Lifetime-risk of alcohol-attributable mortality based on different levels of alcohol consumption in seven European countries. Implications for low-risk drinking guidelines

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Executive summary

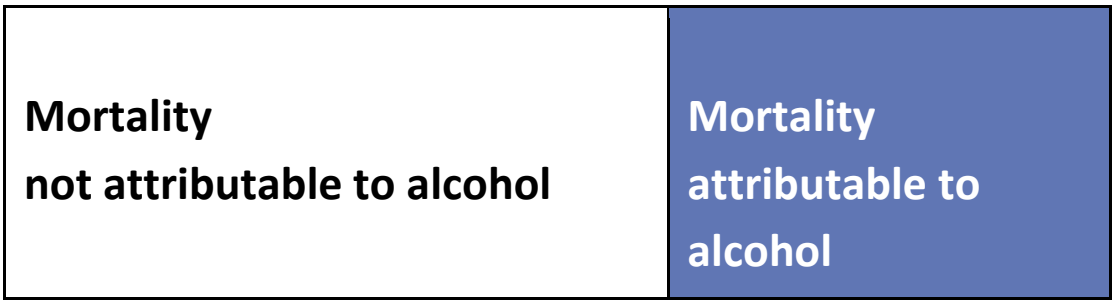
Low-risk drinking guidelines are usually set by blue ribbon committees based on curves showing relative risk of different levels of alcohol use for key alcohol-attributable disease categories such as liver cirrhosis, stroke or various types of cancer. This approach has certain limitations, as there is no easy way to combine the various risk curves and even for a combined risk curve there is no clear threshold, as all summary risk curves for alcohol tend to increase monotonically after small quantities of consumption. Therefore the present report chose to base risk estimations on the (absolute) lifetime risk of dying, following an approach applied by the developers of the Australian low risk guidelines for alcohol consumption. The lifetime risk approach has three advantages: firstly, absolute risks are easier to understand and clearer to communicate. Secondly, there are already standards in many societies and internationally about acceptable lifetime risk, both for voluntary risk and for involuntary risk. Thirdly, it allows comparisons of lifetime risk of alcohol with other risk factors. This report presents calculations for lifetime absolute risk for various levels of drinking for seven European countries.

The schematic figure below shows the principle of the calculations: The first step is to identify the proportion of the cumulative lifetime mortality rate which is attributable to current alcohol consumption (in this case for the year 2012). In the second step this proportion is subtracted from the overall mortality rate and mortality under the scenario of no alcohol consumption is modelled. Based on this rate under the assumption of no alcohol (= “zero alcohol consumption risk”), the third step models the mortality risk for different levels of drinking, i.e., the mortality rate if everybody in a country drank 10g, 20g, 30g and so on. These steps were based on methodology of comparative risk assessment, also used for the Global Burden of Disease and Injury 2010 Study and the Global Status Report on Alcohol and Health 2014 by the World Health Organization. The result gives the best estimates for alcohol-attributable risks for these levels drinking. Patterns of drinking, i.e., the variation of drinking, does not directly enter into the equations. Therefore we give risk curves for acute drinking based on meta-analyses in addition.

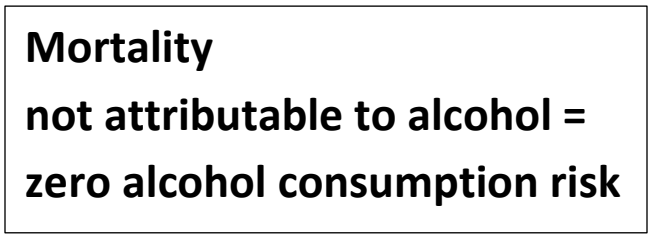
Schematic procedure (simplified) to identify mortality associated with different drinking levels in a country

Step 0: Obtain data on mortality risk for the country under consideration by sex and age.

Step 1: Identify mortality proportion which is attributable to current and past alcohol consumption (in our case, based on Global Status Report on Alcohol and Health, 2014).

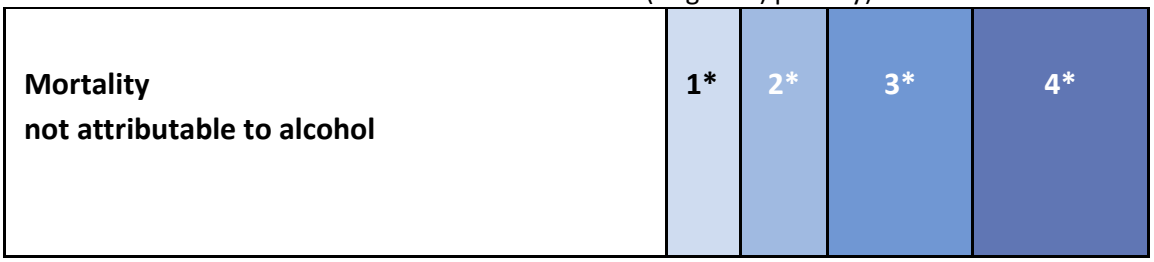


Step 2: Work with the mortality portion not attributable to alcohol consumption (i.e., simulate the country under the counterfactual scenario of no alcohol consumption in the past).



As indicated above, this second step was done by subtracting the mortality attributed to alcohol use as quantified by the WHO Global Status Report on Alcohol and Health (1) from overall mortality.

Step 3: Add mortality which would be resulting under different scenarios of consumption (assuming that drinkers would consume a certain amount of drinks (or grams) per day).



* 1,2,3,4… denote the numbers of drinks a day (as size of standard drinks differ in Europe, we used 10g, 20g, 30g, etc. instead).

The resulting lifetime mortality risks are then compared to the usual acceptable risk standards that high income societies apply to other behavioural risks. It can be shown that the currently accepted risks for customary levels of drinking clearly exceed usual standards, which would be around 1 in 1,000 deaths

lifetime. Usual standards of acceptable risk and the ratio between voluntary and involuntary risks were derived from the literature. For involuntary risks not controlled by the individual such as risks from water, soil or air, nations and international organizations often set standards of 1 in a million (1 in 1,000,000) for lifetime mortality. For voluntary risks stemming from individual behaviours such as hobbies, or lifestyle factors (skiing, smoking), about 1,000 times higher risk is accepted, resulting in an acceptable risk threshold of 1 in 1,000.

Drinking 20 g pure alcohol (2 standard drinks) per day exceeds this threshold for lifetime mortality risk of 1 in 1,000 for both men and women in almost all European countries; and in many of the countries examined, even the 10 times higher risk threshold of a 1 in 100 chance of alcohol-attributable death would be exceeded by this consumption level of 2 standard drinks per day. **In summary, if drinking guidelines were to be based on the usual accepted lifetime mortality risk for voluntary behaviours, the maximum alcohol consumption would be one drink a day (for European Union countries).** In addition, we considered the risk of dying from other people's alcohol use with other involuntary risks in society. Again, the risks accepted for alcohol use by far seem to exceed other involuntary risk thresholds (e.g., lifetime risks from drinking water, soil or air pollution).

Overall, when it comes to alcohol, modern high-income societies seem to accept lifetime mortality risks that are much higher than risks from other behaviours or in case of harm to others, higher than other involuntary risks. The reasons for accepting high risks from alcohol consumption are not fully understood.

A bit of history on low-risk drinking guidelines

Low-risk drinking guidelines, i.e., advice to drinkers on how much alcohol is relatively safe or appropriate[1] to drink, has been largely a concern of the last three decades (2), although earlier efforts can be found—most famously 'Anstie's limit' of 1870, specifying a limit of about three standard drinks (i.e., 34g ethanol) per day for a middle-class man (3). The term "low-risk" guidelines is more and more replacing the earlier terms of "safe" or "sensible" guidelines, as research has indicated that there is no safe limit for the risk of alcohol use for a number of health outcomes such as cancer ((4-6); for risk functions of other diseases see (7); or (8)). The introduction of low-risk drinking guidelines fits well with the modern ideal of a consumer society, with well-informed consumers putatively conforming their behaviour to consumer advice from official or professional sources (2).

In many countries drinking guidelines have been adopted (e.g. (9); http://www.nhs.uk/Livewell/alcohol/Pages/Effectsofalcohol.aspx; http://www.alcool-info-service.fr/alcool/evaluer-consommation-alcool/consommation-a-risque))[2], but the bases for establishing guidelines are not clear. Norfolk described the process of establishing the earlier guidelines in the UK: "[they were] really plucked out of the air…. It was sort of an intelligent guess by a committee" (Norfolk, 2007, cited from (10)). Even the newer guidelines based on different disease specific risk curves (as e.g. the Canadian guidelines (11, 12)) rely on expert judgements when attempting to combine those to one single risk curve. Where to place the threshold (cut-off) to inacceptable risk on this continuous relative risk curve (usually on its monotonically increasing part (see also (13)), is in most cases subject to expert opinion, too. Thus, almost all low-risk drinking guidelines are made by blue ribbon committees[3] determining a consensus based more or less on gut feelings and expected reactions of the public.

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[1] While committees are usually instructed to base their judgements solely on health considerations, inevitably cultural norms about what is appropriate enter the discussion. This can be seen in any public discourse about draft guidelines (e.g., https://www.nhmrc.gov.au/your-health/alcohol-guidelines for Australia).

[2] The current Joint Action on Reducing Alcohol Related Harm (RARHA) has the objective to collect and compare low risk drinking guidelines for the countries of the EU.
http://www.rarha.eu/About/BackgroundPurpose/Pages/default.aspx

[3] From http://en.wikipedia.org/wiki/Blue-ribbon_panel (10.10.2014): "Blue-ribbon panel (sometimes called a blue ribbon commission) is an informal term generally used to describe a group of exceptional persons appointed to investigate or study or analyze a given question. The term generally connotes a degree of independence from political influence or other authority, and such panels usually have no direct authority of their own. Their value

Absolute alcohol-attributable health risk as basis for low-risk drinking guidelines

The Australian low-risk drinking guidelines (https://www.nhmrc.gov.au/your-health/alcohol-guidelines) took a different approach (see also (2); for a general discussion of various approaches see the different contributions to (14)). They tried to identify absolute lifetime mortality risk associated with different levels of drinking (i.e., the probability of dying if one drank at this level the whole adult life). This absolute mortality risk was then compared to other behavioural lifetime mortality risks such as skiing or smoking (see also (10), as background). This still requires some human decision making, to define which lifetime mortality risk level is acceptable for behaviours people choose themselves (i.e., voluntary exposure such as alcohol drinking, smoking, skiing, bungee jumping, etc.) compared to what lifetime mortality risk is acceptable for risks people are involuntarily exposed to (e.g., radon exposure, living with nuclear power; the latter risks are often set in guidelines; for background see (15-19)). We will discuss acceptable risk literature below.

Despite the necessity to define acceptable risk thresholds, the lifetime mortality risk approach has several advantages:

- it explicitly states a criterion for decision making;
- it is based on absolute risks, which are easier to communicate and understand (20, 21);
- the risk analysis for different risk factors can be made comparative, so no sector is differentially treated in policy making.

Based on these considerations, the present analyses will, like the Australian ones, adopt the lifetime approach. In some other, more technical, respects the current approach differs from the Australian approach, which will be explained below.

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comes from their ability to use their expertise to issue findings or recommendations which can then be used by those with decision-making power to act."

[4] We actually modelled the cohort between 0 and 74 years of age, but before age 15, as modelled in the Comparative Risk Analyses of the Global Burden of Disease studies and the Global Status Reports on Alcohol and

Methods

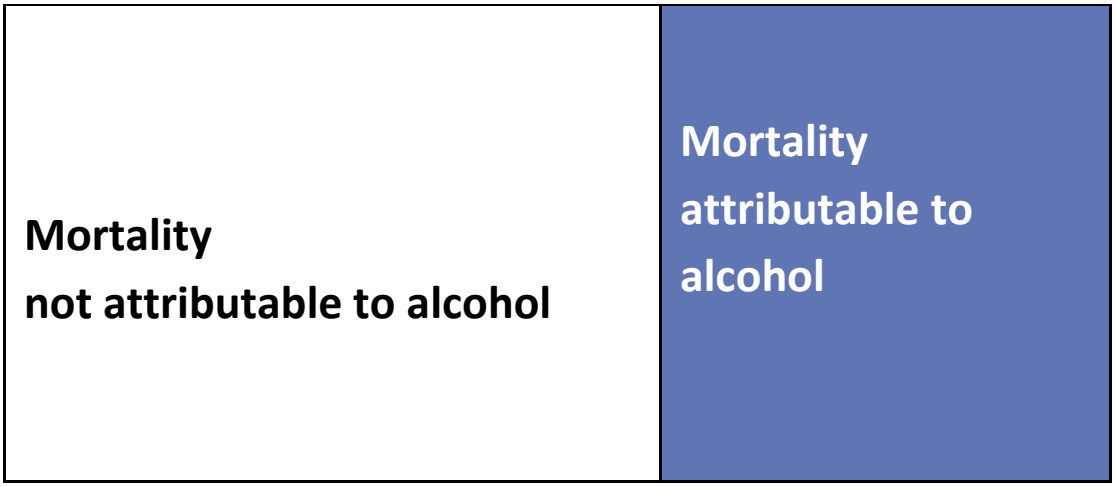
General principles to derive lifetime mortality risks for different levels of alcohol use

Constructing lifetime mortality risks attributable to different levels of alcohol use for European countries requires first a methodology to quantify the risks of alcohol at different levels of drinking. The succession of steps (Figure 1) below schematically outline such a procedure, the details of which are explained and justified in the next sections.

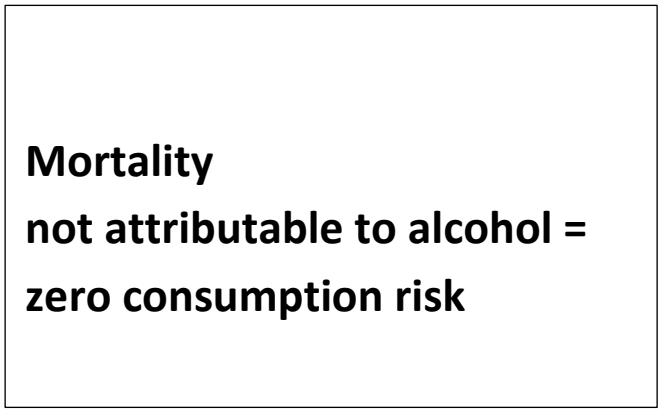
Figure 1: Stepwise procedure to identify mortality associated with different drinking levels in a country

Step 0: Obtain data on mortality risk for the country under consideration by sex and age for each year of the life course.

Step 1: Identify mortality proportion which is attributable to current and past alcohol consumption (in our case, based on Global Status Report on Alcohol and Health, 2014 – (1))



Step 2: Work with the mortality portion not attributable to alcohol consumption (i.e., simulate the country under the counterfactual scenario of no alcohol consumption in the past).



As indicated above, this second step was done by subtracting the mortality attributed to alcohol use as quantified by the WHO Global Status Report on Alcohol and Health (1) from overall mortality.

Step 3: Add mortality which would be resulting under different scenarios of consumption (assuming that drinkers would consume a certain amount of drinks (or grams) per day).

* 1,2,3,4… denote the numbers of drinks a day (as size of standard drinks differ in Europe, we used 10g, 20g, 30g, etc. instead.

Step 4: Steps 1-3 were conducted for one year risks of mortality by sex and age. In order to derive the lifetime risk, we took a hypothetical cohort and artificially "followed" them between ages 15 and 74 (inclusive of age 74) for the impact of alcohol consumption, applying to them the age- and sex specific one-year risks of mortality[4]. The lifetime survival risk can thus be determined based on the multiplication of all yearly survival risks. The lifetime mortality risk is 1-lifetime survival risk.

The lifetime mortality risk approach sketched above requires a number of decisions to conduct the analysis. First of all we defined lifetime as up to age 75 [5]. Further, the following issues were addressed as

[4] We actually modelled the cohort between 0 and 74 years of age, but before age 15, as modelled in the Comparative Risk Analyses of the Global Burden of Disease studies and the Global Status Reports on Alcohol and Health of the WHO, we assumed no alcohol consumption.

[5] Age 75 was taken as a threshold, because death certificate in older age tend to become less accurate with respect to cause of death, which is underlying the calculations in this report. Of course, this decision is conservative, as there are alcohol-attributable deaths after age 74.

described in smaller print below (decisions in short in brackets for readers who would like to skip the technical part):

- Risk for what? Is mortality the best outcome to base guidelines on?
  (cause-specific mortality was taken as the basis of calculations)
- Selection of the dimension of alcohol use to be examined
  (amount of alcohol per day was used)
- Selection of countries – focus on Europe
  (Estonia, Finland, Germany, Hungary, Ireland, Italy, and Poland were chosen as exemplary countries based on the diversity of their drinking cultures)
- Selection of the causes of death causally impacted by different levels of alcohol consumption
  (with only a few small exceptions the same causes as used in the Global Status Report on Alcohol and Health (1), and in the Global Burden of Disease Study (22) were used)
- Selection of operationalizations and methodology
  (method of absolute mortality risk derived from scenarios assuming that all drinkers in a country drink 1 drink, 2 drinks, etc., with different assumptions on mortality)
- Selection of acceptable thresholds for lifetime risk caused by alcohol consumption
  (based on usual thresholds for voluntary risk, thresholds of 1 in 1,000 lifetime mortality risk and a much less conservative risk of 1 in 100 were applied)

Risk for what? Is mortality the best outcome to base guidelines on?

All arguments stated above were based on lifetime mortality risk as the main endpoint for evaluating different levels and patterns of alcohol consumption, but this is not the only possible choice. Any outcome used should be able to summarize across different diseases and injury, without necessarily being a "summary health measure"[6] (24, 25). We decided to use mortality as there is much more literature on acceptable mortality risk compared to acceptable risks for other summary health measures such as disability-adjusted life years (26, 27); or hospitalizations (for some classical reviews on acceptable mortality risks from different disciplines: (17, 28-30)). In other words: only for lifetime mortality could we establish acceptable mortality risk thresholds, which had converged for different high-income countries. Other reasons for taking mortality as major outcome include that it is the most severe outcome, and that mortality data including cause of death information is readily available with reasonable validity and reliability, at least in high-income countries such as all European Union (EU) countries (for more details on these reasons see (31); for review of studies on the reliability of mortality (32)).

[6] Summary measures of population health are measures that combine information on mortality and non-fatal health outcomes to represent the health of a particular population as a single number (23).

This study adopted the methodology to calculate absolute lifetime risk underlying the Australian guidelines (10, 33, 34); for background see also: (31, 35) and https://www.nhmrc.gov.au/your-health/alcohol-guidelines) and refined it as described in the following. At this point we would like to stress, that the chosen methodology does not assume any expert judgements, once the acceptable risk thresholds are set. It is based solely on evidence.

We chose the weighted summation of disease-specific risks rather than using the overall risk function between alcohol use and mortality (e.g., (36-38)), as taking studies on all-cause mortality as the basis for low-risk drinking guidelines for any jurisdiction assumes, that the age- and cause of death distributions of the underlying cohort studies are similar to the respective distributions of the general populations for which the low-risk drinking guidelines should apply (31). This is not likely to be the case; in fact, typical cohort studies differ considerably from European general populations in their mortality mix. Cohorts for prospective studies are usually selected for ease of follow up (39), resulting in a bias favouring stable middle-class populations, unlikely to have the same characteristics as general populations. While this is usually irrelevant when causality between exposure and specific disease outcomes is studied, it does matter when looking at the impact of different levels of exposure on all-cause mortality. In general, cohorts from prospective studies have a much better health profile with higher life expectancies and different causes of death (i.e. fewer injuries, more cardiovascular and other chronic disease death) compared with general populations. Thus, such cohorts will overestimate the protective effect of alcohol use, based on its effects on ischemic diseases and on diabetes (40, 41), and underestimate the detrimental effects.

Selection of dimensions of alcohol use to be examined

From a health perspective it does make a difference if the same amount of alcohol per week (e.g. 14 standard drinks[7] per week) is consumed over a number of days (e.g. 7 days with 2 drinks each day) or concentrated on only a few days (e.g., 5 abstinent days and one day with 8 drinks and one day with 6 drinks; for background see (42, 43)). To account for that, a second dimension of alcohol use often introduced into guidelines is maximal use on each occasion (often labelled as rules for patterns of drinking; for background see (44); for relations to disease see (7, 45)). It is difficult to input such a dimension into lifetime risk calculations, so we chose to indirectly model this via resulting mortality profiles in European countries (see discussion below), and in addition show results for injuries as a function of drinking per occasion.

Selection of countries

The fact that European countries differ considerably with respect to their drinking cultures makes country-specific analyses necessary. A drinking culture comprises preferences with respect to specific beverages, the public demonstration of states of intoxication as well as drinking habits such as drinking with meals. These features are in turn associated with harm (e.g., (46, 47) for the impact of drinking with meals on harm; (48, 49) for the impact of public drinking on harm). Drinking cultures are influenced by traditions, economics and the legal context of a country that both might change over time. Countries and regions were selected to include at least one region with each of the three prototypical drinking pattern traditions in Europe (50-52) as well as European extremes in drinking levels, prevalence of alcohol use disorders (AUD) and life expectancy:

[7] As there are different definitions of standard drinks in European countries, our calculations will be based entirely on grams pure alcohol per day. However, for illustrative examples we still use the term standard drinks, as it is easier understood. Of course, the statement above applies irrespective of how a standard drink is defined.

- Wine-drinking countries in the Mediterranean region, where wine is often consumed daily, usually with meals and avoiding drunkenness. The country selected for this drinking style was **Italy**.

- Central-West and Western regions with also a frequent drinking style, but with beer as the beverage of choice; and proportionally less drinking with meals. The countries selected for this drinking style were **Germany** and **Ireland**.

- Nordic and Central-East and Eastern regions, with a style of irregular heavy drinking, mostly outside meals. We selected four countries with this drinking style representing some variation between wealth and life expectancy[8]: for the Nordic countries: **Finland**; for Central East and Eastern countries: **Estonia** as representative of the Central East/Eastern European EU countries with lowest GDP-PPP and lowest life expectancy; **Hungary** as a medium country for that region; and **Poland** as a relative rich country with one of the longest life expectancies in this region).

In terms of level of drinking, Hungary is among the countries with highest overall use globally (and thus in Europe as well), and Italy one of the countries with lowest drinking level in Europe (1). In terms of prevalence of AUD and especially alcohol dependence, Estonia is among the highest in Europe and Italy among the lowest in Europe (54)

Causes of death causally impacted by different levels of alcohol consumption

Table 1 gives an overview of mortality risks (i.e., disease and injury conditions) causally impacted by alcohol consumption. The list here is identical to the alcohol-attributable causes of deaths, used as a basis of the Global Status Report on Alcohol and Health (1), and to the alcohol-attributable causes used in the Global Burden of Disease Study (22) except the definition of AUD[9] and the impact on HIV/AIDS medication (55). The latter is listed but was not used in our calculations as these risks tend to be very low due to relatively small numbers. In addition to Table 1, the relative risks by sex and level of drinking can be found in-Appendix Table 3.

Harm to others (low birth weight, traffic fatalities) was also not included, as conceptually low risk drinking guidelines are intended to inform drinkers about their risks. In our discussion we will consider harm to others and potential implications for low risk drinking guidelines to protect people other than the drinker.

Table 1: Categories of alcohol-attributable disease and the sources used for determining risk relations

Condition	ICD 10 Code	Sources on risk relations (for calculating alcohol attributable fractions)
Infectious and parasitic diseases		
Tuberculosis	A15-A19	(56); for causal relationship see: (57)

[8] For comparisons of life expectancy see (53) and http://www.oecd-ilibrary.org/sites/9789264183896-en/01/01/index.html?itemId=/content/chapter/9789264183896-4-en

[9] The 2010 GBD did not include "harmful use of alcohol" or "alcohol abuse" into their calculations due to a technical error (see definitions of (22)).

Human immunodeficiency virus/ Acquired immune deficiency syndrome	B20-B24	(55); for estimate on the impact of alcohol on worsening the disease course via disrupting the medication schedule; not relevant for Europe because of small numbers as cause of deaths
Malignant neoplasms		
Mouth and oropharynx cancers	C00-C14	(4, 6)(based on relative risks from (58))
Esophageal cancer	C15	(4, 6) (based on relative risks from (58))
Liver cancer	C22	(4, 6) (based on relative risks from (58))
Laryngeal cancer	C32	(4, 6) (based on relative risks from (58))
Breast cancer	C50	(4, 6) (based on relative risks from (58))
Colon cancer	C18	(4, 6) (combined risk taken from (59))
Rectal cancer	C20	
Diabetes		
Diabetes mellitus	E10-E14	(60)
Neuro-psychiatric conditions		
Alcoholic psychoses (part of AUD)	F10.0, F10.3-F10.9	Special analysis, see text below: section on operationalization and methodology
Alcohol abuse (part of AUD)	F10.1	
Alcohol dependence (part of AUD)	F10.2	
Epilepsy	G40-G41	(61)
Cardiovascular disease		
Hypertensive disease	I10-I15	(62)
Ischemic heart disease	I20-I25	(63-65)
Cardiac arrhythmias	I47-I49	(66)
Ischemic stroke	I60-I62	(65, 67)
Hemorrhagic and other non-ischemic stroke	I63-I66	(67)
Digestive diseases		
Cirrhosis of the liver	K70, K74	(68)
Acute and chronic pancreatitis	K85, K86.1	(69)
Respiratory infections		
Lower respiratory infections	J10–J18, J20–J22	(70)
Conditions arising during the prenatal period		
Low birth weight: as defined by the GBD	P05-P07	(71); cause of death not included, as we only included the harm of drinking to drinkers
Unintentional injuries		
Motor vehicle accidents	§	(58)

Poisonings	X40-X49	(58)
Falls	W00-W19	(58)
Fires	X00-X09	(58)
Drowning	W65-W74	(58)
Other Unintentional injuries	†Rest of V-series and W20-W64, W 75-W99, X10-X39, X50-X59, Y40-Y86, Y88, Y89	(58)
Intentional injuries		(58)
Self-inflicted injuries	X60-X84, Y87.0	(58)
Homicide	X85-Y09, Y87.1	(58)

§ V021–V029, V031–V039, V041–V049, V092, V093, V123–V129, V133–V139, V143–V149, V194–V196, V203–V209, V213–V219, V223–V229, V233–V239, V243–V249,V253–V259, V263–V269, V273– V279, V283–V289, V294–V299, V304–V309, V314–V319, V324–V329, V334–V339, V344–V349, V354–V359, V364–V369, V374–V379, V384–V389, V394–V399, V404–V409, V414–V419, V424–V429, V434–V439, V444–V449, V454–V459, V464– V469, V474–V479, V484–V489, V494–V499, V504–V509, V514–V519, V524–V529, V534–V539, V544–V549, V554–V559, V564–V569, V574–V579, V584–V589, V594–V599, V604–V609, V614–V619, V624–V629, V634–V639, V644–V649, V654–V659, V664–V669, V674–V679, V684–V689, V694–V699, V704–V709, V714–V719, V724–V729, V734–V739, V744–V749, V754–V759, V764–V769, V774–V779, V784–V789, V794–V799, V803–V805, V811, V821, V830–V833, V840–V843, V850– V853, V860–V863, V870–V878, V892.
†Rest of V = V-series MINUS §.

Methodology for estimating alcohol-attributable mortality risk associated with various levels of drinking

The proportions of alcohol attributable mortality by country, age, sex and cause of death were derived from the Global Status Report on Alcohol and Health ((1) steps 1-2 from Figure 1). Steps 3-4 involved the following calculations.

The risk of mortality was estimated for average level of daily alcohol use. The levels of alcohol use for which calculations were made were taken in steps of 10g of pure alcohol up to 100g, i.e., 10 categories of alcohol consumption starting at 10g and ending at 100g. For all disease categories causally related to alcohol consumption we obtained meta-analyses that evaluated the dose-response relationship between alcohol and the risk of disease mortality (i.e. alcohol mortality relative risk functions) (see Table 1). These relative risk functions (where lifetime abstainers were used as the reference category) were used to calculate the relative risk of mortality for each category of alcohol consumption (see appendix Table 1 for RRs). The following equivalent equation was used to derive the risk of death at each alcohol consumption level and in a given sex-age category. All analyses were conducted first subtracting the current impact of alcohol use to obtain a zero alcohol consumption number of deaths ($Deaths\_AA\_Removed_{iz}$), by removing the alcohol-attributable deaths (as obtained from the Global Status Report on Alcohol and Health (1)) from all deaths in that cause of death category i (where i is the index of causes of death (disease and injuries) that are causally impacted by alcohol (except AUD)) for a given sex-age group (z). The absolute risk of dying from an alcohol-attributable death in 2012 for any given sex-age group (z), at alcohol consumption level q, was then calculated as follows:

$$Risk.Death.AA_{zq} = \frac{\sum_{i=1}^{n}((RR_i(q)-1) * Deaths\_AA\_Removed_{iz}) + Deaths_{AUD\_z} * \frac{Prev.AD_{Counterfactual}(q)}{Prev.AD_{Current}}}{Population_z}$$

Where $RR_i(q)$ is the relative risk for mortality at the drinking level q for disease i, $Deaths_{AUD\_z}$ is the number of AUD deaths for sex-age group (z), $Prev\_AD_{Counterfactual}(q)$ is the prevalence of alcohol dependence (AD) under the counterfactual scenario linked to the alcohol level indexed by q, and $Prev\_AD_{Current}$ is the current actual prevalence of AD.

Data on the prevalence of AD for countries under current conditions were obtained from (52) and data for counterfactual scenarios were based on alcohol use data among people with AD from the recent APC-Study (not yet published). From this distribution of alcohol consumption among people with alcohol dependence we were able to estimate the distribution of alcohol consumption among people with AD in Europe (as obtained form (52)). Based on this distribution we were able to estimate the probability of a European having AD given an average daily alcohol consumption amount (q). This prevalence of AD was used as the $Prev\_AD_{Counterfactual}(q)$.

Age groups were split into five-year intervals starting at 15 years of age. Population data and mortality data were obtained from the World Health Organization [(1) based on Global Health Estimates: http://www.who.int/healthinfo/global_burden_disease/en/). All calculations were performed by age group and separately for all countries of interest. Furthermore all calculations were calculated for men and women separately in each country.

There are various potential problems with this approach, which have been dealt with by sensitivity analyses using different assumptions. First, if we used the sex-specific mortality, women would be given too high thresholds. This is because women have, in comparison to men, much higher life-expectancies, i.e. much lower lifetime mortality risk, in all European countries (see (53) and http://www.oecd-ilibrary.org/sites/9789264183896-en/01/01/index.html?itemId=/content/chapter/9789264183896-4-en). Consequently the analyses would be driven more by their overall mortality risk rather than by their alcohol-attributable relative risk, which increases more quickly with increasing consumption than men's relative risk. We included an analysis with sex-specific overall mortality risk (sensitivity analysis 1), but for the main analyses we used the same absolute country and age specific zero consumption mortality risk for both sexes combined derived from the mortality and population data of the WHO for the year 2012 (for methodology used see also above).

Second, the mortality risks for alcohol-attributable diseases other than AUD are based on alcohol-attributable fractions, i.e., on the proportion which is caused by alcohol and which would disappear under the assumption of no alcohol use (for explaining the methodology and background see (72-74); for alcohol see (75)). This model could not be employed for AUD, as these are 100% alcohol attributable by definition (see above). So a different methodology had to be applied, essentially multiplying the probability of alcohol dependence, given different levels of drinking (see above). However, there are additional problems with the mortality from AUD: while AUD are associated with a high level of mortality (76-78), they usually do not appear as a major underlying cause of death in European or global statistics for many reasons including insurance and stigmatization (i.e., insurance in some European countries will not pay, if death is "self-afflicted" by alcoholism; about the stigmatization associated with AUD see (79)).

Third, while the procedure of first removing deaths estimated to be alcohol-attributable successfully removes some of the impact by patterns of drinking (e.g., some of the impact on injury (80) and ischemic heart disease (81)), we suspect that other impacts of patterns of drinking can be found in the country-specific overall mortality even in the zero consumption mortality model, i.e., the . An example here would be the high proportion of misclassified alcohol poisoning deaths in Estonia (82, 83). In other

words: the country differences in overall mortality risk allow us to check on the stability of results from different perspectives.

Lastly, the one-year mortality risks obtained for the various sex-age groups using the equations above were combined to yield lifetime risks (Step 5). For this, we took a hypothetical cohort and artificially "followed" them between ages 0 and 74 (with alcohol consumption being modelled between 15 and 74 years of age), applying to them the age- and sex specific one-year risks of mortality derived in step 3. This was performed using the following formula (where k ≥ 1):

$$POP_k = POP_{k-1} - ((RiskDeathsNonAA_k + RiskDeathsAA_k) * POP_{k-1})$$

where POP_k is the population left at the end of age k (POP_k starts at 1 for 0 years into a person's life course, and decreases as age increases); $RiskDeathsNonAA_k$ represents the risk of a death from a non-alcohol-attributable cause for a person age k; and $RiskDeathsAA_k$ represents the risk of a death from an alcohol-attributable cause for a person age k (and is 0 for ages under 15 years). This formula is applied in an iterative fashion to calculate the population at age 0 to age 74 (inclusive). Using this formula we can then calculate the total risk of an alcohol-attributable death as follows:

$$CumulativeRiskAlcohol_k = \sum_{k=0}^{n} RiskDeathsAA_k * POP_{k-1}$$

where $CumulativeRiskAlcohol_k$ represents the cumulative lifetime risk of dying from an alcohol-attributable death at age k in a person's life course.

Methodological differences between the current approach and the approach taken as basis of the Australian guidelines

As indicated above, this report follows the tradition of calculations underlying the Australian guidelines (https://www.nhmrc.gov.au/your-health/alcohol-guidelines; see also (2)). However, as the analyses have been based on different comparative risk assessments (2004 vs. 2012), there are differences in the methodological details:

- Whereas the lifetime mortality risk calculations of the Australian guidelines were based on the approach of the comparative risk analysis of 2004 (41, 84), the current analyses is based on the comparative risk analysis underlying the GBD 2010 and the Global Status Report on Alcohol and Health for 2012 (1, 22). The former had a categorical approach for different levels of average alcohol consumption (85), whereas the latter had a continuous approach (75).
- In the more recent analyses, more alcohol-attributable disease categories were included, such as tuberculosis and pneumonia, colorectal cancer and pancreatitis; but depression and an unspecific cancer category had been excluded (for details see (86)).

- In the present report, the method to include injury was based on the relationship between **daily average level** of alcohol consumption in the lifetime mortality risks, and reported acute relationships separately on an event basis (see below), whereas calculations conducted for the Australian guidelines were based on **acute risks** for the lifetime risks of injuries as well resulting in two different sets of lifetime risks (https://www.nhmrc.gov.au/your-health/alcohol-guidelines; see also (2, 10, 33, 34)).

Selection of acceptable thresholds for lifetime risk caused by alcohol consumption

The following conclusions are taken from the classic 1969 paper of Starr ((17); p. 1237):

(i) The indications are that the public is willing to accept "voluntary" risks roughly 1,000 times greater than "in-voluntary" risks.
(ii) The statistical risk of death from disease appears to be a psychological yardstick for establishing the level of acceptability of other risks.
(iii) The acceptability of risk appears to be crudely proportional to the third power of the benefits (real or imagined).
(iv) The social acceptance of risk is directly influenced by public awareness of the benefits of an activity, as determined by advertising, usefulness, and the number of people participating.

These conclusions are highly relevant for guidelines for alcohol consumption. Many of the fully involuntary risks such as unsafe water provided to a household have acceptable risk thresholds of 1 in one million (or 1 : 1,000,000; or 1 : 10^6; see also (19)). Indeed, the 1 in one million lifetime mortality risk has become something like a gold standard of acceptable risk for involuntary exposure and has been used in different areas such as water safety in Australia or the US (87, 88) or for increases of exposure to carcinogens in air, sediment or soil (89). It should be noted that other standards have been used, and sometimes we see ranges such as 1 in a million to as 1 in 100,000 (see also http://www.safedriver.gr/studies/KINDYNOS/THE%20MYTH%20OF%2010-6%20AS%20A%20DEFINITION%20OF%20ACCEPTABLE%20RISK.pdf).

Applying the above to determine a threshold for voluntary lifetime mortality risks experienced by the drinker themselves, a threshold of 1 in 1,000 lifetime mortality risk would result. We will additionally apply a much less conservative risk of 1 in 100 in the below, and discuss these numbers in light of empirical evidence of acceptable risk. For involuntary risks to others than the drinkers (90, 91), we will

apply a risk of 1 in a million to 1 in 100,000, analogously to the risks used by US Environmental Protection Agency (see (89)).

Results

Lifetime risks for alcohol-attributable mortality

We will first report on the results of the main scenario with country-specific alcohol-attributable deaths, where the mortality associated with current drinking has first been removed to yield a zero alcohol consumption mortality, and mortality associated with different drinking levels were then re-added. The basic scenario assumes the same zero-consumption mortality risk for both sexes. Tables 2 and 3 and Figures 2-5 below give an overview on the incurring lifetime risks for alcohol-attributable deaths by country, sex and drinking levels, and for all countries combined. The following observations can be made:

- Assuming the same "zero alcohol consumption risk" for both sexes, the same amount of drinking leads to higher absolute mortality risks for women than for men with any distribution of alcohol-attributable causes of death in Europe for any levels of drinking more than 10g. This result reflects the higher relative risks for women compared to men for almost any disease given the same level of drinking.
- An average level of alcohol use of 10g pure alcohol per day over a lifetime is associated with more protective than detrimental effects in most investigated countries; and on average for men and for both sexes combined. For women drinking this amount, the average alcohol-attributable lifetime mortality across countries is 9 in 10,000. As the consequences are below the usually accepted risk standards of 1 in 1,000, low-risk drinking guidelines for European countries for adult populations should tolerate drinking of 10g pure alcohol per day .
- **If the usual risk threshold of 1 in 1,000 for alcohol-attributable lifetime mortality is chosen (see discussions above and below), then 20g pure alcohol on average per day would exceed this threshold in all countries for women and for men with one exception.**
- Even a risk threshold of 1 in 100 for alcohol-attributable lifetime deaths would be exceeded for women in all countries with drinking 20g pure alcohol per day (threshold of 1 in 100 for women across all countries is 14.6g). For men the risk threshold of 1 in 100 for alcohol-attributable lifetime death would be exceeded when drinking 30g on average in all but one European country examined (Ireland). The exact threshold for a 1% risk, across countries, would be 25.9g pure alcohol per day for men.

As indicated above, the results of Table 2 reflect the main scenario of our modelling, where the same country specific non-alcohol-attributable mortality rates were applied to both sexes, and the risk associated with different levels of drinking were added on top of this.

Table 2: Lifetime risk to die from alcohol use for different levels of average daily consumption in Europe in 2012

Average drinking	Average across all seven countries		
	Men	Women	Total
10g	-0.0019	0.0009	-0.0005
20g	0.0043	0.0199	0.0121
30g	0.0138	0.0471	0.0305
40g	0.0269	0.0804	0.0536
50g	0.0444	0.1267	0.0855
60g	0.0664	0.1726	0.1195
70g	0.0962	0.2436	0.1699
80g	0.1292	0.3026	0.2159
90g	0.1718	0.3690	0.2704
100g	0.2298	0.4429	0.3364

Level of alcohol consumption associated with:		
	Men	Women
a 1/1,000 risk of dying	15 g	10 g
a 1/100 risk of dying	26 g	15 g

Coloring:

Green: overall protective effect

Lightest red: overall lifetime risk smaller than 1 in 1,000

Light red: overall lifetime risk smaller than 1 in 100, but larger than 1 in 1,000

Dark red: overall lifetime risk equal to or larger than 1 in 100

Basis: overall country-specific mortality risks for both sexes combined; sex- and age-specific relative risks for different drinking levels

In conclusion, if the approach is taken to base drinking guidelines on the usual thresholds for acceptable risk for behavioural risk factors (i.e. voluntary risks taken with a threshold of 1 in 1,000), one would have to consider drinking guidelines of less than 20g pure alcohol per day for both sexes as justified. If one allows exceptions for drinking compared to other behaviours, e.g. by considering a more lenient mortality risk threshold for alcohol because of its historical tradition in Europe, and accepting a threshold of 1in 100 lifetime risk of alcohol-attributable death, one would have to go to about 15g pure

alcohol per day as a threshold for women, and to 26g as threshold for men. However, modern high-income societies do usually not accept any risks that high for voluntary behaviour not considered necessary for survival.

Table 3: Lifetime risk to die from alcohol use for different levels of average daily consumption in 2012 for men (M) and women (W) – main scenario

Average drinking	Estonia		Finland		Germany		Hungary		Ireland		Italy		Poland	
	M	W	M	W	M	W	M	W	M	W	M	W	M	W
10g	0.0027	0.0051	-0.0015	0.0037	-0.0004	0.0024	-0.0061	-0.0022	-0.0014	0.0014	0.0002	0.0022	-0.0068	-0.0062
20g	0.0138	0.0380	0.0030	0.0185	0.0041	0.0148	0.0028	0.0274	0.0025	0.0126	0.0045	0.0131	-0.0004	0.0148
30g	0.0296	0.0842	0.0102	0.0402	0.0110	0.0327	0.0171	0.0695	0.0084	0.0287	0.0104	0.0279	0.0102	0.0466
40g	0.0504	0.1371	0.0197	0.0655	0.0197	0.0543	0.0373	0.1221	0.0169	0.0492	0.0182	0.0467	0.0259	0.0877
50g	0.0792	0.2175	0.0344	0.1054	0.0322	0.0866	0.0635	0.1888	0.0277	0.0762	0.0278	0.0706	0.0458	0.1418
60g	0.1097	0.2868	0.0522	0.1429	0.0477	0.1179	0.0993	0.2594	0.0425	0.1055	0.0404	0.0964	0.0730	0.1990
70g	0.1625	0.4173	0.0800	0.2141	0.0694	0.1712	0.1408	0.3494	0.0603	0.1468	0.0549	0.1275	0.1058	0.2789
80g	0.2055	0.4955	0.1078	0.2651	0.0928	0.2140	0.1941	0.4370	0.0832	0.1887	0.0739	0.1628	0.1470	0.3549
90g	0.2583	0.5769	0.1447	0.3240	0.1229	0.2641	0.2629	0.5325	0.1140	0.2390	0.0983	0.2048	0.2018	0.4414
100g	0.3255	0.6596	0.1959	0.3920	0.1647	0.3230	0.3550	0.6332	0.1578	0.2997	0.1318	0.2549	0.2782	0.5377

Coloring:

Green: overall protective effect

Lightest red: overall lifetime risk smaller than 1 in 1,000

Light red: overall lifetime risk smaller than 1 in 100, but larger than 1 in 1,000

Dark red: overall lifetime risk equal to or larger than 1 in 100

Basis: overall country-specific mortality risks for both sexes combined; sex-and age specific relative risks for different drinking levels

Figure 2: Lifetime risk for alcohol-attributable mortality for different levels of drinking pure alcohol per day by sex (M=men, W=women) for Estonia (left) and Finland (right)
(based on mortality data for 2012)

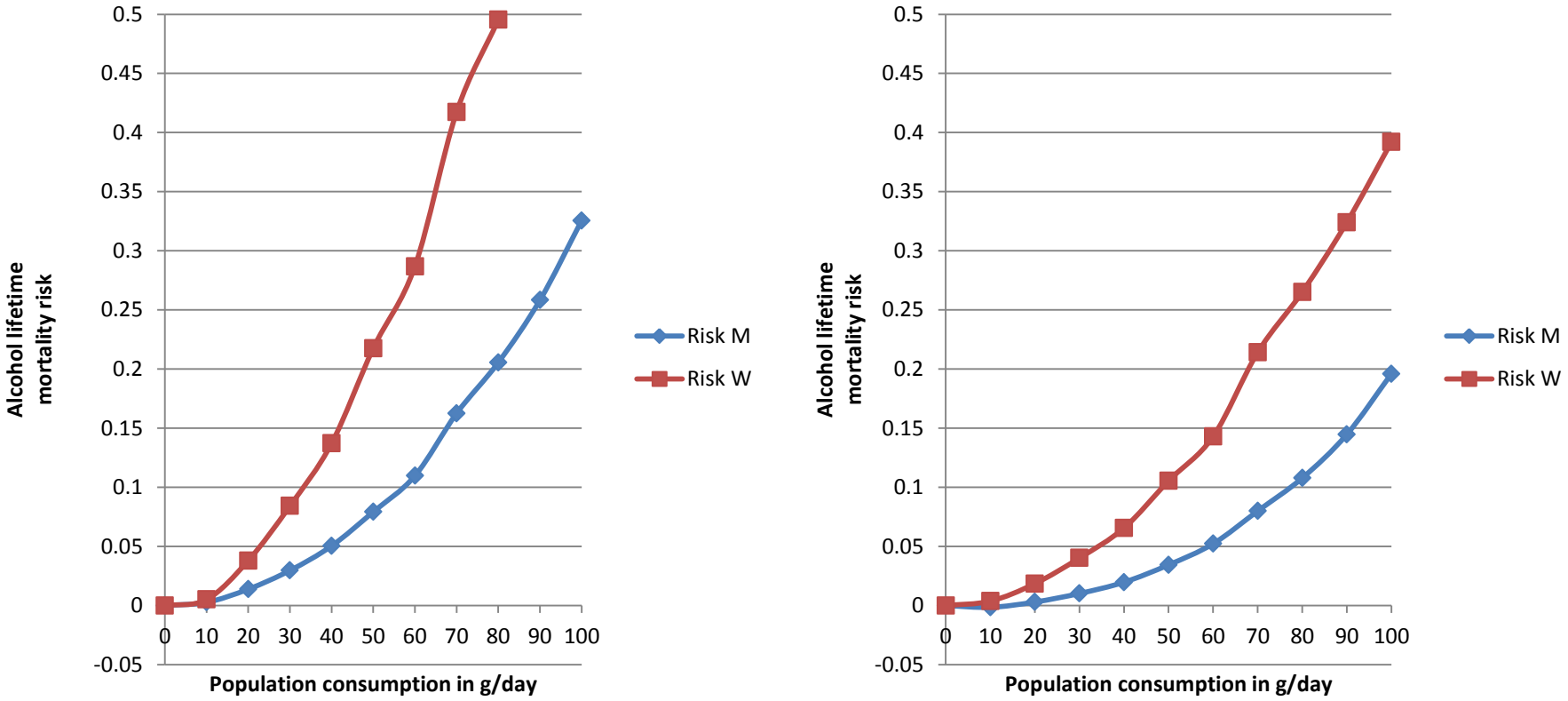


Figure 3: Lifetime risk for alcohol-attributable mortality for different levels of drinking pure alcohol per day by sex (M=men, W=women) for Germany (left) and Hungary (right) (based on mortality data for 2012)

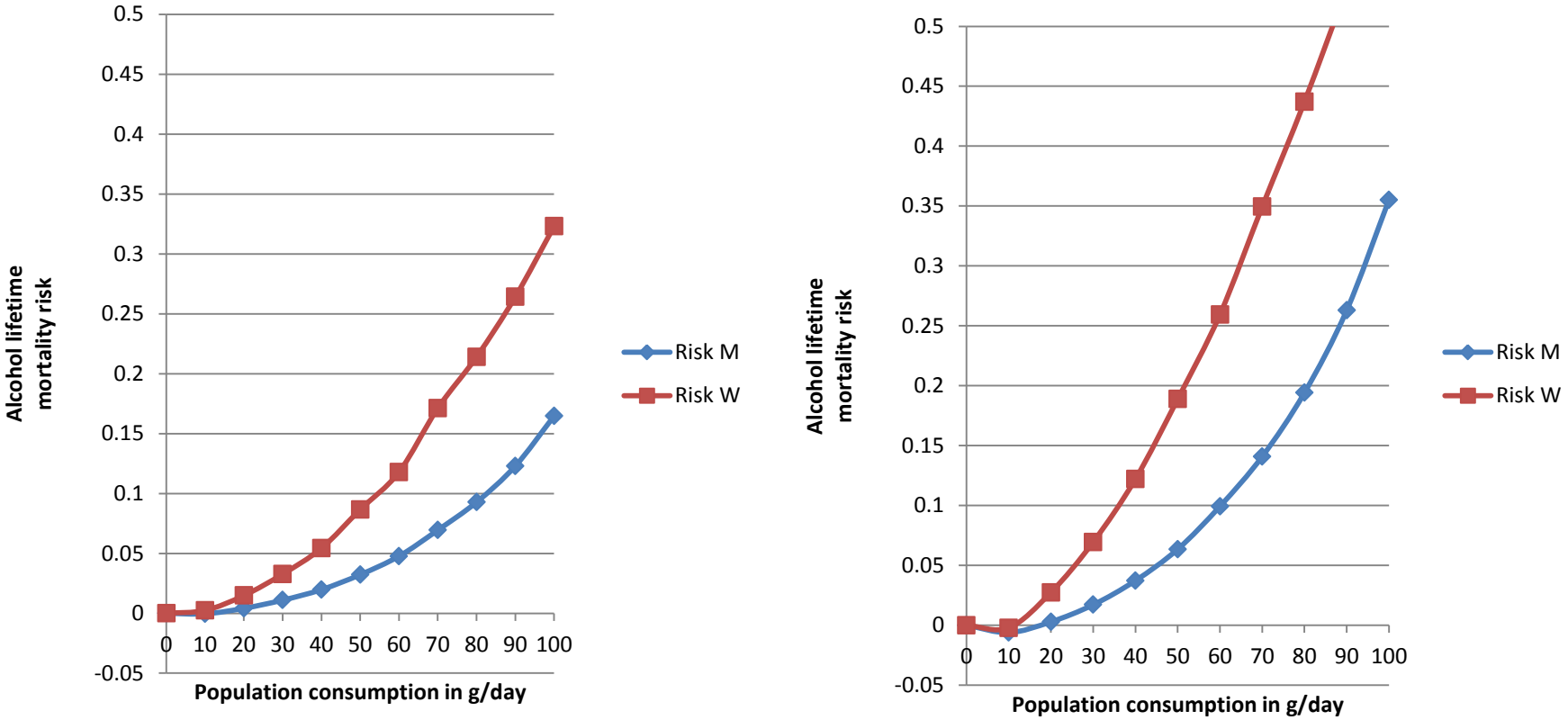


Figure 4: Lifetime risk for alcohol-attributable mortality for different levels of drinking pure alcohol per day by sex (M= men, W= women) for Ireland (based on mortality data for 2012)

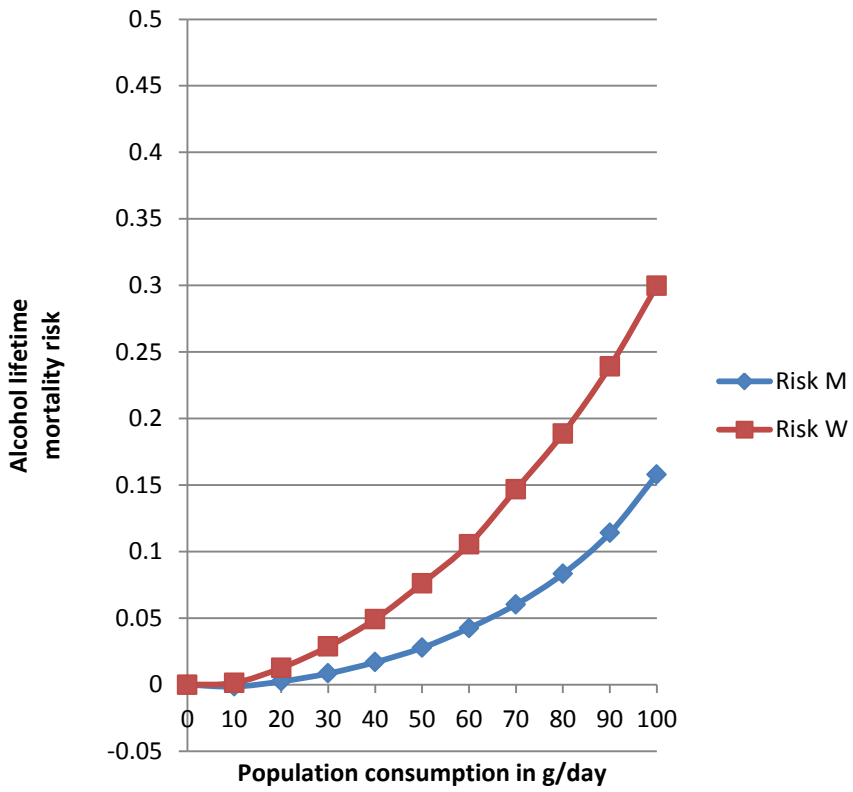
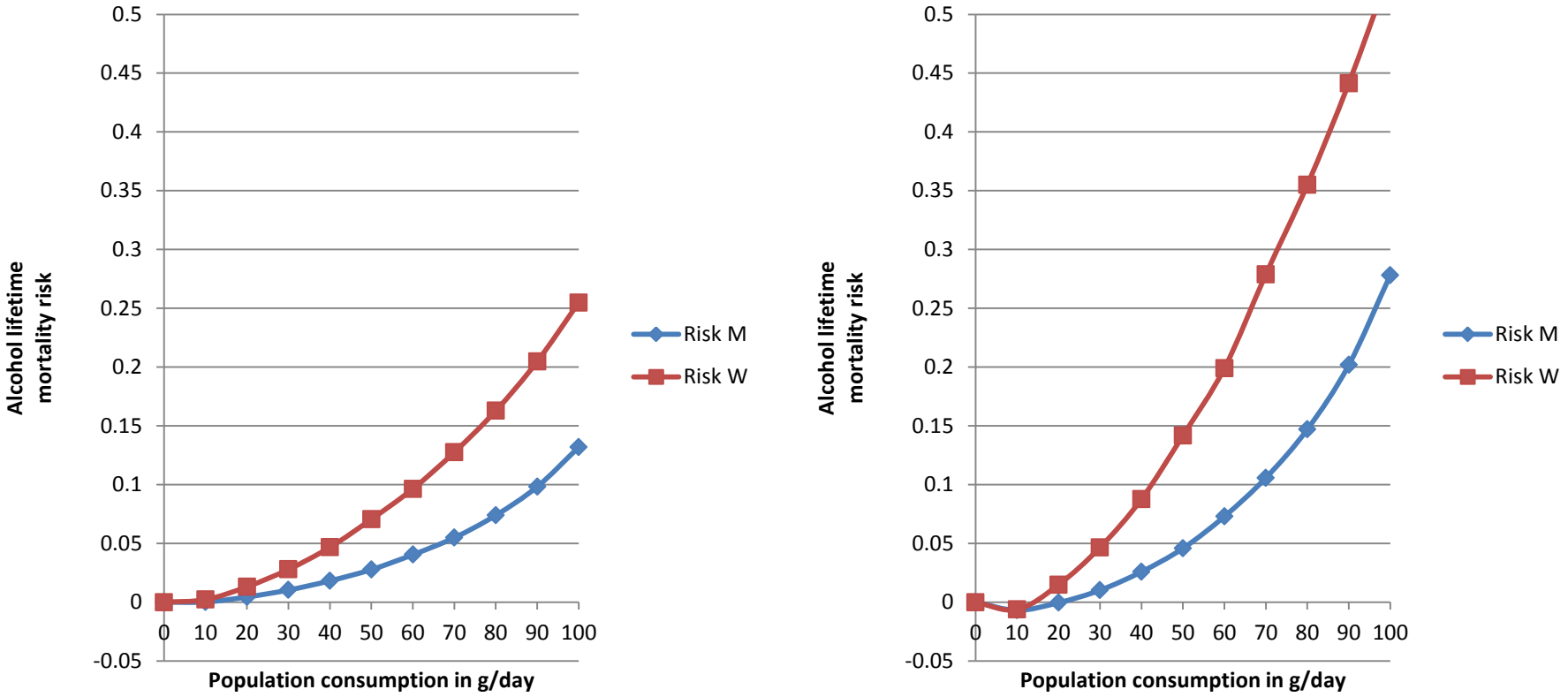


Figure 5: Lifetime risk for alcohol-attributable mortality for different levels of drinking pure alcohol per day by sex (M=men, W=women) for Italy (left) and Poland (right) (based on mortality data for 2012)



Results of the sensitivity analyses

Sensitivity analysis 1 using sex-specific mortality

The first sensitivity analyses used sex-specific "zero alcohol consumption" mortality together with the sex-specific relative risks for alcohol use (the latter being the same as in the main analysis above). Results are summarized below in Table 4 (for all countries combined) and in Appendix Table 1 and the Appendix Figures 1-7 for country-specific results.

The higher **relative** risks for women compared to men for the same level of alcohol use in these analyses are partially cancelled out by the overall mortality risks which are lower among women than among men. However, the mortality risk for men in this scenario are only markedly higher at heavy drinking levels (see Table 4; for the average risk across all countries, the ranking on the genders switches between 80g/day and 90g/day). For the lower levels of alcohol use relevant for guidelines, the same conclusions can be drawn as from the main analyses:

- Use of 10g pure alcohol per day was associated with overall beneficial effects for men and both sexes combined, even if the lifetime mortality risk for women in Europe was not below the acceptable risk threshold of 1 per 1,000(see Table 4).
- **With a threshold for alcohol-attributable lifetime mortality risk of 1 in 1,000, use of 20g pure alcohol on average per day exceeded acceptable risk for both men and women (and in each single instance in all countries except for men in Poland).**
- For women, even a threshold of 1 in 100 was exceeded in most cases with 20g pure alcohol per day on average (across the countries, the exact threshold was 16.7g).
- For men, the threshold of 1 in 100 alcohol-attributable lifetime risk was met at 23.7g.

Table 4: Lifetime risk to die from alcohol use for different levels of average daily consumption in Europe in 2012 – (sensitivity analyses with sex-specific mortality and with alcohol-attributable deaths of current drinking patterns removed and then alcohol-attributable deaths for specific drinking levels added)

Average drinking	Average across all seven countries		
	Men	Women	Total
10g	-0.0040	0.0016	-0.0012
20g	0.0048	0.0141	0.0094
30g	0.0187	0.0312	0.0249
40g	0.0381	0.0522	0.0452
50g	0.0643	0.0804	0.0724
60g	0.0970	0.1097	0.1034
70g	0.1412	0.1518	0.1465
80g	0.1887	0.1911	0.1899
90g	0.2493	0.2366	0.2429
100g	0.3293	0.2891	0.3092

Level of alcohol consumption associated with:		
	Men	Women
a 1/1,000 risk of dying	16 g	10 g
a 1/100 risk of dying	24 g	17 g

Coloring:

Green: overall protective effect

Lightest red: overall lifetime risk smaller than 1 in 1,000

Light red: overall lifetime risk smaller than 1 in 100, but larger than 1 in 1,000

Dark red: overall lifetime risk equal to or larger than 1 in 100

Basis: country-specific mortality risks for both sexes combined; sex-and age specific relative risks for different drinking levels

Sensitivity analysis 2 using combined mortality but additionally adjusting for competing risks from non-alcohol-attributable deaths

Table 5 and Appendix Table 2 provide an overview of the results with the deaths from competing risks (mortality from causes other than alcohol) being taken out. This method takes into account that if a person dies from a cause other than that attributable alcohol, they can not die again of alcohol (i.e in

the unadjusted model mortality from other causes during a person's life course are not taken into account). The impact of accounting for mortality not caused by alcohol, increases with age, but as 75 years is still below the average life expectancy for both sexes in the EU (although barely for men; http://www.oecd-ilibrary.org/sites/9789264183896-en/01/01/g1-01-01.html?itemId=/content/chapter/9789264183896-4-en&_csp_=9e67b2c8fa06d751ee4c494e32bfe3da) this effect would further increase if a life course of 76 years or more were modelled. However, while these analyses changed the results a lot for heavier drinking (lower proportions of deaths being caused by alcohol; see country specific graphs in Appendix Figures 7-12), the main conclusions with respect to low-risk drinking guidelines remain unchanged (Table 5):

- Use of 10g pure alcohol per day is often estimated to have a beneficial effect, dependent on sex and country, and overall leads to a mortality risk below the thresholds of acceptable risk.
- **For women as well as men, the use of 20g pure alcohol per day would exceed the threshold of 1 in 1,000 of lifetime risk for alcohol-attributable death.**
- If a threshold of 1 in 100 is applied, consuming 20g would still exceed that threshold for women, but not for men. The exact amounts of pure alcohol to reach risk of alcohol-attributable mortality of 1 in 100 would be 19.1g for women and 25.6g for men.

Table 5: Lifetime risk to die from alcohol use for different levels of average daily consumption in Europe in 2012 – (sensitivity analyses with sex-combined mortality and with alcohol-attributable deaths of current drinking patterns removed and then alcohol-attributable deaths for specific drinking levels added; competing risks adjusted)

Average drinking	Average across all seven countries		
	Men	Women	Total
10g	0.0001	-0.0007	-0.0003
20g	0.0059	0.0110	0.0084
30g	0.0132	0.0268	0.0200
40g	0.0218	0.0431	0.0324
50g	0.0338	0.0652	0.0495
60g	0.0466	0.0801	0.0634
70g	0.0650	0.1123	0.0887
80g	0.0780	0.1252	0.1016
90g	0.0904	0.1368	0.1136
100g	0.1018	0.1470	0.1244

Level of alcohol consumption associated with:			
	Men	**Women**	
a 1/1,000 risk of dying	12 g	11 g	
a 1/100 risk of dying	26 g	19 g	

Coloring:

Green: overall protective effect

Lightest red: overall lifetime risk smaller than 1 in 1,000

Light red: overall lifetime risk smaller than 1 in 100, but larger than 1 in 1,000

Dark red: overall lifetime risk equal to or larger than 1 in 100

Basis: Overall country-specific mortality risks were taken into account for both sexes combined; sex-and age specific relative risk data for different drinking levels (specifically, RR(q)-1) were applied to the percentage of the population at age k (were k ranges from 15 to 74 years of age) that were still alive as compared to those alive at birth (i.e. 100%). This estimated the risk of dying at age k from an alcohol-attributable case, i.e. the cumulative risk of dying up to age 75 is the lifetime risk of dying from an alcohol-attributable death.

Acute risks as a result of drinking per occasion

In addition to risk associated with average daily alcohol intake, lower risk guidelines should consider acute risk in the drinking situation, e.g. driving under the influence. In the following, we will present data from meta-analyses for acute risks, which is usually illustrated as the relationship between acute alcohol intake and risk of injury[10]. Two contributions summarized this relationship for non-fatal and fatal outcomes (93, 94). The risk curves can be seen in Figures 6 to 8. It should be noted that the risk relationships presented in the following are relative risk relationships (as opposed to the absolute risks reported above). The reported odds ratios indicate the factor by which the odds of an injury increase under different levels of consumption/intoxication compared to the odds of injury when being sober.

[10] Please note that the lifetime risks above are based on the meta-analyses between average level of alcohol use and injury (taken from (58); see Table 1 above). As this association is much less pronounced, and mainly reflects indirectly the association between acute alcohol intake (often measured as blood alcohol concentration and then converted into intake of grams absolute alcohol ingested in the last hours – but see (92), for some caution) and injury, the impact of alcohol use on injury has been underestimated for the main analyses, and thus the impact of injury on overall lifetime mortality risk has been relatively small (for instance compared to regular comparative risk assessments, where this impact is modelled as an interaction between average level of consumption and frequency and quantity of heavy drinking occasions (80)).

Figure 6: Dose-response curve for the amount of alcohol consumed 3 hours prior and the odds of injury other than motor vehicle accident injury (from Taylor et al., 2010)

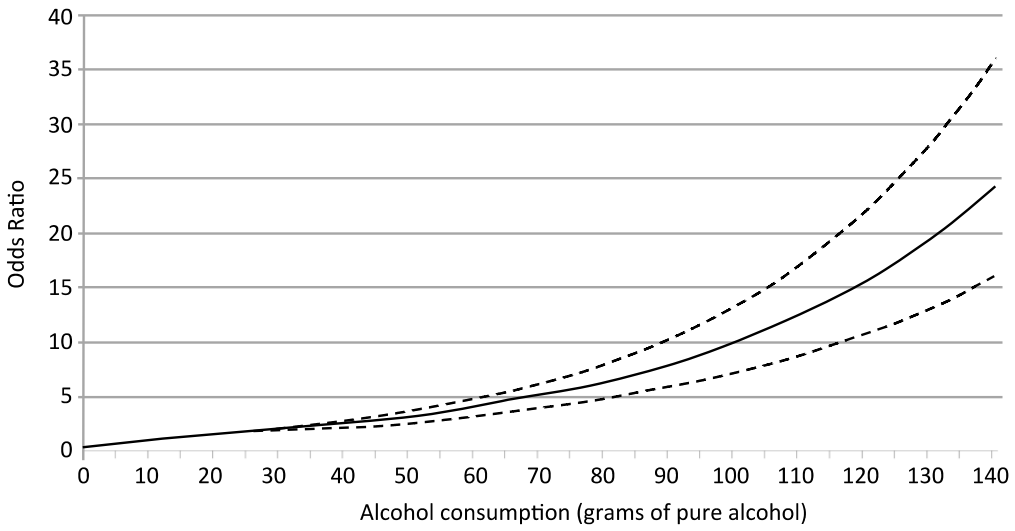


Figure 7: Dose-response curve for the amount of alcohol consumed 3 hours prior and the odds of motor vehicle accident injury (from Taylor et al., 2010).

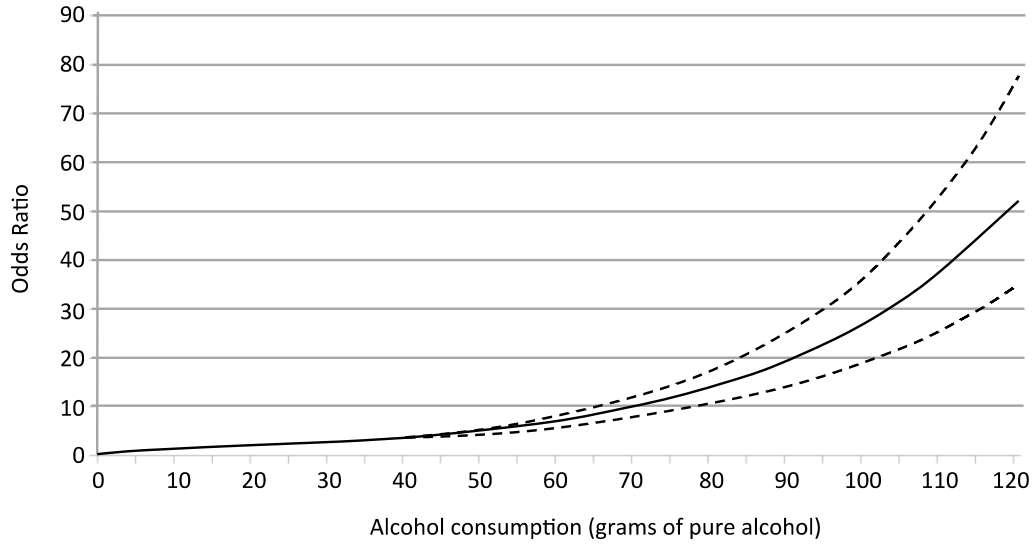
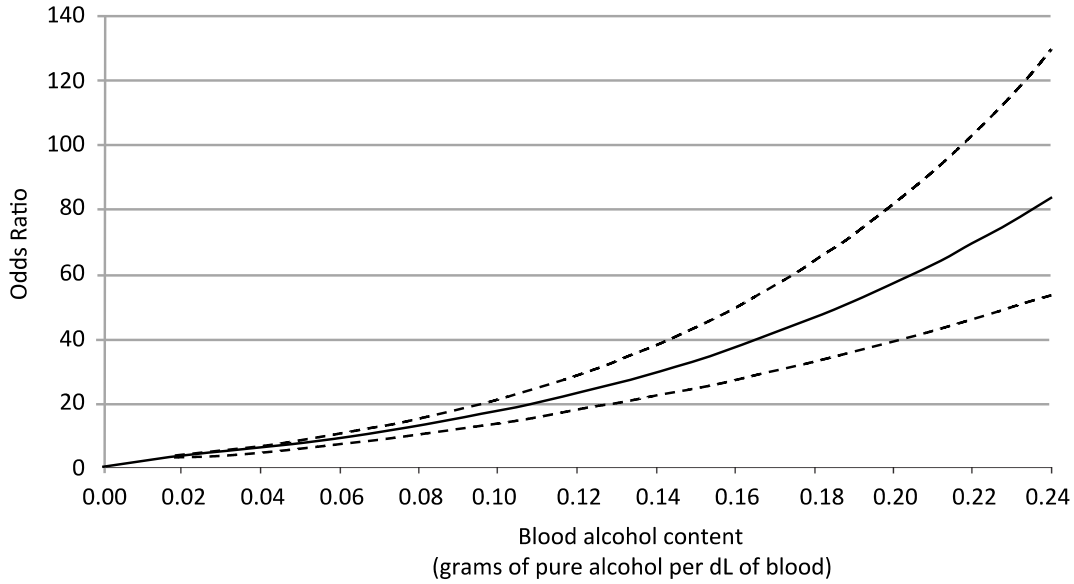


Figure 8: Dose-response curve for the blood alcohol concentration (BAC) levels and the odds of fatal motor vehicle Injury for BAC levels from 0 to 0.24% (from Taylor et al., 2012)



To summarize the results:

- The relationship between alcohol use before injury and the risk of injury is exponential, with considerably elevated risk at higher levels.
- However, even at lower levels of consumption, there is significantly elevated risk, and no indication for a protective effect.
- These results are in line with biological research on the effects of low dose consumption on psychomotor skills and other behavioural effects of the central nervous system (95). The general result of a causal impact of prior alcohol use on injuries has also been corroborated by other reviews and meta-analyses (96-100).

Further considerations about variability of drinking – alcohol free days

Alcohol-free days are part of several guidelines (e.g., (101), and are currently discussed as part of the revision of the UK guidelines (http://www.nhs.uk/change4life/Pages/alcohol-lower-risk-guidelines-units.aspx). The scientific basis for alcohol-free days is scarce, especially for light to moderate drinking. Walsh and Rehm (1996)(43) found lower mortality risk if the same amount of alcohol was spread over all

days compared to fewer days. However, daily drinking has long been considered a risk for AUD (for instance, (102). Also, there are good indications that for heavier drinking, alcohol-free days result in less mortality, in part due to relieving liver functions (103).

Considerations of heterogeneity between people, and consequences for low-risk drinking guidelines

So far, we have concentrated exclusively on population numbers derived on the basis of meta-analyses. This approach is valid as a basis for low-risk guidelines for populations, and we have already pointed to potential differences by sex, which did mainly play a role for higher levels of consumption, but not for the general conclusion that usual acceptable lifetime mortality risks are exceeded with 20g pure alcohol per day for both sexes, which is less than two standard drinks for many European countries (most notable exception UK; for standard drinks size see (104, 105)), and probably less than two poured standard drinks in almost all European countries.

What other characteristics impact on consequences of drinking and what role do they play for considerations of low risk drinking guidelines:

The country-specific alcohol consumption risks were based on alcohol relative risks that did not take into account **genetic differences**. For example, some individuals have a certain type of a gene that causes a flushing response (i.e. their face turns red) when they consume alcohol. This flushing response is due to a reduced breakdown of acetaldehyde after alcohol consumption (106). The genetic difference that leads to the flushing response may also lead to differences in how much alcohol people consume (107), and subsequent differences in risk for alcohol-attributable diseases (107, 108). However, the proportion of the total population with the type of gene that leads to the flushing response is low in Europe (109), and thus the limitation of the relative risks not accounting for this genetic difference will likely have a negligible effect on the country level risks. Other genetic constellations impacting systematically on relative risks of drinking relevant for the population level in Europe are not known.

The detrimental effects of alcohol do not only depend on the amount of pure alcohol consumed but on the resulting blood alcohol concentration and thereby the degree to which organs and tissues are exposed to alcohol. The blood alcohol concentration resulting from a certain alcohol intake is associated with body size. Would it therefore be useful to include body size stratifications in lower risk guidelines? In fact, blood alcohol concentration is also determined by body water content, body weight, body fat, the pace of metabolism and many other factors (110-112). Gender differences in the effects of alcohol

consumption partially go back to systematic differences in those parameters (112). Beyond that, the blood alcohol concentration may be determined by the specific beverage, over and above its alcohol content (113), again differing by gender. Beyond those individual factors blood alcohol concentration and toxicity of alcohol depend on situational factors as being 'fed or fasted' (114). Overall the effects of alcohol on each individual are determined by many other factors than just the pure alcohol consumed. However, in order to be useful, guidelines should be concise, clear and easy to remember. Therefore we do not recommend including measures as body size or weight into new lower risk guidelines.

Discussion

If the threshold for alcohol-attributable lifetime mortality risk is chosen to be 1 in 1,000, which seems to be the standard for other voluntary risks in modern high-income societies, then drinking 20g pure alcohol per day exceeds this threshold for both sexes. This result is consistent for the different European countries examined in the main analysis and both sensitivity analyses. Even if a considerably more lenient lifetime mortality threshold of 1 per 100 was introduced, the guidelines for women would recommend values lower than 20g of pure alcohol per day and those for men less than 30g per day. However, there does not seem to be a good justification for such high thresholds, since alcohol use is a voluntary behaviour, i.e., neither necessary as part of diet nor as part of any needs to survive. The present results corroborate the finding, that overall modern high-income societies accept higher thresholds for mortality risks from alcohol use compared to other voluntary risk factors (19), which is also reflected in current lower risk drinking guidelines in Europe.

As indicated above, two different sensitivity analyses were carried out. The first was based on sex-specific mortality risks, and the second took into consideration competing risks in a more conservative way. Both of these scenarios to test the stability of our finding arrived at similar conclusions for the average levels of drinking to reach predetermined acceptable thresholds, while for higher use levels, the differences between scenarios grew. It should be stressed, that lifetime mortality risk associated with drinking at higher levels (e.g., 50g pure alcohol per day and above) would be similar or exceed the lifetime risk of smoking (115, 116)[11].

It would be an interesting exercise to base low risk drinking guidelines on involuntary risk. From the sparse research on mortality and morbidity caused by others' drinking from Australia, it seems that even the yearly risks of current drinking patterns in this country would exceed lifetime acceptable risk thresholds for involuntary behaviour. Thus, for the year 2008, an Australian study (117) found a yearly burden of 367 deaths and almost 14,000 hospitalizations due to drinking by others, indicating a yearly risk of higher than 1 in 100,000 for mortality, and about 0.5 per 1,000 for hospitalizations, clearly much higher than the usually accepted involuntary risk thresholds stated above (i.e., 1 in 1,000,000 lifetime;

[11] This does not mean that the deaths of current drinking in Europe exceed the deaths of smoking for two reasons:
1) A smaller proportion of the population drinks 50g or above compared to the prevalence of smoking.
2) The analyses here are restricted to 75 years of age. Many of the smoking attributable deaths occur later than this age.

see also (17, 89)). As these mortality and morbidity risks of current drinking on others than the drinker by far exceed acceptable risk, this could be reflected in devising guidelines for alcohol based on involuntary risk. In fact, alcohol-attributable mortality to others (i.e., involuntary risk considerations) could be used as a benchmark for national alcohol policies. Such a benchmark would contribute to the initiation of effective policies to reduce not only the risks to non-drinkers, but to reduce the risk to the drinkers as well. Given the main causes of involuntary risk to others, the following areas should be highlighted:

- Measures to reduce alcohol-attributable injury in traffic.
- Measures to reduce alcohol-attributable injury at the workplace.
- Measure to reduce alcohol-attributable violence.
- Measures to reduce drinking in pregnant women.

In addition to specific measures, some general measures such as increase in taxation or reduction of availability have been shown to be effective in reducing alcohol-attributable injury including violence (118, 119).

In assessing mortality risk and health burden due to alcohol consumption, one should not overlook that the burden of alcohol goes well beyond the health field, including such social consequences to those around the drinker and to the wider society as crime, lost productivity, family problems, child neglect or abuse, and social marginalisation (120). An Australian study found that the reported tangible costs from out-of-pocket expenses and time lost because of others' drinking were of much the same magnitude as the costs to health, social and legal systems of dealing with problems from drinking (117). While it may prove hard to integrate the metrics of social burden with those of health burden, they underline the necessity to change our negligent attitude towards alcohol use and its risks.

Overall, while we found that societies accept much higher lifetime mortality risk for alcohol use compared to other risk factors, both for voluntary risk to the drinker and for involuntary risk to others, the reasons for this acceptance are not fully understood (19). It may be related to lack of knowledge about the true risks of alcohol, especially for cancer, or to historical vagaries, as alcohol use has neither been integrated into food regulations as an ordinary food item, nor into international conventions which exist for all other psychoactive substances, nor has there been a public health action similar to tobacco after the repeal of prohibition (for more details see (19)). However, as current evidence clearly indicates an exceptional role for alcohol use, with higher mortality risks being accepted than for other behavioural

and non-behavioural risk factors, we may well rethink acceptable risk for alcohol, and this rethinking could be reflected in new low-risk guidelines.

Appendices

Sensitivity analysis 1 and 2

Appendix Table 1: Lifetime risk to die from alcohol use for different levels of average daily consumption in 2012 – (sensitivity analysis with sex-specific mortality and with alcohol-attributable deaths of current drinking patterns removed and then alcohol-attributable deaths for specific drinking levels added)

Average drinking	Estonia		Finland		Germany		Hungary		Ireland		Italy		Poland	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
10g	0.0014	0.0029	-0.0036	0.0038	-0.0012	0.0027	-0.0098	-0.0015	-0.0028	0.0031	-0.0001	0.0019	-0.0116	-0.0019
20g	0.0188	0.0217	0.0023	0.0129	0.0050	0.0112	0.0030	0.0185	0.0020	0.0121	0.0059	0.0093	-0.0031	0.0128
30g	0.0444	0.0469	0.0125	0.0253	0.0146	0.0227	0.0238	0.0466	0.0097	0.0242	0.0144	0.0190	0.0117	0.0336
40g	0.0792	0.0760	0.0261	0.0397	0.0270	0.0366	0.0532	0.0824	0.0210	0.0391	0.0257	0.0312	0.0346	0.0603
50g	0.1265	0.1189	0.0478	0.0613	0.0452	0.0560	0.0917	0.1275	0.0354	0.0586	0.0397	0.0465	0.0637	0.0940
60g	0.1766	0.1597	0.0746	0.0820	0.0675	0.0755	0.1435	0.1770	0.0555	0.0793	0.0584	0.0629	0.1032	0.1313
70g	0.2596	0.2309	0.1157	0.1198	0.0994	0.1051	0.2033	0.2377	0.0791	0.1084	0.0797	0.0821	0.1514	0.1783
80g	0.3263	0.2833	0.1570	0.1483	0.1329	0.1316	0.2771	0.3035	0.1102	0.1372	0.1078	0.1040	0.2100	0.2296
90g	0.4057	0.3416	0.2114	0.1815	0.1761	0.1629	0.3695	0.3789	0.1521	0.1715	0.1438	0.1300	0.2866	0.2897
100g	0.5023	0.4057	0.2858	0.2205	0.2353	0.1999	0.4870	0.4641	0.2115	0.2127	0.1932	0.1610	0.3903	0.3600

Coloring:

Green: overall protective effect

Lightest red: overall lifetime risk smaller than 1 in 1,000

Light red: overall lifetime risk smaller than 1 in 100, but larger than 1 in 1,000

Dark red: overall lifetime risk equal to or larger than 1 in 100

Basis: overall country- and sex-specific mortality risks; sex- and age-specific relative risk for different drinking levels.

Appendix Table 2: Lifetime risk to die from alcohol use for different levels of average daily consumption in 2012 – (sensitivity analysis with combined mortality and with alcohol-attributable deaths of current drinking patterns removed and then alcohol-attributable deaths for specific drinking levels added; competing risks included)

Average drinking	Estonia		Finland		Germany		Hungary		Ireland		Italy		Poland	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
10g	0.0005	-0.0049	0.0010	0.0045	0.0027	0.0015	0.0001	0.0008	-0.0003	0.0007	0.0004	-0.0010	-0.0035	-0.0068
20g	0.0079	0.0180	0.0056	0.0142	0.0106	0.0058	0.0085	0.0190	0.0029	0.0081	0.0033	0.0045	0.0023	0.0074
30g	0.0178	0.0473	0.0112	0.0279	0.0216	0.0107	0.0183	0.0428	0.0070	0.0184	0.0067	0.0122	0.0099	0.0282
40g	0.0294	0.0741	0.0175	0.0413	0.0331	0.0161	0.0300	0.0680	0.0122	0.0298	0.0107	0.0212	0.0199	0.0511
50g	0.0481	0.1206	0.0272	0.0636	0.0503	0.0236	0.0445	0.0962	0.0188	0.0431	0.0153	0.0312	0.0326	0.0780
60g	0.0665	0.1466	0.0378	0.0773	0.0610	0.0319	0.0634	0.1165	0.0276	0.0531	0.0212	0.0381	0.0490	0.0972
70g	0.1014	0.2357	0.0544	0.1184	0.0879	0.0436	0.0818	0.1461	0.0364	0.0684	0.0266	0.0452	0.0664	0.1288
80g	0.1209	0.2600	0.0657	0.1316	0.0976	0.0524	0.1006	0.1616	0.0456	0.0766	0.0326	0.0503	0.0832	0.1441
90g	0.1397	0.2820	0.0767	0.1437	0.1065	0.0606	0.1185	0.1749	0.0544	0.0838	0.0381	0.0547	0.0992	0.1574
100g	0.1571	0.3021	0.0869	0.1548	0.1145	0.0683	0.1347	0.1863	0.0627	0.0902	0.0432	0.0585	0.1138	0.1689

Coloring:

Green: overall protective effect

Lightest red: overall lifetime risk smaller than 1 in 1,000

Light red: overall lifetime risk smaller than 1 in 100, but larger than 1 in 1,000

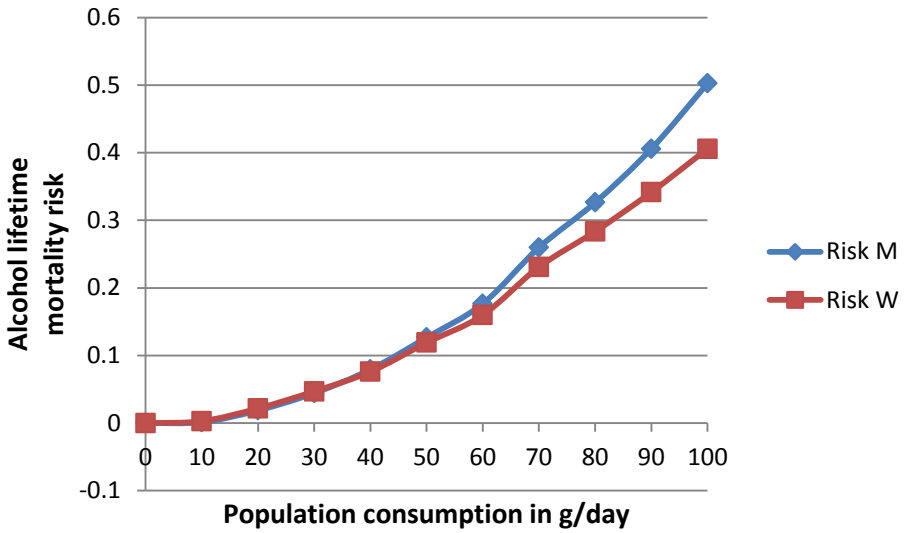
Dark red: overall lifetime risk equal to or larger than 1 in 100

Basis: overall country-specific mortality risks combined for both sexes; sex-and age specific relative risk for different drinking levels; competing risks subtracted

Appendix Figures 1-7: Lifetime risk to die from alcohol use for different levels of average daily consumption in 2012 – sensitivity analyses 1 with sex-specific mortality and with alcohol-attributable deaths of current drinking patterns removed and then alcohol-attributable deaths for specific drinking levels added

Please note of different scales for the y-axis per country

Estonia



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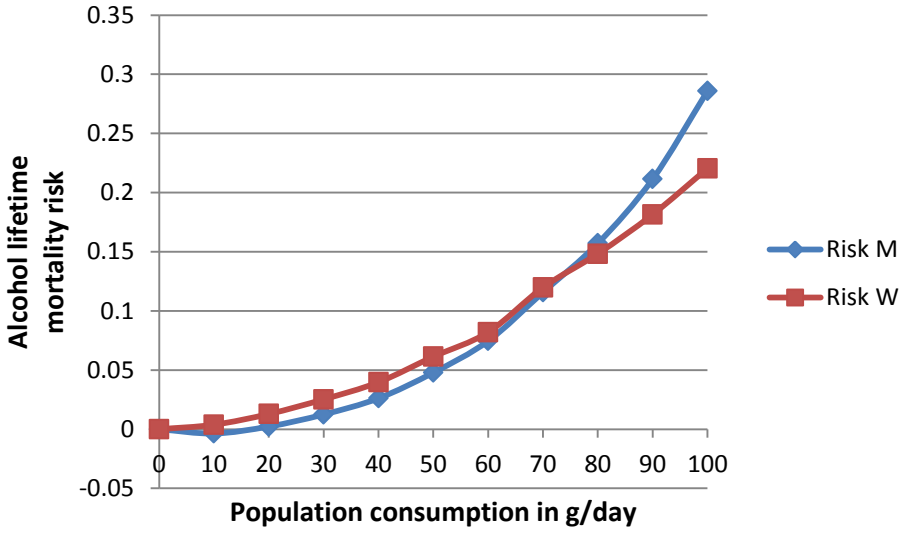
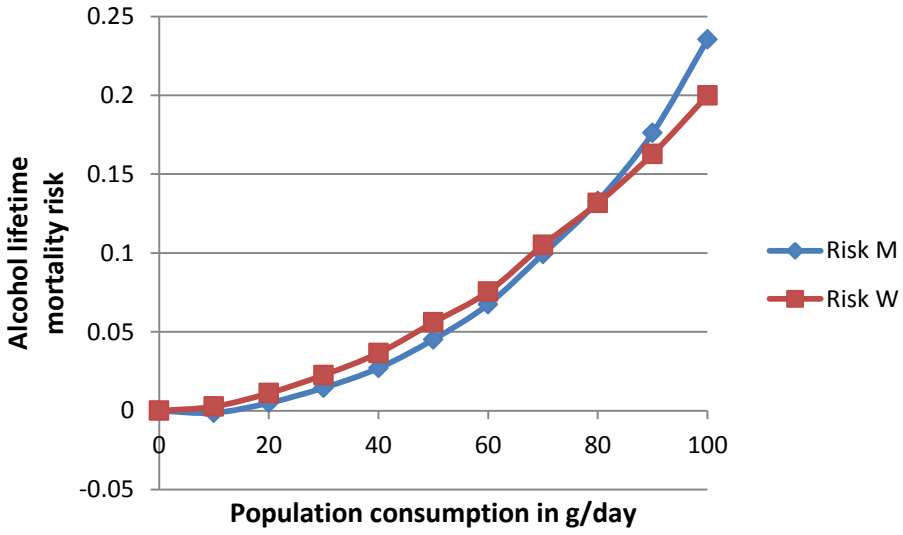
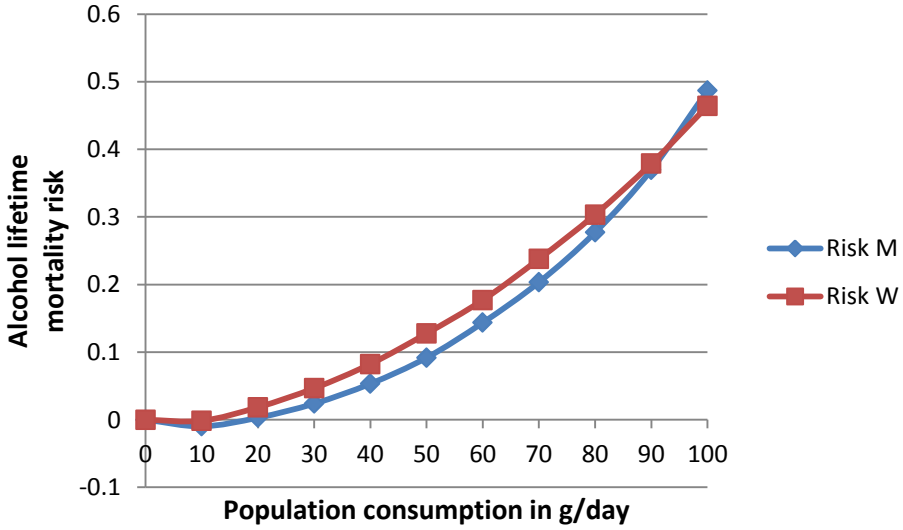


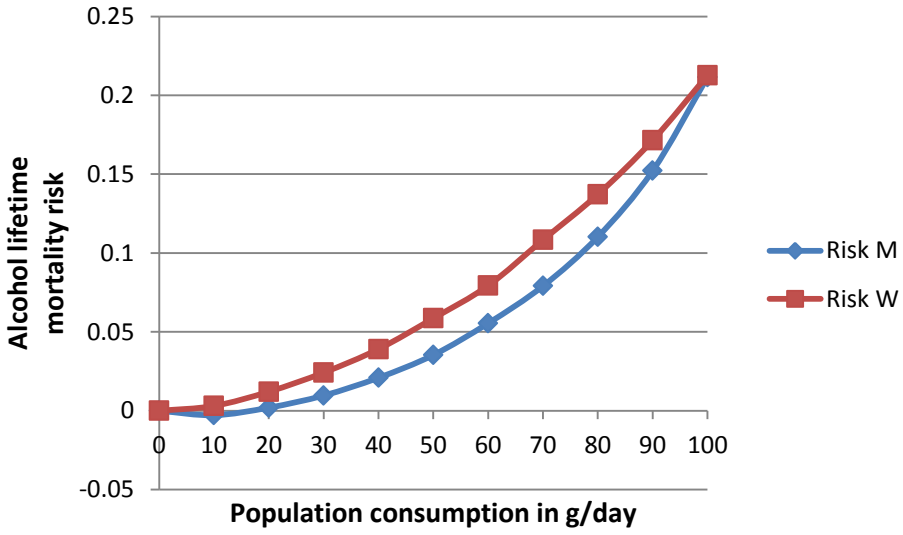
Germany



Hungary



Ireland


0.25
0.2
0.15
0.1
0.05
0
-0.05
Alcohol lifetime mortality risk
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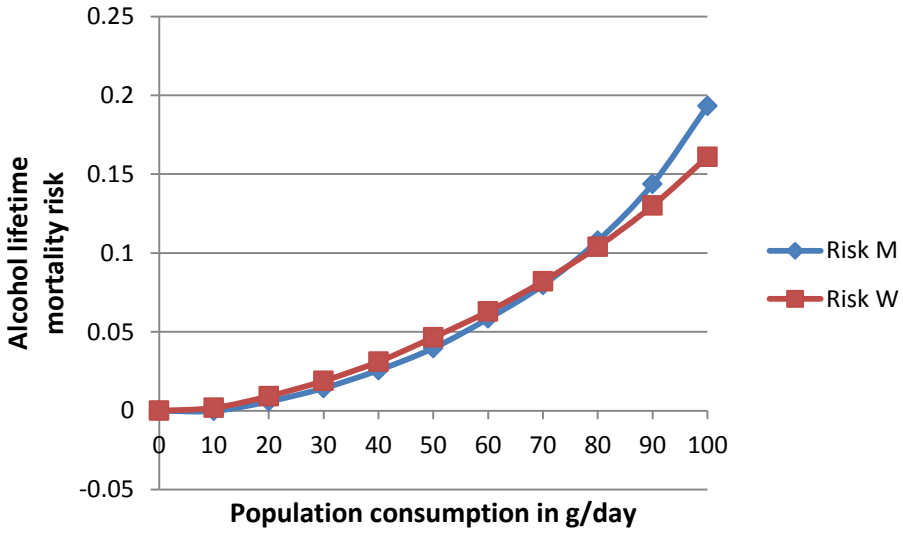
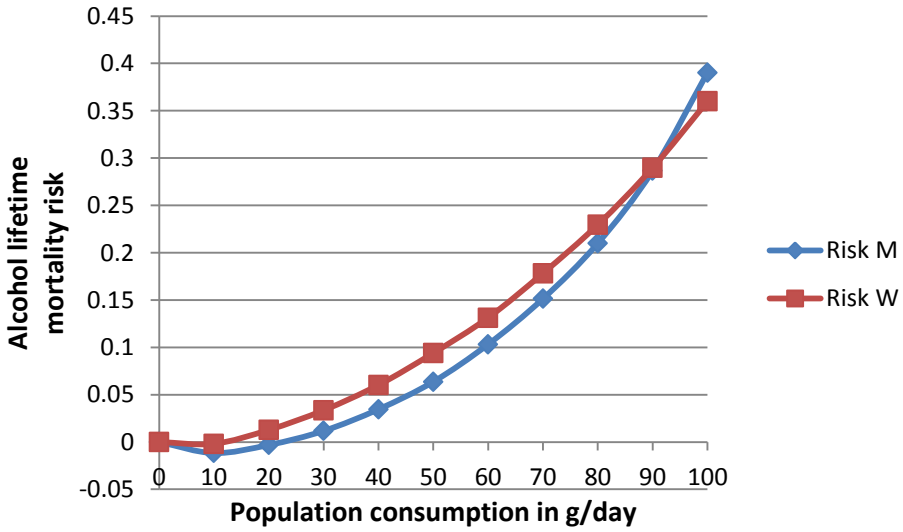
10
20
30
40
50
60
70
80
90
100
Population consumption in g/day
Risk M
Risk W

Italy



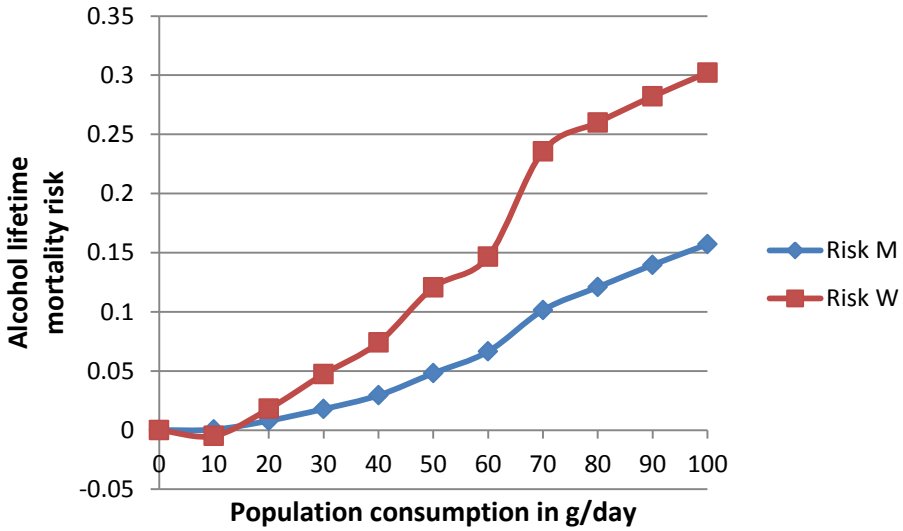
Poland



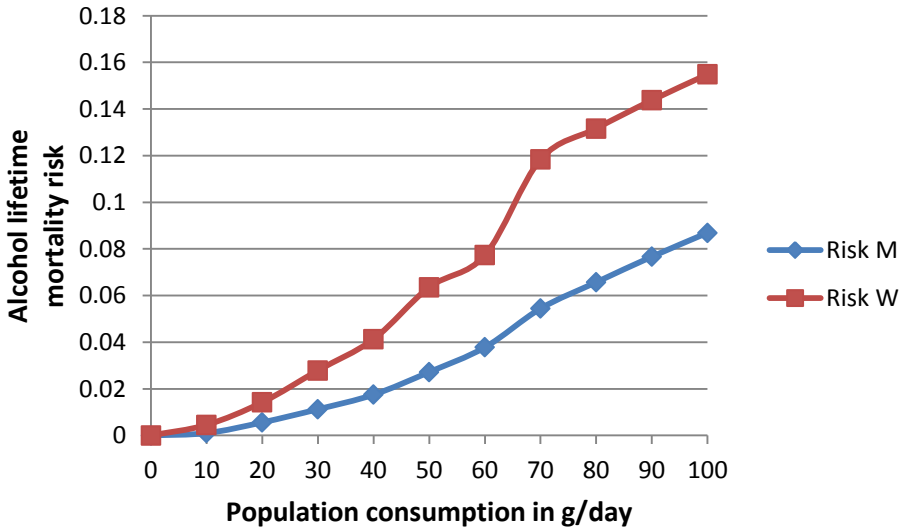
Appendix Figures 8-14: Lifetime risk to die from alcohol use for different levels of average daily consumption in 2012 – sensitivity analyses 2 with sex-specific mortality and with alcohol-attributable deaths of current drinking patterns removed and then alcohol-attributable deaths for specific drinking levels added; competing risks adjusted for

Please note of different scales for the y-axis per country

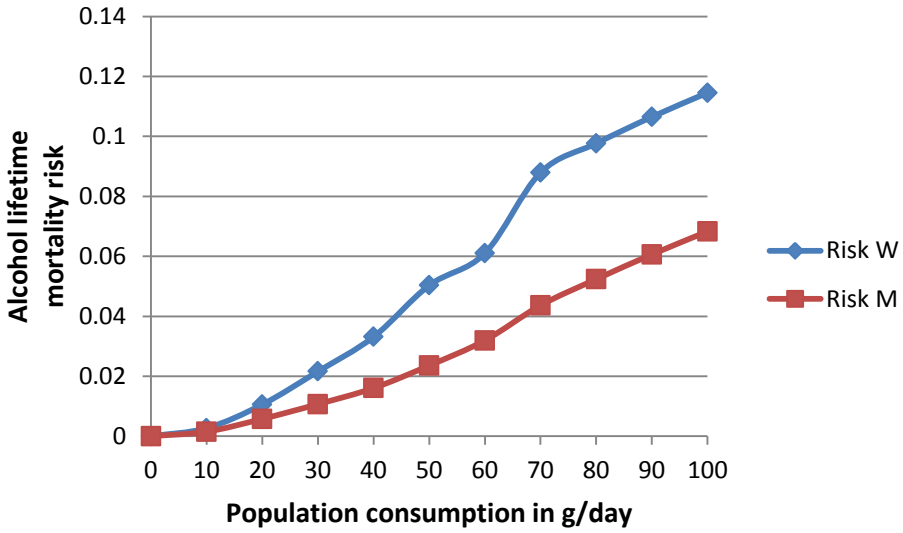
Estonia



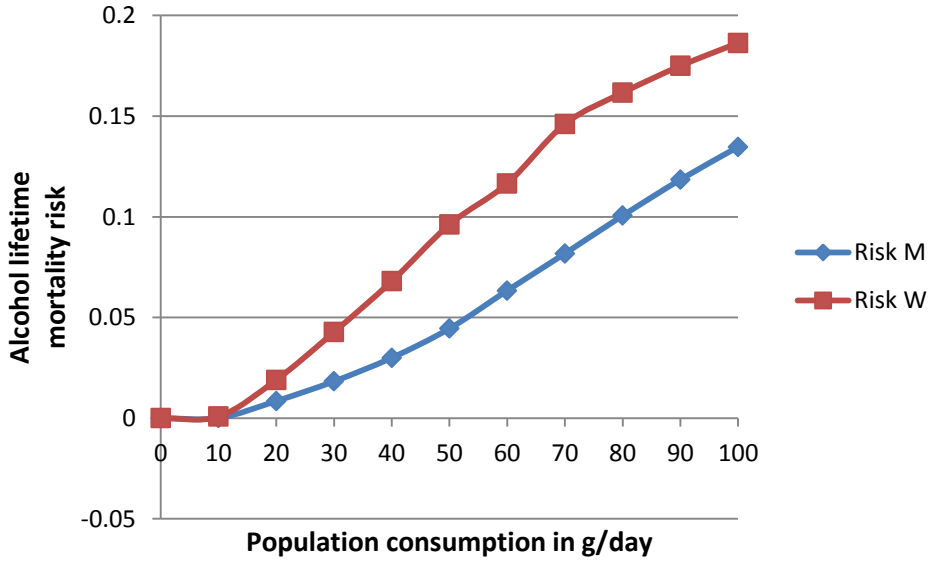
Finland



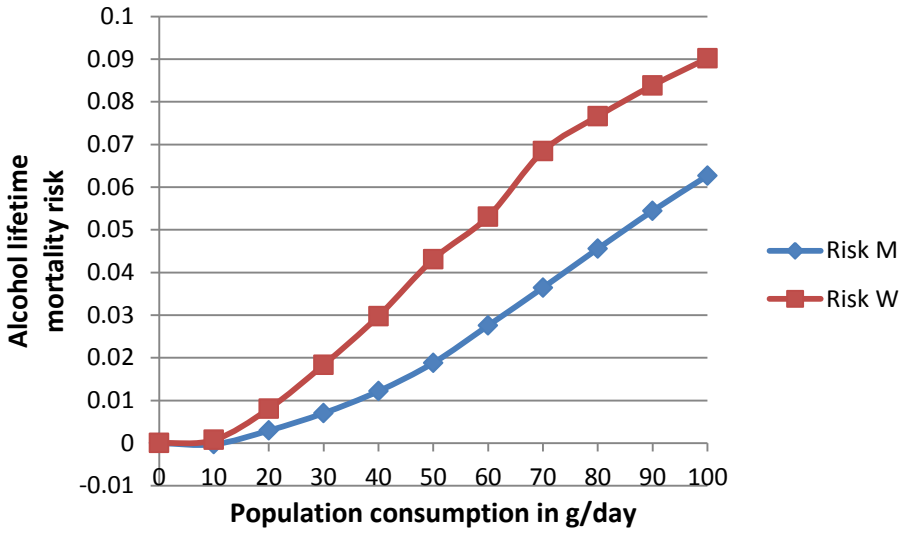
Germany



Hungary



Ireland



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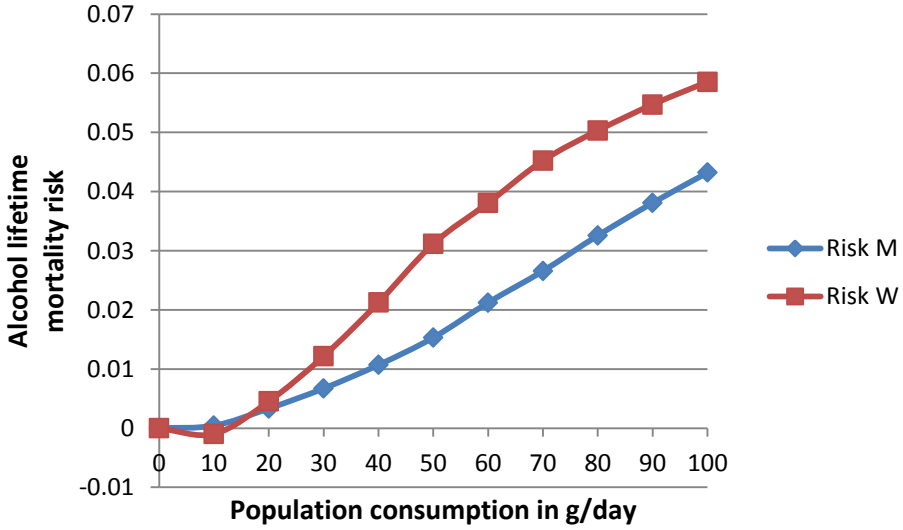
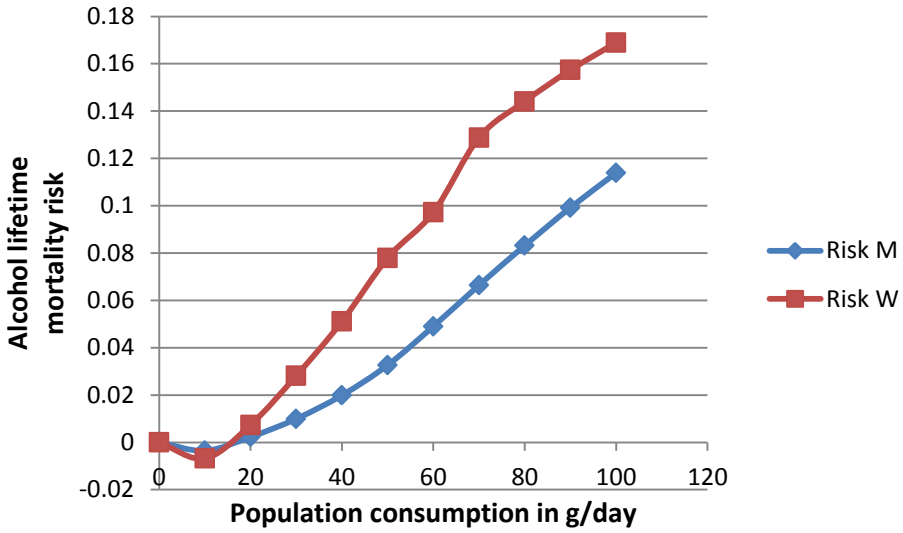


Poland


0.18
0.16
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0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
0
20
40
60
80
100
120
Alcohol lifetime mortality risk
Population consumption in g/day
Risk M
Risk W

Relative risk by sex and level of consumption

Appendix Table 3. Relative risk for alcohol-related diseases given an average daily alcohol consumption amount (as compared to lifetime abstainers)

Disease	Sex	Relative risk (given an average daily alcohol consumption amount in grams of pure alcohol per day)									
		10	20	30	40	50	60	70	80	90	100
Infectious diseases											
Tuberculosis	Men	1.00	1.00	1.00	2.96	2.96	2.96	2.96	2.96	2.96	2.96
	Women	1.00	1.00	1.00	2.96	2.96	2.96	2.96	2.96	2.96	2.96
Lower respiratory infections	Men	1.05	1.10	1.15	1.21	1.27	1.33	1.40	1.46	1.54	1.61
	Women	1.05	1.10	1.15	1.21	1.27	1.33	1.40	1.46	1.54	1.61
Cancers											
Oral cancer	Men	1.30	1.66	2.08	2.56	3.11	3.71	4.36	5.04	5.75	6.46
	Women	1.30	1.66	2.08	2.56	3.11	3.71	4.36	5.04	5.75	6.46
Esophageal cancer	Men	1.14	1.30	1.48	1.69	1.93	2.19	2.48	2.82	3.18	3.59
	Women	1.14	1.30	1.48	1.69	1.93	2.19	2.48	2.82	3.18	3.59
Colorectal cancer	Men	1.06	1.13	1.21	1.29	1.37	1.46	1.55	1.65	1.76	1.87
	Women	1.06	1.13	1.21	1.29	1.37	1.46	1.55	1.65	1.76	1.87
Liver cancer	Men	1.08	1.15	1.23	1.31	1.40	1.48	1.56	1.65	1.73	1.81
	Women	1.08	1.15	1.23	1.31	1.40	1.48	1.56	1.65	1.73	1.81
Pancreatic cancer	Men	1.01	1.02	1.04	1.07	1.10	1.13	1.17	1.21	1.25	1.30
	Women	1.01	1.02	1.04	1.07	1.10	1.13	1.17	1.21	1.25	1.30
Breast Cancer	Men	-	-	-	-	-	-	-	-	-	-
	Women	1.09	1.19	1.30	1.42	1.55	1.69	1.85	2.02	2.21	2.41
Larynx Cancer	Men	1.15	1.33	1.53	1.76	2.02	2.31	2.64	3.00	3.41	3.85
	Women	1.15	1.33	1.53	1.76	2.02	2.31	2.64	3.00	3.41	3.85
Neuropsychiatric conditions											
Epilepsy	Men	1.14	1.29	1.45	1.64	1.86	2.10	2.38	2.69	3.04	3.44
	Women	1.14	1.29	1.45	1.64	1.86	2.10	2.38	2.69	3.04	3.44

Cardiovascular diseases											
Hypertension	Men	1.10	1.20	1.31	1.44	1.57	1.72	1.89	2.07	2.26	2.48
	Women	0.89	1.20	1.61	2.12	2.78	3.59	4.60	5.85	7.39	9.28
Ischemic heart disease	Men	0.77	0.74	0.72	0.71	0.71	1.00	1.00	1.00	1.00	1.00
	Women	0.54	0.55	0.61	0.71	0.86	1.07	1.34	1.72	2.23	2.91
Hemorrhagic stroke	Men	1.08	1.17	1.26	1.36	1.47	1.59	1.71	1.85	2.00	2.16
	Women	0.68	0.77	0.90	1.05	1.22	1.43	1.66	1.92	2.22	2.56
Ischemic stroke	Men	0.84	0.89	0.95	1.02	1.09	1.16	1.24	1.32	1.41	1.50
	Women	0.81	0.82	0.87	0.95	1.04	1.15	1.28	1.43	1.61	1.82
Conduction disorders and other dysrhythmias	Men	1.06	1.12	1.19	1.26	1.33	1.41	1.50	1.58	1.68	1.78
	Women	1.06	1.12	1.19	1.26	1.33	1.41	1.50	1.58	1.68	1.78
Digestive diseases											
Liver cirrhosis	Men	1.19	1.41	1.66	1.97	2.33	2.76	3.27	3.87	4.58	5.42
	Women	2.12	2.88	3.64	4.44	5.29	6.20	7.17	8.21	9.33	10.53
Pancreatitis	Men	1.02	1.06	1.15	1.27	1.46	1.72	2.09	2.62	3.39	4.50
	Women	1.02	1.06	1.15	1.27	1.46	1.72	2.09	2.62	3.39	4.50
Diabetes											
	Men	0.90	0.87	0.88	0.91	0.95	1.00	1.07	1.16	1.16	1.16
	Women	0.68	0.60	0.62	0.74	1.07	1.18	1.18	1.18	1.18	1.18
Injuries and violence											
	Men	1.05	1.10	1.15	1.20	1.26	1.32	1.38	1.44	1.51	1.58
	Women	1.05	1.10	1.15	1.20	1.26	1.32	1.38	1.44	1.51	1.58

*Green represents a protective effect and red represents a detrimental effect

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