Risk relations between alcohol use and non-injury causes of death

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This is an update of the Appendix of the overview paper of Rehm and colleagues on risk relations between alcohol use and mortality outcomes (1), and includes the relative risk of diseases, and conditions among former drinkers, which had been collected as part of the International Model of Alcohol Harms and Policies (InterMAHP; 2). It contains risk relations for drinkers and former drinkers1 for all non-injury causes of death which had been determined as partially attributable to alcohol, i.e., where causality had been established (1, 6, 7). In addition, it denotes formulas for causes of death and burden of disease, which are 100% attributable to alcohol, but for which there had been no reliable global statistics either by World Health Organization (8) or by the Global Burden of Disease and Injury Studies (9). The original sources and full documentation of the formulas are given to comply with GATHER standards (10).

All functions are defined from 0 to 150 g/day pure alcohol/day (for reasoning (11, 12)). For any drinking level above 150g/day pure alcohol, please use the risk for 150 g/day (for sensitivity analyses please see (13)). If you would like to specify over a larger range of exposure, please use the already mentioned InterMAHP model for options (2).

In the function definitions, x refers to the average daily consumption of pure alcohol in g/day.

R-programs for the functions are available upon request from the first author under the conditions:

- that the original work for each formula is cited as per this report;
- that the source of the program is acknowledged as follows:


1 Please note, that the risk relations for former drinkers had been mainly derived from high-income countries where majority consumes alcohol, and quitting drinking is often after having consumed alcohol for decades (e.g., (3, 4)). There are problems in transposing these risks to countries where alcohol use is against the social norms, and former drinkers may have consumed alcohol only sporadically (see e.g., solution in (5) for potential modelling).
## Sources for determining causality

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<th>Diseases or condition (ICD-10 code)</th>
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<td>Rehm et al., 2009 (14)</td>
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<td>Hypertensive heart diseases [I11-13]</td>
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<td>Atrial fibrillation and flutter [I48]</td>
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<td>Rosenberg &amp; Mukamal, 2012 (29)</td>
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<td><strong>Diseases of the respiratory system [J00-99]</strong></td>
<td>Puddey et al., 1999 (30); Mazzaglia et al., 2001(31); Collins et al., 2009 (26)</td>
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<td><strong>Lower respiratory infections: pneumonia [J09–J22, J85, P23]</strong></td>
<td>Samokhvalov et al., 2010 (32); Traphagen et al., 2015 (33), for heavy drinking und alcohol use disorders: Simet &amp; Sisson, 2015 (34)</td>
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<td><strong>Diseases of the digestive system [K00-93]</strong></td>
<td>Gao &amp; Bataller, 2011(35)</td>
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<td><strong>Fibrosis and cirrhosis of liver [K70, K73-74]</strong></td>
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<td><strong>Pancreatitis [K85 K86.0-1]</strong></td>
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6
Infectious disease [A00-B99]

Tuberculosis [A15-19, B90]

**Current drinkers:**

\[
\ln(RR(x)) = 0.0179695 \cdot x
\]

Source: Imtiaz et al., 2017 (36)

**Former drinkers:**
Women and men; \(RR_{FD} = 1.0^*\)

* There is no increased risk of former drinkers, due to the biological pathways, which are based on infection due to acute consequences of use (14).
HIV/AIDS (effect via behavioural intentions) [B2-24]

Current drinkers:

\[
\ln(RR(x)) = \begin{cases} 
0, & x \leq 49 \\
\ln(1.54), & x > 49 
\end{cases}
\]

Women

\[
\ln(RR(x)) = \begin{cases} 
0, & x \leq 61 \\
\ln(1.54), & x > 61 
\end{cases}
\]

Men

Source: Rehm et al., 2017 (15) based on Scott-Sheldon et al., 2016 (37); for the effect via medication adherence see Gmel et al., 2011 (38)

Former drinkers:

Women and men; RR_{FD} = 1.0*

*There is no increased risk of former drinkers, due to the biological pathways, which are based on infection due to acute consequences of use (15, 16).
Malignant neoplasms [C00-97]
For all alcohol-attributable cancers, causality has been determined by International Agency for Research on Cancer (IARC) monograph conferences (17, 18). Only cancers with the highest level of evidence for carcinogenicity in humans (group 1) were included (39).

Oral cavity, salivary glands, oropharynx and hypopharynx cancer [C01-14]

Current Drinkers:

![Graph showing the relationship between RR and ethanol consumption](image)

\[
\ln(RR(x)) = 0.02474 \cdot x - 0.00004 \cdot x^2
\]

Source: Bagnardi et al., 2015 (40)

Former drinkers:
Women and men; \(RR_{FD} = 1.20\) (95% CI: 0.63-2.30)
Source: Marron et al., 2010 (41)
Oesophagus cancer [C15]

**Current Drinkers:**

\[ \ln(\text{RR}(x)) = 0.05593 \cdot x - 0.00789 \cdot x \cdot \ln(x) \]

Source: Bagnardi et al., 2015 (40)

**Former drinkers:**
Women and men; \( \text{RR}_{FD} = 1.16 \) (95% CI: 0.72-1.87)
Source: Marron et al., 2010 (41)
Colon and rectum cancer [C18-20]

Current drinkers:

\[
\ln(\text{RR}(x)) = 0.006279 \cdot x
\]

Source: Bagnardi et al., 2015 (40)

Former drinkers:
Women; \( \text{RR}_{FD} = 1.05 \) (95% CI: 0.79-1.40)
Men; \( \text{RR}_{FD} = 2.19 \) (95% CI: 0.99-4.83)
Source: Schütze et al., 2011 (42)
Liver and intrahepatic bile duct cancer [C22]

Current drinkers:

\[
\ln(RR(x)) = 0.00017 \cdot x^2 - 0.00069 \cdot x^{0.5}
\]

Source: Bagnardi et al., 2015 (40)

Former drinkers:
Women; \(RR_{fd} = 2.28\) (95% CI: 0.88-5.85)
Men; \(RR_{fd} = 1.54\) (95% CI: 1.20-1.98)

Source: Schütze et al., 2011 (42)
Larynx cancer [C32]

Current drinkers:

\[
\ln(RR(x)) = 0.01462 \cdot x - 0.00002 \cdot x^2
\]

Source: Bagnardi et al., 2015 (40)

Former drinkers:
Women and men: \( RR_{FD} = 1.18 \) (95% CI: 0.67-2.08)
Source: Marron et al., 2010 (41)
Female breast cancer [C50]

**Current drinkers:**

\[
\ln(RR(x)) = 0.01018 \cdot x
\]

Source: Bagnardi et al., 2015 (40)

**Former drinkers:**

Women and Men RR_{FD} = 1.00*

* The RR_{FD} = 1.03 (0.88-1.21) as measured by Schütze et al., 2011 (42) falls inside the range of 0.95 and 1.05 where the former drinker RRs were not modelled.
Diabetes mellitus [E10-14]

Current drinkers:

Women
\[
\ln(RR(x)) = -1.3133910 \cdot \left(\frac{x}{100}\right)^{0.5} + 0.0728256 \cdot \left(\frac{x}{100}\right)^{3}
\]

Men
\[
\ln(RR(x)) = 0.1763703 \cdot \left(\frac{x}{100}\right)^{2} - 0.0728256 \cdot \left(\frac{x}{100}\right)^{3}
\]

Source: Knott et al. (2015) (43)

Former drinkers:
Women: \(RR_{FD} = 1.14\) (95% CI: 0.99-1.31)
Men: \(RR_{FD} = 1.18\) (95% CI: 0.89-1.52)
Source: Rehm et al., 2010 (6)
Diseases of the nervous system [G00-99]

Epilepsy [G40-41]

Current drinkers:

\[
\ln(RR(x)) = 1.22861 \cdot \frac{x + 0.5}{100}
\]

Source: Samokhvalov et al., 2010 (44)

Former drinkers:

Men and women: \( RR_{FD} = 1.00^* \)

* The observed \( RR_{FD} \) were 0.9 (95% CI: 0.1, 5.0) for women and 0.9 (95% CI: 0.2, 3.0) for men as measured by Leone et al., 1997 (45). However, there is no evidence that former drinking is correlated to the risk of an epileptic seizure.
Diseases of the circulatory system [I00-I99]

Hypertensive heart diseases [I11-13]

Current drinkers:

\[
\ln(\text{RR}(x)) = \begin{cases} 
0, & x < 18.9517 \\
-0.0154196 \cdot x + 0.0217586 \cdot \frac{x^3 - (x-10)^3 \cdot 20 - (x-20)^3 \cdot 10}{20^2}, & 18.9517 \leq x < 75 \\
0.9649937, & x \geq 75 
\end{cases}
\]

Men

\[
\ln(\text{RR}(x)) = \begin{cases} 
0.0150537 \cdot x - 0.0156155 \cdot \frac{x^3}{75^2}, & 0 \leq x < 21 \\
0.0150537 \cdot x - 0.0156155 \cdot \frac{x^3 - (x-21)^3 \cdot 75}{75^2}, & 21 \leq x < 75 \\
0.0150537 \cdot x - 0.0156155 \cdot \frac{x^3 - (x-21)^3 \cdot 75 - (x-75)^3 \cdot 21}{75^2}, & 75 \leq x 
\end{cases}
\]

Source: Roerecke et al., personal communication

Former drinkers:

Women: \(\text{RR}_{FD} = 1.00^*\)

Men: \(\text{RR}_{FD} = 1.05\) (95% CI: 0.85, 1.30)

Source Roerecke et al., personal communication

* The \(\text{RR}_{FD} = 1.03\) (95% CI: 0.78, 1.33) for women falls inside the range of 0.95 and 1.05 where the former drinker RRs were not modelled.
Ischaemic Heart Disease [I20-25] (ages 35-64)

Current drinkers:

\[
\ln(RR(x)) = \begin{cases} 
1.897718 \cdot y + 1.593365 \cdot y \cdot \log(y), & x < 30.3814 \\
0.0093 \cdot (x - 30.3814), & x \geq 30.3814
\end{cases}
\]

where \( y = \frac{x}{100} + 0.0099999997764826 \)

The risk relations between alcohol use and ischemic stroke are age-dependent (5). We only show exemplary functions for one age group. In addition, the relative risk is 1 for all people, who consume on average less than 60g of pure alcohol per day, but have at least one heavy drinking occasion per month (27, 46).

Source: Rehm et al., 2016(5) based on Roerecke & Rehm, 2012(47)

Former drinkers:

Women: \( RR_{FD} = 1.54 \) (95% CI: 1.17-2.03)

Men: \( RR_{FD} = 1.25 \) (95% CI: 1.15-1.36)

Source: Roerecke & Rehm (2011) (48)
Cardiomyopathy [I42]

Causality: Not necessary, as there is a distinct category call alcoholic cardiomyopathy [I42.6]; for an on overview see Rehm et al., 2017(49)

Meta-analysis and modelling: No meta-analysis possible due to lack of epidemiological data (49). An alternative strategy to model the data can be found in Manthey et al., 2017 (50).

Atrial fibrillation and flutter [I48]

Current drinkers:

\[
\ln(RR(x)) = 0.0575183 \cdot y
\]

where \( y = \frac{x + 0.0499992370605469}{10} \)

Source: Samokhvalov et al., 2010 (51)

Former drinkers:
Women and men: \( RR_{FD} = 1.00^* \)

*The \( RR_{FD} = 1.01 \) (95% CI: 0.88-1.16) measured Larsson et al., 2014 (52), falls inside the range of 0.95 and 1.05 where the former drinker RR's were not modelled.
Haemorrhagic stroke and non-ischaemic stroke [I60-62, I69.0-2]

Current drinkers:

\[
\begin{align*}
\text{Women} \\
\ln(RR(x)) &= \begin{cases} \\
\ln(1 - x \cdot (1 - 1.014815)), & x \leq 1 \\
1.466406 \cdot \frac{x + 0.0028572082519531}{100}, & x > 1 \\
\end{cases} \\
\text{Men} \\
\ln(RR(x)) &= \begin{cases} \\
\ln(1 - x \cdot (1 - 1.006943)), & x \leq 1 \\
0.6898937 \cdot \frac{x + 0.0028572082519531}{100}, & x > 1 \\
\end{cases}
\end{align*}
\]

Source: Patra et al., 2010 (53)

Former drinkers:
Women and men: \(RR_F = 1.36\) (95% CI: 0.92-2.02)
Source: Larsson et al., 2016 (54)
Ischaemic stroke [I63-67, 69.3] (ages 35-65)

**Current drinkers:**

\[ \ln(RR(x)) = \begin{cases} \ln(1 - x \cdot (1 - 0.8029366)) & , x \leq 1 \\ 1.035623 \cdot (-2.48768 \cdot y^{0.5} + 3.7087240 \cdot y), & x > 1 \end{cases} \]

where \( y = \frac{x + 0.0028572082519531}{100} \)

**Men**

\[ \ln(RR(x)) = \begin{cases} \ln(1 - x \cdot (1 - 0.8665101)) & , x \leq 1 \\ 1.035623 \cdot (0.4030081 \cdot y^{0.5} + 0.3877538 \cdot y^{0.5} \cdot \ln(y)), & x > 1 \end{cases} \]

where \( y = \frac{x + 0.0028572082519531}{100} \)

The risk relations between alcohol use and ischemic stroke are age-dependent (5). We only show exemplary functions for one age group. In addition, the relative risk is 1 for all people, who consume on average less then 60g of pure alcohol per day, but have at least one heavy drinking occasion per month (55, 56).

Source: Rehm et al., 2016(5) based on Patra et al., 2010 (53)

**Former drinkers:**

Women and men : \( RR_{FD} = 1.00^* \)

* The \( RR_{FD} = 0.97 \) (0.83-1.14) measured Larsson et al., 2016 (54), falls inside the range of 0.95 and 1.05 where the former drinker RRs were not modelled.
Diseases of the respiratory system [J00-99]

Lower respiratory infections: pneumonia [J09–J22, J85, P23]

Current drinkers:

\[
\ln(RR(x)) = 0.4764038 \cdot \left( \frac{x + 0.0399999618530273}{100} \right)
\]

Source: Samokhvalov et al., 2010 (32)

Former drinkers:

Women and men: \(RR_{FD} = 1.00\)

*There is no increased risk of former drinkers, due to the biological pathways, which are based on infection due to acute consequences of use (32, 33).
Diseases of the digestive system [K00-93]

Fibrosis and cirrhosis of liver [K74]

**Current drinkers:**

\[
\ln(RR(x)) = \begin{cases} 
\ln(1 + x \cdot (1.421569 - 1)) & , x \leq 1 \\
3.252035 \cdot \sqrt{\frac{x + 0.1699981689453125}{100}} & , x > 1
\end{cases}
\]

**Women**

\[
\ln(RR(x)) = \begin{cases} 
\ln(1 + x \cdot (1.033224 - 1)) & , x \leq 1 \\
2.793524 \cdot \frac{x + 0.1699981689453125}{100} & , x > 1
\end{cases}
\]

Source: Rehm et al., 2010 (57)

**Former drinkers:**

Women and men: \(RR_{FD} = 3.26\) (95% CI: 1.38-7.74)

Source: Roerecke et al., personal communication
Pancreatitis [K85-86]

Current data:

\[
\ln(\text{RR}(x)) = \begin{cases} 
-0.0272886 \cdot x & , x > 3 \\
-0.0272886 \cdot x + 0.0611466 \cdot \frac{(x-3)^3}{(40-3)^2} & , 3 \leq x < 15 \\
-0.0272886 \cdot x + 0.0611466 \cdot \frac{(x-3)^3 - (x-15)^3 \cdot (40-3)}{(40-15) \cdot (40-3)^2} & , 15 \leq x < 40 \\
-0.0272886 \cdot x + 0.0611466 \cdot \frac{(x-3)^3 - (x-15)^3 \cdot (40-3) - (x-40)^3 \cdot (15-3)}{(40-15) \cdot (40-3)^2} & , 40 \leq x < 108 \\
2.327965 & , x \geq 108 
\end{cases}
\]

Source: Samokvalov et al., 2015 (58)

Former drinkers:

Women and men: \( \text{RR}_{FD} = 2.20 \) (95% CI: 1.45-3.34)

Source: Samokvalov et al., 2015 (58)
Fetal alcohol syndrome (FAS)

The fetal alcohol syndrome (FAS) is a condition which is per definition caused by alcohol (for all such conditions see (1)). However, mortality due to FAS is not routinely collected by either WHO (8) or IHME ((9); for more background see (59)). Mortality due to FAS will be calculated based on prevalence, which is calculated based on the number of pregnant women who consume alcohol (60).
References