The relationship between different dimensions of alcohol use and the burden of disease—an update

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ABSTRACT

Background and aims Alcohol use is a major contributor to injuries, mortality and the burden of disease. This review updates knowledge on risk relations between dimensions of alcohol use and health outcomes to be used in global and national Comparative Risk Assessments (CRAs). **Methods** Systematic review of reviews and meta-analyses on alcohol consumption and health outcomes attributable to alcohol use. For dimensions of exposure: volume of alcohol use, blood alcohol concentration and patterns of drinking, in particular heavy drinking occasions were studied. For liver cirrhosis, quality of alcohol was additionally considered. For all outcomes (mortality and/or morbidity): cause of death and disease/injury categories based on International Classification of Diseases (ICD) codes used in global CRAs; harm to others. **Results** In total, 255 reviews and meta-analyses were identified. Alcohol use was found to be linked causally to many disease and injury categories, with more than 40 ICD-10 three-digit categories being fully attributable to alcohol. Most partially attributable disease categories showed monotonic relationships with volume of alcohol use: the more alcohol consumed, the higher the risk of disease or death. Exceptions were ischaemic diseases and diabetes, with curvilinear relationships, and with beneficial effects of light to moderate drinking in people without heavy irregular drinking occasions. Biological pathways suggest an impact of heavy drinking occasions on additional diseases; however, the lack of medical epidemiological studies measuring this dimension of alcohol use precluded an in-depth analysis. For injuries, except suicide, blood alcohol concentration was the most important dimension of alcohol use. Alcohol use caused marked harm to others, which has not yet been researched sufficiently. **Conclusions** Research since 2010 confirms the importance of alcohol use as a risk factor for disease and injuries; for some health outcomes, more than one dimension of use needs to be considered. Epidemiological studies should include measurement of heavy drinking occasions in line with biological knowledge.

Keywords Alcohol use, average volume, chronic disease, injury, patterns of drinking, risk-relations, systematic review, unrecorded consumption.

INTRODUCTION

Alcohol consumption has been identified as a major contributor to the burden of disease and mortality in all the global Comparative Risk Assessments (CRAs [1]) conducted thus far as part of the Global Burden of Disease (GBD) studies [2–7], and in the World Health Organization (WHO) Global Status Reports on Alcohol and Health and their predecessors [8–10]. All CRAs restricted themselves to modifiable risk factors [11], where the modifications could be linked to reductions in the disease burden [12]. As a consequence, they have become crucial for guiding health policy [13], not only in terms of primary prevention [14–16], but also in terms of secondary prevention and health systems management [17–19].

At the core of any CRA are the risk relations between different dimensions of exposure (in the present case, alcohol use) and particular diseases, disorders or injuries. Each of these relative risks is then combined with the extent of the respective exposure in a particular population to create alcohol-attributable fractions (AAFs) for that population [20,21]. In most CRAs, including for alcohol, both the relative risk and the prevalence of exposure are continuous functions [22]. Knowledge on and estimates of these risk relations have been evolving during the past 15 years (compare the overview from 2003 [23], and especially since 2010 when the last overview on this topic in *Addiction* appeared [24], which the current review will update with the latest evidence. It will follow the structure of the previous reviews [23,24]: first, we will list disease and injury categories which are 100% alcohol-attributable; secondly, we will address disease categories partly attributable to alcohol, and finally, injury categories which are partly attributable to alcohol will be discussed. In the discussion, we not only outline the limitations of our review, but also look to future research developments.

METHODS

Search strategy

For this systematic review, we (a) searched the WHO International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) 2016 databank [25] for the term 'alcohol*' to identify disease and injury categories fully attributable to alcohol (see Table 1), and (b) updated all estimates of alcohol use–disease or injury relationships for partially attributable outcomes from the estimates in the most recent preceding publication [24], following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26,27].

We conducted a systematic literature search on AMED, CAB Abstracts, Embase, Health and Psychosocial Instruments, Healthstar, OVID Medline, PsycINFO, PubMed and Social Work Abstracts databases to identify systematic reviews and/or meta-analyses. Key words were different alcohol categories and the respective outcome category, along with either 'systematic review' or 'meta-analysis'. All databases were searched from January 2008, the time limit of the last review of this series [24], to October 2016. Supporting information, Appendix S1 gives an overview on the exact search terms used and full results. To identify the appropriate studies from the search results, one author reviewed independently all titles and abstracts at the initial stage. The results were compared with previous searches and reviews conducted independently by other authors who were part of this overview for each health outcome category. Discrepancies between the authors after the title and abstract review were resolved by discussing the full text. No language or geographical restrictions were applied. In assessing and summarizing the results of the searches, our emphasis was on causality, pathophysiology and the key meta-analyses.

Assessment of causality

We used the epidemiological definitions of causality, where alcohol had to be necessary, either alone or in combination with other antecedent conditions as a component cause [28]. This translates into AAFs for partially attributable outcome categories, i.e. for outcome categories for which alcohol is a component cause. AAFs can be interpreted as the proportion of an outcome in a specific population, which would not occur if there had been no alcohol use [11,29]. In discussing the various conditions, we also refer to the Bradford Hill criteria [30], with most emphasis on pathophysiology.

Terminology

Unless specified otherwise, we will use the term 'heavy drinking occasion' for consuming quantities of 60+ g of pure alcohol on one occasion. Chronic heavy drinking indicates consumption on average per day of 60+ g of pure alcohol for men and 40+ g for women (for similar thresholds in alcohol exposure classifications, see [31,32]). Light to moderate drinking is used to refer to drinking patterns which, on average, entail fewer than 60 g of pure alcohol per day in men and fewer than 40 g in women.

RESULTS

Disease and injury categories fully (100%) attributable to alcohol use

In the ICD-10 [25], alcohol is mentioned as part of several diseases and injuries, as well as in the chapter 'Factors influencing health status and contact with health services' (Z codes). Table 1 gives an overview of the over 40 codes in ICD which include 'alcohol' or 'alcoholic'.

While there are more than 10 000 disease and injury codes, for only a small fraction (310) of the most frequent and important categories are there global data on cause of death or morbidity. All the 100% alcohol-attributable categories in Table 1, except alcohol use disorders (F10), are too infrequent to be included in these 310 global cause of death or burden of disease statistical categories, either by the Institute for Health Metrics and Evaluation (IHME) [33] or the WHO [34]. However, GBD CRA adds estimates for alcohol poisoning (X45) and fetal alcohol syndrome (Q86.0) to this label. The WHO Global Status Reports summarize F10 and X45 only under alcohol use disorders. The choice of broad categories in all global CRAs is based on the availability and quality of data. For most of the population world-wide, affecting 38 million of 56 million annual

Table 1 ICD-10 categories with maximal one decimal with mention of alcohol or alcoholic.

E24.4	Alcohol-induced pseudo-Cushing's syndrome
F10	Mental and behavioural disorders due to use of alcohol
F10.0	*Acute intoxication*
F10.1	*Harmful use*
F10.2	*Dependence syndrome*
F10.3	*Withdrawal state*
F10.4	*Withdrawal state with delirium*
F10.5	*Psychotic disorder*
F10.6	*Amnesic syndrome*
F10.7	*Residual and late-onset psychotic disorder*
F10.8	*Other mental and behavioural disorders*
F10.9	*Unspecified mental and behavioural disorder*
G31.2	Degeneration of nervous system due to alcohol
G62.1	Alcoholic polyneuropathy
G72.1	Alcoholic myopathy
I42.6	Alcoholic cardiomyopathy
K29.2	Alcoholic gastritis
K29.20	Alcoholic gastritis, without mention of haemorrhage
K29.21	Alcoholic gastritis, with haemorrhage
K70	Alcoholic liver disease
K70.0	*Alcoholic fatty liver*
K70.1	*Alcoholic hepatitis*
K70.2	*Alcoholic fibrosis and sclerosis of liver*
K70.3	*Alcoholic cirrhosis of liver*
K70.4	*Alcoholic hepatic failure*
K70.9	*Alcoholic liver disease, unspecified*
K85.2	Alcohol-induced acute pancreatitis
K86.0	Alcohol-induced chronic pancreatitis
O35.4	Maternal care for suspected damage to foetus from alcohol
P04.3	Foetus and newborn affected by maternal use of alcohol
Q86.0	Fetal alcohol syndrome (dysmorphic)
R78.0	Finding of alcohol in blood
T51	Toxic effect of alcohol
T51.0	Ethanol
T51.1	Methanol
T51.2	Propanol
T51.3	Fusel oil
T51.8	Other alcohols
X45	Accidental poisoning by and exposure to alcohol
X65	Intentional self-poisoning by and exposure to alcohol
Y15	Poisoning by and exposure to alcohol, undetermined intent
Y90	Evidence of alcohol involvement determined by blood alcohol level—different subcategories as defined by thresholds in mg/100 ml
Y91	Evidence of alcohol involvement determined by level of intoxication
Y91.0	Y91.0—Mild alcohol intoxication
Y91.1	Y91.1—Moderate alcohol intoxication
Y91.2	Y91.2—Severe alcohol intoxication
Y91.3	Y91.3—Very severe alcohol intoxication
Y91.9	Alcohol involvement, not otherwise specified
Z04.0	Blood-alcohol and blood-drug test
Z50.2	Alcohol rehabilitation

(*Continues*)

Table 1. (Continued)

Z71.4	Alcohol abuse counselling and surveillance for alcohol use disorder
Z72.1	Alcohol use
Z81.1	Family history of alcohol abuse

deaths globally [35], there are no vital registries with cause of death information. For these deaths without vital registries, cause of death is estimated on the basis of verbal autopsies of subsamples and then scaled-up [36]. Verbal autopsy denotes a method of gathering health information concerning deceased individuals to determine their cause of death. Relevant health information and a description of symptoms and events preceding the death are determined based on interviews with next of kin, neighbours or friends of the deceased. This information is then analysed by trained health professionals or computer-based algorithms to assign a probable cause of death. The resulting cause of death categories have to be broad, as it is impossible to determine a detailed cause of death via verbal autopsy [37]. For any non-fatal health categories, such as morbidity or disability, the data situation is worse than for mortality [38].

While almost all disease or injury categories 100% attributable to alcohol cannot be included in the global CRAs, they are often assessed in high-income countries with national hospital records and vital registries and, thus, these categories should be included in national CRAs where possible. For example, alcoholic cardiomyopathy (I42.6) as a cause of death is available in approximately half of the countries as a cause of death [39], and thus could be included as part of alcohol attributable mortality in these countries.

Alcohol use disorders

For alcohol use disorders, as defined in the F10 category of ICD-10, causality is clear by definition, as there would not be alcohol use disorders without alcohol use. The most important category of alcohol use disorders in terms of public health impact is alcohol dependence (F10.2), which is linked both to regular and irregular heavy drinking occasions (see the almost straight linear relationship between average level of drinking and number of symptoms for dependence [40]). The link to irregular heavy drinking occasions is most evident in drinking cultures such as those in eastern Europe, where daily drinking is not common, not even among people with alcohol dependence [41]. Alcohol dependence and other alcohol use disorders are usually assessed based on general population surveys as

part of mental disorders (such as by the World Mental Health Survey [42]). As such surveys are relatively infrequent or absent for many countries, for most CRAs to date the prevalence of alcohol use disorders had to be estimated, often using the level of per-capita alcohol consumption or prevalence of heavy drinking predictors in the estimation [43,44].

Accidental poisoning by and exposure to alcohol

Alcohol poisoning, which is the short term for the above-specified injury category, is handled as part of alcohol use disorders in global CRAs. Alcohol poisoning is often assessed in hospitals for emergency room entries. Any blood alcohol concentration above 3 g/l should be considered as potentially life-threatening, with increasing mortality risks associated with increasing blood alcohol concentrations [45]; in many countries, cause of death from 'alcohol poisoning' may be given regularly for concentrations above 4 g/l. However, alcohol poisonings are underestimated markedly for two main reasons. First, alcohol use disorders in general are stigmatized, even over and above the general stigma of psychiatric disorders [46]. As a consequence, death certificates may mention more neutral categories, such as heart disease categories, as the cause of death ([47]; see also the discussion on alcoholic liver cirrhosis below). The amount of misclassification can be substantial in some countries or regions. For example, Zaridze and colleagues [48] reported that in a series of more than 22 000 autopsies in a Russian city, 16% of decedents had more than 4 g/l and 8% had more than 5 g/l blood alcohol concentrations. Some of the deaths reported by Zaridze and colleagues [48] should have been coded as alcohol poisoning instead of the other codes given, often cardiovascular deaths. Similar misclassifications were found in other regions of Russia and surrounding countries [49]. However, while this means that alcohol poisoning deaths have been under-reported, this effect is too small to explain the positive association between heavy drinking and cardiovascular mortality in countries with irregular drinking of very large amounts of alcohol, such as the eastern European countries [50,51]. The second reason for the underestimation of alcohol poisoning are the rules applied to classify drug overdose deaths in ICD-10 or earlier versions of the ICD [52], which give a priority for coding other substances than alcohol in case of involvement of multiple types of substance use in deaths (see also [53,54]). While polydrug use is common in drug overdose situations (e.g. [55]), and alcohol is one of the substances often present with other illicit substances, alcohol is rarely recorded as the cause of death, even when it has been specified and reported as the most toxic component by the medico-legal pathologist, and based on this should have been coded as the underlying cause of death [56].

Fetal alcohol spectrum disorders

Fetal alcohol spectrum disorders (FASD) are the leading known cause of preventable birth defects and developmental disabilities. FASD is an umbrella term that describes the full spectrum of deficits that can occur in prenatally alcohol-exposed individuals. The most severe and important form of FASD in terms of public health, fetal alcohol syndrome (FAS), is characterized by clear morphological changes, functional deficits and high prevalence of comorbidities [57]. FAS is the only expression of FASD in the ICD-10 (see Table 1). While FASD is not yet in ICD, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders included 'Neurobehavioral disorder associated with prenatal alcohol exposure' under 'conditions for further study' as the first step before including it as a formal diagnosis for clinical use (see Supporting information, Appendix, Section III [58]). Studies by May and co-workers [59–61] give some indication of the full spectrum of FASD.

While human research has not delineated, and perhaps cannot delineate fully, the pattern, amount and/or critical period of alcohol exposure necessary for structural and/or functional teratogenesis, animal models have shown that all stages of embryonic development are vulnerable to the teratogenic effects of ethanol, and that the type and severity of ethanol-induced birth defects are dependent largely upon the pattern, dose and developmental stage of the embryo at the time of ethanol exposure [62,63]. Animal models demonstrate clearly that even low levels of prenatal alcohol exposure may lead to brain dysfunction which, in turn, contributes to behavioural abnormalities [64].

In human research, the link between heavy drinking occasions during pregnancy and the risk of FAS is well established [65–70]. For low amounts of alcohol (8–28 g per occasion), several studies have found that there is no increased risk of behavioural and/or developmental deficits in children [69,71–73]. However, there is some evidence that the consumption of 42–56 g per week during pregnancy may have adverse effects on neurodevelopment [70]. To date, however, there are no longitudinal human studies that have followed alcohol-exposed individuals over a sufficient amount of time and used FASD diagnostic criteria to establish the relationship between dose and/or pattern of alcohol intake during pregnancy and FASD.

For estimation of the prevalence of FAS and FASD, Popova and colleagues developed a methodology based on the prevalence of drinking during pregnancy, which will be used in future CRAs [74]. However, disability weights [75] need to be established for both categories to estimate the burden of disease (currently only available for FAS [76]).

Disease and injury categories partially attributable to alcohol use

In total, 255 unique reviews and meta-analyses were identified (see Supporting information, Appendix S1). Table 2 gives an overview of global cause of death and outcome categories causally impacted by alcohol, as well as the most important meta-analyses, including those used for the CRA of the upcoming WHO Global Status Report on Alcohol and Health (to be prepared in 2017; for graphs on the relationships between average level of alcohol use and disease, see Supporting information, Appendix S2).

In the following sections, we discuss the underlying reasons and pathways for major disease, injury and cause of death categories where causality has been established. An important consideration for each disease and mortality outcome are the questions of (a) which dimension of alcohol use is causally related; (b) if there are dose–response relationships within the respective dimension; and (c) whether there are gender differences (see also Supporting information, Appendix S2 for gender specific formulas). The overall results on modelled and biological relationships are summarized in Table 3.

Infectious diseases

Alcohol's effects on the immune system

Alcohol impacts the innate and the acquired immune system and, thus, increases vulnerability to infectious disease [77,78]. Alcohol exposure impairs the functioning of phagocytes such as polymorphonuclear leucocytes (especially neutrophils) and macrophages [79]. These cells are responsible for the ingestion of dead cells and can be considered the immune system's first responders to inflammation [80]. Alcohol exposure has a suppressive effect on the release of cytokines responsible for cell signalling and critical for regulation of the host defence [80,81]. This includes chemotactic signals that trigger the migration of polymorphonuclear leucocytes into the infected area. The effects of chronic alcohol use on the immune response are probably also to increase the risk of infectious disease [82,83]. Overall, the biological pathways suggest a more pronounced effect of heavy drinking occasions and, thus, more exponential pathways and a specifically high risk for alcohol use disorders.

Tuberculosis

Alcohol's impact on the immune system described above is immediately relevant to infection with tuberculosis (TB), as approximately one-third of people in the world have been infected with *Mycobacterium tuberculosis* but are not yet ill and cannot transmit the disease (latent TB [84]). However, only 10% of those infected develop active TB; for the rest, the immune system will be able to fight off the infection.

Accordingly, a weakened immune system is critical for increasing susceptibility to TB infection, or for reactivation of latent TB, and alcohol plays a prominent role here [85]. As a second important pathway, alcohol use may lead to a presence in social environments that facilitate the spread of tuberculosis infection [85]. As a consequence, alcohol is one of the major risk factors for TB, especially in countries with high population densities and high infection rates of *M. tuberculosis*, with poverty being linked to both. Regarding for average level of consumption, there is clearly a dose–response relationship, with some indication that, for lower levels of consumption, the increase is less steep than for higher levels [86,87].

Given the aetiology, one may suspect an impact of patterns of drinking, especially of irregular heavy drinking occasions, but the empirical evidence is scarce [88]. In addition, the higher relative risks for alcohol use disorders or alcohol problems may serve as an indirect indicator [86,87], as both are usually linked to heavy drinking occasions [40,89,90].

HIV/AIDS

The status of alcohol use as a cause for HIV infection, separate from its general impact on the immune system (see above), and of the effects of alcohol use on the course of HIV/AIDS, separate from non-adherence to anti-retroviral medications [91,92], have been discussed in recent years [93–96]. Indeed, the evidence on both mechanisms was found to be non-conclusive in most publications, and also at a meeting to discuss the causal role of alcohol use in HIV/AIDS organized by the WHO and the South African Medical Research Council in 2008 [97]. However, since 2008, considerable new scientific evidence has emerged which supports a causal role of alcohol. Systematic reviews and meta-analyses are now available to allow the quantification of the impact of alcohol use on HIV/AIDS. In the following, we try to summarize recent developments (following closely [98]; see also [99]), and suggest an operationalization to quantify the causal impact of alcohol use on HIV/AIDS.

Alcohol use was found to be associated with HIV incidence and prevalence in systematic reviews and meta-analyses [100–106]. This association may have resulted, in part, from the causal impact of acute alcohol use on sexual decision-making [107], resulting in condomless sex [105,108–114]. Alternatively, other variables could be causally responsible for the associations between alcohol use and HIV/AIDS, especially the effect of risk-taking behaviours and other personality traits [96,115].

To exclude such alternative explanations and corroborate the causal role of alcohol on HIV incidence via impacts on decision-making concerning safer sex practices, a

Table 2 Potentially alcohol-attributable broad disease categories.

Disease category	GBD 2015 Cause Name (Cause ID) [354]	ICD-10 codes for cause of death[a]	Causality and reference to meta-analyses/selected systematic reviews	Effect
Infectious diseases				
Tuberculosis	Tuberculosis [297]	A10–A14, A15–A19.9, B90–B90.9, K67.3, K93.0, M49.0, P37.0	Causality: Rehm *et al.*, 2009 [85] Meta-analyses: Lönnroth *et al.*, 2008 [86]; Patra *et al.*, 2014 [355]; Imtiaz *et al.*, 2016 [87] CRA calculations: Imtiaz *et al.*, 2016 [87]	Detrimental
Human immunodeficiency virus/Acquired immune deficiency syndrome (HIV/AIDS)	HIV/AIDS [298]	B20–B24.9	Causality: Rehm *et al.*, 2016 [98]; Williams *et al.*, 2016 [99] Meta-analyses: Shuper *et al.*, 2009 [112]; Baliunas *et al.*, 2010 [102]; Lan *et al.*, 2016 [100] CRA calculations: Rehm *et al.*, 2016 [98], for impact of alcohol on HIV incidence based on [113]; Gmel *et al.*, 2011 [92], for the effect of alcohol use on mortality via medication non-adherence	Detrimental
Other sexually transmitted diseases	Sexually transmitted diseases excluding HIV (393)	A50–A58, A60–A60.9, A63–A63.8, B63, I98.0, K67.0–K67.2, M03.1, M73.0–M73.1, N70–N71.9, N73–N74.8	Causality: Cook & Clark, 2005 [121] Meta-analyses, CRA calculations: the behavioural causal pathway via alcohol's impact on decision making should be the same [98,99], so we suggest the same AAFs as for HIV/AIDS, but without the effect of alcohol use on mortality via medication non-adherence	Detrimental
Lower respiratory infections: pneumonia	Lower respiratory infections [322]	A48.1, A70, J09–J15.8, J16–J16.9, J20–J21.9, P23.0–P23.4	Causality: Samokhvalov *et al.*, 2010 [142]; Traphagen *et al.*, 2015 [356], for heavy drinking und alcohol use disorders: Simet & Sisson, 2015 [357] Meta-analysis and CRA calculations: Samokhvalov *et al.*, 2010 [142]	Detrimental
Cancers				
Lip and oral cavity cancer	Lip and oral cavity cancer (444)	C0–C08.9, D00.00–D00.07, D10.0–D10.5, D11–D11.9, D37.01–D37.04, D37.09[c]	Causality: International Agency for Research on Cancer (IARC), 2010; 2012 [145,146]: sufficient evidence for carcinogenicity in humans[b] Meta-analysis: Corrao *et al.*, 2004 [170]; Bagnardi *et al.*, 2015 [169] CRA calculations: Bagnardi *et al.*, 2015 [169]	Detrimental
Nasopharynx cancer	Nasopharynx cancer (447)	C11–C11.9, D00.08, D10.6, D37.05[c]	Causality: IARC, 2010; 2012 [145,146]: sufficient evidence for carcinogenicity in humans[b] Meta-analysis: Corrao *et al.*, 2004 [170]; Bagnardi *et al.*, 2015 [169] CRA calculations: Bagnardi *et al.*, 2015 [169]	Detrimental
Other pharynx cancer	Other pharynx cancer (450)	C09–C10.9, C12–C13.9, D10.7[c]	Causality: IARC, 2010; 2012 [145,146]: sufficient evidence for carcinogenicity in humans[b] Meta-analysis: Corrao *et al.*, 2004 [170]; Bagnardi *et al.*, 2015 [169] CRA calculations: Bagnardi *et al.*, 2015 [169]	Detrimental

(Continues)

Table 2. (Continued)

Disease category	GBD 2015 Cause Name (Cause ID) [354]	ICD–10 codes for cause of death[a]	Causality and reference to meta-analyses/selected systematic reviews	Effect
Oesophagus cancer	Oesophageal cancer (411)	C15–C15.9, D00.1, D13.0[c]	Causality: IARC, 2010; 2012 [145,146]: sufficient evidence for carcinogenicity in humans[b] Meta-analysis: Corrao et al., 2004 [170]; Bagnardi et al., 2015 [169] CRA calculations: Bagnardi et al., 2015 [169]	Detrimental
Stomach cancer	Stomach cancer (414)	C16–C16.9, D00.2, D13.1, D37.1[c]	Causality: IARC, 2012 [146]: probably carcinogenic in humans[b] Meta-analysis: Bagnardi et al., 2015 [169] CRA calculations: Bagnardi et al., 2015 [169]; stomach cancer may be included in CRA calculations where the threshold is set to include 'probably carcinogenic'	Detrimental
Colon and rectum cancer	Colon and rectum cancer (441)	C18–C21.9, D01.0–D01.3, D12–D12.9, D37.3–D37.5[c]	Causality: IARC, 2010; 2012 [145,146]: sufficient evidence for carcinogenicity in humans[b] Meta-analysis: Corrao et al., 2004 [170]; Bagnardi et al., 2015 [169] CRA calculations: Bagnardi et al., 2015 [169]	Detrimental
Liver cancer	Liver cancer (417)	C22–C22.9, D13.4[c]	Causality: IARC, 2010; 2012 [145,146]: sufficient evidence for carcinogenicity in humans[b] Meta-analysis: Corrao et al., 2004 [170]; Bagnardi et al., 2015 [169] CRA calculations: Bagnardi et al., 2015 [169]	Detrimental
Pancreatic cancer	Pancreatic cancer (456)	C25–C25.9, D13.6–D13.7[c]	Causality: IARC, 2012 [146]: probably carcinogenic in humans[b] Meta-analysis: Bagnardi et al., 2015 [169] CRA calculations: Bagnardi et al., 2015 [169]; pancreatic cancer has been included in some CRA calculations where the threshold was set to include 'probably carcinogenic'	Detrimental
Larynx cancer	Larynx cancer (423)	C32–C32.9, D02.0, D14.1, D38.0[c]	Causality: IARC, 2010; 2012 [145,146]: sufficient evidence for carcinogenicity in humans[b] Meta-analysis: Corrao et al., 2004 [170]; Bagnardi et al., 2015 [169] CRA calculations: Bagnardi et al., 2015 [169]	Detrimental
Trachea, bronchus and lung cancer	Tracheal, bronchus, and lung cancer (426)	C33–C34.92, D02.1–D02.3, D14.2–D14.32, D38.1[c]	Causality: IARC, 2010; 2012 [145,146]: neither sufficient evidence nor probably carcinogenic in humans[b] Meta-analysis: Bagnardi et al., 2015 [169] CRA calculations: not relevant, as not yet established as causal pathway	Detrimental
Female breast cancer	Breast cancer (429)		Causality: IARC, 2010; 2012 [145,146]: sufficient evidence for carcinogenicity in humans[b]	Detrimental

(Continues)

Table 2. (Continued)

Disease category	GBD 2015 Cause Name (Cause ID) [354]	ICD–10 codes for cause of death[a]	Causality and reference to meta-analyses/selected systematic reviews	Effect
		C50–C50.929, D05–D05.92, D24–D24.9, D48.6–D48.62, D49.3, N60–N60.99[c]	Meta-analyses: many meta-analyses with similar results (for an overview see Shield et al., 2016 [151]) CRA calculations: Bagnardi et al. 2015 [169]	Detrimental
Other neoplasms	Other neoplasms (488)	C17–C17.9, C3–C31.9, C37–C38.8, C4–C41.9, C47–C5, C51–C52.9, C57–C57.8, C58–C58.0, C60–C60.9, C63–C63.8, C66–C66.9, C68.0–C68.8, C69–C7, C74–C75.8, D07.4, D09.2–D09.22, D13.2–D13.39, D14.0, D15–D16.9, D28.0–D28.1, D28.7, D29.0, D30.2–D30.22, D30.4–D30.8, D31–D33.9, D35–D36, D36.1–D36.7, D37.2, D38.2–D38.5, D39.2, D39.8, D41.2–D41.3, D42–D43.9, D44.1–D44.8, D45–D45.9, D47–D47.0, D47.2–D47.9, D48.0–D48.4, D49.6, D49.81, K31.7, K62.0–K62.1, K63.5, N84.0–N84.1	Too diverse a category to establish any causal pathways from alcohol as a whole or to quantify any risk-relations; thus, this category will not be quantified as a cause of death or morbidity category causally impacted by alcohol.	
Diabetes mellitus				
Diabetes mellitus	Diabetes mellitus (587)	E10–E10.11, E10.3–E11.1, E11.3–E12.1, E12.3–E13.11, E13.3–E14.1, E14.3–E14.9, P70.0–P70.2, R73–R73.9	Causality: Howard et al., 2004 [188] Meta-analyses: Baliunas et al., 2009 [191]; Knott et al., 2015 [192]; Li et al., 2016 [193]; in addition there were intervention studies with mixed results [194,195] CRA calculations: Baliunas et al., 2009 [191]; currently in revision	Beneficial or detrimental, depending on patterns of drinking and populations
Neuropsychiatric disorders				
Alzheimer's disease and other dementias	Alzheimer disease and other dementias (543)	F00–F03.91, G30–G31.1, G31.8–G31.9	Causality: Collins et al., 2009 [212] for potential pathways of protective effects of light to moderate use; Ridley et al., 2013 [210]; Daulatzai, 2015 [211], for mechanism of detrimental effects of heavy use Meta-analyses: Beydoun et al., 2014 [207] CRA calculations: not yet included in CRA	Detrimental; potential beneficial effect for light to moderate drinking

(*Continues*)

Table 2. (Continued)

Disease category	GBD 2015 Cause Name (Cause ID) [354]	ICD–10 codes for cause of death[a]	Causality and reference to meta-analyses/selected systematic reviews	Effect
Unipolar depressive disorders	Major depressive disorder (568)	Has not been modelled in GBD as cause of death	Causality: Rehm et al. 2004 [5]; Boden & Fergusson, 2011 [219]; Meta-analyses: Boden & Fergusson, 2011 [219]; Foulds et al. 2015 [358] CRA calculations: suggested to use Fergusson et al. 2009 [221] to be conservative, based on prevalence of alcohol use disorders	Detrimental
Epilepsy	Epilepsy / Epilepsy impairment envelope (545)	G40–G41.9	Causality: Bartolomei, 2006 [359]; Barclay et al., 2008 [236]; Leach et al., 2012 [237] Meta-analysis and CRA calculations: Samokhvalov et al., 2010 [230]	Detrimental
Cardiovascular diseases				
Hypertensive heart disease	Hypertensive heart disease (498)	I11–I11.9	Causality: Puddey & Beilin, 2006 [360]; O'Keefe et al., 2014 [239]; in addition we have good evidence that interventions leading to reductions of alcohol use subsequently lead to reductions in blood pressure and hypertension [361,362] Meta-analyses: Chen et al., 2008 [363]; Taylor et al., 2009 [241]; Briasoulis et al., 2012 [242] CRA calculations: Taylor et al., 2009 [241]; new meta-analyses in preparation	Detrimental, may depend on patterns of drinking for low volume in women
Ischaemic heart disease	Ischaemic heart disease (493)	I20–I25.9	Causality: Mukamal & Rimm, 2001 [364]; Collins et al., 2009 [212]; Roerecke & Rehm, 2014 [248] Meta-analyses: Ronksley et al., 2011 [256]; Roerecke & Rehm, 2011 [365]; Roerecke & Rehm, 2012; 2014 [248,257] CRA calculations: Rehm et al. 2016 [268]	Beneficial or detrimental, dependent on level and patterns of drinking
Cardiomyopathy	Cardiomyopathy and myocarditis (499)	A39.52, B33.2–B33.24, D86.85, I40–I43.9, I51.4–I51.5	Causality: Iacovoni et al. 2010 [244]; George & Figueredo, 2011 [366]; Rehm et al. 2017 [39] No meta-analyses found. There is a separate category for alcoholic cardiomyopathy, which is responsible for 3–40% of all cardiomyopathies [244]. Rehm and colleagues recently introduced a method to estimate AAFs for this condition [367] CRA calculations: Manthey et al. 2017 [367]	Detrimental
Atrial fibrillation and flutter	Atrial fibrillation and flutter (500)	I48–I48.92	Causality: Rosenqvist, 1998 [368]; Rosenberg & Mukamal, 2012 [369] Meta-analyses: Samokhvalov et al., 2010 [370]; Kodama et al. 2011 [245]; Larsson et al., 2014 [371] CRA calculations: Samokhvalov et al. 2010 [370]	Detrimental
Heart failure	No GBD category; ICD codes are redistributed	I50, I11.0, I13.0, I13.2	Although there are many reviews about alcohol use and heart failure, including meta-analyses (Supporting information, Appendix S1), this does not	

(*Continues*)

Table 2. (Continued)

Disease category	GBD 2015 Cause Name (Cause ID) [354]	ICD–10 codes for cause of death[a]	Causality and reference to meta-analyses/selected systematic reviews	Effect
	to other GBD categories, mainly to ischaemic heart disease		affect CRAs, as the category of 'heart failure', since the first GBD study, has been redistributed to other GBD cardiovascular categories, mainly to ischaemic heart disease [372]	Beneficial or detrimental, dependent on level and patterns of drinking
Ischaemic stroke	Ischaemic stroke (495)	G45–G46.8, I63–I63.9, I65–I66.9, I67.2–I67.3, I67.5–I67.6, I69.3–I69.398	Causality: Puddey et al., 1999 [255]; Mazzaglia et al., 2001 [373]; Collins et al., 2009 [212] Meta-analyses: Reynolds et al., 2003 [374]; Patra et al., 2010 [375]; Zhang et al., 2014 [376] CRA calculations: Patra et al., 2010 [375]; Rehm et al., 2016 [268]	Beneficial or detrimental, dependent on level and patterns of drinking (similar to IHD)
Haemorrhagic and other non-ischaemic stroke	Haemorrhagic and other non-ischaemic stroke (496)	I60–I61.9, I62.0–I62.03, I67.0–I67.1, I68.1–I68.2, I69.0–I69.298	Causality: Puddey et al., 1999 [255]; Mazzaglia et al., 2001 [373]; Meta-analyses: Reynolds et al., 2003 [374]; Patra et al., 2010 [375]; Zhang et al., 2014 [376] CRA calculations: Patra et al., 2010 [375]	Mainly detrimental, except for low doses
Oesophageal varices	No GBD category	I85	No meta-analyses found Global CRA calculations: not applicable, as category is too small. National CRA calculations: should be done with relative risk of liver cirrhosis	Detrimental
Gastrointestinal diseases				
Cirrhosis of the liver	Cirrhosis and other chronic liver diseases (521)	B18–B18.9, I85–I85.9, I98.2, K70–K70.9, K71.3–K71.51, K71.7, K72.1–K74.69, K74.9, K75.8–K76.0, K76.6–K76.7, K76.9	Causality: a causal impact of alcohol is by definition as for many liver diseases there are alcoholic subcategories in the ICD (see Table 1); pathogenesis: Gao & Bataller, 2011 [279] Meta-analyses and CRA calculations: Rehm et al., 2010 [280]	Detrimental
Gall bladder and bile duct disease	Gallbladder and biliary diseases (534)	K80–K83.9	Causality: not clear for the overall category (for gallstones see [377]) Meta-analyses: Shabanzadeh et al., 2016 [378] CRA calculations: not relevant, as causality is not clear and the only meta-analyses showed no association between alcohol use and gallstones	Potentially beneficial, but no relation to alcohol use in the only meta-analyses for gallstones
Pancreatitis	Pancreatitis (535)	K85–K86.9	Causality: not necessary, as there are two conditions of pancreatitis which are 100% alcohol attributable (see Table 1); for pathogenesis: Braganza et al., 2011 [299]; Yadav et al., 2013 [300]; Lankisch et al., 2015 [301]; Majumder & Chari, 2016 [302] Meta-analyses: Irving et al., 2009 [308]; Sankaran et al., 2015 [303]; Samokhvalov et al., 2015 [309] CRA calculations: Samokhvalov et al., 2015 [309]	Detrimental

(*Continues*)

Table 2. (Continued)

Disease category	GBD 2015 Cause Name (Cause ID) [354]	ICD–10 codes for cause of death[a]	Causality and reference to meta-analyses/selected systematic reviews	Effect
Other digestive diseases	Other digestive diseases (541)	I84–I84.9, K20–K24, K31.0, K31.81–K31.819, K38–K38.2, K57–K62, K62.2–K62.6, K62.8–K62.9, K64–K64.9, K66.8, K67, K68–K68.9, K75.2–K75.4, K76.1–K76.5, K76.8–K76.89, K77–K77.8, K90–K90.9, K92.8–K92.89	Too broad a category for quantifying the impact of alcohol use; there are no studies on the impact of alcohol use on this specific group of diseases	Mainly detrimental
Other disease categories considered				
Psoriasis	Psoriasis (655)	Not a cause of death in GBD	Causality: Farkas & Kemény, 2010 [379]; Brenaut *et al.*, 2013 [380]; Richard *et al.*, 2013 [381]; even though alcohol use has been shown to affect the immune system in general, the conclusion has been that causality for psoriasis has not yet been fully established (see also [382]). Most studies are not about alcohol use as a risk factor for psoriasis, but about comorbidity of psoriasis and alcohol use disorders and increased risk of mortality [383]. A large cohort study found high excess mortality of people with psoriasis mainly with alcohol-attributable cause of deaths [384] Meta-analysis: Zhu *et al.*, 2012 [382] CRA calculations: not relevant, as causality has not been established	Detrimental
Abortion	Maternal abortion, miscarriage, and ectopic pregnancy [371]	N96, O00–O07.9	While there are a number of reviews, no quantitative meta-analyses have been carried out on this category (see Supporting information, Appendix S1 for details)	Detrimental
Preterm birth complications	Neonatal preterm birth complications [381]	P01.0–P01.1, P07–P07.39, P22–P22.9, P25–P28.9, P61.2, P77–P77.9	The only meta-analyses on preterm birth complications covered low birth weight, preterm birth and small for gestational age [385], and the relative risk for preterm birth was not significant CRA calculations: not relevant, as relative risk is not significant	Detrimental for some complications

[a]ICD codes for non-fatal disease outcomes are slightly different in the Global Burden of Disease (GBD), but for this overview table we did not want to introduce this distinction (for the respective ICD codes by the GBD, see [386]); [b]for definitions, see [148]; [c]The relationships between alcohol use and the respective cancer sites are based on studies with ICD-10 C codes; the D codes were listed only, as we wanted to show compatibility with the GBD; Shaded rows indicate a causal impact of alcohol, whether or not the relationship could be quantified. CRA = Comparative Risk Assessment; HIV = human immunodeficiency virus; AAF = alcohol-attributable fractions.

Table 3 Biological pathway and Comparative Risk Assessment (CRA) modelling of alcohol use and health outcomes.

Disease category	Statistical model		Biological pathway	
	General regression of alcohol use on logarithmized RR	*Irregular HD*	*HD*	*Irregular HD*
Infectious diseases				
Tuberculosis	Linear	−	+	+
Human immunodeficiency virus/ acquired immune deficiency syndrome (HIV/AIDS)	Modelled indirectly via sexual decision making and impact on medication adherence	+	+	+
Other sexually transmitted diseases	Modelled indirectly via sexual decision-making	+	+	+
Lower respiratory infections: pneumonia	linear	−	+	?
Cancers				
Lip and oral cavity cancer	Almost linear	−	−	−
Nasopharynx cancer	Almost linear	−	−	−
Other pharynx cancer	Almost linear	−	−	−
Oesophagus cancer	Almost linear	−	−	−
Colon and rectum cancer	Almost linear	−	−	−
Liver cancer	Accelerated	−	−	−
Larynx cancer	Almost linear	−	−	−
Female breast cancer	Slightly accelerated	−	Some indications	−
Diabetes mellitus				
Diabetes mellitus	Curvilinear	+	+	?
Neuropsychiatric disorders				
Alzheimer's disease and other dementias	Not clear; indications for curvilinear	−	+	−
Unipolar depressive disorders	Threshold	−	+	?
Epilepsy	Linear	−	+	?
Cardiovascular diseases				
Hypertensive heart disease	Accelerated	−	+	?
Ischaemic heart disease	Curvilinear	+	+	+
Cardiomyopathy	Modelled indirectly via the proportion of alcoholic cardiomyopathy to cardiomyopathy in the countries with data	+	+	+
Atrial fibrillation and flutter	Linear	−	+	+
Ischaemic stroke	Curvilinear	+	+	+
Haemorrhagic and other non-ischaemic stroke	Linear for women; accelerated for men	−	+	+
Gastrointestinal diseases				
Cirrhosis of the liver	Accelerated	−	+	−
Pancreatitis	Curvilinear for women; linear for men	−	+	+
Injuries				
Unintentional injuries	Modelled mainly via drinking level in the situation	+	+ (tolerance)	+
Violence	Modelled mainly via drinking level in the situation	+	?	+
Suicide	Modelled based on both volume of drinking and drinking in the situation	+	+	+

RR: relative risk; HD: chronic heavy drinking; irregular HD: irregular heavy drinking.

number of experiments have been conducted. Alcohol use was manipulated experimentally to assess its impact on condomless sex intentions. Systematic reviews and meta-analyses of the results of these experimental trials clearly indicated the causal impact of acute alcohol use (clearly shown for a blood alcohol concentration of 0.07 g/dl or more, but possibly even below) use on decisions/intentions about condomless sex, above and beyond the influence of expectations about alcohol and of underlying risk-relevant personality traits [113,114]. It should be noted that these experiments have been conducted in a number of key populations, including HIV-positive people [116].

Clearly, any experimental studies on alcohol use and HIV can only use surrogate end-points, i.e. intention for unsafe (condomless) sex rather than condomless sex itself or HIV infection. However, the results of the experimental studies corroborate the results of epidemiological cohort

and cross-sectional studies with condomless sex [105,108–112,117–120], sexually transmitted diseases [121,122] or HIV incidence [102] as end-points. Moreover, there are meta-analyses that show a clear link between intentions for condomless sex and actual sexual risk behaviour [123,124], as well as between condomless sexual practices and HIV seroconversion [125–127].

Besides this pathway of sexual decision-making, there are findings of biological effects of alcohol use on HIV transmission and disease progression ([128] gives an overview; see also [129–131]). These include clear evidence that heavy drinking or alcohol use disorders are associated with viral load increases and/or CD4 count declines, mediated partly by treatment adherence and partly by the pharmacological interactions with anti-retroviral and other medications to treat comorbidities (for mechanisms see [99,128,130,132–134]; for pharmacological interactions see [135,136]). It should be noted, however, that delineation and quantification of causality in these biological pathways is difficult, as many factors interact [128,134,136,137].

The above considerations allow only a conservative operationalization of the causal impact of alcohol use on HIV/AIDS based on its causal effect on decision making, assuming that there is a threshold for alcohol's effect on decision-making of four drinks for women and five drinks for men (approximately 48+/60+ g on one occasion). A further causal impact is the effect of alcohol on impeding adherence to anti-retroviral medications [92]. The estimation of relative risk based on these two mechanisms is conservative in its assumptions, and the resulting AAFs are markedly lower than those from modelling exposure with relative risk for incidence [102] using the usual methodology for CRAs (see [98] for a comparison; for usual modelling strategies see [11]).

Sexually transmitted diseases excluding HIV

Other sexually transmitted diseases have been found to be associated with alcohol use, especially with heavy drinking occasions [121]. While some specific biological pathways may vary, the general impact of alcohol use on the immune system (see above) is also relevant for the incidence of these diseases. Moreover, the behavioural causal pathway of alcohol's impact on decision-making should be the same [98,99], so we suggest the same AAFs as for HIV/AIDS (excluding the AAF for the effect of alcohol use on mortality due to medication non-adherence). The latter effect was specific for HIV/AIDS, as missing anti-retroviral medications was shown to have marked effects on mortality [92], an effect not applying to medications for other sexually transmitted diseases. Moreover, the interactions between medications for HIV/AIDS and alcohol are not observed for medications for other sexually transmitted diseases and alcohol.

Lower respiratory infections: pneumonia

The constant exchange with the environment presents a specific challenge to the immune defences of the lower respiratory tract. Apart from the general immunosuppressive effects explained above, chronic alcohol exposure specifically impairs the immune defences and functioning of the lower respiratory tract, increasing the risk of both viral and bacterial pneumonia. Chronic alcohol exposure decreases saliva output, which leads to an increased colonization of bacteria in the oropharynx [138]. Ciliary movement that is responsible for the transportation of trapped airborne particles and microorganisms can be impaired by heavy alcohol use, and the normal cough reflex can be weakened, increasing the risk of aspiration of oropharyngeal bacteria [80]. Finally, chronic alcohol use severely impairs alveolar macrophages that constitute the first line of the cellular immune defence of the lungs [79,138,139]. For an overview of the physiological mechanisms, see [138] and [140].

While the effect of alcohol use on pneumonia has been recognized since the 18th century [141], there has been a scarcity of systematic reviews and meta-analyses quantifying the relative risk associated with different levels of alcohol use. The work of Samokhvalov and colleagues still seems to be the best review and quantitative summary [142]. In line with what would be expected, based on the physiological effects, heavy and prolonged alcohol use and alcohol use disorders have been linked specifically to a high risk, while evidence of the effects of lower levels of use is less clear.

Cancers

The carcinogenic effects of ethanol (the main carcinogenic compound in alcoholic beverages [143]) and its metabolites have been acknowledged by the International Agency for Research on Cancer (IARC) in three monographs [144–146], as well as by the Continuous Update Project of the World Cancer Research Fund and the American Institute for Cancer Research [147]. Specifically, the biological, animal and epidemiological evidence has resulted in alcohol being classified as a group 1 carcinogenic agent for humans (i.e. the highest level of evidence of carcinogenicity; for guidelines and evaluation criteria see [148]). Furthermore, the most recent IARC monographs found sufficient animal and epidemiological evidence to conclude that alcohol consumption plays a causal role in oral cavity, pharyngeal, laryngeal, oesophageal (limited to squamous cell carcinoma (SCC), liver, colon, rectal and female breast cancers [149], as well as some evidence for a probable relationship between alcohol consumption and stomach and pancreatic cancers [146]. Lastly, there is limited epidemiological evidence of a relationship between

alcohol consumption and kidney, thyroid, prostate, ovarian and endometrial cancers and Hodgkin's and non-Hodgkin's lymphoma [149]. Thus, the causal role of alcohol in the development of these cancers is uncertain.

There are various biological pathways by which the use of alcohol increases (and possibly decreases) the risk of cancer; the exact pathways are often unknown and likely to vary by cancer site. Based on current evidence, the main pathway by which alcohol use is hypothesized to increase the risk of cancer is through the metabolism of ethanol into its carcinogenic metabolite acetaldehyde, which forms DNA adducts leading to the development of cancer (see review in [143]). There are at least four other pathways by which alcohol use may increase the risk of cancer. First, alcohol may alter the one carbon metabolism by inhibiting folate absorption, leading to increased homocysteine concentrations [150,151], and by inhibiting folate cycle enzyme methionine synthase and the trans-methylation enzymes methionine adenosyltransferase and DNA methyltransferase [150,152]. Secondly, alcohol may affect serum levels of hormones and related signalling pathways, leading to an increased risk of breast cancer, and possibly of prostate, ovarian and endometrial cancers [153–155]. Thirdly, alcohol consumption may lead to alterations in serum levels of insulin-like growth factor (IGF); however, this relationship is complex, with moderate chronic alcohol consumption increasing serum levels of IGF, and acute alcohol consumption leading to a decrease in IGF levels [156]. Lastly, alcohol also has a strong interaction with tobacco smoking, particularly in terms of its carcinogenic effects on the oral cavity and oesophagus (SCC). Specifically, alcohol acts as a solvent for tobacco carcinogens [157,158].

Conversely, alcohol may prevent the development of cancer through two biological pathways. First, by increasing insulin sensitivity, alcohol may decrease the risk of kidney cancer [159,160]; in contrast, insulin resistance has been observed to be a risk factor for cancer independent of other risk factors such as obesity [161,162]. Furthermore, the World Cancer Research Fund has found that there is strong evidence to suggest that alcohol consumption below 30 g per day on average is related causally to a decrease in the risk of developing kidney cancer [163]. Secondly, resveratrol (the 'red wine chemical') has gained attention for its protective effects on the development of cancer [164–166] through its ability to inhibit nuclear factor kappa B (NF-κB) (thus creating an anti-inflammatory effect) and activator protein-1 (AP-1) transcription (thus inhibiting the conversion of procarcinogens into carcinogens [167]). However, the effect of resveratrol in decreasing the risk of cancer is minimal, at best. To exhibit a protective effect against cancer (i.e. reduce the incidence of certain cancers of colon, liver and female breast) a certain minimum daily dose of resveratrol is required, and below this

dose there will be no possible protective effect. The amount of resveratrol in wine is approximately a factor of 100 000 or more below this minimal effective daily dose and, thus, no protective effect is to be expected from such a low dosage (this would be similar to ingesting 1/100000 of an aspirin tablet [168]).

The increase in the risk of developing cancer (stratified by cancer site) for increasing average daily amounts of alcohol consumed (measured in grams of pure alcohol consumed per day) has been observed to be linear on an exponentiated scale; however, the magnitude of these risk increases varies by cancer site [169–171]. Furthermore, as with other diseases related causally to alcohol consumption, the relative risks for cancer are dependent upon the systematic search strategy, inclusion and exclusion criteria, reference group (and if this includes former drinkers) of the underlying studies [172–174], use of case–control and/or cohort studies [175] and use of categorical or continuous estimates for alcohol consumption [169] (for relative risk graphs see [176] and Supporting information, Appendix S2).

No threshold for the effects of alcohol use on the risk of cancer has been detected; however, especially for breast cancer, there is ample evidence of alcohol's effects even at low levels of average consumption [177–179]. This results in a large breast cancer burden from relatively low doses (< 21 g per day) of alcohol [179]. Furthermore, there is currently not enough epidemiological evidence to assess if the pattern of alcohol consumption modifies the risk of breast cancer [151]. The main biological pathway seems to be through overall tissue exposure to acetaldehyde, which may not be affected by drinking patterns; however, through modifications of insulin-like growth factor (IGF) serum levels, drinking patterns may have an effect on the risk of developing breast cancer (as well as other cancers, where modifications to IGF serum levels play a role [180]).

The risk relationship between alcohol consumption and the development of cancer has been shown to be modified by genetic variations in the carbon metabolism pathway and the ethanol–acetaldehyde metabolic pathways [181,182]. Specifically, genetic variations in the *aldehyde dehydrogenase 2* gene have been shown to affect the risk relationship between alcohol consumption and oral cavity and oesophageal cancer [175,181,183]. As the prevalence of these genetic variations differs in different national populations, cancer is the first alcohol-attributable disease category where genetic considerations play a role in modelling the effect of alcohol use in global CRAs of the GBD and the WHO (for a first such attempt, see [184]).

Overall, the alcohol-attributable cancer disease and mortality burden is high [8,178]. However, current estimates of the number of cancer cases and cancer deaths caused by alcohol are limited due to the inability to incorporate biological latency which, for many cancer sites, can be 20 years or more [185,186]. Future CRA studies

will need to take into account this latency and the competing risks from alcohol-related and -unrelated deaths [187].

Diabetes mellitus

There seems to be a beneficial effect of alcohol use on diabetes mellitus type 2 incidence [188], as evidenced in meta-analyses and in systematic reviews [189–193]. However, this seemingly unambiguous picture must be qualified by different results by gender and ethnicity. For instance, stratification of available data in the latest and most comprehensive meta-analyses by Knott and colleagues [192] revealed that reductions in risk may apply to women only and may be absent in studies sampled in the Asian region. In addition, Knott [192] found that some beneficial effects disappeared when compared to life-time abstainers, a problem not unique to diabetes ([174]; see below and discussion in [173]). Also, intervention studies about the effects of reductions in the consumption of alcohol on glucose and insulin biomarkers in people with and without diabetes showed mixed results [194,195]. Irregular heavy drinking occasions may play a role in explaining the differences between studies and in the reviews (e.g. [196,197]), but there are not enough epidemiological studies on diabetes including this dimension of alcohol exposure to settle this question.

Whether a beneficial effect of alcohol on diabetes should be modelled in future CRAs will be a discussion in the respective technical advisory committees. This decision has important public health relevance (see [198] for additional considerations), as the effect is fairly large, given the prevalence of diabetes mellitus world-wide [199,200] and the relatively high effect size found in epidemiological studies on alcohol use and the incidence of type 2 diabetes mellitus [191,192].

Neuropsychiatric disorders

Alzheimer's disease, other dementias and cognitive decline

The relationships of alcohol use to Alzheimer's disease, other forms of dementia and cognitive decline seem to be complex. On one hand, there is a possible protective effect of light to moderate drinking [201–203]. On the other hand, systemic reviews revealed inconsistent results about a potential protective effect of alcohol use [204,205]. Several subtypes of dementia are clearly related detrimentally and causally to heavy drinking [206], and the most comprehensive review exhibited a J- or U-shaped relationship between the intensity of alcohol use and the direction of the effect [207]. A recent review also found evidence that heavy alcohol use predicts conversion from any type of mild cognitive impairment to dementia, and inconsistent evidence about whether moderate alcohol use predicts risk of dementia [208]. In addition, a Mendelian randomization

study did not provide any evidence of a causal impact of alcohol use on cognitive performance, although admittedly this is a more general concept than the disease categories discussed above [209].

Overall, while the negative impact of heavy drinking on dementia and cognitive functioning seems indisputable, with identified biological pathways [210,211], a protective effect of light to moderate drinking has some biological plausibility [212], but evidence on this is inconsistent. This is due partly to the multitude of methodological problems which every review describes (e.g. see discussion in [213]), such as inconsistent measurement of exposure and outcomes, inconsistent control of potential confounders and lack of consideration of sample attrition due to mortality.

Major depressive disorders

Most mental disorders, including major depressive disorders, have consistent associations with alcohol use, and especially with heavy drinking and alcohol use disorders [79–81,214–217]. In addition to these associations, both the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [58] and the ICD-10 ([25]; see also [218]) list alcohol-induced mental disorders, including alcohol-induced depressive disorders, thus building causality into the disorder category. However, these codes are not used in most countries (an exception is the United States, where it is a billable code for medical services), so we need to establish estimates of the causal impact of alcohol use on major depressive episodes in other ways.

There are three possible descriptions of the potential causal pathways that underlie the association between heavy alcohol use and alcohol use disorders and major depressive disorders [5,219]: (a) heavy drinking/alcohol use disorders cause depressive disorders; (b) depressive disorders increase alcohol use and cause alcohol use disorders (often discussed under the heading of a 'self-medication' hypothesis [220]); and (c) a reciprocal causal relationship or causation by another mechanism such as genetic vulnerability. Two reviews on this topic came to the same conclusion: that all three mechanisms are possible and probably existing, but the first mechanism—that alcohol use (especially heavy use and alcohol use disorders) causes depression—is stronger and more prevalent than the other pathways ([5,219]; see also [221,222]).

How to estimate the causal impact of alcohol use on major depressive disorders remains in question. Given the current scarcity of meta-analyses on alcohol use as a risk factor for major depressive disorders, this probably has to be performed indirectly from the risk relationships of alcohol use disorders and depressive disorders [219]. To be conservative, these risk relationships should be applied only to depressive disorders with later onset

than alcohol use disorders. Alternatively, the confounder-controlled risks from Fergusson and colleagues [221] could be used [odds ratio (OR) = 1.66, 95% confidence interval (CI) = 1.08–2.55]. Both suggested solutions are conservative, as it has been demonstrated that alcohol use levels below heavy drinking are associated with higher risks than abstention [223].

In addition to its role in the aetiology of depressive disorders, alcohol use has been associated with worsening the depression course, and worse outcomes such as suicide/death risk, social functioning and health care utilization ([214]; specifically for suicide, see section on injury below). However, the literature on this is not detailed enough to derive reliable quantitative risk relationships.

Unprovoked seizures and epilepsy

The association between alcohol use and seizures has been known since ancient times, with alcohol withdrawal seizures being the best studied and described aspect [224,225]. However, in terms of public health, the effect of alcohol use on the development of epilepsy and seizures not resulting directly from alcohol withdrawal is more important ([224–228]; for an exact definition see [229]). A meta-analysis of the data on unprovoked seizures from six available studies showed an overall association between alcohol use and the risk of epilepsy with a pooled relative risk (RR) of 2.19 (95% CI = 1.83–2.63). In addition, there was a dose–response relationship, with RRs of 1.81 (95% CI = 1.59–2.07), 2.04 (95% CI = 2.00–2.97) and 3.27 (95% CI 2.52–4.26) for consuming 48, 72 and 96 g pure alcohol per day, respectively [224,230]. Alcohol use also fulfilled other Bradford Hill criteria, such as temporality and biological plausibility [225,228]. The time for developing epilepsy or repetitive unprovoked seizures in heavy drinkers is 10 or more years [228]. The most plausible biological pathway is described by the 'kindling effect', which postulates that repeated withdrawals, even subclinical, may lead to gradual lowering of the seizure threshold and eventually to the development of epilepsy, or unprovoked seizures that occur even in those who no longer consume alcohol [231,232]. Other theories postulate cerebral atrophy, cerebrovascular infarctions, lesions, traumas, neuroplasticity and chronic electrolyte imbalances as leading to the onset of seizures [233–235]. In addition, alcohol use may affect the clinical course of pre-existing epilepsy either by changes in anti-epileptic drug pharmacokinetics or by non-compliance with prescribed medication [236,237].

Cardiovascular diseases

The relationship between alcohol use and cardiovascular disease outcomes is complex, as different dimensions play a role for different outcomes [238–240]. Clearly, chronic heavy drinking is detrimental (for blood pressure/hypertension [241,242]; ischaemic heart disease [243]; cardiomyopathy [244]; atrial fibrillation and flutter [245]; all types of stroke [246]), but there is also evidence for an increased risk associated with irregular heavy drinking, even in people who are on average light to moderate drinkers (ischaemic heart disease [247–249]; ischaemic stroke [250]; all types of stroke [251]; different cardiovascular outcomes [252]). For the effects of irregular heavy drinking occasions on cardiovascular disease, there are potentially four main mechanisms [253]. First, irregular heavy drinking increases the risk of coronary artery disease via unfavourable impacts on blood lipids. Secondly, there are effects on clotting, increasing the risk of thrombosis. Thirdly, irregular heavy drinking affects the conducting system, leading to a greater risk of arrhythmias [254]. Finally, any heavy drinking increases blood pressure, leading to acute or sustained hypertension [255].

With respect to non-heavy drinking, there are beneficial and detrimental effects. Beneficial effects are seen mainly for ischaemic diseases, i.e. ischaemic heart disease and ischaemic stroke [256,257]. While these beneficial effects have been put into question for different reasons (e.g. [174,258,259]), and while they may be overestimated using standard epidemiological methodology because of biased comparison groups [260], biological pathways corroborate some protective effect. The basic biological pathways for beneficial effects on ischaemic diseases are favourable changes in several surrogate biomarkers for cardiovascular risk, such as higher levels of high density lipoprotein cholesterol and adiponectin and lower levels of fibrinogen [255,261,262]. However, the situation may be more complex, as there are indications that the beneficial effect on ischaemic outcomes cannot be found in certain countries such as India [263,264]. It remains to be seen if this reflects different drinking patterns among those who are, on average, light to moderate drinkers, or if there are genetic influences on the biological pathways leading to cardioprotection of light to moderate alcohol use (see also [249]).

As different dimensions of alcohol use impact upon cardiovascular outcomes, instrumental variable approaches such as Mendelian randomization cannot answer questions of causality easily, as they assume linear relations with one dimension (for Mendelian randomizations studies see [259,265]; for a discussion of different dimensions of alcohol use with divergent predictions see [266]).As a result, modelling of alcohol use on cardiovascular disease outcomes also has to take different dimensions of exposure into account. In the most recent CRAs, this was solved as follows [22,267]:

- For hypertensive heart disease, ischaemic heart disease and both stroke types, the risk relations are

specified for fatal and non-fatal outcomes. Moreover, for ischaemic diseases, we used age-specific risk relations [268].

- For countries in eastern Europe (Russia and surrounding countries with similar drinking patterns), different relative risk estimates were used ([269], based on [270]). In particular, no beneficial effect was modelled because of detrimental drinking patterns and higher relative risk per heavy drinking occasion, as the average quantity per heavy drinking occasion in these countries is higher (see [41,271–273] as background).
- For all countries, for ischaemic heart disease and ischaemic stroke, we used risk relations which changed the risk function below 60 g of pure alcohol per day based on the presence or absence of heavy drinking occasions [268].

Modelling the impact of alcohol use this way for all countries in the WHO European Region between 1990 and 2014 revealed that alcohol-attributable cardiovascular mortality was key to understanding the trends in alcohol-attributable mortality as a whole [178,274]. For most countries in the region, alcohol-attributable cardiovascular mortality was close to zero, as the detrimental effects on hypertensive heart disease, atrial fibrillation and haemorrhagic stroke more or less balanced the beneficial effects on ischaemic heart disease and ischaemic stroke [178]. However, for countries with more heavy drinking occasions in the eastern part of the region, there was considerable alcohol-attributable cardiovascular mortality; in some countries such as Russia, this even constituted the highest category of alcohol-attributable mortality ([178]; see also [275]).

Gastrointestinal diseases

Liver cirrhosis

Liver cirrhosis and the wider GBD category with other liver diseases is a major cause of death globally [200], even though it has not been included into the WHO targets for non-communicable disease [276]. Liver disease is linked clearly to alcohol [277], evidenced by several ICD codes for alcoholic liver diseases (Table 1), including simple alcoholic steatosis, hepatitis, fibrosis and cirrhosis and superimposed hepatocellular carcinoma, which is part of alcohol-attributable cancers (see above). Globally, approximately half of all liver cirrhosis deaths and disability-adjusted life years were estimated to be attributable to alcohol in 2012 [8].

The pathogenesis of specific forms of alcoholic liver disease can be summarized as follows [278,279]. Alcohol use, especially heavy drinking occasions, induces changes in lipid metabolism (increases lipogenesis and mobilization of lipids and simultaneously decreases hepatic lipid catabolism), resulting in the accumulation of lipids in hepatocytes

called fatty liver. Alcohol use can also cause an inflammatory response known as alcoholic hepatitis, or steatohepatitis if it is accompanied by hepatic lipid deposition. Although hepatic steatosis does not normally cause irreversible hepatic changes, persistence and severity of alcoholic hepatitis or steatohepatitis leads eventually to fibrosis and sclerotic changes in the liver that result in insidious replacement of hepatocytes with connective tissue (liver cirrhosis) and subsequent liver failure.

The dose–response relationship between average volume of alcohol use and liver cirrhosis is exponential, with the curve more pronounced for mortality than for non-fatal morbidity [280]. The more accelerated dose–response curve for mortality is due to the fact that liver damage can have different aetiologies (most prominently, hepatitis B or C [281]), but if the liver is damaged continuation of alcohol use, even at relatively low quantities, can lead to death. Most research about the relationship between alcohol use and liver disease examined the overall tissue exposure (i.e. overall volume of alcohol consumption) following the tradition of Lelbach [282]. However, there are also indications that patterns of drinking matter [283]. More specifically, given the same amount of overall alcohol exposure, days without any alcohol consumption ('liver holidays') have been shown to be associated with a lower risk than daily drinking [284,285].

Another dimension of alcohol use has been discussed specifically for liver cirrhosis: the quality of the alcoholic beverage, and particularly potential problems with hepatotoxic ingredients in unrecorded consumption (e.g. [286]). Unrecorded consumption denotes all alcohol that is not registered and thus not controlled by routine state activities, such as home-made, illegally produced or smuggled alcohol (for a definition see [287]). While there have been some instances where ingredients of unrecorded alcohol have been found which could cause liver problems over and above the impact of ethanol [288,289] these instances are limited, and the overall conclusion of relevant reviews has been that there is not sufficient evidence to link a sizable portion of liver cirrhosis mortality to unrecorded alcohol ([290,291]; see also [292]).

Another issue is the fact that alcoholic liver disease cannot be measured reliably via usual death registries or via verbal autopsies, as the assessment of whether a liver disease is due to alcohol use or other risk factors is impacted highly by socio-cultural factors, in particular by stigma [46]. In their seminal study in 12 cities in 10 countries, Puffer & Griffith [293] found that after triangulating data on death certificates with data from hospital records and interviews of attending physicians or family members, the number of deaths with alcoholic liver cirrhosis more than doubled, with the majority of new cases being recoded from categories of cirrhosis which do not mention alcohol. This underreporting of alcoholic liver cirrhosis has persisted in later

studies [294–296]; this seems to be the case for all disease categories fully attributable to alcohol use [296,297] including, but not limited to, the disclosure of alcohol use disorders. As a consequence, in national CRAs based on death registries, estimations of alcohol-attributable liver diseases should not be based on routine data from these registries, but estimated indirectly via measures which have no or less bias (such as attributable fractions of liver cirrhosis or liver disease in general). Exceptions should be made only for countries where there had been empirical studies on the validity of alcoholic liver disease as a cause of death.

Pancreatitis

As is the case for liver diseases (see above), there are ICD-10 codes for alcoholic pancreatitis (see Table 1). The pathogenesis is different for acute and chronic pancreatitis, but alcohol use has a significant impact on the pathophysiology of both [298–302] and in the transition from acute to chronic pancreatitis (see [303]). Specifically, in chronic pancreatitis, metabolism of alcohol leads to production of reactive oxygen species [304] and fatty acid ethyl esters [305,306] that activate stellate cells and damage acinar cells of the pancreas. This process is mediated by sustained elevation of the cytosolic Ca2+ levels [307] and results ultimately in releasing pancreatic enzymes into the interstitium and in chronic inflammation [299]. In acute pancreatitis a similar cascade of intra- and extracellular reactions leads to fatty acid ethyl esters (FAEE)-induced increase of the Ca2+ release which results in massive necrosis of pancreatic acinar cells [307] and acute inflammation.

Regarding epidemiological results, the dose–response relationship seems to be accelerated for higher doses [308,309], more pronounced in women, and in acute pancreatitis. There were not enough data to evaluate the impact of irregular heavy drinking occasions in those who are on average light to moderate drinkers, however.

Injuries

Alcohol use has long been identified as a major contributor to injuries of all kinds, with established causal links (for details see previous reviews [23,24]). Blood alcohol concentration is the most important dimension to impair vision, psychomotor skills/abilities and reaction-time; all these processes and others in the central nervous system can be affected negatively, starting at as low as 0.03% blood alcohol concentration by volume [310]. In addition, as already mentioned above, judgement about risk-taking and other behavioural actions is impacted by alcohol use, again dose-dependent. The dose–response relationship between acute alcohol use, measured through the blood alcohol concentration and injury, seem exponential for all

injury types, albeit varying slightly by type of injury [311–313].

However, there is also interindividual heterogeneity, based in part on usual drinking habits. For instance, Krüger and colleagues found that for any given blood alcohol concentration, the risk for traffic injury would be lower for a driver who is a regular heavy drinker than for a light drinker [314]. In other words, average volume of alcohol use also plays a role, even though this complexity of an interaction between acute and typical alcohol use is not modelled in current CRAs [315] or in other modelling of alcohol-attributable injury harm [316].

The impact of alcohol use on suicide may be different from other types of injury, as it seems to be determined more by long-term drinking patterns, such as heavy drinking or alcohol use disorders (e.g. [317,318], even though there are also acute effects of alcohol use, e.g. on judgement [319,320]. Thus, it should be considered to model suicide in future CRAs differently from other types of injury, with more emphasis on chronic patterns of drinking, in particular heavy drinking.

Current modelling of alcohol-attributable injuries in CRAs takes into account the number of drinking occasions of different sizes and the relative risks associated with these different exposures (for the most comprehensive analyses on risk relations see [311]; for others see [312,313]; for the exact methodologies see [321,322]). The last estimation, as part of the larger study for the WHO European Region estimating alcohol-attributable mortality in more than 50 countries for 25 years, revealed [178] that alcohol-attributable injury rates did not decrease in the time-period in the same way as injuries in general [323].

The final consideration about alcohol-attributable injury is the estimation of harm to others than the drinker from injuries, which is described below.

Overview on biological pathways and CRA modelling strategies for each cause of death

Table 3 gives an overview of biological reasoning and CRA modelling for all partially attributable disease and injury categories. To explain further how to interpret this Table, let us give one example: haemorrhagic and other non-ischaemic stroke. As indicated, the current statistical model is based on average volume of alcohol consumption only [375]; see also the graphs in Supporting information, Appendix S2. However, the biological pathways (see above and Table 2) would clearly indicate an additional role for irregular heavy drinking occasions which could not be included to date into the model due to lack of data.

As can be seen, for several disease categories biological pathways would suggest more complex statistical models, which cannot be realized via the usual meta-analytical

procedures because of lack of data from underlying medical epidemiological studies.

Overview on different dimensions of alcohol use and disease and injury outcomes

Figure 1 tries to summarize our knowledge about the strength of the relationships between volume of alcohol consumption, on one hand, and specific heavy drinking occasions, on the other hand, and major disease categories. On one end of the spectrum are cancers, which all show a more or less linear relationship between alcohol use and risk of cancer as expressed in logarithmized relative risk compared to life-time abstention: the higher the (average) volume of alcohol use, the higher the risk for cancer. The use of logarithmic scales for risk relations is customary for the statistical techniques used, meaning that a linear relationship in logarithmized relative risks actually translates into exponential risk relations in the real scales.

At the other end of the spectrum are ischaemic diseases (i.e. ischaemic heart disease and ischaemic stroke), where there is a curvilinear relationship between average volume of alcohol use and risk, which is modified by heavy drinking occasions. Heavy drinking occasions seem primarily to determine the adverse risk and subsequent harm. In societies where most of the alcohol is consumed in non-heavy drinking occasions, we expect an overall beneficial relationship of alcohol use on ischaemic diseases and an overall very small net impact of alcohol use on cardiovascular disease and mortality; in societies where most of the alcohol is consumed via heavy drinking occasions, the overall relationship should be detrimental for ischaemic disease, and even more so for cardiovascular disease and death. This hypothesis was also corroborated by the recent 25-year trend analyses on alcohol-attributable mortality in 52 countries of the WHO European Region [178]. While such a hypothesis is based on individual-level studies, it could not always be confirmed in ecological analyses such as time–series analyses (for confirmation see [5,324]; for essentially no relations in a number of countries in the European Union, see [325]; for a result contrary to the hypothesis, see [326]). However, ecological analysis may be impacted by other factors which cannot be controlled [327]. For the disease categories in between, the ranking from top to bottom may be interpreted as deviation from a straight line (linear relationship) between alcohol use and relative risk of the respective disease category: the higher the impact of heavy drinking occasions, the more accelerated is the curve.
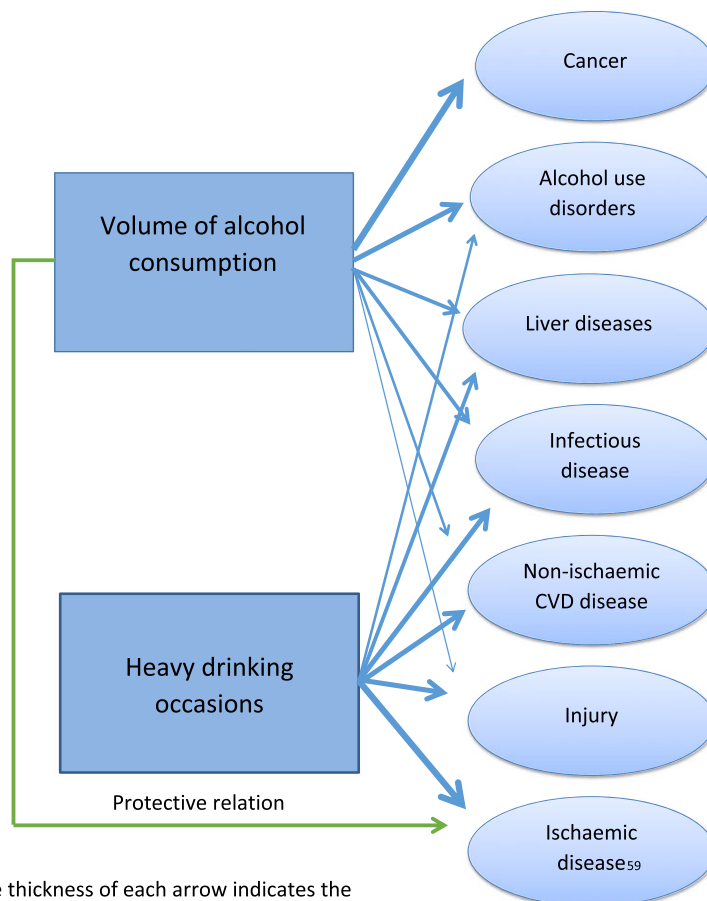
The thickness of each arrow indicates the strength of the relationship

Figure 1 The impact of volume of alcohol use and heavy drinking upon major attributable disease outcomes.

Table 4 Changes to the last review in partially attributable disease categories.

Disease category	Causality	Risk relations	Comments (changes suggested for GSRAH 2017 versus 2014)
Infectious diseases			
Tuberculosis	As in 2010	New meta-analysis	New risk relations suggested to be included for GSRAH 2017
Human immunodeficiency virus/ Acquired immune deficiency syndrome (HIV/AIDS)	New data on establishing causality for incidence	New methodology	Incidence suggested to be additionally included for GSRAH 2017
Other sexually transmitted diseases	New data on establishing causality for incidence	New methodology	New disease category suggested to be included for GSRAH 2017
Lower respiratory infections: pneumonia	As in 2010	As in 2010	As in GSRAH 2014
Cancers			
All cancer categories cancer	No change in cancer categories with sufficient evidence for carcinogenicity in humans; two new categories where evidence indicates probably relationships (stomach, pancreatic cancer)	New meta-analyses	Discussion whether newly established categories where alcohol has been judged as probably carcinogenic in humans should be included; new risk relations suggested for GSRAH 2017
Diabetes mellitus			
Diabetes mellitus	Discussion based on new reviews and meta-analyses	New meta-analyses	Currently in revision to evaluate the new evidence; probably too late for GSRAH 2017
Neuropsychiatric disorders			
Alzheimer's disease and other dementias	Discussion based on new reviews and meta-analyses	New meta-analyses	Currently in revision to evaluate the new evidence; probably too late for GSRAH 2017
Unipolar depressive disorders	New reviews	New meta-analyses	New disease category suggested to be included for GSRAH 2017
Epilepsy	New review (conducted in 2010 but not included in [24])	New meta-analysis (conducted in 2010 but not included in [24])	As in GSRAH 2014
Cardiovascular diseases			
Hypertensive heart disease	New reviews	As in 2010	As in GSRAH 2014
Ischaemic heart disease	New reviews	New meta-analyses	New risk relations suggested to be included for GSRAH 2017
Cardiomyopathy	New reviews	New meta-analyses	New disease category suggested to be included for GSRAH 2017
Atrial fibrillation and flutter	As in 2010	As in 2010	As in GSRAH 2014
Heart failure	As in 2010	As in 2010	Not included, as cases are distributed to clearer disease and cause of death categories
Ischaemic stroke	New reviews	New meta-analyses	New risk relations suggested to be included for GSRAH 2017
Haemorrhagic and other non-ischaemic stroke	As in 2010	New meta-analyses	As in GSRAH 2014
Gastrointestinal diseases			
Cirrhosis of the liver	As in 2010	As in 2010	As in GSRAH 2014

(*Continues*)

Table 4. (Continued)

Disease category	Causality	Risk relations	Comments (changes suggested for GSRAH 2017 versus 2014)
Gall bladder and bile duct disease	Not included as in 2010	Not included as in 2010	Neither in GSRAH 2014 nor suggested for GSRAH 2017
Pancreatitis	As in 2010	New meta-analysis	New risk relations suggested to be included for GSRAH 2017
Other disease categories considered			
Psoriasis	New reviews but causality not yet established	Not relevant	Neither in GSRAH 2014 nor suggested for GSRAH 2017
Abortion	New reviews	No meta-analyses	Neither in GSRAH 2014 nor suggested for GSRAH 2017
Preterm birth complications	New review	New meta-analysis	No significant effect of alcohol –> should not be included

The last review in this series was published in 2010 [24]. GSRAH = World Health Organization Global Status Reports on Alcohol and Health.

Summary of changes since the last review

Table 4 gives an overview of changes for partially attributable disease categories since the 2010 review [24]. Fewer changes can be seen for injury, although there have been new meta-analyses (see above) which are to be included in the planned new Global Status Report. Alcohol epidemiology is clearly a fast-moving field, and our knowledge about alcohol's impact upon disease and mortality has increased. Clearly, as there have been no major updates in the ICD during the time from the last review, these categories have been stable.

Health harm to others

Like tobacco, alcohol has a marked impact upon the health of others than the drinker [328–331]. Drinking of others as an external cause is usually not measured in health system classifications [332], so these impacts have to be estimated otherwise. In terms of CRAs, minimally three categories need estimation:

- The impact of alcohol use during pregnancy on the health of the child: this can be captured mainly via FASD and FAS, as described above, and new algorithms for estimating incidence and prevalence of these conditions based on mother's drinking during pregnancy have been developed [74]. Prevalence can then be multiplied with disability weights to derive burden (see above). Regarding fatal outcomes of FAS: while a recent study has found a life expectancy of 34 years [333], the overwhelming majority of these deaths are coded as resulting from comorbidities [57], and are not coded to FAS as a cause of death.
- Alcohol use of others can have marked impact on all unintentional injuries. For instance, drinking by a parental care-giver increases the chances of unintentional injury to a toddler [334], and parental alcohol misuse is a powerful predictor of a child's traumatic brain injury [335]. Although others' drinking can impact upon a wide variety of unintentional injuries, it has been studied most fully in the context of driving and other traffic participation under the influence of alcohol (e.g. [329,336]). The burden in traffic injuries and fatalities, at least, can now be estimated more accurately, as there are global statistics by sex of driver and average number of passengers in each car [337].
- The impact of alcohol on aggression and violence to others has been well established [23,338,339]. However, its quantification becomes extremely complicated, as drinking of the victim [311,340,341] and drinking of the perpetrator seem to impact upon the risk and severity of violent acts [340,342], the latter possibly in a curvilinear fashion [340]. Moreover, the impact of alcohol use on violence is mediated by other variables [342,343], including by

culture [344]. While all these mediating and moderating variables complicate estimation (for a first try within the framework of the CRAs see [345]), the estimates found so far seem to indicate large effect sizes: thus, English and colleagues estimated that approximately half the hospitalizations due to assault were attributable to alcohol [31], and male homicide deaths in the Soviet Union dropped by 40% when per capita consumption dropped by 25% [346].

DISCUSSION

This systematic review has shown that many disease and mortality outcomes are impacted causally by alcohol, most often in an accelerated dose–response fashion. Since the last review [24], many new reviews and meta-analyses have appeared (see Table 4 and Supporting information, Appendix S1 for a complete listing), but while new alcohol-attributable disease categories have been added, the general picture of alcohol use being a major contributor to the burden of mortality and disease has not changed.

Any systematic review is limited by the underlying literature. While the depth and quality of the literature varies by disease and mortality category, it is unfortunately still true that exposure measurement in many epidemiological studies is restricted to one measure of average volume of consumption, e.g. from a food frequency questionnaire or from simple quantity–frequency measures (for an explanation of these measures and their strengths see [347]). Even though in recent years there have been more attempts to quantify other dimensions such as irregular heavy drinking occasions, these changes have come slowly, and for many outcomes meta-analyses on patterns of drinking are not possible. Moreover, many studies measure alcohol use only once at baseline, and no changes of use over time can be incorporated into the models. Finally, the comparison group still is a problem [174]: while using last-year abstention may bias results by introducing sick-quitters [348], life-time abstention may be the theoretically preferred measure but has been proven to be unreliable [173], and in many high-income countries life-time abstainers are special groups which also differ on other outcome-relevant measures. In summary, very little has changed since 2000, when these points had been already listed as barriers for improving knowledge on alcohol use and mortality outcomes [349]. Mendelian randomization studies were added to our methodological arsenal [224,259], but their assumptions are problematic if two dimensions are to be analysed simultaneously with one instrumental variable, as in the analyses on the impact of alcohol use on ischaemic heart disease ([266]; see also the discussion in the *British Medical Journal* [259]). Improving measurement of alcohol exposure (including but not limited to measurement of chronic and irregular heavy drinking), as described in the limitations above, should be one of the research priorities. Other research priorities (see also [1]) include:

- Improving incorporating time lags [186] into future CRAs: this applies not only to effects of alcohol use, but also to all risk factors, as CRAs need to be comparative.
- Improving our knowledge about risk relations: as indicated above, for most countries with the exception of Russia and surrounding countries [269], we assume that risk relations taken from the most comprehensive meta-analysis are applicable. Given the genetic and environmental differences, we would expect some differences in risk relations between alcohol use and disease/ mortality outcomes in different regions (see the example of genetically based varying cancer risks described above, which had marked implications for the population-level burden of oesophagus cancer in Japan [175]; see also some indications that alcohol use has different risk for cardiovascular events in Asians versus non-Asians [263,350]). The biggest difference in risk relations will probably be found in injury outcomes, as these depend more upon environment than disease [311,344]. However, for any regional differences in risk, it has to be checked if these cannot be ascribed to differences in drinking patterns first, before they are applied to CRAs.
- Improving our knowledge on health harm to others: currently, only a few studies exist on harm to others which can be translated into a CRA framework, and this should be a priority for future research. In particular, efforts to improve the recording of alcohol's involvement in injuries in hospital or emergency service records (e.g. [351,352]) should include attention to the involvement of others' drinking in the occurrence of the injury.

We would like to finish this review with a reminder that while the alcohol-attributable burden of disease and mortality is large, it is only part of the harm of alcohol use. Social harm outside of health harm is impacted by similar dimensions of alcohol use (e.g. [90,353]), and should be included in any considerations of the overall impact of alcohol use in our societies.

Declaration of interests

None.

Acknowledgements

dose–response relationship between level of alcohol use and cancer based on [169]. Finally, we would like to thank contributors for sending more than 100 mails and requests regarding the previous review, which helped to shape the current version.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Results of the systematic searches.
Appendix S2 Dose Response-relationships between average volume of alcohol use and relative risk for mortality for partially alcohol-attributable disease categories.