The relation between different dimensions of alcohol consumption and burden of disease: an overview

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ABSTRACT

Aims   As part of a larger study to estimate the global burden of disease and injury attributable to alcohol: to evaluate the evidence for a causal impact of average volume of alcohol consumption and pattern of drinking on diseases and injuries; to quantify relationships identified as causal based on published meta-analyses; to separate the impact on mortality versus morbidity where possible; and to assess the impact of the quality of alcohol on burden of disease. **Methods**   Systematic literature reviews were used to identify alcohol-related diseases, birth complications and injuries using standard epidemiological criteria to determine causality. The extent of the risk relations was taken from meta-analyses. **Results**   Evidence of a causal impact of average volume of alcohol consumption was found for the following major diseases: tuberculosis, mouth, nasopharynx, other pharynx and oropharynx cancer, oesophageal cancer, colon and rectum cancer, liver cancer, female breast cancer, diabetes mellitus, alcohol use disorders, unipolar depressive disorders, epilepsy, hypertensive heart disease, ischaemic heart disease (IHD), ischaemic and haemorrhagic stroke, conduction disorders and other dysrhythmias, lower respiratory infections (pneumonia), cirrhosis of the liver, preterm birth complications and fetal alcohol syndrome. Dose–response relationships could be quantified for all disease categories except for depressive disorders, with the relative risk increasing with increased level of alcohol consumption for most diseases. Both average volume and drinking pattern were linked causally to IHD, fetal alcohol syndrome and unintentional and intentional injuries. For IHD, ischaemic stroke and diabetes mellitus beneficial effects were observed for patterns of light to moderate drinking without heavy drinking occasions (as defined by 60+ g pure alcohol per day). For several disease and injury categories, the effects were stronger on mortality compared to morbidity. There was insufficient evidence to establish whether quality of alcohol had a major impact on disease burden. **Conclusions**   Overall, these findings indicate that alcohol impacts many disease outcomes causally, both chronic and acute, and injuries. In addition, a pattern of heavy episodic drinking increases risk for some disease and all injury outcomes. Future studies need to address a number of methodological issues, especially the differential role of average volume versus drinking pattern, in order to obtain more accurate risk estimates and to understand more clearly the nature of alcohol–disease relationships.

Keywords   Alcohol, average volume, burden of disease, injury, morbidity, mortality, patterns of drinking, risk relation.

INTRODUCTION

The present paper can be seen as an update of Rehm and colleagues' work [1], addressing the direction, form and strength of the relationship of different dimensions of alcohol consumption to a whole range of chronic and infectious diseases and injuries. The relationship between alcohol consumption and health outcomes is complex and multi-dimensional. In the 6 years since the previous comprehensive overview [1], however, the field has been transformed substantially by an accumulation of new studies, partly by expansion into new areas of research, such as alcohol and infectious diseases, but particularly by the widespread use of systematic reviews and meta-analyses. While the general conclusions from previous research have been confirmed, some new relationships between alcohol consumption and disease/injury have also been identified and others have been clarified.

Figure 1 provides an overview of the conceptual model used for the current analysis of alcohol within the Global Burden of Disease and Injury (GBD) 2005 study. The GBD 2005 study is a comprehensive effort to estimate and analyse mortality and disability on a global level, including measuring the impact of major risk factors in a comparative fashion [2]. In our conceptual model for the impact of alcohol consumption on disease morbidity and mortality, two separate but related dimensions of individual level drinking are hypothesized as exerting the main causal impact on burden of disease: overall volume of alcohol consumption and pattern of drinking. Volume, operationalized usually as the total absolute alcohol consumed over a time-period, such as 1 year, has been the traditional measure of exposure in alcohol epidemiology [3], and has been linked causally to many International Classification of Diseases (ICD) codes following the seminal work of English and colleagues [4]. Specifically,
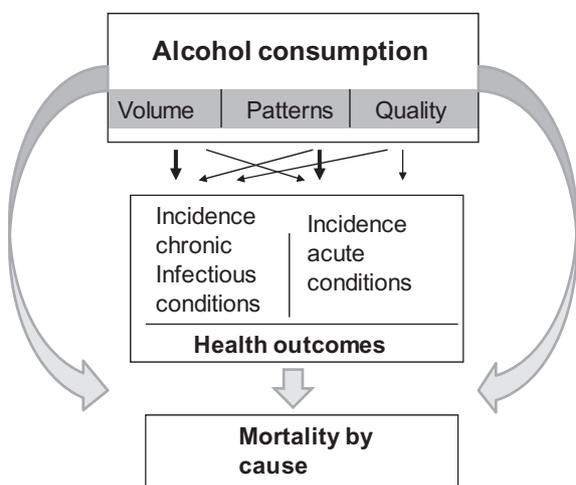

Figure 1 Causal model of alcohol consumption, intermediate mechanisms and long-term consequences

more than 30 ICD-10 (version 10) three- or four-digit codes include alcohol in their name or definition [5], indicating that alcohol consumption is a necessary cause (these are listed later in this paper in Table 1). In addition, alcohol has been identified as a sufficient component cause for more than 200 ICD-10 three-digit disease codes (these are listed later in the paper in Tables 2 and 5). The sufficient component model states that a sufficient component cause consists of a number of components, none of which is sufficient alone for causing the disease. When all the components are present, the sufficient cause is formed. For each disease, different sufficient component causes may be relevant (for a more thorough definition of component causes see [6]). In epidemiological practice, researchers focus mainly upon one component of the sufficient component cause, such as alcohol consumption, often with a counterfactual model, examining what proportion of a disease under consideration would disappear if the risk factor was absent, or what proportion would disappear when the population distribution of the risk factor shifted to a level associated with lower harm [7]. This type of model also underlies the calculation of attributable fractions (see below; [8]).

Pattern of drinking has often been linked to two main categories of disease outcome, injuries (both unintentional and intentional) and cardiovascular risk [mainly ischaemic heart disease (IHD); [1,9]]. Within the context of the current comparative risk assessment (CRA), pattern of drinking was operationalized mainly as the presence of heavy drinking occasions, defined as 60+ g of pure alcohol on one single occasion (corresponding to five or more drinks in most countries; for details on previous definitions see [9,10]). Thus, in this paper, heavy alcohol consumption will be defined as 60+ g per occasion, unless noted otherwise.

The three main intermediate mechanisms between average volume of drinking, pattern of drinking and diseases have been identified: (1) toxic and beneficial biological effects of alcohol on organs and tissues; (2) intoxication; and (3) dependence [1]. In addition, the quality of alcoholic beverages may impact health outcomes and mortality (Fig. 1), for instance via methanol or lead poisoning outbreaks. However, the latter pathway seems to be of less importance from a public health perspective [11,12] because the documented impact is much lower compared to the impact of volume and pattern (described below).

This paper reports the first stage of the process of deriving new estimates of alcohol's role in the burden of mortality and disease, based on research completed as part of the ongoing GBD 2005 study [2]. This process includes evaluating the existing evidence for a causal impact of the dimensions of alcohol on different categories of disease as a first step, then identifying

meta-analyses to quantify the corresponding dose–response relationships. As in previous estimates [13], alcohol consumption is but one of a number of risk factors for the GBD study, with the teams working on the different risk factors coordinating their work in the common frame of a CRA. The conceptual model shown in Fig. 1 is different from previous models in that it separates the impact of alcohol consumption on morbidity from the impact on mortality. This carries the implication that, wherever possible, we tried to find or conduct separate meta-analyses for morbidity and mortality.

Because the alcohol analyses in the CRA process are still proceeding, we indicate in the text the direction to be taken in those analyses that are not yet completed. To allow cross-referencing with other analyses, we also indicate in Tables 2 and 5 both the ICD-10 codes and the GBD 2005 codes for the disorders considered.

METHODS

A six-step procedure was used for the systematic review and article-selection phases of this project: (1) disease case definition; (2) computer-assisted search for systematic reviews and existing meta-analyses; (3) decision about causality; (4) decision about whether a new meta-analysis is necessary; (5) selection of individual articles, including hand searches, for conducting new meta-analyses; and (6) extraction of information about dose–response relationships from existing or new meta-analyses.

Case definition (step 1)

Case definitions were always based on clinical descriptions related to ICD coding schemes and the case definitions in the GBD 2005 operations manual (http://www.globalburden.org/gbdops.html), except for some outcomes (injury, for example) where articles may not have included ICD-10 codes and relied instead upon other diagnoses or descriptions which can be coordinated with the codes. Uncorroborated self-reports were excluded.

Computer-assisted search for systematic reviews and existing meta-analyses on alcohol and disease (step 2)

A systematic review of the literature published between 1980 and the 4th week of January 2008 was completed using computer searches of the following databases: Ovid Medline, EMBASE, Web of Science (including Science Citation Index, Social Sciences Citation Index, and Arts and Humanities Citation Index), CINAHL, PubMed, Cochrane Database of Systematic Reviews, CABS (BIDS), WHOLIST, SIGLE, ETOH, Alcohol in Moderation (alcohol industry database) and Google Scholar. The searches were not restricted geographically or by language.

For each disease outcome, findings were extracted from all available systematic reviews and quantitative meta-analyses and added to the results already included in the previous review [1]. In addition, individual studies and reviews on biological pathways or underlying mechanisms were analysed.

Selection of disease conditions related causally to alcohol (step 3)

As described in the following sections, disease conditions related to alcohol can be grouped into three categories, reflecting the nature of the conditions and the form of aetiological influence of alcohol.

Wholly alcohol-attributable health conditions

Wholly attributable conditions can be identified easily by the inclusion of 'alcohol' or 'alcoholic' in their names, or by an ICD definition which identifies alcohol consumption as a necessary cause. With regard to the attribution of alcohol-relatedness these conditions are, by definition, wholly attributable to alcohol with an alcohol-attributable fraction (AAF) of 100%, where AAF denotes the proportion of a certain disease category which would not have occurred had there been no alcohol consumption [14].

Chronic and infectious disease conditions where alcohol is a component cause (i.e. with AAFs lower than 100%)

In the present analyses, sufficient evidence of causality was defined as meeting all the following criteria: (1) evidence of an association (positive or negative) between alcohol consumption and the disease or injury; (2) chance, confounding variables and other bias can be ruled out with 'reasonable confidence' as factors in this association; and (3) evidence of a plausible mediating process [4]. Reasonable confidence in the present analyses was operationalized using two criteria: first, that the meta-analyses showed effects significantly different from no relations; and secondly, that there was no empirical evidence of confounders or biases that eliminated the relationship. The latter was usually tied to study design and methodology. Usual criteria for establishing causality in epidemiology [6,15] were applied, with the most weight placed on the following four criteria (for example, see [1]):
• established experimental biological evidence of mediating processes or at least physiological plausibility (biological mechanisms);
• temporality (cause before effect);
• strength (effect size); and
• consistency of the association (dose–response relationship) across different studies.

Acute conditions where alcohol is a component cause (i.e. with AAFs lower than 100%)

With respect to acute conditions, most researchers have agreed that alcohol has a causal impact on almost all injury categories if the above criteria are applied [4,9,16–21]. Detailed reasoning could also be found in the previous review [1]. Thus, we will mainly identify and discuss the exceptions from this rule.

Decision about new meta-analyses (step 4)

For all disease/injury categories where causality was considered likely, we looked for existing meta-analyses to quantify the dose–response relationship. Because alcohol consumption can have different curvatures with different diseases (linear, J-shaped, exponential), we looked for meta-analyses that allowed second- or third-order polynomials or fractional polynomials instead of simply fitting a linear relationship. In addition, we sought meta-analyses that separated morbidity from mortality, especially for disease and injury conditions with long survival time. If no such analyses could be found, our group conducted a meta-analysis for these conditions. The final decisions on causality were made based on knowledge of all the literature, including the articles underlying the new meta-analyses and the results of the meta-analyses.

Selection of relevant literature for conducting new meta-analyses to determine dose–response relationships (step 5)

The same databases as for step 2 were searched, with the time-frame extending until January 2009. For disease outcomes where we conducted new meta-analyses, we examined all published evidence on the relationship between alcohol and the disease outcome. For this step, a priori exclusion criteria included any of the following.
1. No measure of association between outcome and appropriate alcohol exposure.
2. Fewer than three levels of alcohol consumption reported.
3. Cross-sectional design.
4. Duplicate data already identified in the search.
5. Outcome data not specific to disease ICD codes.
6. Inability to acquire data (e.g. unavailable thesis or dissertation).

Further technical details for quantitative meta-analyses for specific disease outcomes are provided in Table 3 of the Results section.

Hand search

All the reference lists in pertinent existing reviews and meta-analyses were hand-searched to identify any relevant studies that may have been missed in the main search. Each identified article was obtained, translated into English where necessary, and analysed.

Extraction of information from analyses (step 6)

The following information was extracted from existing meta-analyses or calculated in new meta-analyses:
- quantitative information on the number of underlying studies and dose–response relationship on average volume of alcohol consumption and the respective outcome; and
- fit of fractional polynomial models to determine the dose–response relationship: this involved two main steps—(1) testing for heterogeneity, publication and other bias between the studies identified in the systematic review [22–26] and (2) generating curves. The latter employed a fixed or random-effects model (depending on results of the first step) of 1st- and/or 2nd-order polynomials to define the curve, with goodness-of-fit determined by decreases in overall deviance compared to linear respectively quadratic referent models [27].

In order to check for reliability in extracting data in our own meta-analyses, a sample of 15 articles were extracted by two independent reviewers. In cases where the systematic review resulted in less than 15 articles, all the selected articles were reviewed independently by two reviewers. Table 3 shows the percentage of agreement between the two raters for each completed meta-analysis.

RESULTS

Health conditions wholly attributable to alcohol

Table 1 lists all conditions 100% attributable to alcohol or, in other words, disease conditions which could have occurred only as a result of alcohol consumption. Global prevalence data do not exist for most of the wholly attributable conditions, and thus these conditions were neither included in the GBD 2000 nor will they be included in the GBD 2005: the exceptions are alcohol use disorders (AUD) and fetal alcohol syndrome (FAS). Although relevant data on the mortality, morbidity and disability of other conditions of Table 1 may exist for specific countries [28], even when the information exists for a country there are often problems in records of alcohol diagnoses. Specifically, in addition to usual problems with coding smaller categories, disease categories including alcohol in their name are often stigmatized, leading to under-recording and underestimates [29,30]. Because of these problems with data on alcohol conditions wholly attributable to alcohol, we used broader categories (e.g. all liver cirrhosis) in our calculations, and determined AAFs indirectly.

While these disease categories by definition involve some alcohol consumption, the specific impact of

Table 1 Disease conditions which are by definition alcohol-attributable (AAF = 100%).

ICD-10	*Disease*
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
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 fetus from alcohol
P04.3	Fetus 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*
T51.8	*Other alcohols*
T51.9	*Alcohol unspecified*
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

AAF: alcohol-attributable fraction; ICD: International Classification of Diseases. Note: ICD codes in italic type represent subcodes within a main code of classification.

patterns of drinking is less clear, even for AUD, although a recent review identified a pattern of heavy drinking occasions as a potential cause of FAS [Gmel G., Kuntsche E., Rehm J., unpublished].

Chronic and infectious disease conditions where alcohol is a component cause

Table 2 provides an overview of mainly chronic non-communicable and infectious disease conditions that are not wholly attributable to alcohol, but where at least one review has found significant relations to alcohol. The shaded rows in Table 2 indicate conditions for which the current analyses concluded sufficient evidence for a causal relationship and sufficient data on outcomes and risk relations to be included into the CRA 2005. Table 3 provides an overview of the technical details of the quantitative meta-analyses from which the information on dose–response relationships was extracted for these diseases.

In the following, we describe briefly the evidence of the relationship, including biological pathways, for those conditions which had sufficient evidence for causality and which have been proposed for inclusion in the GBD 2005 (discussed in order of their ICD-10 codes). In addition, we describe briefly two conditions where relatively strong and consistent associations were found, but we could not exclude confounding for human immuno-deficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or we did not find enough evidence for a biological pathway (psoriasis). The dose–response relationships for all conditions with a causal impact of alcohol and evidence for a differential effect for mortality versus morbidity are summarized in Table 4.

Tuberculosis (TB)

A technical meeting was hosted by the South African Medical Research Council and co-sponsored by the World Health Organization at Cape Town in July 2008 to review evidence about a potential causal impact of alcohol consumption on human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and tuberculosis (TB). After reviewing the evidence from epidemiology, social sciences and immunology, the meeting concluded that there was sufficient evidence for a causal impact of alcohol on TB incidence and on worsening the disease [31].

It has long been known that alcohol has been associated with TB [32]. The association between heavy drinking and risk of TB incidence is both strong and consistent, with a risk ratio of approximately 3 ([33]; see also Table 3). Heavy drinking in the underlying meta-analysis and most other studies in the TB area was defined as either drinking more than 40 g pure alcohol per day or 'alcoholism' [33]. Despite its strength, however, the causality of this association had not been established [34].

Our analyses identified two plausible pathways between heavy alcohol consumption and TB. First, heavy alcohol consumption affects the immune system, thus facilitating susceptibility to infection as well as conversion to active TB in infected individuals [35–37]. Secondly, alcohol use may lead to being in social environ-

Table 2 Disease conditions which are not wholly attributable to alcohol identified by various meta-analyses and reviews (at least one review has concluded that there is a relationship of the condition with alcohol).

GBD category	No. of GBD 2005 code	ICD-10[a]	Reference to meta-analyses/systematic reviews	Effect
Tuberculosis	IA	A15–A19, B90	[31,33,38] Technical meeting 2008 concluded sufficient evidence for a causal impact [31]	Detrimental
Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS)	IB	B20–B24	[31,42,43,45,47] There is not sufficient evidence to conclude a causal impact on incidence, but there is sufficient evidence of causal impact on course of disease, which can in part be modelled	Detrimental
Mouth, nasopharynx, other pharynx and oropharynx cancer	IIA1–IIA2b	C00–C13	[4,9,16–20,240,241] Enough data to calculate RR for subcategories of disease, e.g. [67,242]. IARC confirmed cancers of the oral cavity and pharynx to be related causally to alcohol drinking in monograph meeting of February 2007 [58]	Detrimental
Oesophagus cancer	IIA3	C15	[4,9,16–20,67,240,243] IARC confirmed oesophagus cancer to be related causally to alcohol drinking in monograph meeting of February 2007 [58]	Detrimental
Stomach cancer	IIA4	C16	[244] IARC concluded inadequate evidence that alcohol causes stomach cancer because of the inconsistency of the research evidence. Last IARC meeting concluded a possible relationship but confounding of smoking and dietary habits could not be excluded [58]	Detrimental
Colon and rectum cancer	IIA5	C18–C21	[9,66–68,242,245] IARC newly included colorectal cancer as related causally to alcohol drinking in monograph meeting of February 2007 [58]	Detrimental
Liver cancer	IIA6	C22	[4,9,16–20,67,242] IARC confirmed primary liver cancer as related causally to alcohol drinking in monograph meeting of February 2007 [58].	Detrimental
Larynx cancer	IIA9	C32	[4,9,16–20,67,240–242,246,247] IARC confirmed larynx cancer to be related causally to alcohol drinking in monograph meeting of February 2007 [58]	Detrimental
Trachea, bronchus and lung cancer	IIA10	C33, C34	Was excluded from the list of outcomes related causally to alcohol by [4]. This decision has not been revised by any further meta-analysis. Recent meta-analyses on alcohol and lung cancer found mixed results [242,248–250], but even when RRs were elevated for heavy consumption, confounding by smoking could not be fully excluded [248]. The last substantive reviews found no sufficient support for a causal relation [251,252]. Last IARC meeting concluded a possible relationship but confounding of smoking and dietary habits could not be excluded [58]	Detrimental
Breast cancer (female)	IIA13	C50	[9,16–20,67,69–72,242,253–255] [4] Concluded there was only limited evidence for causality, although they found a consistent relationship. Subsequent studies using the same criteria concluded that there was sufficient evidence of a relationship. IARC newly included breast cancer as related causally to alcohol drinking in monograph meeting of February 2007 [58]	Detrimental
Other neoplasms	IIB	D00–D48 (except D09.9, D37.9, D38.6, D39.9, D40.9, D41.9, D48.9)	[9] Mixed category, no assessment of causality possible	Detrimental
Diabetes mellitus	IIC	E10–E13	[4,9,16,17,19,256–258] [4] found only inadequate evidence of causality. Subsequent studies using the same criteria for causality revised this decision (see also [259]).	Mainly beneficial
Alzheimer's disease and other dementias	IIF1	F01–F03, G30, G31	[260–263] Overall, studies showed a beneficial effect, with the beneficial effects on the ischaemic system being the main potential explanation [264]. However, studies show substantial heterogeneity and confounding and other explanations could not be ruled out [259,262,265]	Mainly beneficial
Unipolar depressive disorders	IIE1	F32, F33, F34.1	[9] Available data is not sufficient for meta-analyses, for estimating RRs or AAFs. While there is agreement that some of the unipolar depressive disorders are caused by alcohol consumption (for a examination of causal criteria see [1]), the determination of the AAF was not possible, as it could not be determined which portion of the association between alcohol consumption and depressive disorders was caused by alcohol consumption, which portion by depression and which portion by a third cause impacting both alcohol consumption and depression	Detrimental
Epilepsy	IIF3	G40, G41	[4,9,16–20,88] Meta-analyses did not distinguish between primary epilepsy/unprovoked seizures and provoked seizures such as alcohol withdrawal-induced seizures. We will conduct a new systematic review and meta-analysis consistent with GBD definition of primary epilepsy/unprovoked seizures	Detrimental
Hypertensive heart disease	IIH2	I11–I13	[4,9,10,16–20,67] Because of lack of data for I11–I13 only, we included essential hypertension in our analyses (110)	Detrimental, may depend on patterns of drinking for low volume

Disease	GBD code	ICD codes	Notes / References	Effect
Ischaemic heart disease	IIH3	I20–I25	[4,9,16–20,67,107,112,266] Most recent meta-analysis [107] found heterogeneity among studies. Pattern of drinking must be included in analysis [9,114,115,117] to reduce this heterogeneity	Beneficial or detrimental, depending on patterns of drinking for low to medium volume; detrimental effect for high volume
Cardiomyopathy	IIH6	I42	Not clear if alcohol has a relationship to cardiomyopathy over and beyond the subcategory of alcoholic cardiomyopathy I42.6. Systematic review is ongoing	Detrimental
Conduction disorders and other dysrhythmias	IIH7	I47–I48	[4,9,16–20] Not yet included into previous CRAs, but as GBD 2005 has established a new code for dysrhythmias, the epidemiological assessment of underlying causality applies	Detrimental
Heart failure (no GBD category)		No GBD code; the respective ICD codes will be redistributed in GBD 2005	[4,9,16,17,19,20] This is an unspecific category with no identification of underlying pathology. Therefore, the relationship between average volume of consumption and outcome was usually not determined by meta-analyses, but indirectly from other circulatory diseases	Detrimental
Ischaemic stroke	IIH4a	I63–I67, I69.3	[4,9,16–20,67,154,221,267,268]	Beneficial or detrimental dependent on patterns of drinking (similar to IHD)
Haemorrhagic and other non-ischaemic stroke	IIH4b	I60–I62, I69.0, I69.1, I69.2	[4,9,16–20,67,154,159,221,267–269]	Mainly detrimental, except for low doses
Oesophageal varices (no GBD category)		No GBD code; the respective ICD codes will be redistributed in GBD 2005	[4,9,16–20] Not based on meta-analyses. As most oesophageal varices are due to liver cirrhosis, the AAFs derived for unspecific liver cirrhosis are usually applied. No GBD category	Detrimental
Lower respiratory infections: pneumonia	IK1	J09–J22, J85, P23	Influenza and pneumonia had not been included into GBD so far. However, the transfer to GBD is only possible for disease categories with J10–18 as definition, as the epidemiological studies are usually restricted to these codes. Also, the impact of alcohol use is restricted to community-acquired pneumonia	Detrimental
Cirrhosis of the liver	IIJ6	K70, K73–K74	[4,9,16–20,67] The other meta-analyses included studies on all kinds of liver cirrhosis, included the ones defined as caused by alcohol by definition (see Table 1 above)	Detrimental
Gall bladder and bile duct disease	IIJ7	K80–K83	[4,16–20] Beneficial effect only found for K80 (cholelithiasis); the above references are limited to this	Beneficial
Pancreatitis	IIJ8	K85–K86	[4,9,16–20,67] Usually determined by clinical case studies (but see [221]). There are subcategories of alcohol-induced acute (K85.2) and chronic pancreatitis (K86.0). We are currently conducting a new meta-analysis which will include all forms of pancreatitis	Detrimental
Other digestive diseases	IIJ9	K20–K22, K28–K31, K38, K57–K63, K75.2, K75.3, K75.4, K76–K77, K90–K92 (except K92.0, K92.1, K92.2, K92.9)	[4,9,16–20] Detrimental effect of alcohol has only been found for K22.6 (gastro-oesophageal haemorrhage). AAFs for this category were not based on meta-analyses but documented clinically. The above references are limited to K22.6	Detrimental
Psoriasis	IIL2	L40–L41	[4,9,16,17,19,20,183–185,188] Overall insufficient evidence on the causal impact of alcohol on the association with psoriasis. As this condition had been included in other analyses of alcohol on burden of disease, we included an overview on the evidence as part of the text	Detrimental
Abortion	IIN1	O00–O08	[4,9,16,17,19,20] To be applied to the fraction of women with alcohol consumption during pregnancy	Detrimental
Preterm birth complications	IM1	P05–P07, P22, P25–P28, P77	[4,9,16,17,19,20,270–274] To be applied to the fraction of women with alcohol consumption during pregnancy; [4] concluded that for all birth defects combined (ICD-10: Q00–Q99) there was inadequate evidence for a causation of alcohol during pregnancy. Other reviews, based on the same criteria for causality as [4], concluded sufficient evidence for a causal effect	Detrimental

AAF: alcohol-attributable fraction; CRA: comparative risk assessment; GBD: Global Burden of Disease and Injury; IARC: International Agency for Research on Cancer; ICD: International Classification of Diseases; IHD: ischaemic heart disease; RR: relative risk. aThe ICD-10 code refers to the respective categories as defined by GBD 2005. These may include fewer codes than elsewhere, as GBD identifies ill-specified codes [so called garbage code(s)] separately, which are to be redistributed to more meaningful codes based on specified procedures. The shaded rows indicate conditions for which the current analyses concluded sufficient evidence for a causal relationship and sufficient data on outcomes and risk relations to be included into the CRA 2005.

Table 3 Details of the quantitative meta-analyses from which estimates on dose–response relationships were extracted.

Disease	No. of articles from main search	Exclusion criteria[a]	No. of articles in analysis	% Agreement for data abstraction	Total n	% Male	Notes
Tuberculosis (TB)	16 527 articles in a comprehensive private collection of scientific TB publications were screened; PubMed revealed 2 007 abstracts	1, 3, 4.	21	Not reported	166 893 (calculated from Table 1 of [33])	Not reported	[33]
Incident HIV	856	1, 3, 6	10	NA	28 584	67	This will not be included in the CRA because insufficient proof of causality
Mouth, nasopharynx, other pharynx and oropharynx cancer	58[b]	1, 2, 3, 4, 5	15	Discrepancies to include an article and in quality score assignment were resolved in conference	4 507	Not reported	[67]
Oesophagus cancer	51[b]	1, 2, 3, 4, 5	14	Same as above	3 233	Not reported	[67]
Colon cancer	16[b]	1, 2, 3, 4, 5	16	Same as above	5 360	Not reported	[67]
Rectum cancer	49[b]	1, 2, 3, 4, 5	6	Same as above	1 420	Not reported	[67]
Liver cancer	43[b]	1, 2, 3, 4, 5	10	Same as above	1 321	Not reported	[67]
Larynx cancer	38[b]	1, 2, 3, 4, 5	20	Same as above	3 789	Not reported	[67]
Breast cancer (female)	65[b]	1, 2, 3, 4	53	Not reported	153 582	0	[70]
Diabetes mellitus	1 615	1, 2, 3, 4, 6	20	91.1	437 447	33	[275]
Epilepsy	1 360	1, 2, 3, 4	6	NA	2 332	56	[96]
Hypertensive disease	1 194	1, 2, 3, 5	12	90.4	282 977	46	[276]
Ischaemic heart disease (volume)	196[b]	1, 2, 3, 4, 5	51	NA	2 109 607 (calculated from [107]): 66 118 cases	Not reported	[107] New meta-analysis by Rehm and colleagues ongoing
Ischaemic heart disease (irregular heavy drinking occasions)	734	1, 2, 3, 4, 5	14	NA	55 677	91	[277]
Conduction disorders and other dysrhythmias	1 431	1, 2, 4, 6	8	NA	11 5931	33	New meta-analysis by Rehm and colleagues
Ischaemic stroke	190	1, 2, 3, 4, 5	20	92.0	571 277	56	New meta-analysis by Rehm and colleagues
Haemorrhagic and other non-ischaemic stroke	143	1, 2, 3, 4, 5	16	92.0	536 685	55	New meta-analysis by Rehm and colleagues
Lower respiratory infections: pneumonia	1 580	1, 2, 3, 4, 5	5	NA	112 100	27	New meta-analysis by Rehm and colleagues
Cirrhosis of the liver	3 238	1, 2, 3, 4, 5	17	95.6	1 477 887	38	[169]
Pancreatitis	2 712	1, 2, 3, 4, 5	6	NA	146 517	46	[170]
Preterm birth complications: low birth weight	1 342	1, 2, 3, 4, 5	19	NA	277 300	0	New meta-analysis by Rehm and colleagues
Injury	323	1, 2, 3, 4, 5	28	94.2	177 300	57	New meta-analysis by Rehm and colleagues

CRA: comparative risk assessment; HIV: human immunodeficiency virus; NA: not applicable. [a]Exclusion criteria: (1) no measure of association between outcome and appropriate alcohol exposure; (2) fewer than three levels of alcohol consumption; (3) cross-sectional study; (4) duplicate data already identified in the search; (5) outcome data not specific to disease ICD codes; (6) inability to acquire data (e.g. unavailable thesis dissertation). [b]The search criteria of Corrao *et al.* [67,107] were narrower compared to most searches of our group, as our search was intended not only to elicit papers for a quantitative meta-analysis on dose–response relations, but also to give insight into other causal criteria (see text above).

Table 4 Quantitative dose–response relationships between alcohol consumption and causally impacted disease conditions.

Disease	Monotonic relationship	Threshold	Dose–response relationship RR (95% confidence interval)	Differential effect mortality versus morbidity	RR for ex-drinker compared to life-time abstainers
Tuberculosis	Not enough data to model dose–response relationship	Yes, modelled at 40 g/day or diagnosis of alcoholism	After exclusion of small studies because of suspected publication bias from Lönnroth *et al.*, 2008: 2.94 (1.89–4.59). [33]	Hypothesized [38] but not modelled	Not computed: CRA will use all-cause mortality RRs
Mouth, nasopharynx, other pharynx and oropharynx cancer	Yes	No	From Corrao *et al.* (2004) (based on 14 case–control and one cohort studies): 25 g/day: 1.86 (1.76–1.96); 50 g/day: 3.11 (2.85–3.39); 100 g/day: 6.45 (5.76–7.24). [67]	No data from any of the meta-analyses	Not computed: CRA will use all-cause mortality RRs
Oesophagus cancer	Yes	No	From Corrao *et al.* (2004) (based on 13 case–control and one cohort studies): 25 g/day: 1.39 (1.36–1.42); 50 g/day: 1.93 (1.85–2.00); 100 g/day: 3.59 (3.34–3.87) [67]	No data from any of the meta-analyses	Not computed: CRA will use all-cause mortality RRs
Colon and rectum cancer	Yes	No	From Corrao *et al.* (2004) colon (based on 12 case–control and four cohort studies): 25 g/day: 1.05 (1.01–1.09); 50 g/day: 1.10 (1.03–1.18); 100 g/day: 1.21 (1.05–1.39); rectum (based on four case–control and two cohorts): 25 g/day: 1.09 (1.08–1.12); 50 g/day: 1.19 (1.14–1.24); 100 g/day: 1.42 (1.30–1.55) [67]	No data from any of the meta-analyses	Not computed: CRA will use all-cause mortality RRs
Liver cancer	Yes	No	From Corrao *et al.* (2004) (based on eight case–control and two cohort studies): 25 g/day: 1.19 (1.12–1.27); 50 g/day: 1.40 (1.25–1.56); 100 g/day: 1.81 (1.50–2.19) [67]	No data from any of the meta-analyses	Not computed: CRA will use all-cause mortality RRs
Larynx cancer	Yes	No	From Corrao *et al.* (2004) (based on 20 case–control studies): 25 g/day: 1.43 (1.38–1.48); 50 g/day: 2.02 (1.89–2.16); 100 g/day: 3.86 (3.42–4.35) [67]	No data from any of the meta-analyses	Not computed: CRA will use all-cause mortality RRs
Breast cancer (female)	Yes	No	From Hamajima *et al.* (2002) (58 515 women with invasive breast cancer and 95 067 controls from 53 studies): 35–44 g/day: 1.32 (1.19–1.45); ≥45 g/day: 1.46 (1.33–1.61) compared with abstainers. The RR of breast cancer increased by 7.1% (5.5–8.7%) for each additional 10 g/day intake of alcohol, i.e. for each extra unit or drink of alcohol consumed on a daily basis [70]	No data from any of the meta-analyses	Not computed: CRA will use all-cause mortality RRs
Diabetes mellitus	No	No	From Baliunas *et al.* (2009): men: nadir at 22 g/day: 0.87 (0.76–1.00); deleterious >60 g/day: 1.01 (0.71–1.44); women: nadir at 24 g/day: 0.60 (0.52–0.69); deleterious at >50 g/day: 1.02 (0.83–1.26) [275]	No data to establish comparison (almost all risk relations between alcohol consumption and diabetes were based on morbidity)	Men: 1.18 (0.89–1.52); women: 1.14 (0.99–1.31)
Epilepsy	Yes	No	From Samokhvalov *et al.* (in press): not enough data to model separate by sex: 25 g/day: 1.37 (1.28–1.47); 50 g/day: 1.86 (1.62–2.13); 100 g/day: 3.44 (2.61–4.52) [96]	Not enough data to model	Not enough data to estimate. CRA will use all-cause mortality RRs
Hypertensive disease	Men: yes, women: no	No	From Taylor *et al.* (2009): men: 25 g/day: 1.25 (1.19–1.32); 50 g/day: 1.62 (1.46–1.81); 100 g/day: 2.64 (2.14–3.26); women: <5 g/day: 0.82 (0.73–0.93); 25 g/day: 1.24 (0.87–1.77); 50 g/day: 1.81 (1.13–2.90), 100 g/day: 2.81 (1.56–5.05) [276]	Insufficient data for mortality, so the relationship was only modelled for hypertension morbidly	Both genders: 0.94 (0.49–1.39)

Table 4 *Cont.*

Disease	Monotonic relationship	Threshold	Dose–response relationship RR (95% confidence interval)	Differential effect mortality versus morbidity	RR for ex-drinker compared to life-time abstainers
Ischaemic heart disease	No	No	From Corrao et al. (2000): curvilinear relationship for average consumption; based on all 54 studies: nadir at 25 g/day: 0.75 (0.73–0.77); protective effect up to 90 g/day: 0.94 (0.90–1.00); harmful effect at 113 g/day: 1.08 (1.00–1.16); based on 28 high-quality cohort studies: nadir at 20 g/day: 0.80 (0.78–0.83); protective effect up to 72 g/day: 0.96 (0.92–1.00); detrimental effect >89 g/day: 1.05 (1.00–1.11) [107] Bagnardi et al. (2008) estimated an RR for irregular heavy drinking patterns compared to abstainers of 1.10 (1.03–1.17) [117] From Roerecke & Rehm (2010): heavy drinking occasions (>60 g per occasion) compared to non-heavy drinking occasions: 1.45 (1.24–1.70) [277]	Yes, stronger relationship with mortality	Men mortality: 1.21 (1.12–1.30); morbidity: 0.99 (0.90–1.08) Women mortality 1.39 (1.17–1.66); morbidity 1.11 (0.94–1.32)
Ischaemic stroke	No	No	From Reynolds et al. (2003): <12 g/day: 0.80 (0.67–0.96); 12–24 g/day: 0.72 (0.57–0.91); 24–60 g/day: 0.96 (0.79–1.18); >60 g/day: 1.69 (1.34–2.15) [154]	Men: no, women: yes	Strokes combined: men 1.33 (0.91–1.96); women 1.15
Haemorrhagic and other non-ischaemic stroke	Men: yes, women: no (only for morbidity)	No	From Reynolds et al. (2003): <12 g/day: 0.79 (0.60–1.05); 12–24 g/day: 0.98 (0.77–1.25); 24–60 g/day: 1.19 (0.80–1.79); >60 g/day: 2.18 (1.48–3.20) [154]	Men: no, women: yes	(0.71–1.92); both 1.22 (0.87–1.76)
Conduction disorders and other dysrhythmias	Yes	Not clear; volumes of average consumption <36 g have RR of about 1, but based on few studies	From own meta-analysis (not enough data to model separate by sex): <24 g/day: 1.02 (0.94–1.12); 24–36 g/day: 1.13 (0.98–1.30); 36–48 g/day: 1.19 (1.03–1.37); 48+ g/day: 1.45 (1.24–1.69)	Not enough data to model	Not enough data to estimate
Lower respiratory infections: pneumonia	Yes	Not clear, as lower volumes of average consumption have RR of about 1: mechanism similar to TB	From own meta-analyses (not enough data to model separate by sex: 25 g/day: 1.13 (1.03–1.24); 50 g/day: 1.27 (1.05–1.53); 100 g/day: 1.61 (1.10–2.35)	Not enough data to model	Not enough data to estimate
Cirrhosis of the liver	Yes	There are good indications for a threshold for morbidity as end-point, but not for mortality [169]	From Rehm et al. (in press) mortality: men: 30 g/day: 2.8 (2.3–3.4); 54 g/day: 7.0 (5.8–8.0); >60 g/day: 14.0 (11.7–16.7); women: 30 g/day: 7.7 (6.3–9.5); 54 g/day: 14.7 (11.0–19.6); >60 g/day: 22.7 (17.3–30.1); Morbidity men: 30 g/day: 0.7 (0.5–1.0); 54 g/day: 2.3 (1.7–3.2); >60 g/day: 5.0 (3.9–6.4); women: 30 g/day: 2.4 (1.8–3.2); 54 g/day: 5.9 (3.7–9.3); >60 g/day: 6.1 (4.6–8.0). From categorical analysis [169]	Yes, higher risks for mortality [169]	Morbidity and mortality combined: women: 6.50 (2.21–19.08); men: 1.31 (0.67–2.57); women only based on one study [278]
Pancreatitis	Yes, but risk for lower doses of average volume of drinking may not be significantly different from risk of abstention	Yes, a threshold effect at about 48 g/day or four drinks average volume was found [170]	From Irving et al. (2009): not enough data to model separately by sex: 25 g/day: 1.10 (1.08–1.12); 50 g/day: 1.46 (1.34–1.59); 100 g/day: 4.50(3.22–6.31) [170]	Not enough data to model	Not enough data to estimate. CRA will use all-cause mortality RRs
Preterm birth complications	Yes	No	From Rehm et al. (2004): men <40 g/day: 1.00; 40–60 g/day: 1.40; 60+ g/day: 1.40; women <20 g/day: 1.00; 20–40 g/day: 1.40; 40+ g/day: 1.40 [9]	Not relevant	Not meaningful, as only drinking during pregnancy can affect newborns
Injury	Yes	No	From Corrao et al. (1999): 25 g/day: 1.4 (1.2–1.6); 50 g/day: 2.0 (1.5–2.6); 100 g/day: 4.0 (2.4–6.6) Corrao et al. (1999) was based on average volume in g/day [221]	Yes, higher risks for mortality	Not meaningful, as risk is mainly determined by drinking before injury

CRA: comparative risk assessment; RR: relative risk; TB: tuberculosis.

ments which facilitate the spread of TB infection [38]. Other common cause factors (e.g. poverty) may impact the association, but this does not invalidate the conclusion that alcohol is one component in a sufficient component causal mechanism for incidence of TB [38].

Regarding the course of the disease, there is sufficient evidence indicating that heavy alcohol consumption disrupts medication intake regimens and affects help-seeking and treatment processes negatively, leading to worse treatment outcomes compared to abstinence [31,39]. This would indicate the necessity to derive separate relative risk (RR) estimates for alcohol and TB mortality, which should be higher than for morbidity if the above finding is true.

HIV/AIDS

At the Cape Town meeting mentioned above, it was concluded similarly that there is conclusive evidence of a causal linkage between heavy drinking patterns and/or AUD and the worsening of the disease course for HIV/AIDS (for more detailed reasoning see [40,41]). While alcohol use is associated consistently with the prevalence and incidence of HIV [42–44], however, further research is needed to substantiate causality [45]. As indicated above, alcohol use, especially heavy use, weakens the immune system, thus creating a larger vulnerability for infections. However, in contrast to TB which can be acquired through essentially *passive* behavioural means, in order to become infected with HIV there must be an additional *active* behavioural component, which in most cases involves engaging in unprotected sex. Although generalized alcohol use has been shown to be associated with overall reports of unprotected sex [46–48], when the relationship between alcohol consumption and unprotected sex is examined within event-level contexts (e.g. based on daily diary assessments), the relationship weakens and, in many cases, disappears [46,48–51]. These findings suggest therefore that alcohol consumption on its own may not be linked *causally* to the active behaviours that are required in order for HIV acquisition to take place. Rather, alcohol use may serve as a marker for other variables that potentially underlie the association between alcohol and unprotected sex, including personality characteristics such as sexual compulsivity [52] or sensation seeking [53,54], and/or psychiatric conditions such as antisocial personality disorder [55] Thus, sufficient evidence for causality of the impact of alcohol on HIV incidence could not be concluded (see also the reasoning in [44]). Without going into further details, the same kind of reasoning would hold for other sexually transmissible diseases.

However, there is enough evidence to conclude a causal impact of alcohol on the course of the disease [31]. Similarly, as with TB, alcohol consumption was shown to disrupt HIV treatment, with markedly higher dropouts and more treatment failures associated with this exposure [56]. There is also an indication of a dose–response relationship, where problem drinking or alcohol use disorders interfere more strongly than does alcohol exposure *per se* [56]. A conservative quantification of this impact is possible based on the effect of alcohol consumption on antiretroviral treatment adherence [56] combined with the impact of failed adherence on survival [57].

Cancer (in general)

In February 2007, the Monograph Working Group of the International Agency for Research on Cancer (IARC) concluded that there was 'sufficient evidence' for the carcinogenicity of ethanol in animals and classified alcoholic beverages as carcinogenic to humans. Specifically, the group confirmed or newly established the causal link between alcohol consumption and the following malignant neoplasm categories: oral cavity, pharynx, larynx, oesophagus, liver, colorectal and female breast cancer ([58]; see Table 2). However, the working group also confirmed a lack of carcinogenicity of alcoholic beverages for renal-cell cancer and non-Hodgkin's lymphoma. For stomach and lung cancer, the verdict was that carcinogenicity was possible but not established, while evidence on causality between alcohol consumption and risks of other types of cancer was sparse or inconsistent (these results are summarized in Table 2). All cancers showed evidence of a dose–response relationship (shown in Table 3).

The molecular and biochemical mechanisms by which chronic alcohol consumption leads to the development of cancers of various organs are not understood fully. It is suggested that these mechanisms differ by target organ and include polymorphisms in genes that encode enzymes responsible for ethanol metabolism (e.g. alcohol dehydrogenase, aldehyde dehydrogenase and cytochrome P450 2E1), increased oestrogen concentration and changes in folate metabolism and in DNA repair [59]. For the digestive tract cancers, especially those of the upper digestive tract, acetaldehyde, both from alcohol metabolism in the human body and ingested as a component of alcoholic beverages, has been highlighted recently as an important likely causal pathway [58,60–64].

Several of the cancers that were identified as alcohol-attributable in the latest review had already been included in previous studies of the alcohol-attributable disease burden, such as the 2000 or 2004 CRAs [10,65]. The following sections provide more details on colorectal and female breast cancers that had not been included consistently in previous analyses.

Colorectal cancer

A causal relation between alcohol and colorectal cancer was established only recently by the IARC [58]. Several meta-analyses [66–68] observed a positive linear relation between alcohol consumption and colorectal cancer. The studies provide evidence for an increased relative risk (RR) of approximately 10–20% for colorectal cancer with regular consumption of approximately 50 g of alcohol per day, compared with abstainers. This association is similar for both colon cancer and rectal cancer [66,68].

A potential mechanism is that alcohol may act through folate metabolism or synergistically with low folate intake (as low folate intake increases the risk of colorectal cancer); however, the effects might be modest [59,68]. Moskal and colleagues [68] also suggested a genotoxic effect of acetaldehyde, a metabolite of alcohol, and genetic polymorphism as factors for enhancing the risk of colorectal cancer.

Breast cancer (female)

Many epidemiological studies have indicated a positive relation between alcohol consumption and incidence of breast cancer [67,69–71]. The risk exists even at a moderate level of alcohol drinking [72] and increases monotonically with the level of alcohol consumption [67,70]. Based on several epidemiological studies, each additional 10 g (less than one standard drink in most countries) of alcohol per day is associated with an increase of 7% in the RR of breast cancer [70] or higher (an increase of 10% was estimated [71]). Hamajima and colleagues [70] estimated that about 4% of the female breast cancer cases in developed countries may be attributable to alcohol drinking.

The mechanism of association between alcohol and breast cancer may involve increased levels of oestrogen [59,73] or increased levels of plasma insulin-like growth factor (IGF) produced by the liver due to moderate consumption of alcohol ([74]; see also [69,71]).

Diabetes mellitus

Moderate alcohol consumption is associated with a reduced risk of type 2 diabetes. Several possible biological mechanisms may explain the observed relationship. Development of insulin resistance is a key factor in the pathogenesis of type 2 diabetes [75] and the risk reduction may be explained by an increase in insulin sensitivity after moderate alcohol consumption [76], which has been found in observational studies [77–79] as well as randomized controlled trials [80,81]. Alternatively, ethanol oxidation produces measurable downstream metabolites such as acetaldehyde and acetate [82], which

may reduce the risk of type 2 diabetes. Moderate alcohol consumption is also known to increase high-density lipo-protein (HDL) cholesterol concentrations [83], although at higher consumption levels body weight, triglyceride concentration and blood pressure may increase ([84,85]; see also IHD below). Another plausible protective mechanism is through the anti-inflammatory effect of alcohol [86,87]. However, whether moderate alcohol intake is itself a protective factor for diabetes or whether it is a marker for other healthy life-style choices is not certain. We decided to include diabetes into the CRA as impacted causally by alcohol consumption, but the overall level of evidence for this was considered as borderline between sufficient and limited.

Epilepsy

Although it has long been known that alcohol withdrawal can lead to seizures [88], these provoked seizures have been excluded in the GBD 2005 definition of epilepsy. Consistent with the GBD 2005 definition, we used the definitions of epilepsy from the International League against Epilepsy and the International Bureau for Epilepsy, which describe epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. The cited definition of epilepsy requires the occurrence of at least one epileptic seizure [89]. In line with this definition we used the studies which had unprovoked or other *grand mal* seizures as an outcome, in addition to those that used physician-diagnosed epilepsy as their outcome. We found a consistent relationship between alcohol consumption and increased risk of thus-defined epilepsy, especially for higher doses of alcohol [90–96].

The consistent dose–response relationship is rooted in plausible pathways. In particular, chronic alcohol consumption has diverse effects on the central nervous system, affecting its structure and functioning in different ways. There are several major theories explaining the effects of alcohol consumption on the development of epilepsy. One postulates a 'kindling' effect [97]. According to this theory, repeated withdrawals, including natural withdrawal through sleep over the years, may lead to the gradual lowering of the epileptogenic threshold [97]. Epileptogenesis in heavy alcohol users may also be explained by cerebral atrophy [98]. Additional hypothesized causes of epilepsy in alcohol users include cerebrovascular infarctions, lesions, head traumas (from alcohol-attributable injuries) and changes in neurotransmitter systems and ionic imbalances leading to the onset of seizures [98–101]. Our analyses indicated that the strongest evidence was for the 'kindling' hypothesis for cerebral atrophy and for brain lesions each linking direct irreversible central nervous system (CNS) changes to alcohol

consumption, leading potentially to the onset of epilepsy or spontaneous seizures not related immediately to alcohol intake.

Additionally, it has been shown that heavy alcohol consumption may worsen the clinical course of existing epilepsy via increased clearance of anti-epileptic drugs and non-compliance to treatment regimen [100].

Hypertensive disease

The only relevant disease or cause of death in GBD for this category is hypertensive heart disease (see Table 2 for exact definition). As there were no studies on alcohol consumption and hypertensive heart disease fulfilling the inclusion criteria, we substitute the studies on alcohol consumption and a wider definition of hypertensive diseases, including essential hypertension. The relationship between alcohol consumption and hypertensive disease is relatively complex. On one hand, an overall consistently detrimental dose–response effect has been shown [67] for men, while moderate consumption of alcohol has, in some studies, shown to be protective for women. However, despite the consistent effect of chronic alcohol use on increasing blood pressure [102,103] the mechanism of action is unclear, although a number of theories about potential pathways have been proposed [103]. These include activation of the sympathetic nervous system to constrict blood vessels and increase the contractile force of the heart [104], or a possible role of sensitivity of baroreceptors in vessel walls that results in a diminished ability to regulate blood pressure via arterial contraction and relaxation [105]. The protective effect, seen only in moderate doses and among women, may be explained in the same way that alcohol is protective for IHD by changing concentrations of high- and low-density lipoproteins (HDL and LDL, respectively) in the blood or reduction in platelet aggregation on vessel walls. The fact that it is not seen in men may be a result of higher rates of binge drinking in men resulting in an overall detrimental effect, but the literature is equivocal.

Ischaemic heart disease

IHD is a major cause of death and disease burden around the world, and its impact is projected to increase in the future [106]. The relation of alcohol consumption to IHD is complex, with mechanisms for both beneficial and detrimental causal impact, depending on drinking pattern. Light to moderate regular alcohol consumption has been linked to reduced risk and severity for incidence of coronary events, with greater risk reduction for non-fatal events; however, most of the effect can be achieved with consumption of 12 g pure alcohol (about one standard drink in the United States and many other countries) every other day, with no benefits obtained for consump-

tion of more than 20 g pure alcohol per day (less than two standard drinks) [107,108]; as IHD constituted the main beneficial effect in medical cohorts, the relationship between alcohol and total mortality showed about the same form [109]. The pattern of light to moderate regular alcohol consumption with no heavy drinking occasions also reduces the risk for recurrence after an IHD event [110] and among people with existing IHD risk factors such as diabetes [111,112] or hypertension [113], whereas a drinking pattern that includes heavy drinking occasions, even when usual consumption is light or moderate, has been related to an increase in IHD risk [114–117]. Chronic heavy alcohol use, on the other hand, has been associated with adverse cardiac outcomes, not only IHD but also dilated cardiomyopathy or cardiac dysrhythmias (see below and [118]).

The epidemiological evidence that regular light to moderate alcohol consumption protects against IHD is strengthened by growing and, in some instances, substantial evidence concerning the biological mechanisms by which a protective effect could be mediated [83,119–122]. First, moderate alcohol intake has been linked clearly to favourable lipid profiles, especially an increase in HDL [83,123]. It has been estimated that as much as 40–50% of the protective effect may be attributable to this mechanism [124,125]. Gene interactions may also play a role in influencing HDL levels [126–128], but more work may be required to explain this complex pathway more fully [129].

Secondly, moderate alcohol intake affects coagulation profiles favourably [83], in particular through its effects on platelet aggregation [130] and fibrinolysis [131]. A meta-analysis of 42 published short-term trials confirmed the influence of alcohol both on serum lipid profiles and on blood-clotting factors [83]. Other mechanisms for the cardioprotective effect of light to moderate consumption have been discussed [116,128] but, based on current knowledge, appear to play less prominent roles in explaining the beneficial effects of regular light to moderate drinking.

Due to the complexity of processes leading to IHD and general limitations of observational studies, the protective effect of alcohol on IHD risk remains a highly debated topic. In many of the older studies on IHD risk, alcohol measurement failed to take into account variability of alcohol consumption over time by relying upon one baseline measurement. In addition, a recent review by Fillmore and colleagues [132] suggested that the cardiac protection caused by alcohol might have been overestimated. According to the authors, many studies had used contaminated abstainer groups by not excluding former drinkers from this group. Because former drinkers have a significantly different risk profile from true life-time abstainers, risk estimates may have been inflated (the

so-called 'sick quitter' effect; see [133]). This led Fillmore and colleagues to infer that regular light to moderate drinking might be a marker for good health among older people, but not a cause of it [132]. While this effect would bias risk estimates seriously when abstainers (including former drinkers with substantial previous alcohol consumption) are the reference category, three major points underline the cardioprotective effect despite this theoretical argument [134]. First, experimental evidence has confirmed mediating pathways for a cardioprotective effect of moderate regular drinking [83]. Secondly, studies where life-time abstainers were separated from former drinkers confirmed a cardioprotective effect [135,136]. Thirdly, a cardioprotective effect also has been reported among participants with existing IHD risk factors [110–113].

Nevertheless, classification of life-time abstainers is indeed a difficult task and, when measured carefully at more than one point in time, a substantial fraction of 'life-time abstainers' reported alcohol consumption at other different time-points [137]. However, those who were drinkers of small quantities on rare occasions would not bias the results of the comparison group as there is no plausible biological pathway for an effect of such drinking [138]. The best comparison group for alcohol epidemiology with respect to chronic disease outcomes would thus be a combination of life-time abstainers with those who never consumed alcohol in quantities which could have a biological impact [137].

The relationship between alcohol and IHD risk is complicated further by the fact that at least two dimensions of consumption have to be taken into account in determining IHD risk. Heavy drinking occasions, not captured adequately by measurement of average consumption, have been linked to adverse cardiovascular events for some time [107,116,139]. Unfortunately, most epidemiological studies on alcohol and IHD risk have used average consumption as the exposure measure, and it is only recently that studies have been conducted with methodologically rigorous assessment of IHD as an end-point, and with control for average volume as a confounder and/or with life-time abstention as reference (e.g. [140–143]). All these recent studies found a protective effect for daily average light to moderate drinkers but no or detrimental effects for people whose drinking patterns included heavy drinking occasions (even if their usual pattern was moderate). A review by Agarwal [144] and a study conducted by Mukamal and colleagues [136] also found drinking patterns to be important to the risk of IHD for a given volume of alcohol consumption. The detrimental effects of heavy drinking occasions on IHD are consistent with the physiological mechanisms of increased clotting and a reduced threshold for ventricular fibrillation after heavy drinking occasions (see review [114]).

In summary, heavy drinking occasions are associated mainly with physiological mechanisms that increase the risk of sudden cardiac death and other cardiovascular outcomes, in contrast to the physiological mechanisms triggered by steady low to moderate consumption that are linked to favourable cardiac outcomes. The relationship between alcohol and IHD will thus be modelled based on two dimensions: average volume of consumption and patterns of drinking, operationalized by heavy drinking occasions.

Dysrhythmias

The association between alcohol consumption and cardiac rhythm disorders has been recognized for some time [145]. In two studies, alcohol was identified as a cause of new-onset atrial fibrillation in 30–60% of patients [146,147]. Several mechanisms explaining the development of dysrhythmias due to alcohol consumption have been proposed, including direct alcohol cardiotoxicity, hyperadrenergic activity during drinking and withdrawal, impairment of vagal tone and increased intra-atrial conduction time [148].

Existing estimations of the association between alcohol consumption and the onset of cardiac dysrhythmias vary in different studies, including several large-scale prospective studies—the Framingham Heart Study [149], the Manitoba study [150], the Multifactor Primary Prevention Study [151] and others. The Framingham Heart Study revealed a low association with moderate alcohol consumption, but the association became significant among individuals consuming more than 36 g pure alcohol per day (about three drinks) [149]. In the Copenhagen City Heart Study increased risk of atrial fibrillation was described for people consuming more than 35 drinks per week [152]. A recent study by Planas and colleagues showed an increased risk of the re-occurrence of atrial fibrillation with moderate alcohol consumption [153].

Overall, existing studies show increased risk of development of dysrhythmias related to heavy alcohol consumption, whereas the effects of light to moderate alcohol consumption are inconclusive.

Stroke

The two most recent meta-analyses [67,154] indicate that alcohol use both reduces and increases the risk of stroke depending on the type of stroke, quantity of alcohol consumed and drinking pattern. Both these studies found a positive, almost linear relation between alcohol consumption and logarithmized RR of haemorrhagic stroke (corresponding to an exponential relationship between consumption and the RR of haemorrhagic stroke, when not logarithmized), but observed a curvi-

linear relationship between alcohol consumption and the logarithmized RR of ischaemic stroke. According to these meta-analyses, low to moderate alcohol consumption (one to two drinks per day) seemed to have a protective effect on ischaemic stroke, and then the risk curve turned upwards.

The variation in the effect of alcohol consumption on different types of stroke may be ascribed to the difference in the causes of haemorrhagic and ischaemic stroke. Ischaemic stroke is caused by the blockage in a blood vessel in the brain, arising commonly from a blood clot formed somewhere else, and therefore has a similar aetiology to that of IHD (for biological pathways see IHD above). Consequently, a pattern of irregular heavy drinking occasions should also have the same detrimental effects as for IHD. Thus, combining fatal and non-fatal ischaemic strokes in a Finnish cohort study, Sundell and colleagues [155] reported a RR of 1.99 (95% CI: 1.39–2.87) for ischaemic stroke among participants whose drinking pattern included binge drinking occasions (defined as six or more drinks in one setting for men or four or more drinks for women, equivalent to 72 g and 48 g of pure alcohol, respectively) compared to non-binge drinkers after adjusting for long-term average alcohol consumption, age and sex. An RR of 1.56 (95% CI: 1.06–2.31) was estimated, when hypertension, study area, smoking, diabetes, BMI, education, history of MI, and study year were also taken into account.

Haemorrhagic stroke, on the other hand, is caused by a rupture of a blood vessel supplying the brain, thus releasing blood into the brain. Two major subtypes of haemorrhagic stroke can be distinguished: intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). The impact of alcohol on both types of haemorrhagic stroke is high. For instance, in a study conducted in Germany, more than one-third of men with ganglionic ICH were alcoholics [156]. Mechanisms by which alcohol could impact on ICH and SAH include hypertension [157]. However, the risk for ICH remains elevated even when alcohol-induced hypertension has been accounted for, due to alcohol-induced vasospasm [157]. For SAH, heavy drinking occasions seem to play a specific role [157]. The vasospastic mechanism discussed for ICH may also play a role with SAH. Finally, the same mechanisms leading to a detrimental effect of heavy alcohol consumption on IHD also come into play in explaining the effect of heavy alcohol consumption on haemorrhagic stroke [155].

Based on the above evidence, the relationship between alcohol consumption and stroke will be modelled separately for these two major types of stroke, as specified by the GBD categories. The epidemiological evidence allows mainly for differentiation of these two main types (for further differentiation see [158] and [159]).

Lower respiratory infections: community-acquired pneumonia

Community-acquired pneumonia (CAP), distinguished from hospital-acquired pneumonia because of its different aetiology, has been recognized as caused by heavy alcohol consumption since the seminal work of Rush in the late 18th century [32]. An association between CAP and alcohol intake has been found [160], and plausible biological pathways have been identified. As already indicated above (see section on TB), heavy alcohol consumption can cause alterations of the immune system, thereby increasing host susceptibility to CAP. Also, because of the sedative properties of alcohol which lead to diminished oropharyngeal tone, an increased risk of aspiration and diminished cough reflex and mucociliary clearance [37,161], alcohol intake can facilitate the development of CAP. A preliminary meta-analysis by our group indicated that the risk curve is relatively flat for lower consumption, and reaches a RR of 1.3 only at a consumption level of about five drinks per day (equivalent to 60 g pure alcohol per day). On the other hand, older studies showed that patients defined as 'alcoholics' according to clinical symptoms showed an eightfold increased risk for CAP [162,163]. Also, in a recent study in Russia, drinkers of more than three bottles of vodka per week showed an RR of 3.29 (95% CI 2.83–3.83) for men and 3.42 (95% CI: 2.64–4.44) for women, both compared to drinkers of half a bottle of vodka weekly or less [164].

Liver cirrhosis

Liver cirrhosis has been linked to alcohol consumption in every review of alcohol-attributable disease, and the underlying mechanisms have been described previously in detail [165–167]. Thus, we will restrict our present discussion to the differential relationship of alcohol with liver cirrhosis mortality versus morbidity. Specifically, evidence suggests that alcohol consumption is linked more strongly to cirrhosis mortality than to morbidity because drinking, especially heavy drinking, has been shown to worsen existing liver disease considerably and to have detrimental effects on the immune system, thus affecting negatively the course of existing liver disease and increasing the chance of death [37,165,168]. Our own meta-analyses confirmed clearly that for both men and women the impact of alcohol was stronger on liver cirrhosis mortality compared to morbidity [169].

Pancreatitis

Alcohol consumption has been shown to be associated consistently with an increased risk of pancreatitis, and plausible biological mechanisms have been identified for the effect (see [170]). In particular, the metabolites of

alcohol, such as acetaldehyde and fatty acid ethyl esters, may initiate and/or enhance pancreatic injury. Alcohol may also attenuate or augment inflammatory cell activation, leading to fibrosis in the pancreas [37,171–174]. All these mechanisms come into place particularly with heavy consumption. Thus, the meta-analysis of Irving and colleagues cited above found that, compared with non-drinkers, alcohol consumption of two or fewer drinks per day (≤24 g pure alcohol/day) was almost identical to the risk of non-drinkers (RR = 1.0, 95% CI: 0.8–1.2; $P = 0.887$). Drinking three to four drinks was associated with only marginally significant higher risk than for abstention (RR = 1.2, 95% CI: 1.0–1.5, $P = 0.059$), but overall the dose–response relationship increased monotonically (see Table 3).

Psoriasis

Psoriasis is a chronic, autoimmune, inflammatory, sometimes disfiguring, skin and joints disease, which has a high impact on health-related quality of life. Epidemiological studies from around the world have estimated the prevalence of psoriasis to be 0.6–4.8% [175]. Current evidence suggests that psoriasis is caused by the interaction of genetic–environmental factors and the immune system [176–178].

Medical literature for practitioners and patients describes alcohol as a psoriasis trigger. Most of the studies and reviews conducted in the past decades support a detrimental impact of alcohol consumption on psoriasis, especially in male patients [4,19,179–186]. In addition to the finding of a clear dose–response relationship [186–188], the prevalence of psoriasis among alcoholics was between two and 10 times greater than in the general population [179,189–191]. In one recent study, between 17% and 30% of patients with psoriasis (depending upon the measure of alcohol consumption) were classified as having difficulties with alcohol [192]. However, part of the association between alcohol and psoriasis could, alternatively, be attributed to higher alcohol consumption as a consequence of the disease [179,193]. Abstinence from alcohol was found to be related to psoriasis remission, whereas restarting alcohol consumption has been associated with the recurrence of psoriasis [194,195]. Alcohol consumption is also associated with less favourable responses to treatment and decreased compliance with the treatment of psoriasis [196,197].

The mechanism by which alcohol consumption affects psoriasis has not been clarified fully. Most researchers suggest that alcohol affects psoriasis mainly by affecting the immune system adversely, thus predisposing drinkers to infections ([198–200], but see [201]). It has also been suggested that the stimulatory effect of ethanol and acetone (which exceeds its normal endog-

enous level in the blood of heavy drinkers) on keratinocytes, causing epidermal hyperproliferation, may be one of the reasons why psoriasis can be precipitated by alcohol use in genetically predisposed individuals [198–200]. In sum, consistent with [201], we conclude that there is a consistent association between alcohol consumption and psoriasis, but that the overall level of evidence for causality is insufficient, especially with respect to biological pathways.

Preterm birth complications

Heavy ingestion of alcohol has been implicated in an increased risk of preterm birth [202–206]. However, some studies reported modest inverse associations between low levels of alcohol consumption and preterm delivery with low birth weight (e.g. [205,207]), although this may be a result of a higher prevalence of such drinking behaviour among women who are more advantaged socio-economically [202,203]. Further, the risks associated with different dimensions of drinking during different phases of pregnancy are unclear. For example, moderate amounts of alcohol increased the risk for preterm delivery during late pregnancy, but not during early pregnancy in one study [205], whereas another study also found elevated risk of preterm birth complications with drinking in early pregnancy [208].

The biological mechanism responsible for the association between alcohol use and preterm birth complications may be explained in terms of an enhanced prostaglandin level among drinkers, because a rise in prostaglandin level can cause preterm birth [209]. Progesterone hormone has been shown to suppress prostaglandin production [210–212], which is an important regulator of prostaglandin synthesis during parturition. Heavy alcohol exposure decreases the progesterone synthesis and level [213,214], hence resulting in failure to control the prostaglandin level and leading eventually to the onset of the physiological events associated with parturition [209,215].

The biological mechanisms through which maternal drinking affects fetal growth are not understood completely. However, acetaldehyde, the major metabolite of alcohol, affects the human placenta exposed to this toxic metabolite, consequently causing various problems such as fetal hypoxia, impaired cell proliferation or delayed placental development [216].

Acute conditions where alcohol is a component cause

As detailed in the previously published review based on the GBD 2000 project [1], alcohol consumption has been shown to have a causal impact on different forms of injury, both unintentional and intentional. In the present review, we focus upon two additional issues: whether

Table 5 GBD 2005 injury categories and alcohol.

No. of GBD 2005 code	Category	ICD-10 code[a]
IIIA	Unintentional injuries	V01–V98, W00–W52, W65–W74, X00–X19, X34–X44, X46–X49, Y40–Y84, Y85.0, Y88
IIIA1	Transport injuries (including road traffic accidents)	V01–V98, Y85.0
IIIA2	Poisonings	X40–X44, X46–X49
IIIA3	Falls	W00–W19
IIIA4	Fires, heat and hot substances	X00–X19
IIIA5	Drowning	W65–W74
IIIA6	Exposure to mechanical forces (including machinery accidents)	W20–W52
IIIA7	Natural disasters	X34–X39
IIIA8	Adverse effects of medical treatment	Y40–Y84, Y88
IIIA9	Injuries due to animal bites or contact with a marine animal	W53–W64, X20–X29
IIIA10	Other unintentional injuries	W75–W99, X30–X33, X50–X58
IIIB	Intentional injuries	X60–Y09, Y35–Y36, Y87.0, Y87.1, Y89.0, Y89.1
IIIB1	Self-inflicted injuries	X60–X84, Y87.0
IIIB2	Interpersonal violence	X85–Y09, Y87.1
IIIB3	Collective violence	Y36, Y89.1
IIIB4	Legally sanctioned deaths	Y35, Y89.0

CRA; comparative risk assessment; GBD: Global Burden of Disease and Injury; ICD: International Classification of Diseases. [a]The ICD-10 code refers to the respective categories as defined by GBD 2005. These may include fewer codes than elsewhere, as GBD identifies ill-specified codes [so called garbage code(s)] separately, which are to be redistributed to more meaningful codes based on specified procedures. The shaded rows indicate conditions for which the current analyses concluded sufficient evidence for a causal relationship and sufficient data on outcomes and risk relations to be included into the CRA 2005.

there is evidence of a causal relationship between alcohol and injury for all categories of injury, and how best to estimate AAFs for each injury outcome. Table 5 provides an overview of the GBD 2005 categories for injury.

For the shaded categories, causality has been established by the earlier review [1]. For fire injuries and related conditions, while alcohol has been established as a component cause and its contribution has been estimated quantitatively in some countries based on insurance or police records (e.g. [28]), global estimates seem to be impossible. For natural disasters, while it may certainly be true that intoxicated people may be more vulnerable when disaster strikes, this effect has never been estimated, and therefore natural disasters are not part of the current CRA. Similar reasoning was used for injuries due to animal bites.

For the categories of adverse effects of medical treatment as well as war and other forms of collective violence, including legally sanctioned deaths, there is insufficient evidence for a causal impact of alcohol, although there is ample anecdotal evidence of alcohol intoxication as the source of 'liquid courage' in collective violence [217] and as being used to amplify cruelty in wartime (e.g. [217,218]). Thus, Mueller [217] notes that the killing squads at Srebrenica were often shored up with generous quantities of liquor, as was typical for the wars in former Yugoslavia. In the Rwanda genocide, massacres were

often committed by drunken militia bands, fortified with assorted drugs from pharmacies [219]. Similarly, there are reports documenting the intoxication involved in the purposive violence of football hooligan crowds [220].

The second issue is how best to estimate AAFs for injury categories? One way would be to apply the same procedure as with chronic disease categories, based on average volume of consumption with risk relations taken from the meta-analyses of Corrao and colleagues [221]. However, this procedure cannot take into consideration the cultural differences between societies in the relationship between alcohol consumption and injury, involving both the physical and social context of drinking and the proportion of heavy drinking occasions in the overall volume of drinking. Particularly for intentional injuries, cultural differences in the meaning of drinking are also involved [222]. For example, Rossow [223] found a considerably greater increase in homicide per litre of alcohol per capita consumption in Nordic countries compared to countries in southern Europe.

To include this important effect of patterns of drinking (see also Gmel G., Kuntsche E., Rehm J., unpublished), we will base the estimates of AAFs for injury categories on the number of heavy drinking occasions as estimated by survey and the RR associated with each heavy drinking occasion. Recently, we have developed the methodology for estimating such AAFs [224,225]; however,

this methodology accounts only for injury effects of drinking on the drinkers themselves. Further adjustments still need to be developed to estimate the overall effect of drinking on injury including, for example, the effect of drunk driving on innocent bystanders who did not consume alcohol.

Quality of alcohol

There are few reviews about the effects of quality of alcohol, and the available reviews are all linked to unrecorded alcohol [12,226–228]; for a definition of unrecorded alcohol see [228,229]. Despite evidence of methanol poisoning outbreaks and some problems with potentially harmful levels of other ingredients such as acetaldehyde [230], ethyl carbamate [231] and coumarin [229], overall there is no evidence of a large impact of unrecorded consumption over and above the effects of alcohol *per se* [11,228]. However, even though research activity has increased in recent years, mainly in countries of the ex-Soviet Union and in Africa, there are still too few systematic large-scale investigations of quality of alcohol in different parts of the world to conclude definitively that quality of alcohol does or does not have a significant impact on health.

DISCUSSION

The present analyses are consistent with previous conclusions that the average volume of alcohol consumption is associated with increased risk for many disease outcomes. They also confirm the protective role of light to moderate drinking with certain diseases, and clarify that this protection only occurs if the pattern of average light–moderate drinking does not include episodes of heavy drinking. In addition, heavy drinking was found to add additional risk to that of average volume for certain disease and injury categories. While these findings provide a strong basis for establishing the importance of alcohol consumption for public health, a number of methodological issues and research gaps prevent more precise estimates and a greater understanding of the relationship between alcohol consumption and disease/ injury. In particular, future research needs to address the role of drinking pattern, use better measures of exposure and outcome and use stronger research designs and more representative samples.

First, it is probable that additional disease outcomes are influenced by a drinking pattern that includes episodes of heavy drinking. However, there is still relatively little focus upon drinking patterns in medical epidemiological research to date, and many potential links have not yet been explored. For many chronic disease outcomes, no research has yet been conducted to examine the impact of other dimensions of alcohol consumption besides average

volume. In addition, although there are now studies in which drinking patterns were explored, no standardized measure of drinking pattern has been adopted, thus making comparisons and pooling of studies difficult [Gmel G., Kuntsche E., Rehm J., unpublished].

Secondly, in addition to a bias in the literature that does not allow a clear separation of the effects of drinking pattern from those of overall consumption, there are other measurement problems in alcohol epidemiology that affect the interpretation of findings. Typically, cohort studies have measured alcohol consumption at just one point or period in the respondent's life. In particular, even though it has been argued and demonstrated convincingly that separating ex-drinkers from life-time abstainers or very light drinkers is essential for identifying both beneficial and detrimental effects [133], many studies in medical epidemiology continue to fail to make this crucial distinction. Furthermore, aside from not being able to capture variability in consumption (see above), many of the largest cohorts used a single-item semi-quantitative food frequency questionnaire, which depicts either frequency or volume of consumption depending upon the answer category. These and other problems have long been recognized [232–234], but are still overlooked in much of the relevant research. In addition, measurement of alcohol consumption is not always in line with theoretical assumptions. For example, studies postulating accumulated volume as causally relevant for the disease outcome assess average volume of alcohol at baseline only, and do not include measures of alcohol consumption during the theoretically relevant time-period (e.g. cumulated alcohol intake in the 6 years before the outcome as a relevant period for some cancers). Similarly, studies postulating blood alcohol concentration (BAC) as a causally relevant measure often measured usual alcohol consumption, but not quantity of alcohol consumed at the specific occasion of incidence.

On the outcome side, outcomes such as chronic disease end-points are measured poorly—often only by self-report—and there is often a lack of control for relevant non-substance use-related confounders in many studies in alcohol epidemiology specifically (as distinct from general medical epidemiology). Clearly, alcohol epidemiology needs to improve dramatically in outcome measurement in order to obtain better estimates of the relationships between alcohol consumption and disease risks.

The effects of these problems for the final estimates of alcohol-attributable burden are not clear. Analyses for some European countries have shown that the volume indicator had about twice as much variance explained as the patterns indicator, independent of each other [235]. This is probably an underestimate, but we will know the real numbers only when there are studies combining

better exposure measures of alcohol epidemiology with state-of-the-art outcome measures. Determining the relative importance of volume and patterns of drinking is not only crucial for understanding the aetiology of disease and injury, but also for tailoring prevention measures [236].

Thirdly, a greater understanding of the relationship between alcohol consumption and adverse outcomes is hampered by the use of weak study designs. In particular, most of the underlying evidence, even if exposure and outcomes are measured properly, is based upon non-experimental studies (e.g. case–control or cohort studies). There are limitations to such study designs, as is indicated clearly by the recent failures to confirm the protective effect of various antioxidants on mortality which had been found in observational studies. In contrast to the observational studies the intervention trials with placebo control groups showed no protective effect, and even some indication of a detrimental effect [237]. This is a limitation that is unlikely to be overcome, however, because long-term intervention trials with alcohol are problematic for a number of reasons, and long-term placebo control groups are impossible. Thus, plausible mechanisms from experimental and clinical studies remain an essential aspect of interpreting epidemiological findings and such studies warrant further development. As has been argued before [45], one way to settle the question concerning a true causal impact of alcohol would be to conduct trials in the tradition of Kalichman and colleagues [238,239], with populations with a high risk of HIV infection, such as clients in clinics for sexually transmitted disease in countries with high HIV prevalence, and determine whether proven effective interventions for problem drinking do, in fact, lower the infection rate.

Fourthly, the sampling used in many cohort studies is problematic for studying alcohol. Many cohort studies are restricted to established market economies, and cohorts are selected typically for ease of follow-up and the resulting high retention rate. As a result, many samples used for cohort studies are comprised of nurses, medical doctors, other health professionals, members of the American Cancer Society or other middle to upper middle-class professionals. While such cohorts may have enough variation in average volume of drinking for analyses, they are unlikely to have enough variation in terms of patterns of drinking and potential moderating life-style factors.

Finally, we would like to comment on the new systematic reviews and meta-analyses conducted by our group that are referenced in this paper. We believe that the current effort has been the most comprehensive and systematic to date to examine the relationships between alcohol consumption and disease/injury. Although we have controlled systematically for quality of the analyses by conducting inter-rater studies on random subsamples, there will be errors. However, all the meta-analyses will be published in peer-reviewed journals, including full specification of included articles for each disease/injury condition, the full methodology and the statistical model, so that all steps can be criticized and improved upon via the usual scientific procedures of replication and additional analyses.

In summary, there are limitations to our current ability to estimate the disease burden of alcohol. The CRA can only try to develop the best possible estimates given the current state of knowledge. It is likely that new confounders will be found for some of the relationships described above and, as new evidence emerges, there will be additions to and deletions from the list of alcohol-related disease and injury categories. None the less, these limitations cannot change the overall conclusion that alcohol is related to many disease outcomes, both chronic and acute, and causes a considerable part of the global burden of disease [65].

Declarations of interest

None.

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