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Alcohol and Human Health: What Is the Evidence?

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Abstract

Alcohol consumption has long been a part of human culture. However, alcohol consumption levels and alcohol consumption patterns are associated with chronic diseases. Overall, light and moderate alcohol consumption (up to 14 g per day for women and up to 28 g per day for men) may be associated with reduced mortality risk, mainly due to reduced risks for cardiovascular disease and type-2 diabetes. However, chronic heavy alcohol consumption and alcohol abuse lead to alcohol-use disorder, which results in physical and mental diseases such as liver disease, pancreatitis, dementia, and various types of cancer. Risk factors for alcohol-use disorder are largely unknown. Alcohol-use disorder and frequent heavy drinking have detrimental effects on personal health.

INTRODUCTION

Alcohol has been produced and consumed for a very long time, making alcohol "the best known and most used means of altering human consciousness" (Marshall 1979, p. 2). Some of the oldest indications of the production and consumption of alcoholic beverages date back to the seventh millennium before Christ (McGovern et al. 2004). Alcohol has been consumed as part of rituals and religious occasions but also as a safe, nutritious, and healthy beverage, as it has antimicrobial properties and contains calories. However, alcohol is a toxic substance; it is not produced by the body and is poisonous in high concentrations.

Genetic changes, such as gene duplications and mutations, have provided humans with a more efficient set of alcohol-degrading enzymes than other species have (Carrigan et al. 2012). These genetic changes allowed humans to consume partly fermented fruits and process alcohol produced by their own intestinal microbiomes. Also, this more efficient detoxification may have enabled the consumption of alcoholic beverages as an alternative to water.

Most people consume and enjoy some alcohol, and in the Western world alcohol forms a common constituent of the diet. However, consumption levels and drinking patterns vary greatly, and a significant portion of the population abuses alcohol, which causes problems for both individual and societal health. This review provides an overview of the associations between alcohol consumption and health. Both the beneficial health aspects of moderate drinking habits and the detrimental health effects of alcohol abuse are discussed. The main focus is on those relations that are substantiated by scientific evidence.

FOOD SCIENCE APPROACHES TO MODULATING THE IMPACTS OF ALCOHOL CONSUMPTION

Alcoholic Beverages

Alcoholic beverages are produced in three main groups, i.e., beer, wine, and distilled spirits. Beer is typically produced from grains, wine is produced from grapes, distilled spirits are produced by concentrating via distillation the alcohol content of wines or other fermentation products. The alcohol content of beer, wine, and distilled spirits is typically around 5% (v/v), between 12% (v/v) and 15% (v/v), and 30–40% (v/v), respectively.

Alcohol (ethyl alcohol or ethanol) is produced using yeast fermentation to break plant and fruit sugars down into ethanol and carbon dioxide. Alcohol is a colorless, volatile fluid with a density lower than water (~0.8 g/mL). Because ethanol is hygroscopic, it is usually not 100% pure; the most commonly used highest purity is 96%. The chemical structure is characterized by a simple carbohydrate structure of two carbon atoms, one of which is coupled to a hydroxyl group.

Alcoholic beverages mainly contain alcohol and water, along with low quantities of vitamins and minerals and other nutrients such as proteins, carbohydrates, and fats. Because alcoholic beverages provide energy but hardly any other nutrients, they are not considered an essential part of the human diet and are often referred to as empty calories. However, one gram of alcohol contains approximately 7 kcal (~28 kJ) of energy, which is high compared to the energy contents of carbohydrates (4 kcal/g) and proteins (4 kcal/g).

The size of a serving of alcohol varies depending on the country. For example, a standard glass of wine, beer, and distilled spirits in the Netherlands contains approximately 10 grams of alcohol, whereas a standard glass in the United Kingdom contains 8 grams and in the United States it contains 14 grams. Volume or grams of pure alcohol consumed is preferred to make studies more comparable.

Beverage type has been proposed to be relevant because red-wine-drinking countries, such as France, have lower cardiovascular mortality while having a diet relatively rich in saturated fats

compared to other European countries. This so-called French paradox (Renaud & de Lorgeril 1992) was attributed to the beneficial compounds, such as polyphenols and resveratrol, in red wine that have antioxidant capacity and other beneficial health effects. These health effects are illustrated in in vitro and in vivo animal research, but they are less well-established in humans (Fernandes et al. 2017). Alternatively, epidemiological studies suggest that wine drinkers may have better dietary and drinking patterns than do other drinkers (Tjonneland et al. 1999). Alcohol appears to be a major factor causing beneficial effects when consumed in moderation and a major factor causing detrimental effects when consumed in excess (Klatsky 2015).

Nonalcoholic Beverages

Negative impacts of alcohol consumption may be prevented by consuming low alcohol or nonalcoholic beverages. These beverages fit an emerging trend toward foods with healthy features. Nonalcoholic beverages may be consumed when alcohol is a short-term risk, e.g., when driving, when operating machinery, and before physical activity, but also when alcohol is a long-term risk, e.g., during pregnancy or when breastfeeding. The definitions of alcohol-free and low-alcohol beverages are not fixed. In European countries, the alcohol content in alcohol-free beer is restricted but varies between 0.05% (v/v) in the UK and 1.2% (v/v) in France. In the US, near-beer, or nonalcoholic beer, contains less than 0.5% (v/v) alcohol, and alcohol-free beer contains less than 0.05% (v/v) alcohol.

Nonalcoholic beverages, specifically nonalcoholic beer, may be produced by a large variety of technologies, which could be roughly divided into biological methods and physical methods (Brányik et al. 2012). Biological methods basically modify the brewing process so that fermentation is limited. These methods include the use of special yeasts that cannot ferment specific sugars and therefore limit alcohol production. Alternatively, normal fermentation may be stopped early in the process by, e.g., low temperatures or removing the yeast. Physical methods use evaporation and membrane technology (dialysis) to reduce the amount of alcohol in regular beers.

The aroma and taste of nonalcoholic beverages may differ from the fully fermented counterparts. Such differences depend on the production method. Nonalcoholic beverages produced by physical methods may have less body and a low aromatic profile. Nonalcoholic beverages produced by biological methods may have a sweet and worty off-flavor.

The health impact of the recently introduced nonalcoholic beverages is largely unknown. Nonalcoholic beverages may contribute to a decrease in the average amount of alcohol consumed. Research into their preventive effects on alcohol-related problems and on overall health is limited.

CONSUMPTION LEVEL

Worldwide consumption in 2010 was equal to 6.2 liters of pure alcohol consumed per person aged 15 years or older per year (WHO 2014). Approximately 25% of the alcohol consumed was homemade or illegally produced. Alcohol consumption is widespread. Abstention rates are low (~20%), especially in high-income countries such as the United States and those in Western Europe. Abstention rates are higher (up to ~90%) in countries with large Muslim populations. Men used to drink more than women in most countries. However, this difference is disappearing, as can be best observed among young adults (Slade et al. 2016).

Consumption levels vary greatly between countries. The world's highest alcohol consumption levels are found in the developed world. These countries, however, do not always have the highest incidences of alcohol-related problems and high-risk drinking. Western European countries have some of the highest consumption levels, but their alcohol-attributable mortality rates are low. This

is in contrast to some Eastern European countries where alcohol consumption is also high, but their alcohol-attributable mortality rates are high.

Binge drinking: a pattern of drinking that brings blood alcohol concentration levels to 0.08 g/dL. This typically occurs after four drinks (56 g alcohol) for women and five drinks (60 g alcohol) for men over approximately two hours

BAC: blood alcohol concentration

ADH: alcohol dehydrogenase

DRINKING PATTERN

Apart from consumption level, drinking patterns are also relevant to health. Over the past several decades, various terms have been used to indicate drinking patterns, or categories of alcohol consumption, e.g., light drinking, moderate drinking, heavy drinking, binge drinking, hazardous drinking, excessive drinking, and alcohol abuse. These categories more or less indicate alcohol consumption patterns but are not consistently applied or well-validated. The terms binge drinking and heavy drinking are operationalized in the United States as four or more and five or more standard drinks per occasion for women and men, respectively. These quantities are also used as indicators for nonproblematic (fewer than 4 drinks, i.e., <56 g alcohol, or fewer than 5, i.e., <70 g alcohol) versus problematic (more than four or five) drinking. There is little evidence, however, for these thresholds as indicators for problem drinking (Pearson et al. 2016).

The meaning of the term moderate drinking also varies between countries and institutions. According to the Dietary Guidelines for Americans 2015–2020, moderate drinking is up to 1 drink per day for women and up to 2 drinks per day for men (DHHS 2018), corresponding to 14 g alcohol per day on average for women and 28 g alcohol per day on average for men. It appears to be better for your health to spread these quantities evenly over the week than to imbibe the full quantity once a week (Mukamal et al. 2003).

The term responsible drinking focuses on adherence to certain rules. An important rule is to not drink under specific conditions, including while or just before driving, during pregnancy, while taking specific medication and while underage. Responsible drinking also includes following the official moderate drinking guidelines.

ALCOHOL METABOLISM AND SHORT-TERM EFFECTS

Alcohol Metabolism

Alcohol is absorbed into the blood from the gastrointestinal tract by passive diffusion. Alcohol absorption starts in the stomach, but the majority takes place in the small intestine. Absorption of alcohol is usually at its maximum 30–45 minutes after consumption.

Blood alcohol concentration (BAC) is determined by a number of factors. The most important factors are the dose consumed, gender, and recent food intake. BAC rises to higher levels by consuming larger volumes or higher-percentage alcoholic beverages. Alcohol is distributed throughout the body and is mainly found in blood and other bodily fluids. When drinking the same quantity of alcohol, women usually reach a higher BAC than men because of their lower overall percentage of body water and average body weight compared to men. Similarly, body water is reduced in the elderly, leading to a relatively higher BAC. Another even more important factor determining BAC is recent food intake. The same amount of alcohol can produce a BAC as much as 50% lower in a person who has recently eaten compared with a person who is fasting.

BAC is not constant: The balance between the absorption and breakdown of alcohol determines how BAC changes over time. The majority of the alcohol is broken down or eliminated by the liver (Cederbaum 2012), and less than 3% is excreted through sweat, urine, and breath. The liver detoxifies alcohol into acetate, which can be utilized in the citric acid cycle, in two steps. Alcohol elimination is typically driven by specific alcohol-oxidizing enzymes when drinking in moderation but may be stimulated further by nonspecific enzymes when drinking in excess. The most important and specific alcohol-oxidizing enzyme is alcohol dehydrogenase (ADH), which

converts alcohol into acetaldehyde. The highly toxic acetaldehyde is converted efficiently by the enzyme acetaldehyde dehydrogenase (ALDH) into the harmless acetate.

ADH and ALDH occur in various forms, so-called iso-enzymes. Iso-enzymes are based on genetic variants (alleles) and have different enzymatic activities. The genetic variants determine the individual metabolic capacity for alcohol elimination. In general, it is assumed that alcohol is eliminated at a rate of 80–130 mg of alcohol per kg body weight per hour, which corresponds to approximately 6–10 grams of alcohol per hour. Iso-enzymes vary not only per individual but also per organ. Stomach ADH, for example, is different from liver ADH (Lee et al. 2006).

Alcohol concentrations in blood are usually lower than those calculated on the basis of consumed dosage and body water content. This phenomenon is due to so-called first-pass metabolism. First-pass metabolism occurs when uptake of alcohol is slowed down by food intake. Carbohydrate-rich meals slow down alcohol uptake and fatty meals slow down the peristaltic movements in the gastrointestinal tract, resulting in lower peak BAC (Pikaar et al. 1988). Once absorbed, alcohol passes through the liver, which is where the first round of elimination takes place before alcohol reaches the systemic circulation, where BAC is usually assessed. Possibly, the liver is metabolically more active in the postprandial state as well. Also, stomach ADH may contribute somewhat to first-pass metabolism.

In addition to the specific ADH and ALDH enzyme systems, nonspecific enzyme systems contribute to ethanol elimination specifically when consumption is frequent and high. One important system for alcohol elimination is catalase, which normally breaks down hydrogen peroxide. Another system is the microsomal ethanol-oxidizing system (MEOS), which consists of the cytochrome P450 isoform CYP2E1 (Comporti et al. 2010).

A small fraction of ethanol (<0.1%) undergoes nonoxidative metabolism, yielding ethyl glucuronide, ethyl sulfate, phosphatidylethanol, and fatty-acid ethyl esters. Nonoxidative ethanol metabolites persist for much longer than ethanol itself and may be used as biomarkers for alcohol consumption (Heier et al. 2016).

ALDH: acetaldehyde dehydrogenase

Moderate alcohol consumption: one drink (or 14 g alcohol) per day for women and two drinks (or 28 g alcohol) per day for men

Short-Term Effects

Alcoholic beverages are consumed because alcohol changes our behavior and affects our well-being. These changes occur when alcohol reaches the brain and temporarily affects the transduction of signals. The behavioral effects of alcohol correlate with BAC. In general, one experiences

- increased relaxation and sociability at BACs up to 0.05 g/dL;
- impaired muscle coordination and, consequently, impaired driving skills at BACs above 0.08 g/dL;
- drowsiness and impaired judgment, vision, and balance at BACs above 0.15 g/dL;
- slurred speech, apathy, and lethargy at BACs above 0.25 g/dL;
- unconsciousness, incontinence, and death at BACs higher than 0.4 g/dL; and
- lethality at BACs higher than 0.45 g/dL.

It appears that, generally speaking, alcohol consumption slows down the brain. The most important short-term changes after moderate alcohol consumption are in the neurotransmitters gamma-aminobutyric acid (GABA), glutamate, dopamine, and serotonin. Alcohol stimulates GABA activity and suppresses glutamate activity, resulting in relaxation, calmness, pleasure, and stress reduction. Alcohol also induces a surge of serotonin and stimulates dopamine release, intensifying the pleasurable effects.

ALCOHOL CONSUMPTION AND TOTAL MORTALITY

CVD: cardiovascular disease

Alcohol consumption and health are related. Epidemiological research describes the associations between alcohol consumption and various health outcomes, including mortality. Mortality is considered especially important because it includes all causes of death, including diseases, accidents, and other causes of death (e.g., via suicide, violence, intoxication) occurring in the short-term as well as in the long-term.

The association between alcohol consumption and mortality is a J-shaped curve. Those that do not drink have a baseline mortality, which is the reference risk of dying; their relative risk is set at 1. Light to moderate drinkers have a lower risk of dying than nondrinkers; their relative risk is below 1. Heavy drinkers have an increased risk of dying; their relative risk is well above 1. Recent meta-analyses indicate a reduction of overall mortality of up to 15% at consumption levels higher than 0 g alcohol per day and lower than 30 g alcohol per day (Ferrari et al. 2014, Jayasekara et al. 2014).

This J-curve has been criticized for many decades. Initially, the notion was put forward that those in the nondrinkers' group, referred to as teetotalers, were persons that have had a history of alcohol abuse, so-called sick quitters (Shaper et al. 1988). These persons contribute to higher mortality in the control group. This criticism has led to a reevaluation of the data after excluding former drinkers. The association between alcohol consumption and mortality remained the same (Di Castelnuovo et al. 2006). More recently, sick quitters were again suggested to explain the lowered risk in the J-curves (Fillmore et al. 2007). These conclusions, however, were obtained after selecting a small fraction of the huge number of studies available and using an alternative definition of teetotalers, e.g., those who abstained from drinking alcohol for at least 30 days prior to the interview (Poikolainen 2008). This control group may not be representative of nondrinkers. A recent meta-analysis suggested that sick quitters may explain the J-curve (Stockwell et al. 2016). Interestingly, an initial analysis by these authors confirmed the well-documented J-curve. The J-curve again disappeared only after the authors selected a small number of studies.

Recently, a *Lancet* paper concluded that the threshold of alcohol consumption for the lowest risk of all-cause mortality was approximately 100 g/week and urged a lowering of the currently recommended drinking guidelines (Wood et al. 2018). In two commentaries, it was pointed out that the authors based their conclusions on drinkers only; the nondrinking control group was eliminated from their analysis. It is difficult, however, to establish whether moderate drinking has an effect compared to abstinence when nondrinkers are removed from the comparison (Astrup et al. 2018, Schernhammer 2018).

Another recent *Lancet* paper concluded that at the population level the detrimental effects of alcohol offset the protective effects occurring at low levels of intake (GBD 2016 Alcohol Collab. 2018). The authors of this study used estimates of alcohol-attributable deaths and disability-adjusted life years as their methodology. However, this paper was criticized because total mortality was not considered (Di Castelnuovo et al. 2019) and included several methodological flaws (Abat et al. 2019, Astrup & Estruch 2019, Shield & Rehm 2019).

Unfortunately, observational evidence will never provide conclusive evidence on this widely documented association. It is true that confounding factors, such as socioeconomic status (Jones et al. 2015) and drinking pattern (Greenfield 2016), are sometimes hard to correct for. Therefore, evidence from scientific disciplines other than epidemiology, such as nutrition interventions, is needed to substantiate the observed associations (Mukamal et al. 2016).

ALCOHOL CONSUMPTION AND HUMAN HEALTH

Alcohol consumption is associated with many diseases (GBD 2016 Causes Death Collab. 2017), including cardiovascular diseases (CVDs), type-2 diabetes, dementia, and cancers from moderate

alcohol consumption and alcoholic liver disease and malnutrition, CVDs, pancreatitis, cancers, diseases of the brain, and fetal alcohol spectrum disorder (FASD) from alcohol-use disorder (AUD). Some of the highly prevalent and burdensome diseases like depression, chronic obstructive pulmonary disease, and lower respiratory infections have not been studied in detail in relation to alcohol consumption.

Moderate Alcohol Consumption

The health effects of alcohol strongly depend on dosage. The effects of moderate alcohol consumption on some of the major diseases occurring in the Western world are discussed below. Moderate alcohol consumption is mostly associated with some beneficial health effects, whereas alcohol abuse leads to negative health effects.

Cardiovascular diseases. CVD is the leading cause of death in the United States and the second leading cause of death in Europe. Epidemiological research indicates that lifestyle is an important determining factor for the disease. The Nurses' Health Study showed, as was confirmed in many additional epidemiological studies, that healthy diets combined with smoking avoidance, regular physical activity, normal body mass index maintenance, and moderate alcohol consumption may prevent most (~80%) cardiovascular events (Yu et al. 2016).

There are several CVDs, and they vary in etiology and their association with alcohol consumption. Coronary heart disease (CHD), one of the most prevalent CVDs, is associated with alcohol on a J-curve. The association between light-to-moderate alcohol consumption and stroke is less clear and somewhat controversial, as the association depends on the type of stroke. Recent meta-analyses indicate that moderate alcohol consumption is protective against overall stroke and ischemic stroke (Larsson et al. 2016, Ronksley et al. 2011) but not for hemorrhagic stroke (Larsson et al. 2016). These meta-analyses also showed that alcohol consumption between 2.5 and 60 g alcohol per day is associated with a risk reduction of 24–34% for various outcomes including CVD incidence and mortality and CHD incidence and mortality.

This risk reduction is relative to the existing risk. For example, 1 in 3 or 4 persons will die of CVD in the United States and Europe. If this 25–33% CVD mortality risk is reduced 24–34% by moderate alcohol consumption, CVD mortality risk roughly decreases to approximately 20%, which corresponds to 1 in 5 people dying of CVD. Similarly, moderate alcohol consumption is associated with a reduction in risk of heart failure of approximately 20% (Larsson et al. 2015). However, the immediate risk, i.e., the risk of a cardiovascular event within 24 hours after drinking even in moderation, is increased (Mostofsky et al. 2016). All the above-mentioned beneficial effects concern drinking in moderation, which means regular drinking (almost on a daily basis) at moderate consumption levels. Binge drinking changes these relationships considerably and may increase the risk for CHD by 45% (Roerecke & Rehm 2010).

The association between alcohol consumption and CVD has been extensively described and the mechanisms of action have been elucidated in short-term nutrition intervention studies. The main cause of CVD is atherosclerosis, a progressive multistep pathological process that involves vascular wall damage and allows the precipitation of cholesterol mainly as oxidized low-density lipoprotein (LDL) cholesterol. Subsequent calcification and inflammation lead to increased instability of the so-called vascular plaque, ultimately resulting in its rupture and closure of the blood vessel by clotting. LDL cholesterol, its oxidative modification, and its precipitation in the vascular wall are generally accepted as pivotal to the atherosclerotic process. High-density lipoprotein (HDL) cholesterol is also considered important because of its capacity to prevent oxidation of LDL cholesterol and its ability to export cholesterol from the vascular wall, a process called reverse cholesterol transport.

Fetal alcohol spectrum disorder (FASD): heterogeneous spectrum of clinical manifestations in young children caused by maternal alcohol abuse

Alcohol-use disorder (AUD): also known as alcoholism; refers to a problematic pattern of alcohol consumption that leads to a heterogeneous spectrum of clinical manifestations, significant impairment, or distress

CHD: coronary heart disease

LDL: low-density lipoprotein

HDL: high-density lipoprotein

Glycosylated hemoglobulin (HbA1c): indicator of the average blood glucose values over the last 2–3 months

The significance of HDL cholesterol as a biomarker for counteracting the atherosclerotic process has recently been debated (Rosenson 2016, Tariq et al. 2014). The debate originates from some large epidemiological studies that have shown that using niacin or other drugs to increase HDL cholesterol did not reduce the incidence of cardiovascular events (Keene et al. 2014). Although HDL cholesterol is increased, its function in the associated proteins and enzymes responsible for reverse cholesterol transport and antioxidation may be compromised (Femlak et al. 2017). Recently, the association between reverse cholesterol transport and cardiovascular events was shown to be positive in adults initially free from CVD (Rohatgi et al. 2014). This study illustrated the notion that raising the level of HDL cholesterol must be accompanied by improving its functionality.

Nutrition intervention studies have shown that moderate alcohol consumption not only increases HDL cholesterol concentration but also improves HDL functions. One of the improved functions is reverse cholesterol transport (Sierksma et al. 2004d, van der Gaag et al. 2001). Reverse cholesterol transport was increased by moderate alcohol consumption independent of beverage type. HDL-associated paraoxonase activity, an antioxidative enzyme activity (Brites et al. 2017), was increased by moderate drinking as well (Sierksma et al. 2002b, van der Gaag et al. 1999).

Apart from an increase in HDL (Hendriks et al. 1998) and its functions, other processes (van Tol & Hendriks 2001) that may contribute to the prevention of cardiovascular events are beneficially changed. These include decreases in fibrinogen (clotting) and C-reactive protein (inflammation) (Sierksma et al. 2002a), HbA1c and fasting insulin levels (improved glucose homeostasis) (Schrieks et al. 2015), and arterial stiffness (Sierksma et al. 2004a,b). In addition, fibrinolysis (anticlotting) (Hendriks et al. 1994) and adiponectin (improved glucose homeostasis) (Joosten et al. 2008, Sierksma et al. 2004c) levels increase. The contribution of these mediating factors to CVD events was estimated. It was shown that HDL increase, fibrinogen decrease, and improved glucose homeostasis explain the majority of the protective effect (Mukamal et al. 2005). One of the pathways that needs more research is the role of acetate. Acetate produced from alcohol may stimulate energy metabolism (Pownall & Gotto 2016) and prevent CVD (Pownall et al. 2015).

Nutrition intervention studies have been criticized because they are short-term. Therefore, these interventions do not show a heart attack actually being prevented. A long-term intervention is needed to show the effect of drinking and nondrinking on the incidence of CHD events (Mukamal et al. 2016).

Type-2 diabetes. Type-2 diabetes is a frequently occurring metabolic disease (King et al. 1998). The current obesity epidemic has contributed to a dramatic increase in the incidence of type-2 diabetes (Bhupathiraju & Hu 2016). Diabetes leads to excess mortality (Hu et al. 2001) because of the long-term complications of CVDs (Verges 2015) and renal diseases.

Several meta-analyses have described the association between alcohol consumption and diabetes incidence (Baliunas et al. 2009, Koppes et al. 2005, Li et al. 2016); consumption of up to 24–48 g alcohol per day results in a risk reduction of approximately 20–30%. Some meta-analyses suggest that reductions in risk may differ between men and women (Beulens et al. 2012, Knott et al. 2015).

It may even be more important to investigate the association between moderate alcohol consumption and diabetes complications such as CHD because diabetes mortality is caused by these complications. Meta-analyses studying those relations in diabetics showed that diabetics who consume moderate amounts of alcohol had a 30% lower risk of mortality and a 40% lower risk of total and fatal CHD incidence than nonconsumers (Koppes et al. 2006, Solomon et al. 2000).

The physiological changes occurring after moderate alcohol consumption include improved glucose homeostasis, as suggested by decreased levels of HbA1c and decreased fasting

insulin levels (Schrieks et al. 2015), increased levels of adiponectin (Beulens et al. 2007, Sierksma et al. 2004c), decreased levels of fetuin A (Joosten et al. 2014, Ley et al. 2014), and decreased inflammatory status (Sierksma et al. 2002a).

Although some biomarkers may be more predictive of and more causally related to type-2 diabetes incidence than others (Abbasi et al. 2016), these physiological changes are in line with improvement rather than deterioration of the glucose and insulin homeostasis. Because of this, one may expect that moderate alcohol consumption changes physiology in such a way that it is compatible with type-2 diabetes incidence reduction.

Dementia. Dementia, a neurodegenerative condition, is characterized by a progressive cognitive decline that interferes with independence in everyday activities. The disease is expected to become an important contributor to the overall disease burden by 2030 and beyond (Prince et al. 2013). Alzheimer's disease is the most common type of dementia.

Dementia is associated with alcohol consumption. Meta-analyses indicate a protective effect of moderate alcohol consumption on the incidence of dementia (Anstey et al. 2009, Peters et al. 2008). The risk of all types of dementia, including Alzheimer's disease and vascular dementia, was reduced by approximately 25% in moderate alcohol consumers.

Cancers. Cancer is a leading cause of death in the Western world. The overall cancer death rate has fortunately declined since the early 1990s. In addition to significant progress in cancer treatment, more attention is now focused on cancer prevention. Important risk factors for cancer incidence are lifestyle factors (Kerr et al. 2017), e.g., smoking, obesity, infections, physical inactivity, and unhealthy diet. The contribution of smoking (~30%), obesity (~20%), and infections (~15%) to cancer incidence is relatively large. Physical inactivity, an unhealthy diet, and occupational hazards contribute to approximately 5% each. The remaining risk factors contribute even less, with alcohol's contribution being estimated at approximately 3% (Arteaga et al. 2014).

The association of moderate alcohol consumption with breast cancer incidence has long been a topic of research and initially yielded contradictory results. However, a positive linear association between alcohol consumption and breast cancer incidence was obtained after pooling most of the large epidemiological studies. The first meta-analysis indicated an increased risk of approximately 10% for every 10 g of alcohol consumed per day (Smith-Warner et al. 1998). More recent meta-analyses indicate a risk increase of approximately 5% for every 10 g of alcohol consumed per day (Bagnardi et al. 2013, Hamajima et al. 2002, Tjonneland et al. 2007). This risk increase is in addition to the risk that women usually have to get breast cancer. More specifically, depending on genetic factors and environmental factors such as age of menarche, childbearing, and breastfeeding, 1 in 8 women in the United States and Europe develop breast cancer. In addition to this 12.5% risk, a 5% increase means that a woman's risk increases from 12.5% to 13.1%.

An association between colorectal cancer and alcohol consumption has been suggested to occur at drinking levels of 10 g alcohol per day or more (Fedirko et al. 2011, Ferrari et al. 2007). However, others have shown that an increase in colorectal cancer risk could be observed only at consumption levels exceeding moderate amounts as defined by the US dietary guidelines, i.e., at consumption levels exceeding 30 g alcohol per day (Bagnardi et al. 2015, Klarich et al. 2015). A meta-analysis studying the association between alcohol consumption and colorectal cancer death found an increased mortality risk at alcohol consumption levels higher than 50 g alcohol per day (Cai et al. 2014).

Although the association of heavy alcohol drinking with esophageal cancer has been well established, the association with light and moderate alcohol drinking has been less well substantiated. Because smoking is an important risk factor, studies focusing on never-smokers who drink may not

be confounded by smoking. A review of these studies by Islami et al. (2011) showed that light alcohol drinking (<12.5 g alcohol per day) was associated with an increased risk (~40%) of esophageal cancer in smokers. Among never-smokers, the risk, however, was approximately 25% lower in light drinkers as compared to nondrinkers. Light alcohol consumption appeared to be associated with esophageal cancer mainly in studies in Asia, which suggests a possible role of genetic susceptibility factors.

Light alcohol consumption: consuming alcohol at less than moderate alcohol consumption levels

***Diagnostic and Statistical Manual of Mental Disorders* version 5 (DSM-5):** principal psychiatric taxonomic and diagnostic tool

Similarly, lung cancer is clearly associated with smoking. Several studies have looked into the association between alcohol consumption and lung cancer, most of which included smokers. Recently, a pooled analysis among never-smokers (Fehringer et al. 2017) showed that low to moderate alcohol consumption (0–20 g alcohol per day) is inversely associated with lung cancer risk and induces a risk reduction of approximately 20%.

High concentrations of locally generated acetaldehyde, the first metabolite of ethanol and a more potent carcinogen than ethanol, may play a role in a number of cancers like esophageal cancer. However, acetaldehyde probably does not play a role in, for example, breast cancer. Hormonal changes have been postulated to play a role in alcohol-mediated breast cancer etiology (Brooks & Zakhari 2013). Mechanisms of action for various cancer types by alcohol consumption have not yet been fully established.

Alcohol-Use Disorder

AUD represents the most recent term for a heterogeneous spectrum of clinical manifestations. Previously, alcohol abuse was considered a disorder different from alcohol dependence. The recent fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) has abolished this distinction and defined AUD as a cluster of behavioral and physical symptoms with a continuum or spectrum of severity (APA 2013). Also, the DSM-5 has introduced "craving or a strong desire or urge to use alcohol" as a new criterion. There are eleven criteria for AUD diagnosis that can be divided into several groups, namely impaired control, social impairment, and risky use as well as pharmacological criteria such as the need to drink more to get the same effect and withdrawal symptoms. A minimum of two positive criteria is necessary to establish a diagnosis of AUD. The number of positive criteria indicates the severity of the disease.

In 2004, the World Health Organization (WHO) estimated the global lifetime prevalence of AUD between 0% and 16%, with the highest rates found in Eastern Europe (WHO 2004). More recent estimates based on DSM-5 criteria for the United States were even higher: 13.9% and 29.1% for twelve-month and lifetime prevalence of AUD, respectively (Grant et al. 2015).

The more severe forms of AUD increase an individual's risk of mortality at least three- to fourfold (Laramee et al. 2015). AUD can underlie a constellation of alcohol-related comorbidities, including psychiatric, neurologic, cardiovascular, gastrointestinal, and hematologic diseases.

Because AUD is such a common disorder, it has been recommended that clinicians routinely ask patients about their alcohol use. The tools for fast detection of AUD are numerous and include the CAGE questionnaire [CAGE is an acronym of its four questions: Have you ever felt you needed to Cut down on your drinking? Have people Annoyed you by criticizing your drinking? Have you ever felt Guilty about drinking? Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover? (Ewing 1984)], Michigan Alcoholism Screening Test (Shields et al. 2007), ten-question Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al. 1993) or its shortened versions, and other one- and two-item screening questions. It appears that short screening questions have value but should be followed by a second, more detailed assessment to determine the need for intervention or referral (Mitchell et al. 2014).

Many clinical parameters have been proposed as biomarkers for the identification of AUD. Biomarker-based diagnosis of AUD, however, is far from ideal because the sensitivities and specificities of these markers have remained controversial. Markers such as alanine transaminase (ALT) and gamma-glutamyltransferase (GGT), which are both sensitive to alcohol consumption, are also affected by, e.g., obesity-related morbidity (Niemela 2016).

The most frequently used marker for excessive alcohol consumption is GGT, which has a specificity and sensitivity of approximately 70% at consumption levels above 50 g/day (Seitz 2006). Other markers with lower specificity and sensitivity include mean corpuscular volume and carbohydrate-deficient transferrin. Some of alcohol's metabolites, including fatty-acid ethyl esters and ethyl glucuronide, can be used as a marker for long-term alcohol consumption.

The clinical manifestations resulting from AUD are many and include alcoholic liver disease, malnutrition, CVDs, chronic pancreatitis, cancers, diseases of the brain like Wernicke-Korsakoff syndrome and alcohol-related dementia, and FASD as well as other comorbidities such as depression (Lai et al. 2015), infectious diseases, kidney disease, and infertility (Costin & Miles 2014, Levitsky & Mailliard 2004, Molina et al. 2014).

Alanine transaminase (ALT): a liver enzyme evaluated in blood to determine liver damage and alcohol abuse

Gamma-glutamyltransferase (GGT): a liver enzyme evaluated in blood to determine liver damage and alcohol abuse

Risk factors for alcohol-use disorder. Risk factors for AUD include internal factors, such as genetic factors, and external factors, such as environmental factors; external factors may be more important. Epigenetics seems to play a role in linking these two factor types during adolescence or later in life.

It is well-established that those with a positive family history of alcoholism are at increased risk for developing AUD (Lieb et al. 2002). Identification of specific genes associated with such an increased risk has, however, turned out to be challenging (Claus et al. 2011). It is now recognized that genetic risk for alcoholism may be multifactorial. Several genetic predispositions have been proposed. These include increased or decreased physical sensitivity to alcohol, reward sensitivity (Andrews et al. 2011, Van Leijenhorst et al. 2010), and self-control difficulties (Leeman et al. 2014). Additional genetic predispositions include a constellation of personality characteristics such as impulsivity (Villafuerte et al. 2012), sensation seeking (Weiland et al. 2013), disinhibition, and an impaired ability to easily learn from mistakes (Mayfield et al. 2008). These personality characteristics predispose to a broad range of dependencies. Several genetically influenced syndromes, primarily schizophrenia and manic depressive disease, are associated with an enhanced risk for dependencies, such as alcohol and drug dependencies (Koskinen et al. 2009, Stephen Rich & Martin 2014).

The genes that are considered to contribute the most to AUD predisposition are the genes coding for enzymes involved in alcohol metabolism. The enzymes ADH (which converts ethanol into acetaldehyde) and ALDH (which converts acetaldehyde into acetate) have been investigated extensively. Less active *ALDH* gene forms (alleles) may lead to higher acetaldehyde concentrations and more serious adverse effects, such as facial flushing, nausea, and a rapid heartbeat, explaining the protective association with AUD. The alleles *ADH1B*2*, *ADH1B*3*, *ADH1C*1*, and *ALDH2*2* have been associated with lower rates of alcohol dependence (Edenberg 2007). The prevalence of these alleles differs among ethnic groups: *ADH1B*2* is found frequently in northeast Asians and occasionally in Caucasians, *ADH1B*3* is found predominantly in people of African ancestry, and *ALDH2*2* is found almost exclusively in northeast Asians. Differences in the prevalence of these alleles may account at least in part for ethnic differences in AUD.

External factors contributing to binge drinking, alcohol abuse, and, therefore, AUD include stress (Enoch 2006), childhood experiences, and environment. Stress at an early age has been described as an important factor contributing to substance abuse in general and problem drinking at later ages (Cornelius et al. 2014, Enoch 2011).

Epigenetic mechanisms may mediate gene–environment interactions that play a role in AUD (Schuebel et al. 2016). Epigenetic modifications to DNA change its expression, are reversible, and allow the individual to adapt to a changing environment. Alcohol exposure has been shown to change gene expression, which suggests the involvement of epigenetic mechanisms (Berkel & Pandey 2017, Restrepo et al. 2017).

Also, machine learning was applied to better understand the factors relevant to developing AUD and to construct neuropsychological profiles of alcohol abusers (Whelan et al. 2014). These models appear to be accurate in correctly classifying nondrinkers and binge drinkers. The models also pointed to life experiences, neurobiological differences, and personality as important antecedents of binge drinking (Whelan et al. 2014). It has been noted that the influence of any one feature in isolation is modest. These results underline the multiple causal factors for alcohol misuse and AUD.

Alcoholic liver diseases. It is well established that excess alcohol consumption for decades increases the risk of developing liver disease. Alcoholic liver disease is a direct effect of the toxicity of alcohol and its metabolism and metabolites.

Alcoholic liver disease has a broad clinical spectrum, including steatosis, fibrosis, alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma (Ceni et al. 2014). The pathogenesis of alcoholic liver disease is, however, not well understood. Multiple factors such as gender, obesity (Naveau et al. 1997), and genetics are involved in the progression of alcoholic liver disease, and not all alcoholics develop the full disease spectrum. Some studies report a cirrhosis incidence of approximately 10–15% in alcoholics (Mann et al. 2003). AUD (Rehm et al. 2013) may account for 20–50% of the prevalence of liver cirrhosis.

The earliest response of the liver to long-term alcohol abuse is characterized by steatosis, which is the accumulation of lipids in the hepatocytes. Steatosis is a reversible condition. Alcohol oxidation increases reducing molecules in the cytosol and mitochondria. This increase inhibits the fatty-acid oxidation enzymes and causes steatosis. Also, acetaldehyde may interfere with specific transcriptional activity regulating genes involved in the esterification and export of fatty acids.

Steatosis may progress into hepatic fibrosis, which is still a reversible condition, with continued heavy drinking. Hepatic fibrosis is characterized by increased deposition of components of fibrillar collagen types I and III. Such deposition disturbs the hepatic architecture, leading to portal hypertension. Acetaldehyde is one of the main mediators changing gene expression resulting in hepatic fibrosis (Moshage et al. 1990).

Excessive alcohol consumption causes enteric dysbiosis, resulting in bacterial overgrowth. Enteric dysbiosis increases gut permeability and yields high levels of endotoxin in the circulation. High endotoxin levels induce an inflammatory response in the liver, which contributes to the progression of liver fibrosis to liver cirrhosis. The inflammatory response is usually associated with inflammatory cell infiltration and hepatocellular necrosis, a lesion referred to as alcoholic hepatitis. With continued alcohol abuse, alcoholic hepatitis becomes liver cirrhosis. Histologically, there are no differences between alcoholic cirrhosis and other types of cirrhosis (e.g., obesity induced). Cirrhosis involves the loss of liver cells and irreversible scarring of the liver. Many complications exist with liver cirrhosis, including ascites, bleeding from varices, hepatic encephalopathy, and liver cancer. Liver cirrhosis is the main risk factor for hepatocellular carcinoma. Hepatitis B and C are risk factors for liver cirrhosis as well. The combination of liver cirrhosis and hepatitis leading to hepatocellular carcinoma is common in Asia and sub-Saharan Africa.

Malnutrition. When alcohol replaces food, decreased nutrient intake causes primary malnutrition. Malnutrition is the most frequent complication in alcoholic liver disease, leading to the loss of

skeletal muscle mass and perturbations in energy metabolism (Dasarathy 2016). Also, deficiencies may occur because absorption and digestion of essential nutrients are disturbed. Vitamin deficiencies, mainly of vitamin B1 (thiamine) and C, are commonly observed in AUD (Ijaz et al. 2017). Folate (vitamin B9) and vitamin B12 appear to be affected in many cases as well. All four of these vitamins are important for glutathione production, the principal antioxidant for defense against oxidative liver injury (Halsted 2013). Folate deficiency may lead to anemia, which is frequently observed in AUD.

Heavy alcohol consumption: binge drinking on five or more days in the past month

Thiamine deficiency is the established cause of an alcohol-linked neurological disorder known as Wernicke-Korsakoff syndrome. Thiamine, which plays a critical role in energy metabolism, may also be reduced in alcoholics because of a magnesium deficiency. Some observations suggest that not all persons are equally sensitive to thiamine deficiency and its consequences: Thiamine deficiency may occur in up to 80% of alcoholics, but only approximately 13% of alcoholics develop Wernicke-Korsakoff syndrome (Martin et al. 2003). It is also difficult to correct a thiamine deficiency in alcoholics because alcohol continues to interfere with thiamine absorption and utilization.

Cardiovascular diseases. AUD and long-term heavy drinking may lead to a variety of CVDs. These include alcoholic cardiomyopathy, systemic hypertension, atrial arrhythmias, and stroke (Klatsky 2015).

Cardiomyopathy denotes heart muscle disease. Alcoholic cardiomyopathy indicates that the direct toxic effects of alcohol are involved in the myopathy. A hallmark study evaluating alcoholics that consumed on average more than 200 g of alcohol per day for approximately 16 years indicated that both the heart and skeletal muscle were affected in a dose-dependent manner (Urbano-Marquez et al. 1989).

An association between alcohol consumption and blood pressure elevation was suggested as early as 1915. A more recent meta-analysis indicated that men drinking up to 20 g of alcohol per day had no increased risk of hypertension, whereas an increased risk of hypertension occurred with alcohol consumption higher than 30 g of alcohol per day (Briasoulis et al. 2012). In women, such an increased risk was observed for 20 g of alcohol per day and more.

The risk of atrial arrhythmias increases by approximately 10% even in moderate drinkers (Larsson et al. 2014). Heavy alcohol consumption increases the relative risk of both hemorrhagic and ischemic stroke (Patra et al. 2010). Increasing alcohol consumption consistently increased the risk of hemorrhagic stroke, whereas there was a curvilinear association between alcohol consumption and ischemic stroke, with a protective effect for low to moderate consumption and increased risk for higher consumptions, i.e., more than 3 drinks (36–42 g alcohol) on average per day.

Pancreatitis. Pancreatitis is an inflammatory disorder of the pancreas that leads to a broad spectrum of pancreatic insufficiencies associated with high mortality. Alcohol is the second major leading cause of acute pancreatitis after gallstones. Alcohol is also the most common cause of chronic pancreatitis. Both acute and chronic pancreatitis risk are increased in men and women at consumptions higher than 40 g per day (Samokhvalov et al. 2015).

Cancers. Heavy alcohol consumption and AUD have been associated with an increased risk of cancers of the upper digestive tract, including of the oral cavity, pharynx, larynx, esophagus, and, possibly, stomach. Alcoholics and heavy drinkers also have a higher risk of cancers of the lower digestive tract, e.g., of the liver, pancreas, colon, and rectum. Female breast cancer and male prostate cancer have also been positively associated with heavy alcohol consumption. Consequently, the International Agency on Research on Cancer (IARC) concluded that there is sufficient evidence in

humans for the carcinogenicity of alcohol consumption. Alcohol's contribution to overall cancer incidence is estimated at approximately 3% (Arteaga et al. 2014).

Diseases of the brain. AUD induces complex psychiatric comorbidities, both internalizing disorders, such as mood and anxiety disorders, and externalizing disorders, such as antisocial personality disorder, hyperactivity, and other addictions.

Alcohol addiction. Chronic heavy alcohol consumption may result in addiction through a process called neural adaptation. Neural adaptation changes the response of the brain to alcohol and allows an individual to function normally in the presence of alcohol. One of the possible mechanisms may include permanent changes in the numbers of receptors (see section titled Short-Term Effects) located in areas of the brain associated with addiction.

Wernicke-Korsakoff syndrome. A well-known AUD is the Wernicke-Korsakoff syndrome caused by vitamin B1 deficiency (see section titled Malnutrition). This syndrome typically consists of two components, a short-lived and severe condition called Wernicke's encephalopathy and a long-lasting and debilitating condition known as Korsakoff's psychosis (Martin et al. 2003). Wernicke's encephalopathy is an acute life-threatening neurologic disorder caused by thiamine deficiency. Some symptoms include mental confusion, paralysis of the nerves that move the eyes, and an impaired ability to coordinate movements, particularly of the lower extremities. The majority of alcoholics with Wernicke's encephalopathy develop Korsakoff's psychosis, characterized by behavioral abnormalities and memory impairments. These patients have difficulty acquiring new information and remembering old information.

Alcohol-related dementia. Alcohol-related dementia occurs with an incidence of approximately 1% in both early-onset and late-onset dementia (Cheng et al. 2017). Alcohol-related dementia is difficult to recognize because its pathophysiological profile is not distinct from other dementias. It is also unclear whether dementia can be caused by the direct neurotoxic effects of alcohol. It is difficult to disentangle the effect of alcohol from other underlying pathologies because there are many confounding factors that often accompany the lifestyle of alcohol abusers.

Fetal alcohol spectrum disorder. The adverse effects of alcohol on the developing fetus were first described in the late 1960s. The most severely affected children were observed to have a pattern of malformation initially termed fetal alcohol syndrome (FAS). Later, it became clear that the disabilities associated with heavy alcohol use by the mother represent a spectrum from mild to severe disorders currently referred to as FASD (Hoyme et al. 2016). These disabilities include congenital anomalies, such as growth deficiency and facial malformations such as short palpebral fissures, smooth philtrum, and thin vermilion border of the upper lip. The primary and most serious manifestations of the teratogenic effects of alcohol, however, are in changes in brain structure and/or function diagnosed as cognitive and behavioral deficits. In addition, other physical disabilities may occur, including dysplasia of the cardiac, skeletal, renal, ocular, auditory, and other systems. FASD currently includes FAS, partial FAS, alcohol-related neurodevelopmental disorder, and alcohol-related birth defects. FASD prevalence varies widely between communities, ranging from 0.1% in the Eastern Mediterranean Region to 11% in South Africa, with an overall world average of 0.8% (Lange et al. 2013).

The consequences of maternal alcohol use during pregnancy depend on, among other factors, the amount and pattern of alcohol consumption. Animal studies found that binge-like drinking patterns, in which the fetus is exposed to high BACs over relatively short periods of time, are

particularly harmful. Long-term studies in humans have confirmed that children of binge-drinking mothers exhibited especially severe cognitive and behavioral deficits. Because FASD is preventable and no safe limit for alcohol drinking in pregnancy may exist, mothers are advised not to drink at all during pregnancy or when trying to get pregnant.

Alcohol-use disorder treatment. Although AUD is a frequently occurring disorder (Grant et al. 2015), only a minority of patients gets treatment (Gastfriend 2014). Several medications are FDA approved (acamprosate, disulfiram, oral naltrexone, extended-release injectable naltrexone) for treatment of AUD. Nonapproved antipsychotics, antidepressants, and anticonvulsants are also used to treat AUD. However, all of these medications are only modestly effective. Medications should be prescribed as part of a treatment that includes psychosocial therapies and social support. One of the problems is that AUD is a heterogeneous disease, and therefore no medication works for all in every situation. Using the genetic background of a person may improve treatment efficacy in the future (Seneviratne & Johnson 2015).

SUMMARY POINTS

1. Alcohol has been consumed for a very long time, and its types and patterns of consumption vary widely. Moderate alcohol consumption is defined as one US glass (14 g alcohol) per day for women and two US glasses (28 g alcohol) per day for men.
2. Light and moderate drinkers have a reduced risk for mortality, whereas heavy drinkers, binge drinkers, and alcohol abusers have an increased risk.
3. Moderate alcohol consumption is associated with a risk reduction of approximately 30% for CVDs, approximately 30% for type-2 diabetes, and approximately 25% for dementia.
4. Heavy alcohol consumption for several decades leads to AUD. Lifetime prevalence of AUD in the United States is estimated to be almost 30% on the basis of DSM-5 criteria.
5. AUD is associated with increased risk of alcoholic liver disease, malnutrition, CVD, pancreatitis, cancers, diseases of the brain, and FASD.

DISCLOSURE STATEMENT

The author works as an independent consultant for food companies, the alcohol industry, universities, and government.

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