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REVIEW ARTICLE

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Alcohol and Noncommunicable Diseases: Part II Cancer, Diabetes Mellitus, Kidney Diseases, Alzheimer's Disease, Arthritis

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Abstract

Excessive alcohol consumption is common. It leads to the development of several NCDs and is associated with considerable disability and high mortality. Its intake has been linked with an increase in many cancers, including the common breast and prostate cancer. Light-to-moderate drinking is associated with a lower incidence of type 2 diabetes, but excessive alcohol consumption leads to increased morbidity and mortality in these patients. Compared with no consumption, moderate consumption of alcohol-associated with a reduced risk of CKD. However, the association with heavy alcohol intake and CKD is not clear, although it also appears to be overall inverse in nature. Excessive alcohol intake also targets the brain and promotes AD – although mild to moderate intake may be safe. Alcohol consumption is negatively associated with the prevalence of knee OA. There appears to be an inverse association between alcohol consumption and RA incidence. Alcohol consumption, usually when taken in more than a moderate amount. may also trigger gout. In general, alcohol intake in low to moderate amounts appears to be safe for NCDs described in this communication, except for cancer, where no amount is a safe amount.

Keywords: alcohol, non-communicable diseases, cancer, diabetes mellitus, kidney diseases, Alzheimer's disease, arthritis

1 | INTRODUCTION

Alcohol consumption is common in our society[1]. It is estimated that in 2016, 32.5% of the world's population had at least one alcoholic drink in the past 12 months[2]. Globally, men tend to drink more than women[3]. A standard drink contains 12–15 g of pure ethanol and this is found in 12 ounces of regular beer, 5 ounces of wine, and 1.5 ounces of distilled spirits[4]. In most European

countries, alcoholic drinks are often referred to as by units, with one unit being equivalent to 8-10 grams of alcohol, with typical drinks containing 1–3 units of alcohol[5]. Moderate alcohol intake is considered as two standard drinks a day for men and one standard drink a day for women[6,7]. Heavy drinking is defined as a long-term, high-dose intake, of >60 g/day in men and >40 g/day in women[8]. Binge drinking is considered as 4 or more drinks for women and 5 or more drinks for men over a 2-hour period[9,10]. Compulsive excessive alcohol intake leads to alcohol use disorder[11]. It is estimated that 20% of patients seen by primary care physicians consume alcohol in amounts that are harmful to their health[12]. Alcohol was responsible for 8.9% in males and 2.3% in females for disability-adjusted life years in 2016, globally[13]. Griswold et al also calculated that in 2016, alcohol consumption was responsible for 6.8% of male deaths and 2.2% of female deaths all over the world[13]. Of these deaths in 2016, 21.3% were due to digestive diseases, 19% due to cardiovascular diseases and diabetes, 12.9% due to infectious diseases, and 12.6% due to cancers[14]. The health-related financial burden attributable to alcohol misuse is also extremely high, and in 2010, it cost the United States $249 billion[15].

The relationship between alcohol consumption and cardiovascular diseases (CVDs), respiratory diseases, depression, and liver diseases was discussed in Part I of this manuscript.

2 | DISCUSSION

Noncommunicable diseases (NCD) are common conditions affecting humans[16]. This part of the manuscript discusses the relationship between alcohol and cancer, diabetes mellitus (DM), chronic kidney disease (CKD), Alzheimer's disease (AD), and arthritis. Cancer is expected to replace CVDs as the number one killer in the world[17]. The most common global cancers are those involving the lung, colorectum, stomach, and liver[18]. However, many common cancers can be 'cured' if caught early[19]. Breast cancer, the most common nonskin cancer among women, if detected while still in localized form has a 5-year survival rate of 98%, compared with a survival rate of 72% by Stage III and just 22% by Stage IV[20,21]. Many other cancers demonstrate a similar prognosis depending on the time of their diagnosis[22]. Basal cell carcinoma and squamous cell carcinoma of the skin are the most common human cancers and are 100% treatable if found early. Diagnosing cervical cancer in a pre-cancerous stage can assure a near 100% survival rate. However, if discovered in Sate III, the rate drops to just 32% and if diagnosed in Stage IV, it is a dismal 16%. Prostate cancer is 98% survivable for 5 or more years if it is diagnosed when it is limited to the prostate gland. while if diagnosed at Stage IV, the survival rate is only about 28%. Colon cancer can be 90% survivable if detected early; the survival drops to 39% if it is detected when it has spread[22]. DM is one of the most common metabolic disorders worldwide[23]. and its prevalence is rapidly rising in low- and middle-income countries[24]. According to the World Health Organization, the number of people with diabetes rose from 108 million in 1980 to 422 million in 2014[24]. In the United States, 9.3% of Americans had diabetes (29.1 million persons) in 2014, with a lifetime risk calculated at almost 40%[25]. It is caused by a combination of defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to insulin[26]. Diabetes mellitus is associated with significant microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary artery disease, stroke, peripheral artery disease complications[27,28]. DM reduces the life expectancy of the affected individual by approximately six years[29]. CKD refers to kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 mt2, persisting for 3 months or more, irrespective of the cause[30]. It is a worldwide public health[31]. In 2017, CKD affected almost 700 million

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people in the world[32]. Those affected with CKD exceed those with diabetes, osteoarthritis, COPD, asthma, or depressive disorders[33]. Hypertension and diabetes mellitus are the main causes[34]. CKD is a progressive disease, ultimately resulting in the need for peritoneal dialysis or hemodialysis, or kidney transplantation[35]. The major cause of morbidity and mortality in CKD is due to cardiovascular events[36]. CKD also leads to frequent hospitalization[37]and poor quality of life[38]. CKD results in more deaths than tuberculosis or HIV and is presently ranked as the 12th leading cause of death out of 133 conditions in the world[33]. Dementia is a common worldwide disease[39], with AD being responsible for 50% to 70% of these cases[40,41]. It is characterized by pathologies: β-amyloid plaque deposition and neurofibrillary tangles of hyperphosphorylated tau[42]. This disorder continues to increase in low- and middle-income countries[43]. Its etiology is unclear but appears to be related to a complex interplay between genetic and environmental factors[44]. AD produces cognitive impairment and functional decline, often leading to institutionalization[45,46]. There is no cure for AD, and treatment remains symptomatic[47]. The QOL of these patients is markedly reduced and AD remains a major cause of death[48]. Arthritis is of many types, and osteoarthritis is the most common[49]. It is a major health concern, affecting about 240 million people globally[50]. It reduces the quality of life and results in considerable disability and mortality[51]. It usually affects the knees and the hip, resulting in chronic pain, stiffness, joint instability, and joint deformities[52]. It is associated with considerable disability[53]. Pathologically, it is characterized by progressive cartilage degradation, synovitis, osteophyte formation, and subchondral bone sclerosis[54]. Osteoarthritis (OA) cases are predicted to rise in the coming decades due to the aging population, increasing obesity, and high rates of traumatic knee injuries[55]. Rheumatoid arthritis (RA) is autoimmune arthritis and is characterized by symmetrical polyarthritis often with systemic manifestations[56,57]. RA is often associated with persistent pain, deformity, and disability[58]. It also accelerates cardiovascular disease in these patients[59]. Gout is an autoinflammatory joint arthritis[60], caused by the deposition of monosodium urate microcrystals in joints and tissues[61]. Hyperuricemia is central to its development[62]. In an acute flare-up, monoarthritis develops rapidly and affects the big toe in 50% of cases (other joints commonly affected include the ankle, midtarsal, knee, wrist, finger, and elbow)[63]. The affected joint is red, tender, hot, and tumid with extreme pain[64]. Diagnosis may be confirmed by finding monosodium urate crystals in synovial fluid or tophus aspirates[65].

2.1 | CANCER

Alcohol is a known carcinogen[66,67]. Its consumption increases the risk of several cancers[68,69], especially those affecting the mouth, throat, larynx, esophagus, liver, colorectal tissues, and breast[70]. Bagnardi et al. reviewed 222 articles in 2013, (comprising of about 92 000 light drinkers and 60 000 non-drinkers with cancer and concluded that light drinking increases the risk of oropharyngeal cancer by 17%; esophageal squamous cell carcinoma by 30% and breast cancer by 5%[71]. In a recent analysis, published in 2018, Islami et al. found that alcohol intake was the third-largest contributor to all cancer cases among women and the fourth largest contributor among men[72]. In women, besides causing 28.4% of esophageal cancers, 27.4% of the oral cavity and pharyngeal cancers and many breast cancers were associated with alcohol[72]. Alcohol was associated with 46.3% of all oral cavity and pharyngeal cancers in men[72]. They estimated that alcohol intake was responsible for 5.6% of cancer cases and 4.0% of all cancer-related deaths[72]. Alcohol intake has also been linked with an increase in other cancers, such as gastric cancer[73], colo-rectal cancer[74], prostate cancer[75], and some skin cancers76. It also increases the risk of a second aerodigestive-tract cancer[77]. There may be a dose-response relationship between alcohol and cancer[78]. However, most people are unaware of the increased risk of cancer even after the first drink[79]. The American Cancer Society recommends not drinking alcohol to lower cancer risk[80]. Despite these recommendations, most people, including cancer survivors continue to drink[81].

Alcohol is an irritant to the upper aerodigestive tract[82]. Acetaldehyde is the first and primary metabolite of alcohol and is strongly implicated in cancer development[83]. Its intake is associated with ab-

normal production of reactive oxygen and nitrogen species, aberrant DNA methylation, altered folate metabolism, disturbed immune surveillance and inflammatory response and increased estrogen levels in breast cancer cases[84−86].

2.2 | DIABETES MELLITUS

Alcohol intake is generally considered beneficial for type 2 diabetes prevention, provided it is consumed in moderate amount[87]. In a large study involving 22,778 twins and 580 incident cases of type 2 diabetes during 20 years of follow-up, Carlsson et al documented this phenomenon[88]. Some previous studies have estimated that moderate alcohol consumption may reduce the incidence of type 2 diabetes by 30%-40%[89−91]. In a recent meta-analysis of 20 observational studies, undertaken by Baliunas et al. in 2009, a peak reduction in risk for type 2 diabetes mellitus (T2DM) was noted at 24 g/day among women and 22 g/day among men, relative to never drinkers, with risk increasing in a dose-dependent manner above these levels[92]. However, in a major meta-analysis of 38 studies representing 1,902,605 participants and 125,926 cases of type 2 diabetes, Knott et al found a risk reduction only in women (<71 g/day) when compared to current non-drinkers and never drinkers93. Irrespective of the level of alcohol consumption, no risk reduction was noted in men[93]. Several biological mechanisms have been proposed to explain the apparent reduction in risk of T2DM among moderate drinkers[94]. These include the anti-inflammatory hypothesis, which posits that alcohol may beneficially alter the expression of inflammatory proteins[94] and a possible stimulatory effect of alcohol upon the synthesis of HDL[95]. After an analysis of results reported by 14 intervention studies, alcohol consumption was associated with reduced fasting insulin concentrations and improved insulin sensitivity among women[96]. Reduced duration of drinking, or initiating alcohol intake at a later age, also appears to decrease the risk of T2DM[97]. Heavy alcohol intake has been associated with a higher risk for DM in many studies[98,99]. In a study of 2366 Koreans monitored over 10 years, consumption of more than 2 units of alcohol per day was associated with an increase in the risk of T2DM[100]. A reduction in the maximum intake of alcoholic beverages not only decreases the risk of development of T2DM but also improves survival among established diabetic subjects especially if this reduction is done in early adulthood[101,102.]

Several mechanisms may cause this harm, including alcohol-related increase in metabolic syndrome[103,104]. The increase in alcohol-related hypertension tends to aggravate cardiovascular complications[103]. Long-term alcohol intake also results in pancreatic islet dysfunction and apoptosis[104]. Overall, the relationship between alcohol consumption and risk of T2DM appears to be J- or U-shaped association[105].

2.3 | KIDNEY DISEASES

Compared with no consumption, moderate consumption of alcohol may be associated with a reduced risk of CKD[106]. Moderate alcohol use was associated with a lower risk of CKD or end-stage kidney disease (ESKD) in several previous reports[107−110]. In a meta-analysis of prospective cohorts. not only moderate but also high amounts of alcohol use have been associated with a lower risk of incident CKD or ESKD[111]. However, heavy alcohol consumption or chronic alcohol consumption is positively associated with CKD[112−116]. A Mendelian randomization study also found a causal link between heavy alcohol intake and an increased risk of end-stage kidney disease[117]. In another Mendelian randomization study, Park et al also confirmed the deleterious role of alcohol on the risk of ESKD[118].

Mechanisms of alcohol-induced kidney damage include oxidative stress injury, increase in blood pressure, and activation of the renin-angiotensin-aldosterone pathway[119−121.] Further alcohol and other substances in alcohol may also influence kidney function by effects on other body systems[122,123]. Bottom line – alcohol is a double-edged sword in CKD. It may be safe to drink to a low or moderate degree with CKD but heavy or binge drinking is harmful[124].

2.4 | ALZHEIMER'S DISEASE

Several studies have documented the protective effects of low to moderate amounts of alcohol on dementia[125−127]. Epidemiological studies have also reported a similar effect in AD[128]. In a recent large meta-analysis of 91 articles on AD, Anstey et al confirmed this association[129]. Animal and cell culture studies also show that low or moderate concentrations of ethanol exhibit a protective effect on AD in vitro and in vivo130-133. Heavy drinking is however harmful to the brain[134−138]. In a 5-year follow-up study of 13,342 men and women, Piumati et al reported that reaction time declined more with alcohol intake of 12 units per week when compared to those who drank less[134]. In a large study (of 31 million people over 5 years), researchers found that alcohol use disorders were associated with increased dementia risk[135]. Heavy alcohol intake induces harmful brain changes, cognitive impairment, and dementia[136,137]. Similar deleterious findings have been noted in AD patients with higher alcohol intake[138]. Changes consistent with increased cognitive deficits have also been noted in AD mice models 1-month post alcohol drinking[139]. In the 23-year UK Whitehall study (9087 participants), abstinence or heavy drinking were both associated with a higher risk of dementia[140]. Overall, the association between alcohol intake and dementia appears to be U-shaped with low or moderate amounts of alcohol being protective against Aβ toxicity in hippocampal neurons and high intake increasing neuronal cell death and neurodegeneration[141]. However, alcohol drinking is not recommended for AD protection[142].

2.5 | ARTHRITIS

There is no concrete evidence of an association, beneficial or otherwise, between moderate alcohol consumption and OA[143,144]. This has been noted in the Finnish cohort study with an observation period of 22 years[143] and the Nurses' Health Study[144]. Moderate amounts of alcohol intake are associated with anti-inflammatory effects[145]. Zhang et al found no evidence of alcohol consumption with hsCRP or knee OA[146]. Some studies have found that chronic and excessive intake of alcohol raises inflammation[147,148]. Kc et al noted pathological OA-like changes in animals with chronic alcohol intake[149]. A similar radiological knee OA effect, rather than a symptomatic effect, was seen in Korea in patients with alcohol consumption[150]. The clinical implications of the relationship between alcohol intake and OA. Therefore. remain unclear. The 2009 the Swedish EIRA study (Epidemiological Investigation of Rheumatoid Arthritis) and the Danish CACORA study (Case-Control Study on Rheumatoid Arthritis) found that limited amounts of alcohol decrease the risk of RA incidence[151]. Lu et al concluded that moderate alcohol intake was associated with a better functional status in RA patients[152]. Another study found that low levels of alcohol consumption (about three drinks per week) over at least ten years lowered the risk of RA incidence by half compared with non-drinkers[153]. However, increased frequency of alcohol consumption may be harmful in RA[154]. In the Västerbotten Intervention Program cohort of 386 individuals, no association was seen between alcohol intake and the risk of RA[155]. Baker et al reported that RA patients tend to reduce alcohol intake with higher disease activity, disability, comorbidity, and poor quality of life[156]. Overall, there appears to be no clear benefit of alcohol consumption in RA. **Alcohol may precipitate gout at lower urate levels**[157]**.** Beer intake appears to be more associated with gout than spirits, and spirits more than wine[158,159]. Chronic alcohol intake also is also harmful to gout patients[160,161.] High alcohol intake may impair the production of oxypurinol and stimulate urate production in the body[160,161].

3 | CONCLUSION

Low to moderate alcohol intake appears to be safe, and even protective in DM, CKD, and AD. There may be no "safe" level of alcohol use when it comes to cancer. No definite association can be gleaned from published studies between alcohol and OA and RA. Gout suffers may consider abstaining from alcohol. High levels of alcohol intake are in general, harmful for NCDs. The 2015 U.S. Dietary Guidelines for Americans strongly suggest restricting consumption to $\leq$2 drinks/day for men and $\leq$1 drink/day

for women. Alcohol consumption can lead to adverse outcomes and therefore, non-drinkers should not start drinking for health reasons.

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