

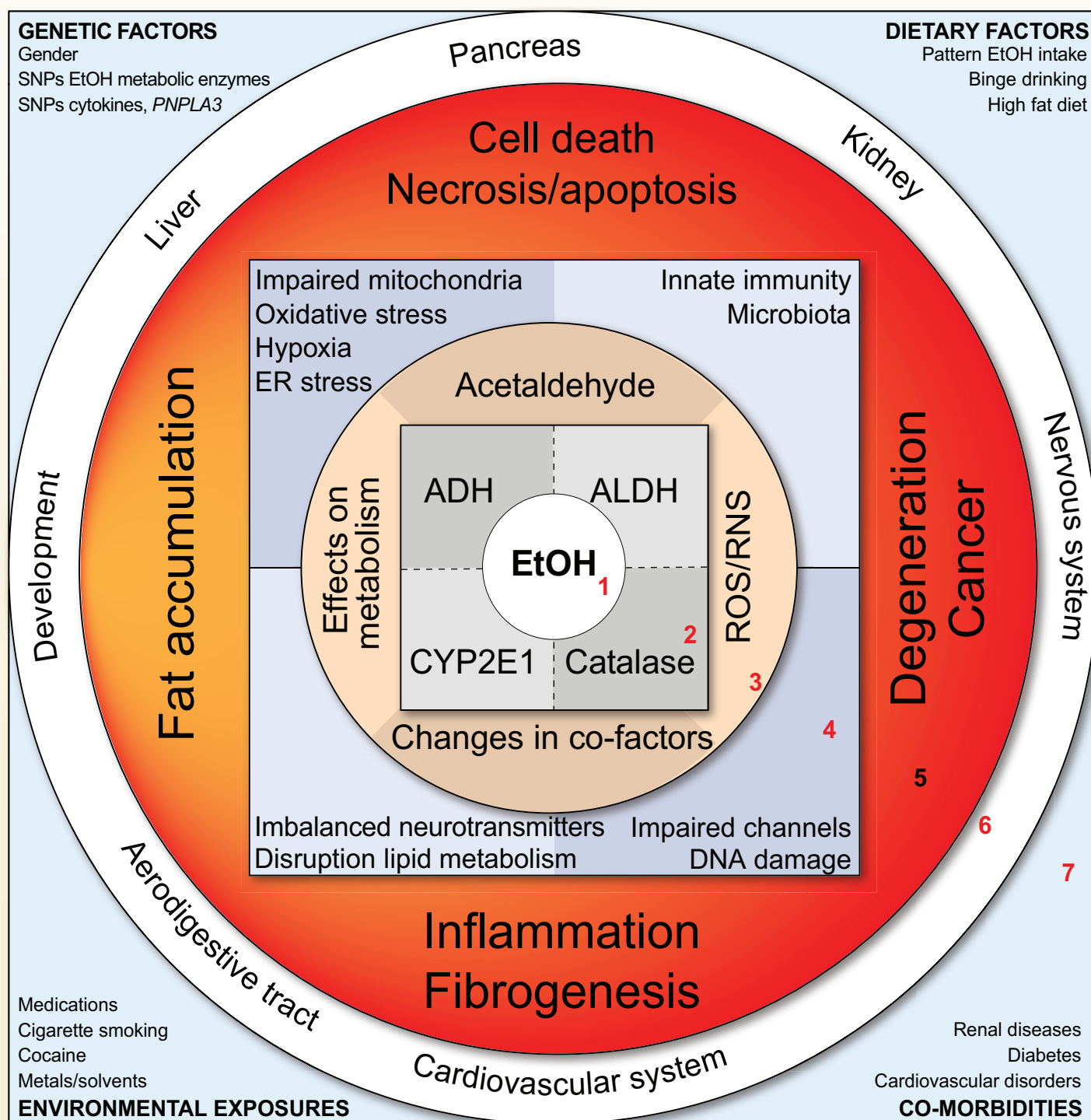
# Alcohol and toxicity

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## Hepatology Snapshot

Excessive alcohol intake is a major public health challenge worldwide and has been identified as one of the main determinants of a variety of non-communicable diseases [1]. The World Health Organization (WHO) estimates that 4.5% of the global burden of disease and injury, and 4% of all deaths worldwide are attributable to alcohol [2]. Alcohol is the leading risk factor for death among males aged 15–59 years, particularly in Eastern Europe [2,3].

Toxic and other adverse effects of alcohol on organs and tissues in humans (see Figure) are largely a consequence of its metabolism to acetaldehyde, and associated formation of reactive oxygen and nitrogen species, depletion of co-factors (e.g., NAD<sup>+</sup>), and impairment in energy homeostasis [4]. Because of the considerable redundancy in the oxidative enzymatic pathways (alcohol dehydrogenases, CYP2E1, and catalase) that can convert alcohol to acetaldehyde, most tissues are capable of alcohol metabolism, even though the liver is the primary site. Likewise, acetaldehyde dehydrogenases are ubiquitous in the mitochondria. A minor, non-oxidative, pathway of alcohol metabolism is to fatty acid ethyl ester (via fatty acid ethyl ester synthase) and phosphatidyl ethanol (via phospholipase D). Alcohol impacts the integrity of the gastrointestinal mucosal barrier. This results in the translocation, via the portal blood flow, of the gut bacteria-derived lipopolysaccharide (endotoxin) and other molecules to the liver, and activation of the innate immune response.

The molecular and cellular sequelae of the toxic mediators of alcoholic injury take many forms. Acetaldehyde and oxidants are highly reactive molecules that can damage DNA, proteins, and lipids. Changes in hepatic respiration and lipid metabolism lead to tissue hypoxia and impairment in the mitochondrial function. Secondary effects include disruption of signaling pathways and ion channel function, unfolded-protein response, and oxidative stress, as well as activation of adaptive immune response largely triggered by acetaldehyde-protein adducts. Cell death triggers additional innate immune response, activation of fibrogenesis, and tissue repair. In addition to pro-inflammatory mediators, other signaling molecules, such as neurotransmitters, are affected by alcohol. Gross pathological changes associated with alcohol drinking include most or all, depending on the affected tissue, of the following: fat accumulation (steatosis), inflammation, necrosis, and fibrosis [5]. Impairment of organ function and carcinogenesis are most advanced pathological effects and are associated with organ dysfunction and increased mortality. As a consequence, alcoholic beverages and ethanol in alcoholic beverages are classified by the WHO International Agency for Research on Cancer as “carcinogenic to humans” (Group 1) [6].

Alcohol is highly diffusible through cell membranes and is metabolized by most tissues. Thus, its toxicity affects most organs. Because the liver is the major site of alcohol metabolism, it is one of the major targets for alcohol-induced organ damage. Alcoholic liver diseases include steatosis, different subtypes of steatohepatitis, cirrhosis, and hepatocellular carcinoma [5]. Of these, cirrhosis of the liver is the third leading (at 16.6%) cause of alcohol-attributable deaths worldwide [2]. In addition, other anatomical sites in the aero-digestive tract are adversely affected by alcohol, with most important morbidity and mortality due to malignant tumors, all causally related to alcohol consumption, of the oral cavity, pharynx, larynx, esophagus, and colorectum [6]. In the pancreas, toxic metabolites of alcohol cause acinar cell injury leading to pancreatitis and subsequent fibrosis [7]. The cardiovascular system is second only to gastrointestinal organs in toxic effects of alcohol [1,2]. Hypertension, ischemic heart disease, stroke, cardiomyopathy, and myocarditis, as well as various arrhythmias, have been associated with alcohol abuse. The linkages between alcohol use and neuropsychiatric disorders have also been established as causal (e.g., for major depression) [8]. In addition, neurobehavioral impairment due to alcohol intoxication is a major contributor to deaths from violence, road traffic accidents, and injuries [2]. In the kidney, excessive alcohol intake has been associated with IgA glomerulonephritis, acute nephropathy, and kidney graft failure [9]. Adverse effects of alcohol on human reproduction and development span the wide range of pathological conditions from impaired fertility to

premature and low-weight births, and fetal alcohol syndrome spectrum disorders [2]. The addition of breast cancer to the list of cancers causally related to alcohol consumption suggested that the proportion of malignancies attributable to alcohol consumption is higher than previously estimated [6]. Indeed, recent studies show that up to 5% of breast cancers are attributable to alcohol in northern Europe and North America for a total of approximately 50,000 alcohol-attributable cases of breast cancer worldwide [10].

Factors affecting susceptibility to alcohol toxicity include genetics, gender, lifestyle/nutrition, exposure to environmental chemicals and drugs, and co-morbidities. Variations in genes encoding metabolic pathways for alcohol or triglycerides, as well as many other genes that may be involved in the pathogenesis or protection from alcohol-induced toxicity, modify the individual's response to alcohol abuse and disease outcomes [4–6]. The effect of gender varies by disease outcome with females being more susceptible to alcoholic liver disease, but most alcohol-attributable deaths occur in males [1,2]. Dietary (e.g., high-fat consumption, patterns of alcohol intake), life style (e.g., cigarette smoking, drugs of abuse), and environmental (e.g., nitrosamines, metals, and chlorinated solvents) factors also affect both morbidity and mortality related to alcohol abuse. Obesity, viral infections, iron accumulation, and other pro-inflammatory conditions, as well as concomitant use of certain drugs (e.g., acetaminophen, isoniazid, and methotrexate), also compound morbidity and mortality due to alcohol abuse.

Finally, while overwhelming evidence exists to conclude that consumption of alcoholic beverages is harmful to human health, many studies observed some beneficial effects of modest alcohol consumption (usually defined as 1–2 servings/day) [1]. Health conditions that have been associated with “beneficial effects” of alcohol on mortality include cardiovascular diseases (e.g., myocardial infarction) and chronic kidney disease [1,9], yet such protection disappears with heavy drinking occasions [2]. No “safe” amount of alcohol consumption has been found for cancer; even consumption of two drinks per day causes a significant increase in risk [6].

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### Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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**Fig. Layered graph showing the mechanisms of alcohol-induced toxicity and organ damage.** Layer #1: the amount of alcohol intake is a main determinant of toxicity. Layer #2: alcohol metabolism is regulated by several enzymes and is a major determinant of alcohol-induced toxicity. Genetic variations and expression of these enzymes regulate systemic and local effects of alcohol intake. Layer #3: alcohol metabolites and molecules released in damaged organs, such as acetaldehyde and ROS, are key toxicity mediators with powerful biological properties. Layer #4: such mediators activate several cellular and molecular mechanisms, such as disrupted lipid metabolism, hypoxia, ER stress, dysregulated immunity, changes in intestinal microbiota and DNA damage. Layer #5: the synergistic effect of the activation of these pathways leads to different histological disturbances in target tissues, such as fat accumulation, inflammation (PMN cells), necrosis/apoptosis, fibrosis and cancer, leading to organ dysfunction. Layer #6: the most susceptible organs to the deleterious effects of alcohol, that account for most of clinical complications, include normal development of the fetus, liver, kidney, nervous system, aero-digestive tract, reproductive system, pancreas, and cardiovascular system. Layer #7: the individual susceptibility to the toxic effects of alcohol in the human body is determined by genetic (gender, SNPs in target genes such as *PNPLA3*), dietary, and environmental exposures. Finally, patients with co-morbidities, such as viral infections or metabolic disorders, are more susceptible to the deleterious effects of alcohol abuse. EtOH, ethanol; ADH, alcohol dehydrogenase; ALDH, acetaldehyde dehydrogenase; ER, endoplasmic reticulum; *PNPLA3*, patatin-like phospholipase domain-containing protein 3; SNPs, single nucleotide polymorphism.