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The alcohol exposome

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ABSTRACT

Science is now in a new era of exposome research that strives to build a more all-inclusive, panoramic view in the quest for answers; this is especially true in the field of toxicology. Alcohol exposure researchers have been examining the multivariate co-exposures that may either exacerbate or initiate alcohol-related tissue/organ injuries. This manuscript presents selected key variables that represent the *Alcohol Exposome*. The primary variables that make up the *Alcohol Exposome* can include comorbidities such as cigarettes, poor diet, occupational hazards, environmental hazards, infectious agents, and aging. In addition to representing multiple factors, the *Alcohol Exposome* examines the various types of intercellular communications that are carried from one organ system to another and may greatly impact the types of injuries and metabolites caused by alcohol exposure. The intent of defining the *Alcohol Exposome* is to bring the newly expanded definition of *Exposomics,* meaning the study of the exposome, to the field of alcohol research and to emphasize the need for examining research results in a non-isolated environment representing a more relevant manner in which all human physiology exists.

Introduction

In response to an evolution in public health research, which demanded more holistic approaches to toxicology, Christopher Wild coined the term *Exposome* as the umbrella term that encompasses all the external environmental exposures a person will encounter from conception throughout the lifespan (Wild, 2005). More recently, environmental health researchers have recently redefined *Exposomics* to mean the study of the exposome (Safarlou et al., 2024). Johnson et al., (2017) reflect on the *Exposome* as a new concept forged out of advancements in bioinformatics to better analyze big data and metabolomics for more detailed biomonitoring, in a quest to provide a realistic toxicological profile for human health (Johnson et al., 2017). However, even with advancements in biotechnology, building multi-variable exposure profiles can be challenging. The concept of the *Alcohol Exposome* seeks to apply the fundamentals of the Exposome using alcohol as the central exposure, but then building a larger context of multiple exposure covariables. While there are many important, well-known external exposure variables, such as organic and inorganic toxins, UV rays, and climate change, the primary variables that make up the *Alcohol Exposome* include cigarettes, poor diet, occupational hazards, environmental hazards, infectious disease, and aging. In addition to representing multiple factors, the *Alcohol Exposome* examines the various inter-organ communications that greatly impact the types of injuries and metabolites produced. Depending upon the dose, alcohol can be a toxic substance and carcinogen (Anderson et al., 2023). The 2022 National Survey on Drug Use and Health (NSDUH) results showed that approximately 29.5 million Americans ages 12 and older have an alcohol use disorder (Alchohol's Effects on Health, 2022), highlighting the importance of continued research on the effects of alcohol on human pathophysiology in public health.

This review examines the multi-organ biochemical interactions that are initiated in response to chronic alcohol exposure, beginning with the initial contact in the oral cavity, where alcohol begins interacting with salivary enzymes (Ferraguti et al., 2022), the first of many enzymes encountered as ethanol permeates various tissues and organs of the body. Alcohol immediately enters the bloodstream, where it is delivered to many organs, particularly the liver, where most of the metabolic processing takes place (Jiang et al., 2020). This speedy journey through the body is commonly referred to as the *first pass* (Jiang et al., 2020). These alcohol

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interactions are significantly impacted by known internal and external covariables such as age, gender, geographic location, lifestyle, socioeconomic class, living conditions, immunological health, mental health, endocrinology, stress, diet, cigarette use, occupation, environmental pollutants, and metabolic byproducts. While there is limited research on finding a significant association between genetic factors and the overall direct impact of alcohol exposure, there is an abundant amount of research evidence showing that genomics can play a significant indirect role in pathophysiological pathways. Many of these pathways will be examined to adequately define the *Alcohol Exposome* to give a comprehensive definition that can be used by researchers to develop models that will better represent the interconnected physiological variables, even when examining only one type of cell or one metabolic pathway. While multiple studies have linked pathophysiological effects of chronic alcohol consumption to specific types of tissue injury (Anderson et al., 2023), an incorporation of the complexities of the *Alcohol Exposome* is required to provide relevant translation of research to human health and disease.

The *Alcohol Exposome* can be defined by the various sources of significant interactions between alcohol and/or any of its metabolites. Furthermore, to qualify a substance as an exposome agent, these interactions with alcohol and its metabolites must result in a significant biological effect on one or more human physiological function(s). Exposure to alcohol may happen as early as conception (Wild, 2005), should a pregnant mother intake alcohol, and may continue until death. Therefore, a proper definition of the *Alcohol Exposome* also requires examining the lifecycle of the exposure. The primary population of concern included in the *Alcohol Exposome* are individuals diagnosed with Alcohol Use Disorders, as defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for Alcohol Use Disorders (AUDs) (Alchohol's Effects on Health, 2022). An AUD is determined by the results of the Alcohol Use Disorder Identification Test – Consumption (AUDIT-C), the gold standard test for qualifying alcohol use disorders (Crabb et al., 2020; Verhoog et al., 2020). While individuals formally diagnosed with AUDs represent a significant number of the population, alcohol misuse does not always involve a formal diagnosis. The intent of developing a universal definition for the *Alcohol Exposome* is to encourage alcohol researchers to increase the scientific translation of their analyses by mirroring the complexities of human life, including the highly significant interactions of alcohol with comorbidities caused by tobacco/substance abuse, poor diet, occupational hazards, environmental toxins, infectious disease, and aging (Fig. 1).

Alcohol metabolism

Though external factors set the stage for the Alcohol Exposome, the internal biological mechanisms translate into toxicity. Alcohol metabolites directly affect all organs, including the kidneys (Byrne et al., 2020), lungs, and, most notably, the liver, where further additional metabolic byproducts are made and then transported to distant parts of the body (Yang et al., 2022). As a hydrophilic substance that easily dilutes in water, alcohol is readily bioavailable to all tissues, including nervous tissue via the gut-brain axis (Sushma et al., 2021). Alcohol is metabolized in several different pathways depending on the organ system (Alchohol's Effects on Health, 2022). The two major enzymes involved in this pathway are alcohol dehydrogenase (ADH), a highly evolutionary conserved pathway going back to primitive yeast (Bowland, 2024) and Cytochrome P450 family member 2e1 (CYP2E1) (Simet et al., 2015). Since 1986, a multitude of studies have shown that ethanol increases expression of CYP2E1, which is the enzyme responsible for many of the hepatocyte-damaging reactive oxygen species (ROS) (Johansson et al., 1986).

ADH and ALDH (aldehyde dehydrogenase) reconfigure the alcohol molecule such that it can be eliminated (Simet et al., 2015). ADH metabolizes ethanol into the toxic carcinogen acetaldehyde, which is then converted into less active acetate (Simet et al., 2015). Acetate is then further broken down into carbon dioxide and water, which are both easily excreted from the body (Simet et al., 2015).

Not only are the metabolites important, but also the site of metabolism and the organ crosstalk that can occur between the various sites. Many metabolites travel between organ systems inside membrane-bound extracellular vesicles (EVs), a key physiological method of organ crosstalk in the body. Armutcu (2019) completed a meta-analysis that focused on organ dysfunction stemming from crosstalk organ interactions with an emphasis on inflammation and fibrosis (Armutcu, 2019). Armutcu searched for

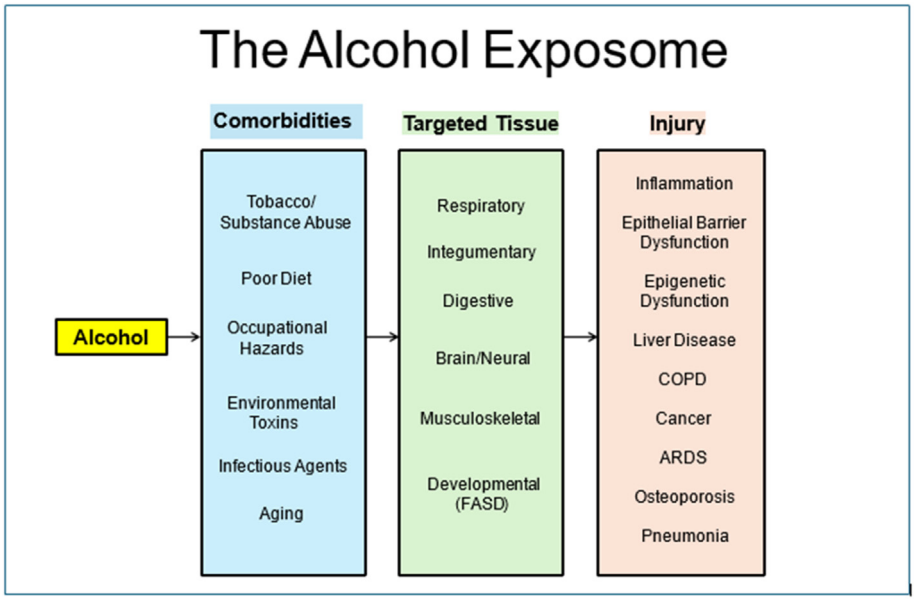

Fig. 1. Diagram of the Alcohol Exposome. Schematic presenting the relationships between the multivariate factors comprising the *Alcohol Exposome*.

research publications that included the words “organ crosstalk” between the years 2000 and 2019 and found a statistically significant association with the exosomal cargo being transported by extracellular vesicles (EV) (Armutcu, 2019), a pathway previously identified as key players in the network of organ-to-organ crosstalk (Corrado et al., 2013). EVs are key modes of intercellular communication. In addition to EVs, Armutcu also points out the important roles of inflammatory chemokines and cytokines for molecular signaling pathways that trigger the “inflammasome” involved in sensing cellular damage, which triggers release of interleukins (ILs) that cause chronic inflammation, leading to tissue injury (Armutcu, 2019).

Organ crosstalk is a key signaling pathway for inflammation due to metabolites of alcohol when it forms axes between different systems of the body. These alcohol metabolite axes include the gut-liver, liver-lung, gut-brain and liver-brain axis. The liver-lung is a crucial axis because the lungs are a direct target organ that excrete alcohol via exhalation. There is a highly significant impact of alcohol on the respiratory system. This relationship has not only been recognized by the scientific community, but it has also been formally accepted by the judicial system in allowing law enforcement to require drivers to take a breathalyzer test that measures alcohol concentrations in the lungs to determine if the amount of alcohol consumed is within the legal limits. The impact begins with direct contact of alcohol with the epithelial tissue lining the oropharyngeal cavity during oral consumption. Within the oral cavity, alcohol readily crosses the phospholipid membrane of the epithelial cells, where it initiates enzymatic reactions (Santos et al., 2023). In the oropharyngeal cavity, alcohol begins to penetrate upper airway tissue, eventually entering even the lungs (Guidotti, 1978). The profound adverse effects of alcohol exposure on the pulmonary system have been well-supported by researchers (Osna et al., 2022). Though the airways are a point of contact for alcohol metabolism, the majority of alcohol metabolism happens in the liver where it induces CYP2E1 (Lu et al., 2008); thereby making the liver-lung axis a critical component of Alcohol Exposome research. The Alcohol Exposome would attempt to determine if hepatocyte EVs carry additional CYP2E1 or even possibly CYP2E1 mRNA to the respiratory tissues as a form of organ crosstalk.

Alcohol and tobacco/substance abuse

While alcohol metabolites directly impact the upper respiratory system, they are also compounded by many exposure variables stemming from cigarette smoke, occupation, diet, viral/pathogen infections, environmental pollutants, and allergens (Wheelock & Rappaport, 2020). There is a limited amount of literature supporting a significant increase in respiratory disease pathology when linking alcohol to cigarette smoke. Being able to examine respiratory effects within the *Alcohol Exposome* will be most challenging due to external tissue exposures, like cigarette smoke, which are covariables that should not be ignored.

Alcohol misuse has a significant association with tobacco products like cigarettes, chewing tobacco, and vape products. Approximately 80% of Americans who misuse alcohol also regularly consume cigarettes (van Amsterdam et al., 2023). Romberger and Grant (2004) observed a positive association between nicotine dependence and a history of alcohol misuse, which often resulted in major health consequences, including additive risks for disease (Romberger et al., 2004). For these reasons, it is most prudent to include cigarette smoke exposure when evaluating chronic alcohol exposure within the *Alcohol Exposome*. While many researchers focus on liver injury with alcohol misuse, the statistically significant association with cigarette smoking suggests that the inclusion of this covariable is essential for human-translatable disease research. The lung is a target for both cigarette and alcohol exposure. Malondialdehyde and acetaldehyde are the products of alcohol metabolism, and the pyrolysis of tobacco leads to the formation of highly stable Schiff Bases known as malondialdehyde–acetaldehyde (MAA) adducts (Sapkota et al., 2015). MAA in the presence of adductable targets such as lung surfactant proteins will form an adducted protein that has the ability to activate lung epithelial cell protein kinase C isoform Epsilon (PKCε) (Wyatt et al., 2012). PKCε activation slows ciliary beating frequency, making it harder for airways to expel trapped foreign matter (Wyatt et al., 2012). However, these MAA adducts are only present in significant amounts in the lungs of cigarette smokers who have AUD; as they are minimal in the lungs of those smokers without AUD (Sapkota et al., 2017). Although the cumulative aldehyde threshold for lung protein adduction is likely only achieved by the combination of smoking and drinking, this scenario defines the importance of co-exposure in creating unique second-hit injuries not seen by either exposure alone. The significant association between cigarette smoking and alcohol use is well-established and therefore must be considered when researching the pathophysiology of either exposure.

In addition to smoked tobacco products, alcohol and chewing tobacco has also been a coexposure of great concern for decades, especially in the etiology of oral cancers (Muwonge et al., 2008; Winn, 2001). While most of the global epidemiology statistics on alcohol and tobacco products exclude smoke-free tobacco usage, the statistic on oral cancer is unambiguous concerning the increased risk of oral, pharyngeal, and esophageal cancers when alcohol use is combined with chewing tobacco given the higher incidence rates of cancer (Znaor et al., 2003).

Comorbidities of AUD, including drug abuse, increase the risks associated with alcohol misuse alone (Yang et al., 2018). One of the most relevant drugs is cannabis. Subbaraman and Kerr (2015) performed a meta-analysis and determined that the prevalence of simultaneous and concurrent use of cannabis was 11.4% for individuals with alcohol misuse and that those using both had higher consumption rates in terms of volume and frequency for alcohol (Subbaraman et al., 2015). This result supports findings in a previous study done by Booth and Kirchner (2001) that cannabis users who were heavy drinkers consumed more alcohol than heavy drinkers who did not use cannabis (Booth et al., 2001). Every year, more states legalize recreational use of cannabis, making it more available to individuals with a history of alcohol misuse. Bailey (2019) found increased Toll-Like Receptors (TLRs) involved in innate inflammatory responses presented on bronchial epithelial cells that were provided by a cohort of individuals clinically diagnosed with alcohol misuse (Bailey, 2022). They concluded that chronic alcohol and cannabis concomitant exposure triggers a host of airway inflammatory responses (Bailey, 2022).

A more recent tobacco product of concern has been vaping products, also known as E-cigarettes. E-cigarettes were first commercially available in China almost 20 years ago and continue to increase in global sales, bringing much debate on product safety for consumers. Since the debut of e-cigarettes, public health officials around the world have been divided on its promotion as a healthier option to combustible tobacco for the delivery of nicotine (Bhatt et al., 2020). This debate is warranted. While there is significant research supporting a reduction in harm when switching from traditional cigarettes to e-cigarettes, the benefits are muted by the fact that over 40% of people who begin vaping had never smoked traditional combustible tobacco products prior to vaping (Park et al., 2016). In recent years, researchers have been analyzing possible compound injuries of alcohol and e-cigarettes, especially as they have been heavily marketed to young consumers. Rothrock et al., (2020) uncovered that more than half of high school students who had used e-cigarettes/vape products were found to also

frequently use alcohol (Rothrock et al., 2020). Hershberger et al., (2021) surveyed 31 adults who stated that vaping increased their alcohol cravings (Hershberger et al., 2021). Like alcohol, e-cigarette fluids also contain acetaldehyde (Muthumalage et al., 2018). In fact, many of the flavoring compounds used in e-cigarettes are aldehyde-based (Cheng, 2014). Given the increasing trends for dual exposures to alcohol and vaping (Hershberger et al., 2021), researchers should consider the additive effects of higher sera levels of acetaldehyde (Muthumalage et al., 2018) and the injuries resulting from a higher dose of this class I toxin. These associations highlight the importance of exposomic methods to evaluate injuries that may otherwise be overlooked. There are voluminous data supporting a behavioral synergy between tobacco-related product use and alcohol misuse that demands more resources be used to research these combined effects.

Alcohol and poor diet

According to the NIAAA, the National Cancer Institute (NCI), and the US Food and Drug Administration, individuals with AUDs often have poor dietary habits lacking in essential nutrients (Breslow et al., 2010). Poor nutrition coupled with an AUD can result in severe injuries to the microbiome, immune system, barrier function, and brain function. Baj et al., (2020) completed a comprehensive examination of multiple trace elements essential to normal functioning human physiology (Baj et al., 2020). The pathways for alcohol metabolism can lead to the formation of free radicals (Zima et al., 2001) causing oxidative injury. The endogenous enzymes that are normally present to protect cells from these free radicals depend on elements such as selenium, manganese, copper, and zinc (Grochowski et al., 2019), which are drastically reduced in chronic alcohol misusers due to poor dietary habits and the reduced absorption caused by alcohol injuries to gut microbiome and architecture (Zima et al., 2001). Zinc deficiency, which is known to impact both epithelial and immune cell functions, has been associated with chronic alcohol use, which leads to altered expressions of zinc transporters and storage proteins in small intestines (Joshi et al., 2009). Zinc deficiency also impairs both alveolar epithelial and macrophage function and renders individuals susceptible to acute lung injury, pneumonia, and other serious lung diseases (Joshi et al., 2009).

Alcohol misuse also creates pathophysiological dysfunction in the gut. Alcohol induces barrier dysfunction that can lead to a leaky gut (Tang et al., 2015). Alcohol and its metabolites incite inflammation in the digestive tract through multiple pathways that affect tissues both locally and systemically (Zhong et al., 2014). Alcohol metabolism involves the microsomal ethanol-oxidizing system (MEOS), which handles a small portion of alcohol metabolism in occasional drinkers, but is responsible for a significant portion of alcohol metabolism when the body needs to process larger amounts of alcohol. MEOS produces oxygen free radicals which can damage cells (Bishehsari et al., 2017). While the majority of alcohol metabolism occurs in hepatocytes, the enzymes involved in the oxidative metabolism of alcohol are also found in the intestinal mucosa (Cederbaum, 2012), and intestinal bacteria also produce acetaldehyde (Bishehsari et al., 2017).

Furthermore, alcohol-induced bacterial overgrowth may exacerbate injuries, as the intestinal bacteria independently metabolize alcohol, producing excess acetaldehyde in the colon, which can compound the rate of proinflammatory alcohol metabolite production (Zhong et al., 2014). In addition, a previous study in mice demonstrated that ethanol exposure promotes the secretion of liver EV containing CYP2E1 via the caspase-3 pathway (Shen et al., 2020). The smallest of these are collectively known as exosomes. They can range in size from 30 to 1000 nm (Shen et al., 2020), and they can carry RNA, DNA, proteins, and lipids from one part of the body to another (Lloret-Llinares et al., 2018) as a form of intercellular communication. As exosomes are carried through the bloodstream, they can be deposited in any tissue or body fluid, including plasma, urine, saliva, synovial fluid, breast milk, bronchoalveolar lavage fluid, and epididymal fluid (Properzi et al., 2013). Knowing that exosomes are found in bronchoalveolar lavage fluid, it could be ascertained that hepatocyte-derived exosomes from alcohol-damaged liver tissue will be in the lung and the bronchoalveolar lavage fluid (BALF). Exosomes from the BALF could be studied to determine whether mRNA for CYP2E1 and ADH is present in these exosomes, to ultimately replicate and be overexpressed in the lung, resulting in compound injury to the respiratory tissue also directly exposed to alcohol.

In addition to exosomal cargo, poor nutrition can lead to unknown pathways that disrupt proper neurophysiology. Heavy alcohol use has been widely recorded to be linked to thiamine deficiency that results in cognitive dysfunction and in extreme cases, a life-threatening condition called Wernicke's Encephalopathy (Listabarth et al., 2023). Poor diet often leads to Type II Diabetes. Vancampfort et al., (2016) large-scale meta-analysis results discovered a highly significant association between alcohol misuse and Type II Diabetes Mellitus (T2DM), with one in 8 individuals diagnosed with an AUD having T2DM (Vancampfort et al., 2016). Some of the association may be due to a lack of diabetic and overall health self-care in persons with AUDs (Thomas et al., 2012). A second large-scale meta-analysis that included data from 1.9 million individuals showed a dose-response association curve indicating a lower risk of developing T2DM with low doses of alcohol (<71 g/day), but a higher risk of developing T2DM with higher amounts of exposure; these results were shown only in women. This highlights the need to explore other covariables in the *Alcohol Exposom*e, including diet and lifestyle to give us new insights beyond our present knowledge.

Alcohol and occupational hazards

Alcohol misuse can have dire physical health effects when combined with occupations that expose the worker to hazardous materials, dangerous work conditions, and/or improper work safety measures. Alcohol consumption is one of the main causes of productivity losses arising from absenteeism, presenteeism, and workplace injuries (Sacks et al., 2010). Occupational pollutants affect workers in many industries, including agriculture, firefighting, and trucking. Ramos et al., (2019) used a cross-sectional data analysis to examine alcohol use disorders among Latino farmworkers; results showed that over 30% of 241 workers included in the study also engaged in heavy, frequent alcohol use in the prior year (Ramos et al., 2019). McCaskill et al., (2012) modeled such exposure using mice to determine whether alcohol and organic dusts from swine production facilities, as a coexposure agent, would result in chronic lung disease (McCaskill et al., 2012). Because alcohol blocks airway epithelial cell cytokine release *in vitro*, it was hypothesized that alcohol feeding would alter mouse lung inflammatory responses to dust inhalation (McCaskill et al., 2012). The experiments revealed that non-alcohol mice and alcohol mice had different effects on the regulation of enzymes that slow cilia in the presence of swine barn dust (McCaskill et al., 2012). Alcohol has other pathways in respiratory dysfunction in handling exposures to organic dust. Using a mouse model, Gerald et al., (2016) determined that chronic alcohol exposure dampens the immune response to exposures to hog barn dust by blocking inflammatory mediators tumor-necrosis factor – alpha (TNF-α), interluekin-8, and Interluekin-12 in mice (Gerald et al., 2016). The combination of slowing the mechanical response to clearing out

dust from the airway, added to the reduced immune responses, has the potential to exacerbate the injuries to the respiratory system. While this study and others published on agricultural exposures are in the context of alcohol exposure, many other occupational co-exposures have yet to be researched.

Firefighting is inherently a high health risk occupation; when coupled with chronic alcohol use, it may have health effects that do not represent what would be most obvious (i.e., burn injury). Bird et al., (2008) research focused on the combined insults from exposure to acute ethanol and burn injury on mortality from a pseudomonas infection presented on the skin or trachea, compared to infected mice given ethanol or burn injury alone (Bird et al., 2008). While mice with dual exposure to ethanol and burn injury had elevated serum levels of proinflammatory cytokines (Choy et al., 2023) IL-6 and TNF-α and marked infiltration of leukocytes into the lung and gut, they also showed immunosuppression at the sites of infection (Bird et al., 2008). This evidence supports a need to examine the prevalence of frequent alcohol use among firefighters who could be at higher risk of mortality beyond the inherent dangers of their profession.

Among occupations most affected by alcohol misuse, truck driving involves multiple risk factors (Trumble et al., 2019) and risky behaviors that can have a serious impact on their health, their work, and general road safety. The use of alcohol during truck-driving activities is a risk factor for traffic accidents (Bragazzi et al., 2018). A systematic review and meta-analysis of truck drivers with AUD who have higher exposures to diesel exhaust (Wendt, 2017) and alcohol (Bragazzi et al., 2018) showed a binge drinking prevalence of 19.0% and an AUD prevalence of 22.7%. Stiegel et al., (2017) completed an environmental exposome study linking environmental exposures of diesel exhaust (DE) and ozone for lung inflammatory cytokine biomarkers (Stiegel et al., 2017). The study results revealed that the combination of DE and ozone significantly increased 10 cytokines compared to either exposure alone. The Stiegel et al., (2017) study only included healthy, young male participants, but future research might apply the *Alcohol Exposome* model to target occupational exposures like those experienced by truck drivers or actively deployed military personnel who have higher than average exposures to DE (Stiegel et al., 2017). This would provide a novel method of measuring the total injury burden for individuals working in these types of conditions.

The *Alcohol Exposome* helps uncover the common routes of injury for alcohol and occupational exposures for farmers, firefighters, and truck drivers to be airway tissues; it also reveals the many non-common routes of injuries not shared between these three occupations. In addition to farming, truck driving, and firefighting, there may be other occupations where alcohol misuse can be detrimental. These occupational co-exposures are worth exploring and further defend the need for alcohol exposures to be examined within the multifactorial concept of the *Alcohol Exposome*.

Alcohol and environmental toxins

One of the most complex aspects of the *Alcohol Exposome* is the many environmental coexposures that may result in compound injuries. These environmental covariates may interplay with alcohol exposure from the earliest stages of development with prenatal alcohol exposure and continue throughout the lifespan with coexposures to toxic metals, chemicals, combustion particulate matter, and microplastics (Gerald et al., 2016; McCaskill et al., 2012; Ramos et al., 2019; Sacks et al., 2010; Vancampfort et al., 2016). Alcohol exposure often occurs during fetal development with maternal alcohol misuse. Pre- and post-conception exposure to environmental toxins such as lead are equally common (Gómez-et al., 2021). The most notable alcohol prenatal exposure outcome is fetal alcohol syndrome (Gómez-et al., 2021), which is associated with several cognitive and physiological abnormalities (Pinkerton et al., 2014). The *Alcohol Exposome* gives researchers the framework to substantiate a credible hypothesis that combined alcohol and lead exposures during prenatal development may have multiplicative or compound deleterious effects. Alcohol exposure by itself has been found to alter gene expression (Zhou et al., 2011) and shorten DNA telomeres (Gómez-et al., 2021), and non-epigenetic libraries of gene expressions are being further analyzed with environmental interactions. Once conceived, the child may continue to be exposed to social and home environment factors such as early age of availability to consume alcohol. Prenatally exposed children are more likely to have access to alcohol (Subramoney et al., 2018). In addition to prenatal and childhood exposure injuries, environmental pollution with alcohol also affects adults. Combustion-derived particulate matter (PM) inhalation causes enhanced disease severity in the alcohol-exposed lung by stimulating the release of latent transforming growth factor-β (TGF-β) within alveolar macrophages. The combinatorial effect of elevated TGF-β and increased oxidative stress increases pulmonary dysfunction by increasing airway by compromising alveolar integrity (Thevenot et al., 2013) at any age. Wahlang et al., (2013) describe the environmental exposures, mostly industrial chemicals, which will exacerbate injuries to the liver in patients already diagnosed with alcoholic liver disease (ALD) (Wahlang et al., 2013). Baek et al. (2023) highlight the additive pathophysiological effect of alcohol misuse with accumulation of microplastics in the gut (Baek et al., 2023). As alcohol disintegrates the tight junctions of the epithelium, it allows for microplastics to travel below the surface and reach the lamina propria, where they accumulate and eventually enter the bloodstream. This increases the amount and rate of accumulated deposits of microplastics in the visceral organs (Baek et al., 2023). The covariables of many toxic substances in water, air, and other parts of the environment should be further analyzed whenever quantifying alcohol-related injuries.

Alcohol and infectious agents

Chronic alcohol misuse is an additive cofactor to injuries for multiple infectious diseases (Bird et al., 2008) such pneumonia, acute respiratory distress syndrome (ARDS), SARS-CoV-2 (COVID-19), respiratory syncytial virus (RSV), human immunodeficiency virus (HIV), alcoholic liver disease (ALD) and gut dysbiosis (Armutcu, 2019; Choy et al., 2023; Trumble et al., 2019; Trumble et al., 2019; Wendt, 2017).

Historical evidence

Throughout history, the negative impact of alcohol misuse on suppressing innate immunity leading to increased susceptibility and prolonged duration of infections has been noted. The positive association between alcohol misuse and infectious disease has been clinically documented for centuries. Dr. Benjamin Rush, the first surgeon general of the United States, observed that individuals with alcohol dependency had a higher incidence rate of pneumonia and tuberculosis (Rush, 1823; Yeligar et al., 2016). In 1975, Lundy et al. performed an experiment using samples from 24 male patients who were admitted for acute alcoholic detoxification (Lundy et al., 1975). The experiments were both done *in vivo* and *in vitro*. The *in vivo experiment* involved skin testing using *de novo* antigen dinitrochlorobenzene and inactive tuberculin. The *in vitro* experiment yielded qualitative and quantitative defects in the thymus-derived lymphocytes. Lundy et al. (1975) also observed that these

defects were not seen with recovered alcoholics, making room for a possible argument that these defects might be reversible (Lundy et al., 1975).

Immune dysfunction

Research performed in the last decade continues to show that alcohol misuse negatively affects the immune system. Simet and Sisson (2015) contend that individuals with AUD are more likely to develop ARDS, pneumonia, RSV, and many other lung diseases (Simet et al., 2015). Chronic alcohol consumption exacerbates systemic oxidative stress (Abbasi-Oshaghi et al., 2022). Locally, in the airway, it reduces antioxidant capacity in the alveolar space, which can cause acute lung injury and alveolar epithelial dysfunction. Alcohol misuse can also increase the risk of aspiration and decrease the cough reflex, requiring the individual to undergo mechanical ventilation (Mehta et al., 2017).

People with ALD also have a higher probability for dysfunctional immune responses to infections due to alterations in the *Matrisome* (Baek et al., 2023). Poole and Arteel (2016) explain the concept of the Matrisome, much the way exposomics has developed in many different fields of biological research, as a new method of characterizing the extracellular matrix (ECM) of a cell (Poole et al., 2016). The Matrisome expands the traditional definition of the ECM to include more than just collagen and structural proteins; it includes more specific proteins like chemokines, enzymes, paracrine signaling proteins, and cytokines. Many of the interactions of cytokines and chemokines in the ECM are critical for the migration of inflammatory cells to the site of damaged tissue where they are required for proper immune responses, including the clearance of infection (Poole et al., 2016).

Molina et al., (2014) alcohol abuse altered the immune responses such that it increased the progression of the disease with adverse outcomes for the patients (Molina et al., 2014). The increased injuries were multisystemic, showing increased adverse effects to the heart, lungs, liver, central nervous system, and musculoskeletal system (Molina et al., 2014). New-Aaron et al., (2021) determined that the pancreas is also greatly affected in patients with HIV who are chronic alcohol users (New-Aaron et al., 2021). Premature alcohol-inducing zymogen activation triggers pancreatitis, and when coupled with the increased oxidative stress caused by the attachment of HIV to the acinar cells of the pancreas, it compounds the injuries (New-Aaron et al., 2021).

Respiratory infections

During the recent COVID-19 pandemic, many hospitals were finding a disturbingly profound association with high mortality rates of patients with alcohol misuse disorders. Data analyzed from a cohort study of 12 Colorado hospitals from 2020 to 2021 revealed that alcohol misusers were at greater risk of requiring mechanical ventilation when infected with SARS-CoV-2 (Jolley et al., 2023). An observational cross-sectional study from January to December 2020 revealed that alcohol misuse led to an 89% higher probability of being a higher severity category patient, which was defined as a patient needing emergency department services with ventilation, or death (Bhalla et al., 2021). Alcohol and SARS-CoV-2 had one of the most profound multiplicative deleterious associations documented during a pandemic. Simultaneously, during the lockdown months in the early stages of the pandemic, alcohol consumption was on the rise, especially in people over 50 (Chodkiewicz et al., 2020). The *Alcohol Exposome* would require further examining a third variable that could possibly exacerbate the alcohol misuse-COVID conundrum by factoring in the drastic increased rate of alcohol consumption during the pandemic.

Alcohol misuse decreases alveolar glutathione levels and depletes antioxidants (González-et al., 2014). In addition to oxidative stress, alcohol also changes the function of normal alveolar barrier and alveolar type II cells. Chronic alcohol consumption may interfere with function of tight junctions within the pneumocytes, which can alter epithelial lining fluid and lead to inflammation, all of which will increase the risk of lung infections (González-et al., 2014). Moss et al. (1996) completed a study of 351 intensive care unit patients with AUDs and discovered they were twice as likely to develop ARDS, and these patients had a 51% mortality rate, as opposed to non-alcohol-abusing patients in intensive care units, who only had 20% mortality (Moss et al., 1996). Self-reported alcohol misuse and COVID-19 exhibited a significant positive association with SARS-CoV-2 susceptibility and longer hospitalization (Burnham et al., 2024). When coupled with smoking, alcohol compounds the risk. Smoking and alcohol increase mortality risk factors for pneumococcal infections that result in invasive pneumococcal disease (IPD) (Grau et al., 2014).

Gastrointestinal infections

Alcohol misuse is also associated with Alcoholic Liver Disease (ALD), which can create a host of immune deficiencies, increasing susceptibility to systemic infections (Riva et al., 2018). In people with ALD, the antibacterial potency of gut cells is compromised, creating what is known as the “leaky” gut that causes patient susceptibility to infection (Riva et al., 2018). Samuelson et al., (2019) discovered that alcohol-associated dysbiosis increases *S. pneumoniae* bacterial burden in HIV-infected mice, which supports previous observations of increased severity of bacterial burden in HIV-infected persons (Samuelson et al., 2019).

The *Alcohol Exposome* encourages further evaluation of the prevalence of alcohol-induced chronic liver diseases’ effects and hepatic encephalopathy resulting from increased levels of cerebral ammonia (Butterworth, 2019) as a part of the Gut-Brain axis.

All of these studies provide evidence supporting the need to view alcohol exposure in the framework of the *Alcohol Exposome* to better understand the increased risk for infectious disease burdens in the presence of chronic alcohol exposure. In addition, there is covariable in the *Alcohol Exposome* that could be explored to give us new insights beyond our present knowledge.

Alcohol and aging

A meta-analysis of six national surveys determined significant increases in the prevalence of alcohol use and binge drinking between 2000 and 2016 among those over age 50 in the United States (Grucza et al., 2018; White, 2023). As people age, alcohol misuse has a greater impact on the stressors that accelerate the decline in cellular functions throughout the body (Hajam et al., 2022). Oxidative stress increases with age as free radical byproducts of metabolism accumulate in many tissues in the body (Hajam et al., 2022). The accumulation of oxidative stressors stemming from recurring tissue injuries of the liver with alcohol misuse is an additive injury to the normal accumulation rates expected with aging. Pneumonia is one of the leading causes of death for people over age 65 (Bailey, 2022; Vila-et al., 2009), which can be partially attributed to age-related reduction in mucociliary clearance. Mucociliary clearance is reduced when PKCε, which slows down the ciliary beat frequency, is activated by oxidative stressors (Bailey et al., 2018). Bailey et al. (2018) compared ciliary function of aging Wild-Type (WT) mice and PKCε knockout (KO) mice and determined that aging knockout mice were protected from age-related cilia slowing (Bailey et al., 2018). Bailey et al. (2018) utilized human epithelial cells to support this finding by using siRNA to inhibit the function of

PKCε and once again determined that oxidative stressors decrease ciliary beat frequencies (Bailey et al., 2018). Furthermore, exposing the cells to antioxidants to restore normal ciliary beat frequency may not be effective. Price and Sisson (2019) were unable to reverse airway ciliary damage using several different antioxidative proteins to repair various pathways of oxidative stress injuries (Price et al., 2019). In addition to oxidative stress, there are systemic effects of long-term alcohol misuse.

Alcohol misuse is a significant exposomic factor that can accelerate neurological, genetic, and physical decline as we age. The deleterious effects of alcohol and aging can result in a worsening of neurological functional capacity for fine motor skill, balance, physical orientation, spatial organization, temporal organization, and general motor neuron signaling (Carvalho et al., 2021). Xu et al., (2023) completed a cohort study of epigenome-wide association study (EWAS) on phosphatidylethanol (PEth), an objective measure of current alcohol consumption in the Veteran Aging Cohort Study (VACS), applied the findings to the Yale Stress Center Cohort (YSCC), and determined that alcohol consumption has a significant impact on DNA methylome and alters epigenetic age (Xu et al., 2023).

Alcohol misuse also has been linked to increased injuries to bone tissue with aging. Bone health deteriorates with age as bones lose the ability to regenerate new cells, while continuing to deplete calcium reserves at the same rate, often leading to osteoporosis and brittle bones (Zioupos et al., 2020). A dose-response meta-analysis completed by Godos et al., (2022). revealed an inverse association between alcohol consumption and bone mass density (BMD) in adults between 48 and 79 years of age (Godos et al., 2022). Decreased BMD increases the likelihood of bone fractures with aging (Godos et al., 2022). Alcohol may affect bone development through many pathways, including the inhibition of osteoblast differentiation and hormone dysregulation (López-Larramona et al., 2013; Luo et al., 2017).

Prolonged exposure to alcohol increases the probability of injuries from the macro-organ system level, all the way down to the micro-system genetic level. Therefore, it is essential to include age, and a wide range of age-related variables, when researching alcohol-related injuries.

Conclusion

The *Alcohol Exposome* helps reshape the framework of alcohol injury and pathophysiology studies by attempting to incorporate external factors like environmental, occupational, diet, and lifestyle choices. The *Alcohol Exposome* also encourages including internal biological factors including age, underlying health conditions and pathogens. There is an abundance of data documenting statistically significant associations with alcohol misuse in combination of one or more these internal and external factors, but not as multifaceted as the one dictated by the *Alcohol Exposome*. Medical research on the health effects of alcohol misuse are well established, and much has been learned; yet, many stones may be left unturned when not expanding the scope of the research to view experiments within the expanded view of the *Alcohol Exposome*. Studies have shown that all cells communicate, sometimes unintentionally, through exosomes that are carried through the bloodstream to distant tissues. Ultimately, this random encounter results in pathologies of one organ system indirectly affecting many others, creating many physiological axes like the gut-lung, gut brain, and the liver-lung axis. The next frontier in alcohol research is in examining all forms of organ-cross talk, starting with intercellular components, such as mRNA or chemokines, which are carried in membrane-bound exosomes from one organ to another, eventually entering new cells through endocytosis, or membrane receptor binding mechanisms. Researchers can explore the possibilities of intercellular mRNA transfers that may result in the introduction of new proteins not normally inherent to a particular cell. Experiments can be done at different stages of the cell cycle to determine cell growth variability in the presence of exosomes. Studies can be done to examine various proteins transported into cells in distant organs that might activate certain kinases not normally activated. Nonetheless, these new frontiers are beginning to surface, and alcohol researchers should not shy away from simultaneously or tangentially including many of the other covariables that will impact pathophysiological outcomes.

CRediT authorship contribution statement

Nousha H. Sabet: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Conceptualization. **Todd A. Wyatt:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare no conflict of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Department of Veterans Affairs. The funders had no role in content, decision to publish, or preparation of the manuscript.

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