Gender differences in alcohol-related impairment: a critical review

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Abstract

Introduction

This article is a critical review about the emerging problems in the field of alcohol research. In particular, the gender peculiarities of alcohol effects are highlighted. Up until now, there have not been many gender studies, but results are consistent with the hypothesis that the severity of alcohol-related damage is greater in females than that in males. Differences are due to the physiological differences that make women more vulnerable than men to alcohol effects. The current trend to start alcohol use at increasingly early age and the evidence of more and more females consuming alcohol, enhance the alcohol related risk in public health, justify the request for gender-targeted studies and raise the question as to how the alcohol drinking today will affect the public health of tomorrow? The issue is crucial because alcohol drinking not only affects the health and the behaviour of the persons but also represents a risk for children whose mothers were drinking during pregnancy. Prenatal alcohol exposure affects embryo development and can cause severe neurotoxicity and permanent birth defects, globally defined as fetal alcohol spectrum disorders (FASDs). This article reports the results of some recent studies about gender differences and underlines the need to improve experimental research to support the evidence-based data on alcohol policies of today and tomorrow.

Conclusion

All people, especially young people, must be informed about how alcohol affects the health by short- and long-term impairment. In particular, women have to be clearly informed about the side effects of alcohol drinking and must be advised to avoid alcohol when they are planning a pregnancy and during pregnancy.

Introduction

Framing the Topic

Alcohol abuse is one of the most pressing problems in Western countries. The widespread alcohol problem is due to several factors including easy availability of alcoholic beverages, social acceptance, traditional use of alcohol in the culture, genetics and environmental factors. In many parts of the world, alcohol drinking is a common feature of social gatherings, but the evolution of new life models that are modifying cultural tradition and changing people habits is favouring the spread of alcohol use/abuse even among vulnerable populations such as young people and women. Alcohol misuse carries a lot of adverse health and social consequences, and new risks for public health are emerging. In a recent paper by David Nutt et al., a multicriteria decision analysis (MCDA) modelling was applied to estimate the social impact related to drug abuse in the United Kingdom. For the first time, the burden of addiction disease was strictly quantified in terms of public harm by the evaluation of the 20 most used drugs including alcohol. Each drug was scored on a scale from 0 to 100 points on the basis of 16 selected criteria. Alcohol was demonstrated the most harmful drug for public health, with an overall harm score 72, followed by heroin (score 55) and crack-cocaine (score 54). The innovative approach of the study and the obtained data represent a milestone for effectively evaluating the burden of alcohol disease on public health and for addressing alcohol policies on the basis of evidence-based data. In May 2013, the American Psychiatric Association published the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) after more than a decade of revisions and refinements. The section dealing with alcoholism has raised several criticisms since in the previous version alcohol use disorders were broken down into two categories—alcohol abuse and alcohol dependence—whilst the new manual will have a single diagnosis of alcohol abuse disorders whose severity will be graded by the number of the 11 selected criteria the person meets. The new criteria of DSM-5 are rising, and it is likely that discussion will increase in the near future. The alcohol problems emerging worldwide are (i) the lowering age of the first use of alcohol, (ii) the increasing number of females who drink alcohol at every age, (iii) the increase of at-risk behaviours that include daily alcohol use exceeding the safe limits of alcohol consumption recommended by WHO, i.e. 3 units per day for men and 2 units per day for women; alcohol consumption outside of meals and binge drinking. The Italian National Institute of Statistics reports that in the year 2012, the higher frequency

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of ‘at-risk behaviours’ occurred among people over 65 (40.7% of men and 10.1% of women, female/male ratio = 0.25), young people 18–24 (21.0% male and 9.5% of women, female/male ratio = 0.45) and adolescents 11–17 (12.4% of men and 8.4% of women, female/male ratio = 0.68). Data show that the lower the age the higher the female/male ratio, thus confirming the tendency to narrow the gender gap among adolescents. Today, 67% of Italian women drink alcohol versus 43% in the 1980s. The age range from 35 to 45 includes the most number of women who abuse alcohol and binge drink both with friends and alone. The education level attained in drinking women is mostly higher degree school (73.7%) compared with primary school (43%), as if it were the higher the culture of woman the stronger the tendency to acquire male behaviours. The significant lowering of the age of first alcohol use represents an alarming risk factor for the development of alcohol disorders in the short and long term. Alcohol misuse by young people is mostly associated with an increased risk of acute health conditions and to be victims of traffic accidents, the first cause of death between young people. But this is only the tip of the iceberg. Alcohol can damage all organs but mostly impairs the central nervous system (CNS) functioning. Early alcohol exposure affects adolescent brain strongly since neuroplasticity, which is a special feature of this age, makes young brains more vulnerable to the toxic effects of alcohol than that of an adult. It has been demonstrated that the younger someone starts to drink, the earlier they are likely to experience memory problems and risk the development of alcohol abuse at a later age. Furthermore, the gender effect must be considered. Evidence-based studies show that women are more vulnerable to alcohol’s impairment of brain health, and it was proved that ‘magnitudes of differences in brain volumes adjusted for intracranial size between alcoholic women and non-alcoholic women were greater than the magnitudes of the adjusted differences between alcoholic men and non-alcoholic men’; women are at risk of blackouts and memory lapses more than men even when they consume comparable amounts of alcohol; the risk of future alcoholism increases with the amount of alcohol consumed for both sexes, but the risk for women increases significantly just at a low consumption of 1–7 drinks/week whilst the risk for men increases significantly when more than 22 drinks/week are consumed. Women who drink, especially if young, are more exposed to heavy health consequences as there are more hospital admissions for acute alcohol intoxications, more sexually transmitted diseases, more hormonal disorders and, last but not least, more unwanted pregnancies under twenty. The evidence that today in the female population neurobehavioral diseases such as eating disorders (globally defined eating disorders not otherwise specified) and depression are significantly spreading deserves to be considered and sounds as a chime of alarm: alcohol drinking, depression, eating disorders, could these problems be connected? The National Association of Anorexia Nervosa and Associated Disorders reports that 72% of women who admit to alcohol abuse also classify as suffering from an eating disorder, thus supporting the hypothesis of a link between the two pathological conditions. Recently, it was described as drunkorexia, the media-coined term that identifies the practice of drastically restricting food intake in order to drink more alcohol without gaining weight or to replace food with alcohol to lose weight. Drunkorexia, which is becoming popular mostly among young women, can lead to an array of heavy physical and psychological consequences since alcohol drinking and malnutrition together can heavily impair individual’s cognitive faculties, can increase vulnerability to alcohol poisoning and health injuries and can make easier to-be victims of violence.

As regards depression, WHO data show that the pathology is spreading mostly among women. The one major study conducted by the National Institute on Alcohol Abuse and Alcoholism reports that nearly one-third of people with major depression also have an alcohol problem. Depression can trigger alcohol use mostly in women who are more than twice as likely to start drinking heavily if they have a history of depression. On the other hand, women who misuse alcohol are more likely to show depressive symptoms than those who do not misuse alcohol. It is observed that mood disorders and alcohol dependence frequently co-occur, and recent studies evaluate the hypothesis that alcohol self-medication of mood symptoms increases the probability of alcohol dependence. Furthermore, many studies show that alcohol increases the risk for depression because of its direct neurotoxic action.

Finally, it’s now emerging the possible role of alcohol drinking in the etiology of neurodegenerative disorders such as dementia, the etiological role of alcohol drinking is now emerging. Recent UK studies show that between 10 and 24% of the cases of dementia in United Kingdom, including cases of Alzheimer disease, could be linked to alcohol drinking. Dementia was considered a disease that happens to people over 65, but today a lot of people under 65 have got cognitive problems. The authors of the study hypothesize that a large proportion of the problems in the group under 65 are related to early alcohol drinking and that women are more prone than men to be affected by these pathologies. The aim of this critical review was to discuss the gender differences in alcohol-related impairment.
**Discussion**

The author has referenced some of its own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Animal care was in accordance with the institutional guidelines.

**The Biological Basis of Gender Differences**

Evidence-based data show that women, on equal terms of alcohol intake, have higher blood alcohol concentration (BAC) than men; that women, on equal terms of BAC, show worse results on cognitive/behavioural tests; that women show a ‘telescoping’ effect, that is, more morbidity and mortality in a shorter time and by smaller alcohol consumption than men; that women who abuse alcohol have more involvement than men in legal actions and in interpersonal approaches and are easily victims of violence. These effects are related to physiological gender differences in terms of (i) body mass index and body water; (ii) sexual hormones and (iii) activity of alcohol dehydrogenase (ADH), the main enzymatic way of alcohol metabolism.

**Body Mass Index and Body Water**

Soon after drinking, alcohol dilutes in body water, but the concentration of water in male body is considerably higher than that in female body. As a result, after the same alcohol intake, alcohol concentration in the female blood is higher. Ely et al. demonstrated that if BAC value is normalized according to the amount of body water, gender differences are flattened.

**Sexual Hormones**

Sexual hormones play a pivotal role in alcohol effects since hormones and alcohol affect each other by several ways. Oestrogens affect enzymatic activity of ADH and worsen inflammatory response to ethanol, thus increasing the risk of alcohol pathologies as steatosis, inflammation and necrosis. Furthermore, hormonal changes also affect alcohol metabolism, and some studies show that BAC varies according to the phases of menstrual cycle, and BAC after the same intake is higher in the premenstrual phase (days 24–28) and ovulation (days 13–15). Differences in hormonal pattern may be responsible for the female lowered threshold of alcohol toxicity and/or of the worse effects of alcohol on the female brain. The use of oral contraceptives may worsen alcohol liver injury by hormonal increase of intestinal-derived endotoxins. On the other hand, alcohol affects the balance of sexual hormones and early alcohol use may be responsible for delay in menarche. The frequency of menstrual alterations is dose related with alcohol use; long-term alcohol use affects fertility and induces early menopause. Clinical studies confirm that alcohol drinking increases significantly the risk of breast cancer in adult women. Noticeably, in 2010, Graham et al. conducted a cohort study involving US drinking girls and not drinking girls aged 9–15 years. Results showed that girls who typically drank 6 or 7 days/week were at significantly higher risk of biopsy-confirmed benign breast disease compared with those who never drank or who drank less than once per week. Steroid hormones can also influence the female responsivity to alcohol that tends to change during menstrual cycle. Animal studies show greater sensitivity to alcohol effects in the premenstrual phase. In particular, allopregnanolone, a prototypic neurosteroid that is the metabolite of progesterone, is involved in modulating alcohol effects. In fact, acute alcohol intoxication significantly increases serum progesterone and allopregnanolone levels in both follicular and luteal phases of the ovarian cycle. Since alcohol and allopregnanolone positively modulate gamma-aminobutyric acid type A (GABA(A)) receptors, allopregnanolone may play a major role in enhancing the anxiolytic and rewarding effects of alcohol, either directly or by influencing the sensitivity of GABA(A) receptors to alcohol.

**Activity of Alcohol Dehydrogenase**

ADH is the main enzymatic way of alcohol metabolism, and its activity is influenced by gender and age. Children and adolescents up to 18–20 years of both sexes have low ADH activity and are more vulnerable than adults to alcohol effects. Frezza first demonstrated that enzymatic activity of the gastric isoform ADH that is responsible of the so-called first-pass metabolism (i.e. the first step of ethanol metabolism in the stomach before reaching the liver) is higher in men compared to that in women. Parlesak et al. showed that the gastric ADH activity in young (20–40 years) men is distinctly higher compared to young women, whilst the opposite holds true in middle-aged (40–60 years) subjects. After 60 years, gender differences tend to flatten. The maximum gender difference occurs at 20–40 years when enzymatic activity reaches the maximum for man and the minimum for woman. So, at this age, women are at a greater risk of being sick by the toxic effects of alcohol and, since it is also the most fertile period, even of damaging the foetal development in consequence of prenatal alcohol exposure.

**Alcohol and Pregnancy**

In western countries, prenatal alcohol exposure is the first preventable cause of mental retardation. Many physical and neurological permanent disabilities called foetal alcohol spectrum disorders (FASDs) can appear in children whose mother was drinking...
during pregnancy. The key features of FASDs are growth deficiency, typical facial features, CNS damage and behavioural impairment, but within one individual exposed to prenatal alcohol the key features can vary widely. This makes a correct definition and diagnosis of FASD very difficult, and in particular the evaluation of the CNS damage lacks clear consensus. Up to today, the conclusive factor for the correct diagnosis is to ascertain that the mother was drinking during pregnancy. For clinical studies, several biomarkers are now available to determine prenatal alcohol exposure in blood, urine, hair of mother and meconium and hair of newborn, but the biomarker for conclusive diagnosis of FASD does not exist yet\textsuperscript{24}. Recently, animal studies investigated the influence of the type of alcoholic drink on the neurotrophic factors nerve growth factor and brain-derived neurotrophic factor in mice brain. Ad libitum pure water solution and red wine at the same alcohol concentration (11%) were administered to two groups of mothers starting 60 days before pregnancy and lasting up to pups' weaning. Results show that ethanol solution but not red wine induced behavioural and brain neurotrophin alterations in young and adult mice pups. These differences suggest that substances other than ethanol may contribute to alcohol effect and that the pattern of alcohol drinking may significantly modulate its teratogenic effects\textsuperscript{25,26}. Does a ‘safe alcohol dose’ in pregnancy exist? As far as we know, a safe dose is quite impossible to define since adverse effects can occur even by moderate drinking. The first few weeks are the most at risk, so alcohol abstinence is strongly recommended not only during pregnancy but also when you plan pregnancy.

\textbf{Gender Differences and Clinical Research}

The importance to evaluate alcohol problems in a gender perspective and the need to develop gender-based studies are emerging more and more in the field of alcohol research. In these last years, the results of clinical studies highlight that alcohol impairment is affected by gender and that alcohol-related damage, including brain damage, is heavier in females compared with males. As detailed before, the differences are due to physiological peculiarities that make women more vulnerable to the effects of alcohol, but many of the involved biological mechanisms need to be better understood. Clinical studies are supported by biomarkers research, but up to today, most studies about alcohol biomarkers included almost only male subjects, and the results have been generalized to both sexes. Only in recent years gender studies have been improving, and gender-oriented research is growing because more and more women consume alcohol. Biomarkers of alcohol impairment are classified as \textit{markers of exposure} such as blood ethanol, methanol, acetaldehyde, ethanol metabolites; \textit{markers of effect} such as acetaldehyde adducts, modified haematological and enzymatic (AST, ALT, GGT) pattern-impaired immunological parameters and \textit{markers of susceptibility} such as genetic polymorphisms of CYP3E1, ADH, serotonin transporters and dopamine receptors\textsuperscript{17}. Only some of these biomarkers were studied in terms of gender comparison. A typical example of gender difference regards the carbohydrate-deficient transferrin (CDT) a very popular alcohol biomarker that increases significantly in case of alcohol abuse. In men, this biomarker shows high specificity and sensitivity, but in women it is less effective since it is affected by iron deficiency and hormonal status. Female CDT decreases after menopause and, when contraceptives are used, increases in premenopausal phase, changes in different menstrual phases and reaches the maximum level during menstruation. Noticeably, during pregnancy, the percentage of the disialotransferrin, which is considered the most significant molecule to evidence alcohol abuse, increases physiologically and it is not dependent on alcohol intake. The CDT reaches the maximum concentration in the last three months of pregnancy and it returns to the reference limit after delivery\textsuperscript{28}.

An important topic in alcohol research is the study of the interplay relationship between a person’s alcohol consumption and nutritional status. Alcohol can alter intake, absorption and utilization of various nutrients and exerts harmful effects through its metabolism and the resulting toxic compound. On the consequences, NIAAA says that ‘Diet quality worsens as alcohol intake increases’\textsuperscript{29}. A severe occurrence in alcohol abusers may be the deficiency of vitamin B1 (thiamine). Thiamine is a coenzyme in three major enzymatic complexes—pyruvate dehydrogenase, alfa-ketoglutarate dehydrogenase and transketolase. In western countries, thiamine deficiency (TD) is due in most cases to alcohol abuse in consequence of poor nutrition, decreased absorption, liver diseases and impaired phosphorylation. The brain receives energy from aerobic oxidation of glucose and so it is the first organ affected by TD that produces heavy damage as the Wernicke–Korsakoff syndrome. Clinical symptoms of TD are frequently ill-defined, and most cases of WKS are diagnosed only post-mortem. Our clinical studies showed that TD may be considered a biomarker of alcohol abuse and that TD is heavier in females than in males, even when the female length of alcohol abuse is significantly shorter than that of males\textsuperscript{30}. This is consistent with the so-called ‘telescoping effect’ mentioned above. TD may be enhanced during pregnancy by poor nutritional status (e.g. due to hyperemesis gravidarum) and may represent a further risk for the development of FASDs. Metabolic impairment due to alcohol abuse
provides a further negative effect: the overgeneration of the so-called reactive oxygen species (ROS) and the consequent condition of oxidative stress (OS), that is the imbalance between the overproduction of ROS and the decreased body antioxidant defence. The presence and the grade of oxidative stress can be evaluated by several biomarkers. Recent studies show that biomarkers of OS can be effectively used as biomarkers of alcohol impairment and that women are more likely to be exposed to OS effects\(^\text{31}\). During pregnancy, even sporadic alcohol exposure can alter the intracellular redox equilibrium. Alcohol OS can directly damage the brain since brain is the greatest oxygen consumer in the body and foetal antioxidant defence is less effective than that of an adult\(^\text{32}\). Furthermore, alcohol-related OS can act indirectly too by impairing the development of placenta and thus affecting the embryo health\(^\text{33}\).

Conclusion

All people, especially young people, must be informed about how alcohol affects the health by short- and long-term impairment. In particular, women have to be clearly informed about the side effects of alcohol drinking and must be advised to avoid alcohol when they are planning a pregnancy and during pregnancy. It is advisable that the development of experimental research in the frame of collaboration research projects will increasingly support by evidence-based data the action and policy against alcohol damage. All people that are responsible for public health are required to make their own contribution to improve knowledge and to promote the prevention of alcohol-related damage.

References