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#### Review

# Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations

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#### ABSTRACT

Aims: To review the contemporary evidence reflecting male/female differences in alcohol use and its consequences along with the biological (sex-related) and psycho-socio-cultural (gender-related) factors associated with those differences.

*Methods*: MEDLINE, PubMed, Web of Science, SCOPUS, PsycINFO, and CINAHL databases were searched for relevant publications, which were subsequently screened for the presence/absence of pre-specified criteria for high quality evidence.

Results: Compared to men, more women are lifetime abstainers, drink less, and are less likely to engage in problem drinking, develop alcohol-related disorders or alcohol withdrawal symptoms. However, women drinking excessively develop more medical problems. Biological (sex-related) factors, including differences in alcohol pharmacokinetics as well as its effect on brain function and the levels of sex hormones may contribute to some of those differences. In addition, differences in alcohol effects on behavior may also be driven by psycho-socio-cultural (gender-related) factors. This is evident by variation in the magnitude of differences in alcohol use between countries, decreasing difference in the rates of alcohol consumption in recent generations and other findings. Evidence indicates that both sex and gender-related factors are interacting with alcohol use in complex manner, which differentially impacts the risk for development of the behavioral or medical problems and alcohol use disorders in men and women. Conclusions: Discovery of the mechanisms underlying biological (sex-related) as well as psycho-socio-cultural (gender-related) differences in alcohol use and related disorders is needed for development of personalized recommendations for prevention and treatment of alcohol use disorders and related problems in men and women.

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#### 1. Introduction

The World Health Organization (WHO) 2014 global status report on alcohol and health indicates that individuals of 15 years and older consume, on average, 6.2 L of pure alcohol per year (or 13.5 g per day), and that 139 million disability-adjusted life years (DALYs), or 5.1% of the global burden of disease and injury, are attributable to alcohol consumption (WHO, 2014).

Substantial male/female differences in risk for acquiring medical or psychiatric diseases as well as their signs, symptoms, pathophysiology, and treatment response have been reported across the lifespan (Becker et al., 2006). In 2012, males/females ratio of current drinkers varied between 1.3 and 4.3 in different countries, while 3.3 million deaths (5.9% of all global deaths), including 7.6% of deaths among males and 4.0% of deaths among females were attributed to alcohol consumption (WHO, 2014). An understanding of the biological (sex-related) mechanisms as well as psycho-socio-cultural (gender-related) factors contributing to such differences is necessary for efficient diagnosis, prevention and treatment of alcohol use disorders and related problems in men and women.

Previously published articles reviewed a considerable body of evidence addressing specific aspects of male/female differences in alcoholic liver injury (Eagon, 2010), alcoholic cardiomyopathy (Fernandez-Sola and Nicolas-Arfelis, 2002), hypertension related to alcohol consumption (Briasoulis et al., 2012), alcohol withdrawal (Devaud et al., 2006), alcohol induced brain damage (Hommer, 2003), alcohol drinking patterns (Holmila and Raitasalo, 2005; Roche and Deehan, 2002), alcohol related behavioral or medical problems (Bradley et al., 1998; Nolen-Hoeksema, 2004; Nolen-Hoeksema and Hilt, 2006; Redgrave et al., 2003), as well as epidemiology of alcohol use and misuse in adults (Keyes et al., 2011; Redgrave et al., 2003), and alcohol use in adolescence (Schulte et al., 2009; Witt, 2007). Reviews of male/female differences in prevalence of alcohol use disorders, physical effects of alcohol, use of treatment services, and recovery (Greenfield, 2002), as well as differences in alcohol consumption, metabolism, effects on the brain and certain receptor systems that could be involved in alcohol abuse (Ceylan-Isik et al., 2010), were also published. In addition, several review papers focused only on women-specific effects of alcohol, such as impact on older women (Blow and Barry, 2002; Epstein et al., 2007), female hormone levels and reproductive system (Dees et al., 2001; Gill, 2000), breast cancer risk (Brooks and Zakhari, 2013; Scoccianti et al., 2014; Seitz et al., 2012; Singletary and Gapstur, 2001), alcohol use in pregnancy (Zelner and Koren, 2013), and alcohol related medical and behavioral problems (Wilsnack et al., 2013). To facilitate a more practical approach to available data and development of sex and gender-specific therapeutic interventions, we present this review of contemporary evidence describing male/female differences in alcohol use and its consequences in the context of biological (sex-related) vs. psycho-socio-cultural (gender-related) factors associated with these differences. For this purpose, and in accordance with the common practice, we used term "sex" while referring to biological and "gender" referring to psycho-social and cultural factors (Alex et al., 2012).

### 2. Methods

The MEDLINE, PubMed, Web of Science, SCOPUS, PsycINFO and CINAHL databases were searched for articles or abstracted published in English in peer  $\,$ 

reviewed journals using two sets of keywords: (1) medical subject headings (MeSH) terms of alcohol drinking, alcoholism, and text words of alcohol consumption, alcohol dependence, and alcohol abuse, (2) MeSH terms of men, women, male, female, and text words of sex differences and gender differences. Boolean indicator "or" was used between the same set of terms. Boolean indicator "and" was used between two sets of terms. Articles meeting the following criteria were included in the review.

#### 2.1. Type of studies

Published articles were reviewed for the presence of a study design description (e.g., inclusion/exclusion criteria), type of data collected (e.g., sample size, baseline population characteristics, and clinical outcomes), methodology (e.g., randomized vs. nonrandomized), and type of outcome measures (e.g., alcohol consumption, alcohol dependency diagnosis, alcohol related disorders diagnosis). No restriction was imposed on studies with respect to blinding, type of design, presence or absence of randomization or the time of publication. We used previously published narrative and meta-analytic reviews to illustrate areas of research addressed in previous publications. We also cited findings from the review articles (alongside with the original research papers) to define contemporary evidence related to the scope of our article.

#### 2.2. Type of participants

Review papers, clinical and experimental studies conducted in humans. No restriction was imposed on studies with respect to age, sex, and racial/ethnic background.

#### 2.3. Type of outcome measures

We included studies that described and compared rates of alcohol drinking, alcohol dependence and alcohol abuse in males and females; studies that described and compared alcohol drinking patterns, course of alcohol drinking and alcohol use disorders, alcohol related behavioral and medical problems, alcohol related morbidity and mortality rates in males and females; studies that described and compared alcohol pharmacokinetics and its impact on the brain in males and females; studies that described and compared the effects of alcohol on sex hormones in males and females.

Studies lacking an adequate description of those above mentioned characteristics as well as duplicated publications were excluded.

#### 3. Results

The initial search identified 5995 articles, which were prescreened in accordance with the step-wise selection process presented in Fig. 1 and inclusion criteria described above. Accordingly, we selected 266 articles (237 original research papers and 29 review papers), which were included for detailed review presented below. Of those, 81 articles described male/female differences in alcohol use and misuse, 121 described differences in alcohol related behavioral or medical problems, 35 addressed differences in alcohol pharmacokinetics and its impact on the brain function, while 29 articles described the effects of alcohol on sex hormones. Table 1 presents a summary of publications addressing behavioral and physiological aspects of alcohol use, its consequences, attribution to sex vs. gender-related effects included in this review. We also indicate geographic area and/or country where research was conducted to reflect the extent of generalizability of findings.

#### 3.1. Male/female differences in alcohol use and misuse

The US National Survey on Drug Use and Health conducted in 2013, estimated that 57.1% of males and 47.5% of females aged 12 or older were current drinkers (SAMHS, 2014). Recent WHO report indicates higher per capita alcohol consumption (between 1.7 and 3.2 in different countries) and lower prevalence of lifetime abstainers in males compared to females (WHO, 2014).

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