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Sex hormones in alcohol consumption: a systematic review of evidence

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ABSTRACT

Sex hormones play an important role in establishing sex-distinctive brain structural and functional variations that could contribute to the sex differences in alcohol consumption behavior. Here, we systematically reviewed articles that studied sex hormone impacts on alcohol consumption and alcohol use disorder (AUD). An extensive literature search conducted in MEDLINE, PubMed, Scopus and CINAHL databases identified 776 articles, which were then evaluated for pre-specified criteria for relevance and quality assurance. A total of 50 articles, including 19 human studies and 31 animal studies, were selected for this review. Existing evidence supports the association of increased testosterone level and increased risk for alcohol use and AUD in males but results are inconclusive in females. In contrast, the evidence supports the association of increased estrogen level and increased alcohol use in females, with mixed findings reported in males. Much less is known about the impact of progestins on alcohol use and misuse in human subjects. Future observational and experimental studies conducted in both sexes with a comprehensive hormone panel are needed to elucidate the impact of the interplay between various sex hormone levels during various developmental stages on alcohol use-related phenotypes and AUD.

Keywords alcohol use, alcohol use disorder, gonadal steroid hormones, sex hormones.

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INTRODUCTION

Sex hormones (also known as gonadal steroid hormones) regulate sexual differentiation, secondary sex characteristics and sexual behavior patterns and are crucial for proper development and body functioning. Gonads (ovaries and testes) are the major sources of sex steroids, although adrenal cortex, placenta, and to a lesser extent other tissues also contribute to their production at various phases of development and in the adult life. Steroidogenesis of the gonadal sex hormones is by definition sexually dimorphic, involving differences in hormonal action, regulation and temporal pattern of production (Svechnikov & Soder 2008). They play a major role in the establishment of sex differences in brain structure and function (Sisk & Zehr 2005), and therefore are primary targets for the investigation of sex-related differences in alcohol effects. Three main classes of sex steroids are known as androgens, estrogens and progestogens (or progestins), of which the most important human derivatives are testosterone, estradiol and progesterone, respectively (Little 2013).

Although present in the body throughout life, the strongest surges of sex hormones typically occur prenatally—driving the development of primary sex characteristics and neuroanatomical organization—and during puberty—driving the development of secondary sex characteristics and affecting the existing neural establishment (Sisk & Zehr 2005). These effects make the prenatal and adolescent brains highly sensitive to time-specific, graded effects of sex hormones (Sisk & Zehr 2005). In females, estradiol and progesterone concentrations are lower during the follicular phase, which starts with menses and ends

with the beginning of ovulation, and are higher during the luteal phase, which starts with ovulation and ends with the beginning of menses (Stricker *et al.* 2006). Estrogen and progesterone are able to interact with neurotransmitters such as dopamine and γ-aminobutyric acid (Barth, Villringer, & Sacher 2015), which are thought to be important in mediating the effects of ethanol (Morrow *et al.* 2001; Garbusow *et al.* 2014). Therefore, it is possible that circulating ovarian hormones may influence not only the acute effects of alcohol but also the long-term alcohol consumption behavior.

Epidemiology studies conducted in the United States and other countries demonstrate huge disparity in the amount and pattern of alcohol use between men and women (Substance Abuse and Mental Health Services Administration 2014; Gowing *et al.* 2015). In our review, we also found contemporary evidence indicating that the differences in alcohol use and related disorders between males and females could be driven by both psycho-socio-cultural (gender-related) and biological (sex-related) factors (Erol & Karpyak 2015). Moreover, the species-specific sex differences in alcohol sensitivity and drinking patterns tend to emerge gradually from late puberty, supporting the notion of gonadal hormones influence on alcohol intake (Witt 2007). Not surprisingly, the relationship between sex hormones, as the major biological factors contributing to sex-related differences, and alcohol-related phenotypes has been extensively explored. There are several review articles summarizing the evidence related to the effects of alcohol consumption on sex hormones (Longnecker & Tseng 1998; Purohit 1998; Shulman & Wolf 1999; Gill 2000; Devaud, Risinger, & Selvage 2006), while several others reviewed the effects of specific sex hormones on specific alcohol-related phenotypes or in certain subgroups of subjects (Morrow *et al.* 1999; Morrow *et al.* 2001; Witt 2007; Lenz *et al.* 2012). Here, we present a comprehensive systemic review on the human and animal studies that investigated the influence of sex hormones on alcohol use and alcohol use disorder (AUD) in males and females, with an emphasis on such influence during different periods of development and on interspecies variations.

MATERIAL AND METHODS

Literature search strategy, article selection and data abstraction

MEDLINE, PubMed, Scopus and CINAHL databases were searched for articles published in English and describing human experimental and clinical studies investigating the influence of sex hormones on alcohol-related phenotypes. Two sets of terms were used: (1) sex hormones (with medical subject headings terms of gonadal steroid hormones, testosterone, androgens, estradiol, estriol, estrone, estetrol, estrogens and progestins); (2) alcohol (with medical subject headings terms of alcoholism, alcohol drinking, ethanol, and text words of alcohol abuse, alcohol dependence, problem drinking and AUDs). Boolean indicator 'and' was used between the two sets of terms, and Boolean indicator 'or' was used in between terms from the same set. Last literature research was conducted in June 2017. Bibliographies of the selected articles were searched for additional relevant studies. Identified articles were reviewed for the presence of characteristics related to study design, type of collected data, methodology and outcome measures defined in Table 1. Studies lacking an adequate description of those characteristics, as well as duplicated publications, were excluded.

RESULTS

Screening results

This systemic review follows the guidelines of the Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA; Moher 2009).

A total of 776 articles were identified using the aforementioned search method. The inclusion/exclusion process shown in Fig. 1 resulted in a selection of 50 articles, which include 19 human studies and 31 animal studies.

Description of the articles selected for review

Of the 50 included studies, 18 examined the effects of androgens, 29 examined the effects of estrogens and 11 examined the effects of progestins. Some studies investigated more than one sex hormone.

The included human studies varied in the use of outcome measures (e.g. alcohol consumption, AUD diagnosis and AUD symptoms), the period of development (prenatal, adolescence or adulthood) where the associations between sex hormone levels and current or later-in-life alcohol use were examined, the source of the measured sex hormone or the biological cause of the sex hormone fluctuation and the sex hormones investigated. All of these human studies were observational except for one experimental trial (Little *et al.* 1980). Descriptions of the methodology and alcohol use-related outcome measures of the 19 selected human studies are summarized in Table 2 and in more details, in Table S1.

In contrast, the included animal studies encompassed both experimental and observational designs and used alcohol intake as well as the rewarding and aversive effects of alcohol as outcome measures. Similar to the human studies, the animal studies also differed in the period of development where the associations between sex hormones and alcohol intake and/or effects were examined, the intervention for generating sex hormone fluctuation

Table 1 Screening criteria for identified articles.

Inclusion Criteria	
Publication language	•English: in full text
Journal type	•Peer reviewed articles •Full text available
Type of studies	•Clinical or preclinical •Observational or experimental •Case/control, healthy subject-only and population-based studies are accepted
Subjects	•Human: no restriction on age, sex, racial/ethnic background or population •Animal: no restriction on species •Detailed descriptions of subject/cohort characteristics, inclusion/exclusion criteria and sample size required
Outcome measures	•Examined the influence of endogenous or exogenous sex hormones on alcohol-related phenotypes, or their associations •Alcohol-related phenotypes: amount or frequency of alcohol intake, diagnoses of alcohol dependency or alcohol use disorders •Detailed definitions of outcome measures required
Exclusion Criteria	•Focused on other substance use •Focused on problems other than alcohol related effects •Investigated effects of alcohol on sex hormone •Focused on influence of sex hormones in alcohol metabolism •Lack of descriptions of study cohort/population or results •Duplicated publications or data

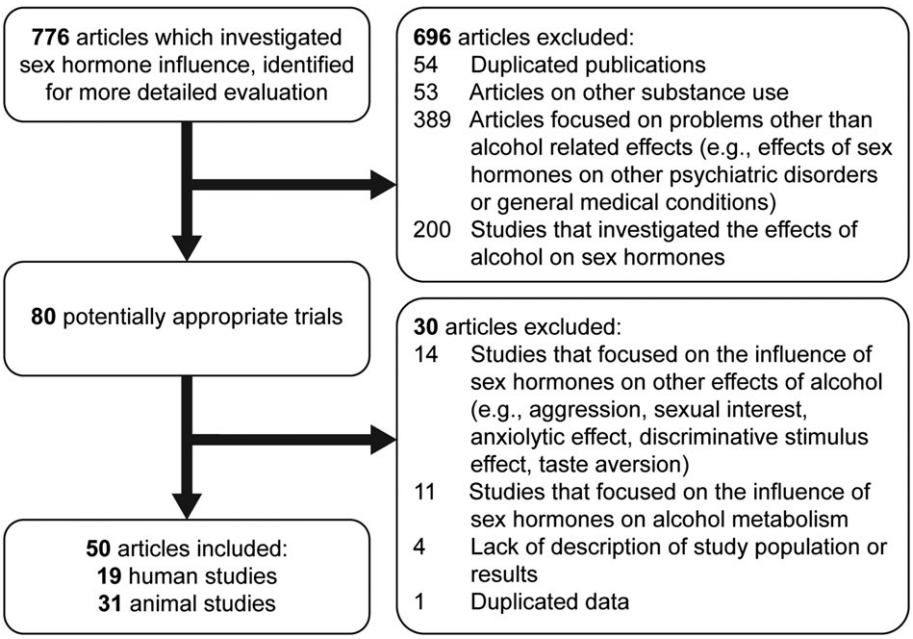

Figure 1 Article screening process

and in the sex hormones investigated. Descriptions of the methodology and alcohol use-related outcome measures of the 31 selected animal studies are summarized in Table 3 and in more details, in Table S2.

The impact of androgen levels on alcohol use and AUD

Four retrospective studies investigated the association of the prenatal exposure to excessive androgen levels with alcohol use or AUD diagnosis in adults (Lenz, Muller, & Kornhuber 2012; Ellingson *et al.* 2013; Falhammar *et al.* 2014; Lenz *et al.* 2017). Using prenatal androgen loads, an index derived from various prenatal androgen markers such as second-to-fourth finger length ratio (2D:4D ratio), transient evoked otoacoustic emissions and the age of puberty onset, Lenz *et al.* (2017) found that prenatal androgen load was higher in male alcohol-dependent patients compared with controls and

Table 2 Methodology and outcome measures of the human studies included in the review.

Reference	*Outcome measures*			*Time of (abnormal) sex hormone exposure*			*Sources of sex hormones or their fluctuation*			*Sex hormone investigated*		
	Alcohol consumption	*Diagnosis of AUD or alcohol dependence*	*Others*	*Prenatal*	*Adolescents*	*Adults*	*Blood/saliva*	*Prenatal*	*Menstrual cycle*	*Androgens*	*Estrogens*	*Progestins*
Braams *et al.* (2016)	Yes				Yes	Yes	Saliva			Yes		
Costello *et al.* (2007)	Yes	Yes			Yes		Blood			Yes	Yes	
de Water *et al.* (2013)	Yes				Yes		Saliva			Yes	Yes	
Ellingson *et al.* (2013)	Yes		AUD symptoms	Yes				Congenital adrenal hyperplasia		Yes		
Eriksson *et al.* (2005)	Yes	Yes			Yes		Saliva			Yes		
Falhammar *et al.* (2014)		Yes	Comorbid psychiatric disorders and suicidality	Yes				Androgen transfer by male co-twin		Yes		
Harvey & Beckman (1985)	Yes					Yes			Yes		Yes	
Holdstock & de Wit (2000)	Yes		Ethanol effects (subjective, behavioral and physical)			Yes			Yes		Yes	
La Grange *et al.* (1995)	Yes					Yes	Blood			Yes		
Lenz *et al.* (2017)		Yes	Alcohol-related hospital readmissions and withdrawal syndrome	Yes		Yes	Blood	2D:4D, TEOAE, age at onset of puberty		Yes		

Table 2. (Continued)

Reference	*Outcome measures*			*Time of (abnormal) sex hormone exposure*			*Sources of sex hormones or their fluctuation*			*Sex hormone investigated*		
	Alcohol consumption	*Diagnosis of AUD or alcohol dependence*	*Others*	*Prenatal*	*Adolescents*	*Adults*	*Blood/saliva*	*Prenatal*	*Menstrual cycle*	*Androgens*	*Estrogens*	*Progestins*
Lenz *et al.* (2012)		Yes		Yes				Androgen transfer by male co-twin		Yes		
Little *et al.* (1980)	Yes					Yes					Yes	
Mello *et al.* (1990)	Yes		Premenstrual symptoms			Yes			Yes		Yes	
Muti *et al.* (1998)	Yes					Yes	Blood				Yes	
Pastor & Evans (2003)	Yes		Mood changes			Yes			Yes		Yes	
Peters *et al.* (2015)	Yes				Yes		Saliva			Yes		
Stalenheim *et al.* (1998)		Yes	Personality and behaviors			Yes	Blood			Yes		
Sutker *et al.* (1983)	Yes		Mood changes			Yes			Yes		Yes	
Wu *et al.* (1995)			Life style			Yes	Blood			Yes		

2D:4D = two-to-fourth finger length ratio; AUD = alcohol use disorder; TEOAE = transient evoked otoacoustic emissions.

Table 3 Methodology and outcome measures of the animal studies included in the review.

Reference	*Species*	*Outcome measures*			*Interventional*		*Observational*	*Stage of intervention/observation*			*Sex hormone investigated*		
		EtOH intake	*EtOH reward*	*EtOH aversion*	*Gonadectomy*	*Sex hormone administration*		*Prenatal*	*Adolescent*	*Adult*	*Androgens*	*Estrogens*	*Progestins*
Almeida *et al.* (1998)	Rats	Yes			Yes	Yes				Yes	Yes	Yes	Yes
Besheer *et al.* (2010)	Rats	Yes				Yes				Yes			Yes
Cailhol & Mormede (2001)	Rats	Yes			Yes					Yes	Yes	Yes	
Ford *et al.* (2002a)	Rats	Yes			Yes	Yes				Yes		Yes	
Ford *et al.* (2002b)	Rats	Yes					Estrous cycle			Yes		Yes	
Ford *et al.* (2004)	Rats	Yes			Yes	Yes				Yes		Yes	
Ford *et al.* (2007)	Mice	Yes				Yes				Yes			Yes
Forger & Morin (1982)	Rats	Yes			Yes					Yes		Yes	
Gurkovskaya *et al.* (2009)	Rats	Yes				Yes				Yes			Yes
Hilakivi-Clarke (1996)	Mice	Yes				Yes				Yes		Yes	
Janak *et al.* (1998)	Rats	Yes				Yes				Yes			Yes
Janak & Gill (2003)	Rats	Yes				Yes				Yes			Yes
Juarez *et al.* (2002)	Rats	Yes			Yes	Yes				Yes		Yes	
Lakoza & Barkov (1980)	Rats	Yes			Yes	Yes				Yes	Yes	Yes	Yes
Llido *et al.* (2016)	Rats	Yes				Yes				Yes			Yes
Mankes *et al.* (1991)	Rats	Yes					Intrauterine sibling contiguity	Yes		Yes			
Marinelli *et al.* (2003)	Rats	Yes				Yes				Yes		Yes	
Mello *et al.* (1986)	Macaque monkey	Yes					Estrous cycle			Yes		Yes	
Quirarte *et al.* (2007)	Rats	Yes			Yes	Yes				Yes		Yes	
Rajasingh *et al.* (2007)	Mice	Yes			Yes	Yes				Yes		Yes	
Reid *et al.* (2002)	Rats	Yes								Yes		Yes	
Reid *et al.* (2003)	Rats	Yes				Yes				Yes		Yes	
Rezvani & Levin (2014)	Rats	Yes				Yes				Yes			Yes
Roberts *et al.* (1998)	Rats	Yes					Estrous cycle			Yes		Yes	
Sandberg & Stewart (1982)	Rats	Yes			Yes	Yes				Yes		Yes	
Sherrill *et al.* (2011)	Rats	Yes			Yes					Yes	Yes	Yes	
Sinnott *et al.* (2002)	Mice	Yes				Yes				Yes			Yes
Torres *et al.* (2014)	Rats		Yes	Yes			Estrous cycle		Yes	Yes		Yes	
Vetter-O'Hagen & Spear (2011)	Rats	Yes			Yes				Yes	Yes	Yes	Yes	
Vetter-O'Hagen & Spear (2011)	Rats	Yes			Yes	Yes				Yes	Yes		
Wolfe *et al.* (2000)	Rats	Yes				Yes				Yes			Yes

was correlated positively with alcohol withdrawal severity. Higher prenatal androgen loads were also correlated with more frequent 12-month hospital readmissions independent of sex (Lenz *et al.* 2017). Falhammar *et al.* (2014) reported an increased frequency of alcohol misuse in 253 males born with congenital adrenal hyperplasia (results in androgen over-production) compared with 25 300 age-matched male controls. *In utero* transfer of sex hormones between fetuses renders the study of opposite-sex twins a valuable tool for prenatal sex hormone exposure (Miller 1994). Using two large-scale twin registries, Lenz *et al.* (2012) reported decreased prevalence and rate of hospitalization for alcohol dependence in males with male co-twin (presumably resulting in exposure to higher testosterone levels) compared with males with female co-twin (interpreted as no additional testosterone exposure throughout pregnancy), while no association with the same phenotypes was found in females regardless of co-twin's sex. In line with these findings was a rodent study by Mankes *et al.* (1991), which demonstrated that male rats developed between male siblings *in utero* had lower alcohol preference in adulthood compared with those rats developed between female siblings; such a difference was not found in female rats of either contiguity group. Nevertheless, in humans, Ellingson *et al.* (2013) observed more lifetime AUD symptoms (not AUD diagnosis or alcohol consumption) in females with male co-twin compared with females with the same-sex twin or females with same-sex twin pairs with close-in-age brother.

Five studies investigated the association between testosterone levels and alcohol use in adolescents. A twin study in adolescent boys found higher saliva testosterone levels to be associated with increased alcohol use, more frequent diagnosis of alcohol dependence and more alcohol dependence symptoms (Eriksson *et al.* 2005). Another large-scale study found that higher salivary testosterone levels correlated with earlier onset of alcohol use in adolescent boys but not in girls (de Water *et al.* 2013). Furthermore, higher total blood testosterone levels were associated with increased risk of alcohol use in adolescent males but not females (Costello *et al.* 2007) and higher salivary testosterone levels were found to predict alcohol use 2 years later in adolescents and young adults (Braams *et al.* 2016). Interestingly, one study reported that in adolescent boys, the effect of testosterone level on alcohol use was indirect and was mediated by amygdala-orbitofrontal cortex intrinsic functional connectivity, which was associated with behavioral approach behaviors such as risk taking (Peters *et al.* 2015).

Another four studies investigated the relationship between testosterone levels and alcohol consumption in adults. In males undergoing forensic psychiatric evaluation, high blood testosterone levels were found to be associated with type II alcoholism, which is characterized by early onset (before age 15), comorbid abuse of other drugs, disruptive behavior and criminality and early efforts at abuse treatment (Stalenheim *et al.* 1998). In a sample of college students, higher blood testosterone level was correlated with higher alcohol use in both male and female subjects, with a stronger effect in males (La Grange *et al.* 1995). In terms of the sex-specific effect of testosterone, another study also reported higher blood dihydrotestosterone level in early abstained alcohol-dependent males than controls, but not in alcohol-dependent females (Lenz *et al.* 2017). However, no association between alcohol use and serum testosterone levels (total, free, bioavailable and dihydrotestosterone levels) was found in a study of 1127 older men (mean age of 69.9), which may be attributed to age-related decline in testosterone levels or other factors including growing levels of sex hormone binding globulin (Wu *et al.* 1995). Lenz *et al.* (2017) found that blood bioavailable dihydrotestosterone levels were reduced in general between early abstinence and 12-month follow up in both male and female AUD patients. Interestingly, AUD patients with elevated dihydrotestosterone levels reported more alcohol-related hospital readmissions and sooner for their first readmission in 12 months compared with those with reduced dihydrotestosterone levels (Lenz *et al.* 2017).

The impact of estrogen levels on alcohol use

Two population-based studies investigated the relationship of estrogens on alcohol use in adolescents (Costello *et al.* 2007; de Water *et al.* 2013). de Water *et al.* (2013) reported higher salivary estradiol level to be associated with earlier onset and higher quantity of alcohol use in boys but not in girls. Costello *et al.* (2007) also found no association between blood estradiol level and alcohol use in adolescent females. It should be noted that while the latter study did not control for menstrual cycle phase, the former study collected samples during early follicular phase during which estradiol level is low.

Two studies investigated the association between estradiol level and alcohol consumption in adult women with precise monitoring of menstrual cycle phase (Harvey & Beckman 1985; Muti *et al.* 1998). Harvey & Beckman (1985) found no changes in the *frequency* of alcohol consumption throughout the menstrual cycle in female social drinkers but it should be noted that the *quantity* of consumption peaked at the luteal phase compared with other phases. Muti *et al.* (1998) measured estradiol level in blood collected from premenopausal women during luteal phase on the same month, day, hour and minute 1 year apart and found a significant positive association between estradiol level

and alcohol intake and a higher prevalence of drinkers in subjects with consistently higher estradiol level. In addition, an observational study reported increased alcohol consumption during menstruation in female social drinkers but not in those using oral contraceptives (Sutker *et al.* 1983). Another observational study also found higher alcohol use during menses compared with follicular and luteal phases in moderately drinking females (5–10 drinks/week) but not in heavy (≥11 drinks/week) or light (1–4 drinks/week) drinkers (Pastor & Evans 2003). It should be noted that the classification of heavy, moderate and light drinkers and the definitions of various menstrual phases were different between those studies. An experimental investigation of the effects of premenstrual dysphoria on alcohol acquisition and use pattern conducted in a clinical research ward demonstrated increased drinking compared with baseline only in women (five out of 14) who also demonstrated an impaired social functioning and emotional dysregulation during premenstrual phase (Mello, Mendelson, & Lex 1990). No difference in alcohol effects and consumption after a priming dose of alcohol during various menstrual cycle phases was found in healthy adult women participating in a human laboratory study (Holdstock & de Wit 2000). Furthermore, no significant change in alcohol consumption after oral intake of estradiol (4 mg/day) was observed in a double-blind experimental study including healthy young women (Little *et al.* 1980).

The majority of animal studies also found positive associations between estrogen levels and alcohol intake in females (Forger & Morin 1982; Mello, Bree, & Mendelson 1986; Reid *et al.* 2002; Ford, Eldridge, & Samson 2002a; Marinelli, Quirion, & Gianoulakis 2003; Reid, Hubbell, & Reid 2003; Quirarte *et al.* 2007; Rajasingh *et al.* 2007; Sherrill *et al.* 2011; Torres *et al.* 2014). For example, an experimental study in female monkeys found decreased ethanol intake during menstrual phase (when estrogen levels are low) compared with mid-cycle or the late luteal phase (Mello *et al.* 1986). However, a study in female rats showed increased ethanol consumption during diestrus (when estrogen levels are low) than both proestrus (when estrogen levels are high) and estrus (when estrogen levels are lowest; Roberts *et al.* 1998). Moreover, findings indicate that the effects of estrogen on ethanol consumption in female rodents may depend on the dose of estradiol, as well as the presence or absence of gonads (Forger & Morin 1982; Sandberg & Stewart 1982; Hilakivi-Clarke 1996; Almeida *et al.* 1998; Ford et al. 2002a; Ford, Eldridge, & Samson 2004; Sherrill *et al.* 2011; Torres *et al.* 2014). On the contrary, in male rodents, estradiol was shown both to stimulate ethanol intake (Lakoza & Barkov 1980; Hilakivi-Clarke 1996) and to reduce voluntary alcohol consumption (Juarez, De Tomasi, & Virgen 2002).

The impact of progestin levels on alcohol use

We found no human studies that examined the relationship between progestins and alcohol use. However, there were reports cited earlier in this review (Harvey & Beckman 1985; Muti *et al.* 1998) that indicate the tendency of adult women to consume more alcohol during the luteal phase, which is characterized by a significant increase of progesterone level compared with other phases of the menstrual cycle.

Animal studies, however, revealed no significant impact of progestins administration (progesterone or allopregnanolone) on alcohol consumption in female rats (Almeida *et al.* 1998; Wolfe, Means, & McMillen 2000; Sinnott, Phillips, & Finn 2002). In male animals, a dose-dependent increase of alcohol intake was reported with progestins use regardless of the route of administration (e.g. subcutaneous, intraperitoneal or interventricular; Ford *et al.* 2007; Gurkovskaya *et al.* 2009; Janak & Gill 2003; Janak, Redfern, & Samson 1998; Sinnott *et al.* 2002), apart from one study in which no significant impact on alcohol consumption was observed after low doses (Lakoza & Barkov 1980), and two studies that observed reduced alcohol intake (Besheer *et al.* 2010, Rezvani & Levin 2014). One of these studies reported that acute pregnenolone administration reduced alcohol intake and preference in male alcohol-preferring rats, but such effect disappeared after 24 hours, while the chronic pregnenolone administration did not show any effect (Rezvani & Levin 2014). One study reported increased alcohol intake in adulthood after neonatal progestin administration (Llido *et al.* 2016).

DISCUSSION

Sex hormone levels, alcohol use and AUD in males

Our review suggests that the nature of the relationship between testosterone levels and alcohol use or AUD in male subjects may vary depending on the age of exposure. Presumed exposure to excessive prenatal testosterone levels *in utero* caused by congenital adrenal hyperplasia or the presence of male co-twin was found to be associated with either increased (Falhammar *et al.* 2014) or decreased risk (Lenz *et al.* 2012) of alcohol dependence later in life, respectively. Another index, prenatal androgen loads, which is derived from various prenatal androgen markers (e.g. 2D:4D ratio), was associated with alcohol dependence and alcohol withdrawal severity (Lenz *et al.* 2017). Despite the findings in the co-twin study supported by similar outcomes in a rodent study of sibling contiguity (Mankes *et al.* 1991), these

results should be taken cautiously, as none of the human studies conducted direct measurements of the testosterone levels *in utero*. On the contrary, ample evidence supports the association of a high testosterone level with increased alcohol intake in adult men (La Grange *et al.* 1995; Stalenheim *et al.* 1998; Falhammar *et al.* 2014). In older males, however, such association did not persist, which might be partly explained by age-related reduction in testosterone level (Wu *et al.* 1995). Less is known about the effects of estrogen level on alcohol use in males, with only one report of a positive association between salivary estradiol level and alcohol use in adolescent boys (de Water *et al.* 2013). Animal studies on the topic were also limited and study design inconsistencies (such as estrogen doses used or presence/absence of gonadectomy) might have contributed to contradictory impact on ethanol consumption (Lakoza & Barkov 1980; Hilakivi-Clarke 1996; Juarez *et al.* 2002). Animal studies also suggest a dose-dependent (inverted U-shape) impact of progestin on alcohol intake with no effect at low dose (Lakoza & Barkov 1980), increased intake at moderate doses (Janak *et al.* 1998; Sinnott *et al.* 2002; Janak & Gill 2003; Ford *et al.* 2007; Gurkovskaya *et al.* 2009) and reduced ethanol self-administration at high dose (Besheer *et al.* 2010). However, no human studies are available to corroborate this effect of progestin level on alcohol use in men.

Sex hormone levels, alcohol use and AUD in females

Similar to studies in males, evidence suggests an age-dependent impact of elevated testosterone levels on alcohol use and related problems in females. A co-twin study demonstrated higher prenatal testosterone exposure in females, presumably caused by a male co-twin, to be associated with more AUD symptoms later in life (Ellingson *et al.* 2013), while a study which used prenatal androgen load markers found no impact of higher prenatal testosterone levels on alcohol dependence in adulthood for females (Lenz *et al.* 2017). Higher testosterone levels were associated with higher alcohol use in young adult females (La Grange *et al.* 1995). Nevertheless, evidence from animal studies is scarce with only one study reporting no association between endogenous androgen levels with alcohol intake in female rats (Mankes *et al.* 1991). A limited number of animal studies also do not support the impact of progestin levels on alcohol consumption in females (Almeida *et al.* 1998; Sinnott *et al.* 2002), but there is no human study yet to refute it.

Compared with androgens and progestins, far more human and animal studies explored the influence of estrogen level on alcohol use and AUD in females. Similar to the impact of testosterone levels on alcohol consumption in males, the impact of estrogen levels on alcohol consumption in females seems to be more pronounced in adult female social drinkers, and especially during the luteal phase when estradiol is sustained at a relatively prominent level (Harvey & Beckman 1985; Muti *et al.* 1998).

Nevertheless, some studies were unable to observe differences in alcohol consumption across menstrual cycle phases in healthy adult women (Sutker *et al.* 1983; Mello *et al.* 1990; Holdstock & de Wit 2000). Moreover, several observational studies reported an increase in alcohol consumption during menses when estrogen level is lowest, and such change was attributed to menstrual-related negative moods and discomforts (Sutker *et al.* 1983; Mello *et al.* 1990; Pastor & Evans 2003). These findings call for the investigation of complex relationships between sex hormone levels and psychological factors in the context of their impact on drinking behavior in females.

Most of the animal studies seem to provide more consistent support for a positive relationship between estrogen levels and alcohol intake (Forger & Morin 1982; Mello *et al.* 1986; Roberts *et al.* 1998; Reid *et al.* 2002; Ford *et al.* 2002a, 2004; Marinelli *et al.* 2003; Reid *et al.* 2003; Quirarte *et al.* 2007; Rajasingh *et al.* 2007; Sherrill *et al.* 2011; Torres *et al.* 2014), except for a few studies, which found opposite or no effect (Sandberg & Stewart 1982; Cailhol & Mormede 2001; Ford, Eldridge, & Samson 2002b; Vetter-O'Hagen & Spear 2011). Careful consideration of the differences in the study methodology, such as the route of estrogen administration and ovariectomy, as well as the inter-species differences in estrous cycles is needed when comparing results between those studies or studies in human females.

Sex hormone levels, alcohol use and AUD in adolescence

The relationship between sex hormone levels and alcohol use appears to be sexually dimorphic as well as specific to developmental phase. In line with studies conducted in adult males, data from adolescence studies support the association of a high testosterone level with increased alcohol intake in adolescent males (Eriksson *et al.* 2005; Costello *et al.* 2007; de Water *et al.* 2013). Furthermore, testosterone levels in adolescent boys could be predictive of future alcohol use (Braams *et al.* 2016) and the relationship between testosterone and alcohol use may be mediated by the functional connectivity between orbitofrontal cortex and amygdala, which play key roles in emotion regulation and goal-directed behavior (Peters *et al.* 2015). Yet the only study to examine the effects of estrogen level on alcohol use in males reported a positive association between salivary estradiol level and alcohol use in adolescent boys (de Water *et al.* 2013). In contrast, population-based studies in adolescent females did not

show a significant association between testosterone level and alcohol use nor between estradiol level and alcohol use (Costello *et al.* 2007; de Water *et al.* 2013). However, it should be noted that these studies were limited by the lack of menstrual cycle stage monitoring or the sole focus on early follicular phase during which estradiol is relatively low. No studies examined the relationship between progestin levels and alcohol use in adolescence.

Limitations of current knowledge

Our review indicates several important limitations in contemporary knowledge about relationships between sex hormone levels and alcohol use. Firstly, both human and animal studies vary greatly in terms of sample size, type of outcome measures and assessments of these measures tailored to the research questions and sample characteristics of each study. These differences are problematic for meta-analysis because the nature and the severity of the outcome measures may not be translatable between studies. Secondly, in addition to interspecies differences in estrous cycle, drinking behaviors and potential sex hormone effects, the inconsistency in the control of menstrual cycle phases in human female subjects and gonadectomy in animal subjects complicate result comparisons between and within human and animal studies, particularly for the study of females. Thirdly, most of the studies focused only on a particular hormone except for a few (see Table 1 and Table 2, for examples). Although such an approach is understandable in the context of limited sample sizes and biological sample availability, it artificially restricts the ability to consider real life circumstances reflecting a complex interaction between multiple hormone levels. Because all gonadal steroid hormones are present in both sexes but at different proportions, the balance between them as well as other hormones that regulate them (e.g. follicle stimulating hormone aka FSH, luteinizing hormone aka LH) could also be important for determining sex-specific alcohol effects and consumption behavior. Fourthly, empirical evidence to establish a causal influence of sex hormones on alcohol use behavior relied mainly on animal studies (for instance, no human studies directly investigated the effect of progestins on alcohol consumption or AUD). This can be due to ethical concerns in human subjects that result in most of the human studies being association studies. Several human studies endeavored to address this issue by focusing on subjects with congenital adrenal hyperplasia and co-twins of the same or alternative sex, or indirect markers of prenatal androgen levels in order to evaluate the dysregulation of steroid hormone production and differential levels of *in utero* testosterone exposure, respectively (Lenz *et al.* 2012; Ellingson *et al.* 2013; Falhammar *et al.* 2014; Lenz *et al.* 2017). Nonetheless, the potential confounding effects of other symptoms associated with a congenital disease and the absence of testosterone measurement should not be overlooked. Last but not the least, only limited studies investigated the influence of sex hormones on alcohol consumption. Moreover, to our knowledge, no studies investigated the influence of estrogens or progestins on AUDs.

Future research considerations

The following aspects and research directions may be considered in future studies investigating the impact of sex hormone levels on alcohol consumption and related phenotypes. Firstly, standardization in outcome measures and their assessments is necessary to facilitate alignment across studies and allows for large-scale meta-analyses. Apart from adopting clinically accredited standards for AUD diagnosis (i.e. DSM-5), current alcohol use pattern and alcohol use history could also be recorded using standardized questionnaires, and the classification of drinkers could follow national organization guidelines. The confounding potential of socioeconomic factors and family role, which relates to perceived stress level, could also be explored. Additionally, for human studies including females, menarcheal history and current menstrual cycle phase should be noted or taken into account. The role of potential confounders such as the intake of oral contraceptive need to be accounted for in a study design (e.g. inclusion as a separate group) or as an adjustment factor in the analyses. For animal studies, gonadectomy accompanied with exogenous administration may allow for better control of effective hormone levels, but need to keep in mind how the procedure will interfere with normal development and functioning that depends on the hormones produced by the gonads, which may reduce the validity of the model. Attention is also required for selection of animal strains and housing conditions because it may interfere with normal behaviors and sex hormone levels. As the balance between various sex hormones and their regulators could be the key to the sex-specific difference in alcohol use behavior, therefore, under the permission of sample abundance and economic consideration, future studies may analyze multiple sex hormones and related hormones/factors (e.g. follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin or SHBG) in the same biological sample, and the interactions among them could be examined. Apart from studying sex hormone effects during various developmental stages, adding the periods of detoxification and prolong abstinence will explore the association between sex hormone levels and propensity to relapse, which may provide insights into sex-specific treatment design. Moreover, instead of focusing on either male or female subjects, including both sexes in a study and

making between-sex comparisons on the same parameter will be crucial in the future to elucidate sex differences in sex hormone effects on drinking behavior. Finally, future larger scale studies and meta-analyses are needed to confirm previous findings and develop statistical models that include potential moderators or mediators (e.g. impulsivity, alcohol craving and mood states) in the association between different sex hormones and alcohol use to elucidate the impacts of sex hormones on drinking behavior.

Conclusions

The contemporary evidence supports a positive association of testosterone and estrogen levels with increased alcohol consumption in adult human male and females, respectively, as well as a positive association of prenatal testosterone level with the risk of alcohol dependence in adulthood. However, these associations are unclear in adolescents, particularly in females, possibly due to dynamic changes in hormonal levels at this developmental stage. Despite animal studies suggested progestin impacts on alcohol consumption, more evidence from human and animal studies are needed to confirm this effect. Future studies that include both sexes with a comprehensive hormone panel and psychosocial assessments, as well as records of menstrual/estrous cycle phase for female subjects, are warranted to elucidate the impact of the interplay between various sex hormone levels during various developmental stages, even during alcohol abstinence, on alcohol use-related phenotypes and AUD.

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None.

Conflict of Interest

None to declare.

Authors Contribution

AE conducted literature search, article screening, analysis and prepare the original manuscript draft. Tables and figure were prepared by AE and AMH. AMH, SJW and VMK edited and critically reviewed the manuscript. VMK conceived the paper. All authors approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 The influence of sex hormones on alcohol related phenotypes (human studies).
Table S2 The influence of sex hormones on alcohol related phenotypes (animal studies).