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Sex, Gender and Alcohol

What Matters for Women in Low-Risk Drinking Guidelines?

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Project Partner

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Executive Summary

Key Messages

- Sex and gender both affect the use, impact and health effects of alcohol.
- Sex-related factors enhance the impact of alcohol on female bodies, causing more harm from lesser amounts of alcohol.
- Gender-related factors contribute to the negative impacts of alcohol consumption, especially for women, including increasing vulnerability to sexual assault and intimate partner violence.
- Sex, gender and factors such as trauma and poverty interact and make dependence on alcohol and recovery more difficult for women.
- Females need to know that their bodies can be more damaged by drinking compared to males.
- Practitioners need to recognize that both biological and social factors affecting alcohol use create differential impacts on, and require tailored responses for women, men and gender diverse people.

Canada's Low-Risk Drinking Guidelines (LRDG) are under review. The current LRDGs have provided sex-specific guidance since their release in 2011, suggesting lower amounts of alcohol per day, week and sitting for women than for men. Specifically, women are advised to limit their consumption to no more than 10 drinks per week and no more than two per day, while men are advised to drink no more than 15 drinks per week and no more than three per day. Sex- and gender-related factors, along with determinants of health and intersectional factors, shape the impact of alcohol. All people living in Canada can benefit from nuanced messages about alcohol and safe drinking, but especially women and girls.

This report is for practitioners in the substance use field, and policy makers or scientists who are designing alcohol-related policies or research. It reviews the evidence on how sex- and gender-related factors can determine the effects and impacts of alcohol use, with a focus on women and women's health. It also reviews the evidence on sex, gender and reproductive health, and how it might inform messages about alcohol use and fertility, pregnancy and breastfeeding. Alcohol use has sex- and gender-specific risks and many reproductive processes including pregnancy are vulnerable to the effects of alcohol. To reach and inform audiences in a meaningful way, it is necessary to share the evidence and create advice and messaging accordingly.

Sex-related factors: In general, males are more likely to develop alcohol use disorder (AUD), but females are more likely to develop organ and other bodily damage from drinking alcohol. There are four main categories of sex-related factors that are important to understanding how alcohol affects male and female bodies: 1) physiology and anatomy; 2) hormones and enzymes; 3) genetics; and 4) neurobiology. Within these factors, various sex-related differences or processes exist. The absorption, distribution and metabolism of alcohol is affected by sex-related factors. For example, females break down ethanol faster than males, and reach a higher blood alcohol concentration due to faster absorption. Significantly, females generally experience more risk of damage or disease at lower levels of alcohol consumption.

Gender-related factors: In general, there are sometimes different impacts on women or men or gender and sexual minorities from consuming alcohol. There are four main aspects of gender that account for these impacts: 1) gender roles and norms; 2) gender relations; 3) gender identity; and 4) institutionalized gender. Gender identity matters in that the strength of adherence to masculinities

and femininities affects style and volume of drinking behaviour, with men and sexual and gender minorities often drinking more and more often than women. Gendered relations often mean that women are influenced by a partner's drinking. The impacts of alcohol reflect gender inequities such as vulnerability to sexual assault and violence. Gender roles lead to women using alcohol to cope with the stresses of caregiving, trauma and intimate partner violence. Institutionalized gender generates greater stigma for women as a group, compared to men, and creates barriers to treatment for women and mothers who use alcohol.

Interactions and intersections: All these factors and processes are exacerbated by sex-gender interactions. Sex- and gender-related factors coincide to produce specific impacts of alcohol during pregnancy on both women's and fetal health. For example, heightened stigma and social policing is applied during pregnancy, and pregnancy-related processes also affect the pharmacokinetics of ingesting alcohol. Vulnerability to sexual assault is heightened by being young, female and intoxicated in the context of pervasive gender-based violence. Intersections with poverty, racialization, past trauma, or sexual and gender minority stigmas synergistically merge to create more harms.

Reproduction: Women's reproductive health is also compromised by alcohol use, particularly during pregnancy and breastfeeding. Long-term damage to children can occur if the fetus is exposed to alcohol in the womb, and alcohol use during breastfeeding can reduce milk production. During pregnancy, increased water and blood volume, along with the impact of alcohol on glucose and insulin lipid metabolism, create complex effects on the body. In general, there is mixed evidence on the impact of alcohol on pregnancy and delivery outcomes, with possible increases in miscarriage and placental abnormalities. With respect to fetal health, exposure to alcohol in the womb results in a well-established risk for learning, health and social effects that have a lifelong impact, including brain injury, birth defects, health problems and diseases. Recent reviews that considered low levels of exposure have found some of the adverse effects persist at these levels, reinforcing the message that it is safest not to drink in pregnancy. Effects of alcohol consumption on breastfeeding include a decrease in milk production, early cessation of breastfeeding and effects on infant sleep patterns.

The collective impact of these sex, gender and interactive and intersectional factors on alcohol use has particular importance for women. It is necessary to communicate this emerging and growing body of evidence to women, service providers, practitioners and policy makers to improve health literacy and inform more specific and tailored prevention, treatment and harm reduction efforts.

Introduction

The Canadian Centre on Substance Use and Addiction (CCSA) produced the first version of the Canadian Low-Risk Alcohol Drinking Guidelines (LRDGs) in 2011. CCSA is currently reviewing them with the goal of producing a revised and updated version. For this revision, it is important that the guidelines address factors and influences related to alcohol consumption specifically for women, for men and for gender diverse people. In 2011, the LRDGs in Canada offered sex-specific advice, recommending that women and men consume alcohol in different amounts and frequencies to safeguard their health. It is also important for practitioners and policy makers to consistently reflect on sex- and gender-based evidence to tailor their own approaches to alcohol-related health promotion, prevention, treatment and policy issues.

This section reports on a review of evidence on sex, gender and reproductive health that has been undertaken to inform messaging about alcohol use by women. Alcohol use has sex- and gender-specific risks for women, and many reproductive processes including pregnancy are vulnerable to the effects of alcohol. To reach and inform audiences in a meaningful way, we need to share the evidence related to sex, gender and alcohol consumption, and create advice and messaging that reflects that evidence.

There is established evidence indicating differential impacts of alcohol on female and male bodies, on pregnancy and fetal development, and on the gendered patterns of harms associated with use. This report collates and analyses recent evidence on these effects, recommends sex and gender-related content for the LRDGs, and provides advice on knowledge mobilization. This section discusses the review of recent literature that addresses and describes three areas: a) sex-related factors affecting alcohol use in females; b) reproductive issues (pregnancy, fetal, infant and child health) and alcohol use; and c) gender-related factors affecting alcohol use and its impact in women. We conclude with a discussion on sex-gender interactions, intersectional issues and knowledge mobilization messaging.

Sex and gender science is nascent, the literature incomplete, and many effects and impacts of sex and gender on alcohol use, especially among sub-populations such as Indigenous Peoples, older people, sexual minorities and gender minorities, remain under-researched or unknown. Nonetheless, reviewing current evidence on these matters is essential. As evidence about alcohol and social patterns of drinking evolves, it will be important to continuously reassess the impact of alcohol on all populations, and to create appropriate public health and health promotion advice.

Methods

We conducted a comprehensive, multi-part review of recent literature focused on identifying evidence on alcohol risk factors and related health outcomes. The topic areas and parameters for risk factors were informed by:

1. The alcohol section of a large 2018 scoping review conducted on sex, gender and four substances: alcohol, cannabis, tobacco, and opioids (Hemsing & Greaves, 2020);
2. Two evidence reviews supporting the recent low-risk drinking guidelines in Australia (Middleton et al., 2018; NHMRC Clinical Trials Centre, 2017);
3. A systematic review of the effects of low-to-moderate prenatal alcohol exposure on pregnancy and child health outcomes conducted in the United Kingdom (U.K.) (Mamluk et al., 2017), and
4. Two searches conducted by a CCSA information specialist described in the next section.

Search Strategy

The results of the base search of literature up until 2018 were consulted. This base search covered the years 2007–2018, but excluded pregnancy, fetal or infant health, and breastfeeding data or outcomes. In addition, two literature searches were conducted by an information specialist at CCSA using health-related databases with international coverage (Medline, Embase, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials via Ovid, CINAHL, PsycINFO, Social Work Abstracts, Women's Studies International, LGBT Life via EbscoHost, and Social Science Citation Index via Clarivate Analytics) for English language articles.

Search 1 identified research published between 2018 and 2021 that addressed sex and gender related factors and alcohol use. Search 2 identified literature published during a longer period, 2015 to 2021, that addressed pregnancy, and fetal and reproductive health. Medical Subject Headings (MeSH) were used where applicable and combined with appropriate keywords for each risk factor topic. The search terms used for Search 1 and Search 2 can be found in appendices A and B.

Inclusion and Exclusion Criteria

Specific inclusion and exclusion criteria were developed for each additional search. In general, the searches included English language, peer-reviewed journal articles, including systematic reviews, meta-analyses and individual studies that contained information on risk factors and health outcomes associated with alcohol use. We primarily focused on recent systematic reviews and meta-analyses. Subject areas where systematic review evidence was limited were supplemented by reviewing individual studies.

To update our previous searches, we included literature published later than 2018 (Search 1) and later than 2015 for reproduction related outcomes (Search 2) from a range of countries, including Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, the United Kingdom and the United States. Studies published in all other countries or that include data from multiple countries where the data were not disaggregated were excluded.

Analysis and Synthesis

Authors met weekly between October and December 2021 to discuss the findings, including alcohol-related risk factors and related health outcomes. A narrative summary approach was used to succinctly synthesize the main findings and implications of the identified literature.

How Do Sex and Gender Matter to Alcohol Use?

According to the Canadian Institutes of Health Research's Institute of Gender and Health, "every cell is sexed and every person is gendered" (2018). The pervasive nature of sex and gender make them essential components in understanding human health and risks of susceptibility to diseases or conditions, generating personalized clinical and consumer advice, and mounting effective health promotion.

Sex refers to a range of biologically based factors, characteristics and processes that affect human health such as genes, anatomy, physiology, metabolism and neurobiology. **Gender** refers to a range of social and cultural factors and processes that affect experiences of health and healthcare, such as gendered roles, relations, identities and institutional practices. Both sex and gender can be broken down into several components. Figures 1 and 2 illustrate sex and gender components with examples related to alcohol use.

In real life experience, **sex and gender interact** with each other, and then with other intersectional characteristics to shape the impacts of alcohol use. Taken together, these concepts contain a range of variables, characteristics and factors that affect the impact of alcohol use or of others' alcohol use. There is a wide range of **intersectional** characteristics (such as age, race, ability, education, socioeconomic status and sexual orientation), **ideologies** (such as sexism, racism and ableism) and **social and political processes** (such as colonization and capitalism) that proscribe and surround sex and gender, and ultimately impact all audiences, in particular, individual women and girls who may use alcohol. Knowledge mobilization messages and approaches need to reflect and encapsulate the entire environment for audiences.

The Impact of Sex-Related Factors on Alcohol Use

The information in this section is based on systematic reviews identified by the CCSA information specialist and published between 2018 and 2021 that addressed sex- and gender-related factors and alcohol use. (See Appendix A for search terms). It also draws on research identified in a scoping review conducted in 2018 of academic literature. The aim of that review was to identify, analyze and synthesize current research in sex- and gender-related factors in substance use (initiation, uptake, patterns of use) and its effects, and prevention, treatment or harm reduction outcomes for four substances, one of which was alcohol. Focused searches for additional individual studies were undertaken to elucidate certain sex-specific factors.

In general, males are more likely to develop alcohol use disorder (AUD), but females are more likely to develop organ and other bodily damage from drinking alcohol. In Figure 1, there are four main categories of sex-related factors that are important to understanding how alcohol affects male and female bodies. With respect to alcohol, these can be sex-related differences, factors or processes. They indicate that females generally experience more risk of damage or disease at lower levels of consumption. For example, one impact is more organ exposure to alcohol in females upon consuming similar amounts of alcohol (Ceylan-Isik et al., 2010). The current LRDGs reflect some of these sex differences and indicate that women (females) should drink less per sitting and fewer drinks per week, given potential differential and negative impacts on their bodies. The pharmacokinetics (PK) of drug ingestion include four main processes and assist in understanding how the body responds to alcohol (Ceylan & Özerdoğan, 2015).

Typical PK processes include the following ADME scheme:

- Absorption (affected by gastric motility: increased bioavailability in females)
- Distribution (affected by water, fat, and body mass: increased blood alcohol concentration in females)
- Metabolism (affected by enzymes; liver and gastric enzymes more active in females)
- Excretion (clearance via urine, breath and sweat: affected by gastric emptying, liver oxidation, hormones in females)

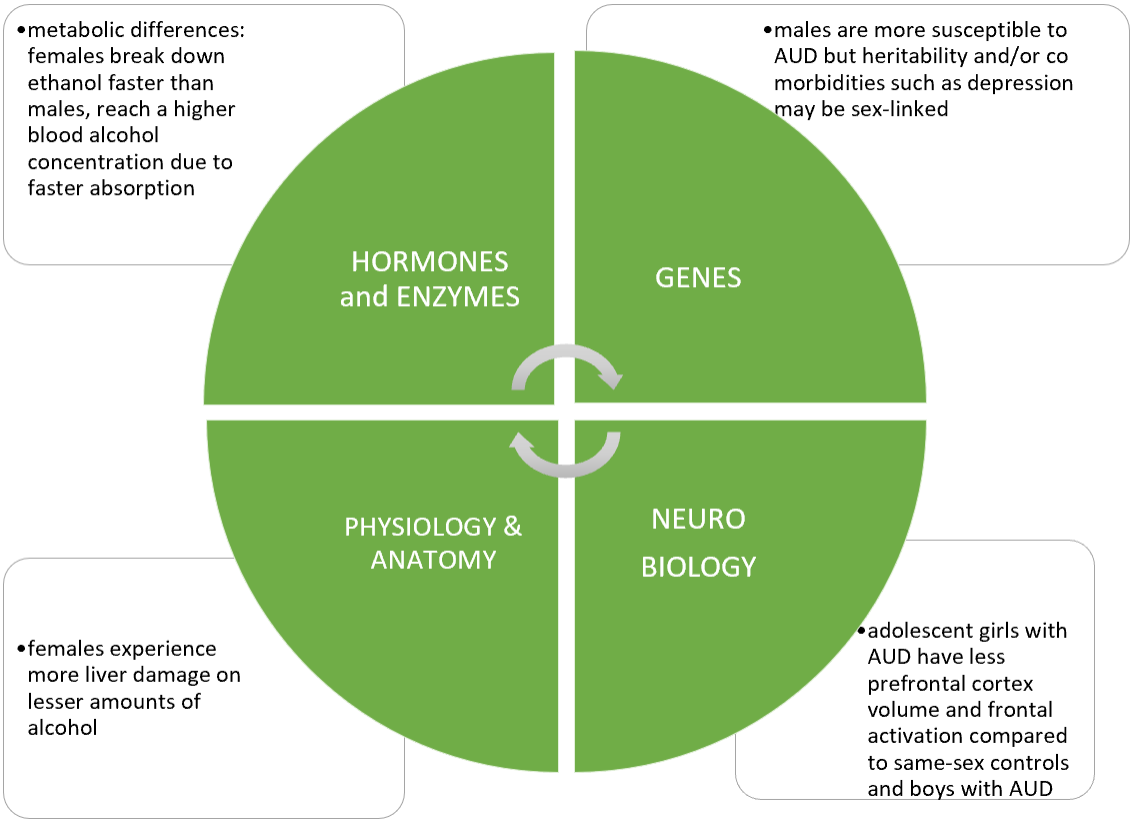
Some PK parameters are different for males and females. For example, first-pass metabolism of ethanol is greater in males than females and the volume of distribution is less in females compared to males (Soldin & Mattison, 2009). These PK differences might explain why women show greater blood concentrations of alcohol (Soldin & Mattison, 2009). Importantly, females break down ethanol faster than males (Dettling et al., 2007) and reach a higher blood alcohol concentration due to faster absorption (Dettling et al., 2009). Hormones might also play an important role as increased serum progesterone levels are associated with faster alcohol elimination rates in women but not in men (Dettling et al., 2008). It is important to consider that these hormonal impacts are fluid over the life course or monthly cycle, and potentially overlapping between males and females as levels fluctuate. Elimination is the sum of the processes of removing a substance from the body in the PK ADME scheme and is frequently used to encompass both metabolism and excretion (Garza et al., 2022). A diagram adapted from Gendered Innovations (n.d., see Appendix C) illustrates this range of components and differences in PK processes with respect to drug ingestion in general, concluding that elimination is generally slower in females.

There are various approaches to building sex-related research. While pursuing sex “differences” research is a limited paradigm, it is an important one, as it often acts as a gateway to understanding

differential impacts and setting research agendas. More broadly, though, it is important to focus on the sex-related factors that affect alcohol use. While sex is often used as a comparator and category in population research, or as an observed characteristic in experimental research or clinical practice, it is vital to understand that a range of sex-related factors affect health that do not rely on comparisons between the sexes (differences) but require research, analysis and consideration in their own right. In this vein, it is useful to clarify which aspect of sex may be of issue and importance in developing specific advice about alcohol consumption. Much sex-related alcohol research is at a developmental stage, where "differences" may be sought and found, but the explanations for underlying mechanisms or potential impacts are not yet discussed or understood.

Figure 1 illustrates some broad overlapping categories of sex-related factors that impinge on alcohol use and its impact, with selected examples for illustrative purposes. This figure indicates some broader conceptual categories of interest to any sex-based analysis of evidence regarding human health. The diagram engages with components of sex that are useful in searching for sex-related factors and mechanisms.

Figure 1: Sex-related factors



Adapted from Greaves & Hemsing, 2020. Sources for examples: Chu, 2014; Prescott, 2002.

Physiology and Anatomy

Alcohol affects a range of disease processes, organs, systems and conditions and there are sex-based differences in the pathophysiological consequences of consuming alcohol. For example, a study that examined cardiac reactivity measures after acute alcohol ingestion revealed that the heart rate variability measure reflected significant interaction between alcohol and sex, with females exhibiting higher values than males (Vatsalya et al., 2014). Further, in a study conducted among women even low to moderate alcohol consumption was associated with an increased risk of cancers of the oral cavity, pharynx, esophagus, larynx, rectum, liver, breast and all cancers combined, (Allen et al., 2009).

Alcohol contributes to various cancers in women, including breast cancer.

Females experience more liver damage at lower levels of alcohol consumption, compared to males.

There is evidence that sex-related factors play an important role in the development of alcoholic liver cirrhosis and in the progression of alcoholic liver disease (Askgaard et al., 2014). In a study conducted with male and female alcohol-dependent subjects admitted to an alcohol treatment program, females showed higher levels of biomarkers of liver injury than males even though they used less alcohol on a daily basis and had been drinking for shorter time periods (Kirpich et al., 2017). These findings suggest that women develop and have more progressive liver injuries, even when consuming lower quantities of alcohol (Vatsalya et al., 2016). Indeed, in a systematic review and meta-analysis on the impact of alcohol as a risk factor for liver cirrhosis, women were more impacted than men by the same amount of drinking in both mortality and morbidity studies (Rehm, 2010).

Hormones and Enzymes

Enzymes break down alcohol differently in females compared to males, with faster action in females.

Processes of metabolism are affected by a range of features including hormones and enzymes. Gastric enzymes perform differently and at different speeds in females and males. Hormonal changes during pregnancy, menopause or after ingesting oral contraception have an impact on PK processes by affecting the performance of enzymes, metabolism and clearance processes for women (Chu, 2014).

Hormones affect and are affected by alcohol in males and females differently.

Alcohol may also act to alter sex hormone levels. For example, alcohol infusions provoked differential responses in women and men when administered in a two-session, single-blinded study. While the level of testosterone decreased in men, the level of estradiol increased in women (Vatsalya et al., 2012). In a different study with pre-menopausal women, evidence suggested that the previous day's alcohol intake, notably of wine and beer, was significantly associated with elevated total and free estradiol, testosterone and luteinizing hormone, and binge drinking magnified these effects (Schliep et al., 2015). Despite these alterations in hormones, there was no risk of menstrual cycle dysfunction (Schliep et al., 2015).

Hormones may also affect the development of AUD. In a systematic review of 50 articles (19 conducted with humans and 31 with animals) on the impacts of sex hormones on alcohol consumption and AUD, Erol et al. found evidence of an association of increased testosterone level and increased risk for alcohol use and AUD in males (2019). Among females, there is support for a positive relationship between increased estrogen level and increased alcohol use with mixed results found in males (Erol et al., 2019). There were no human studies found on the impact of progestins on alcohol use and AUD.

Genetics

The genetic influences on AUD may also be sex specific. In a Swedish study with national data from 787,916 twin and sibling pairs, Kendler et al. (2016) found that there are sex differences in the etiology of AUD with weaker genetic effects among females than males (Kendler et al., 2016). In another study, males showed a stronger externalizing pathway to genetic risk of AUD than females (Kendler et al., 2021).

Females may be less vulnerable to genetically linked AUD, compared to males.

Neurobiology

Alcohol affects female and male brains differently, with more negative impacts on females.

There are numerous indications that brain function after alcohol consumption is different in males and females. These findings have implications for impaired function, inhibition, impulsivity, subjective experiences and behavioural impacts. Experimental studies measured the neurobiological impacts of various levels of administration of alcohol in males and females. For example, Rickenbacher et al. (2011) investigated the effects of acute alcohol intoxication on gray matter perfusion in males and females using arterial spin labeling to specifically examine regional brain impacts. Acute intoxication increased perfusion in bilateral frontal regions in males but not in females. Under placebo, stronger cortical perfusion was observed in women compared with men, primarily in the left hemisphere in frontal, parietal and temporal areas. These results emphasize both sex-related impacts and differences in regional specificity of alcohol's effects of cerebral perfusion, possibly because of interactive influences on hormonal, metabolic and hemodynamic autoregulatory systems. Alcohol-induced perfusion increases correlated positively with impulsivity and antisocial tendencies, consistent with dopaminergic mediation of reward and its effects on cortical perfusion.

Even at lower dosage, experiments reveal impacts on inhibition. For example, Hoppenbrouwers et al. (2010) examined sex differences in frontal interhemispheric connectivity in response to alcohol, with 12 female and 10 male healthy volunteers who received a single administration of 0.5% alcohol in a placebo-controlled counterbalanced crossover design. Paired-pulse transcranial magnetic stimulation was applied to measure transcallosal inhibition between the left and right primary motor cortex. Administration of a single oral dose of alcohol resulting in a blood alcohol concentration of 0.05% reduced transcallosal inhibition between the right and left primary motor cortex in females, but not in males.

Sex related factors and differences in the neurobiological impacts of alcohol use also have potential implications for behavioural patterns between men/boys and women/girls. A recent narrative review of neuroimaging findings in alcohol use over the last 10 years found that, overall, adolescent girls demonstrated smaller prefrontal cortex volumes and less frontal activation compared to same-sex controls. Among boys the opposite findings were found, suggesting that these findings may have implications for sex-related cognitive deficits associated with alcohol use (Verplaetse et al., 2021). For example, in a study on the associations between binge drinking and the spatial working memory brain activation, males with adolescent-onset AUD or who binge-drink had greater frontal activation in response to a spatial working memory task compared to same-sex controls. Females with adolescent-onset AUD or who binge-drink had less frontal activation to a spatial working memory task compared to same-sex controls (Squeglia et al., 2011). For females who binge drink, less frontal activation was associated with poorer working memory and attention on the spatial working memory task (Squeglia et al., 2011).

Sex-related differences and factors may also impact both subjective and objective experiences of alcohol ingestion and may manifest differently in those with AUD compared to binge or a range of self-identified social drinkers. For example, a controlled study on alcohol cue-induced activation showed that women with AUD activated different reward circuits, cognitive control circuits and regions of the default-mode network compared to same-sex controls (Arcurio et al., 2015). The authors suggested that these results might indicate a problem with switching between different neural networks. The impacts of binge drinking are also sex specific as acute intoxication increased cortical perfusion in bilateral frontal regions in men, but not in women (Rickenbacher et al., 2011). Another study conducted with healthy social drinkers (0.60 g/kg ethanol for men, 0.55 g/kg for women). On average, these participants reported light-to-moderate drinking patterns imbibing 1.8 ± 1.2 times per week and 2.5 ± 1.0 drinks per occasion, with men and women reporting similar amounts and frequencies of drinking. The study found that women reported feeling more intoxicated than men and had lower activity in their anterior cingulate cortex than men (Marinkovic, et al., 2012).

It is possible that neurobiological sex differences persist after recovery from AUD, influencing ongoing brain health. Evidence from a study that examined drinking history associations with regional white matter volumes in abstinent men and women (who were at least four weeks abstinent after prior diagnoses of alcohol abuse or dependence that involved drinking more than 21 drinks per week), reported differences by sex. Women were more impacted in the frontal, temporal, ventricular and corpus callosum regions, while men showed effects mainly in the corpus callosum (Ruiz et al., 2013.

Subjective reports from men and women indicate women feel more intoxicated after equivalent drinking.

Finally, alcohol may have sex-differential impacts on impairment, measured both subjectively and objectively. Administration of a single oral dose of alcohol resulting in a blood alcohol concentration of 0.05%, reduced transcallosal inhibition between the right and left primary motor cortex in women but not in men (Hoppenbrouwers et al., 2010). An experiment by Miller et al. (2009) revealed that men and women respond differently to a single dose of alcohol (0.65 g/kg) that impaired the simulated driving performance as well as measures of three behavioural and cognitive functions important to driving performance: motor coordination, speed of information processing and information-processing capacity. Alcohol significantly impaired all aspects of performance. However, women displayed greater impairment than men on all behavioural tests and reported higher levels of subjective intoxication compared with men (Miller et al., 2009).

Escalation and Telescoping Effects

A key impact of sex-specific PK processes combined with the impact and interactions of processes of metabolism and modified by gender is the escalation of use, sometimes referred to as the telescoping effect, which is more pronounced in treatment samples compared to population-based samples (Becker et al., 2017). For those in treatment, the length of time of progression from first alcohol use to the onset of alcohol-related problems and their consequences is shorter among women than men (Fama et al., 2020). Women have shorter intervals between the initiation of alcohol use to entering treatment, and experience medical and health-related problems earlier, even when they consume the same amount of alcohol as men. Women also have different severity of cognitive consequences than men, reflecting both sex- and gender-related factors such as emotional and social factors (Fama et al., 2020).

There are sex-related factors associated with the telescoping effect such as the rate at which alcohol is metabolized producing a greater sensitivity to alcohol in women (Diehl et al., 2007). There are also life-stage factors that determine use of hormonal contraception or hormone levels that also interact

with gendered and social factors. For example, women with a history of childhood maltreatment are particularly vulnerable to an accelerated time from initiation of alcohol use until dependence (Oberleitner et al., 2015). Taken together, the causes and effects of sex-related differences and influences linked to alcohol use are complex and interact in influential ways with gender-related factors on women's health.

The Impact of Alcohol on Reproductive Health: Pregnant Women, Fetal and Child Health, and Breastfeeding

There has been a long history of research and public education on fetal outcomes after alcohol use during pregnancy, and in some countries on the development of fetal alcohol spectrum disorder (FASD) and its impact on child development and adult disability. There has also been a focus on pregnancy and birth outcomes, but generally from a fetus-centric stance, with less attention paid to the health of pregnant women. Similarly, links between alcohol use and breastfeeding have been researched to derive public education messages about infant health. Some specific examples of each are discussed in this section in the context of outcomes of pregnancy, fetal outcomes and infant development.

In pregnancy a range of PK processes shift, reflecting changes in maternal metabolic processes that evolve throughout pregnancy and differ by month and trimester. For example, increased blood volume and total body water, along with prolonged gastric emptying impact the PK of alcohol during pregnancy. The underlying explanations for these changes are still obscure but alcohol use during pregnancy changes and disrupts metabolic processes. Specifically, ethanol alters glucose, insulin and lipid metabolization, all of which can lead to abnormal fetal development and growth. Alcohol in pregnancy can also inhibit CYP2E1, a liver enzyme that metabolizes ethanol and other carcinogens in the body (Lee et al., 2020).

Although pregnancy and birth outcomes are sex-related matters in research and clinical practice, real-world experience indicates that health impacts often result from a combination of sex and gender interactions, experienced in an intersectional context. For example, low nutrition or tobacco use during pregnancy combine with the effects of alcohol ingestion and may be associated with trauma, poverty, low socioeconomic status or other social conditions or experiences such as intimate partner violence, all contributing to maternal and fetal health outcomes. This confluence of factors can make it hard to untangle the impact of alcohol on such outcomes. More recent research in this realm is focusing on such contextual factors, along with sex-based impacts.

The findings in this section reflect the two systematic reviews conducted by Cochrane Australia and the South Australian Health and Medical Research Institute, and the University of Sydney's NHMRC Clinical Trials Centre (Middleton et al., 2018; NHMRC Clinical Trials Centre, 2017) that informed the Australian Guidelines to Reduce the Risks from Drinking Alcohol, as well as a systematic review and meta-analysis conducted in the U.K.

The authors of the Cochrane Australia and South Australian Health and Medical Research Institute systematic review examined the association between levels and patterns of alcohol consumption during pregnancy and while breastfeeding to identify select health outcomes (Middleton et al., 2018). The authors reported on pregnancy outcomes: birth defects and congenital malformations (e.g., spina bifida, cleft palate, anencephaly, club foot, heart defects); behavioural problems (e.g. conduct, hyperactivity, personal-social behaviour); and breastfeeding outcomes: cognitive impairment, sudden infant death syndrome (SIDS) or sudden unexplained death of an infant; sedation; child neglect; maternal bonding; and failure to thrive. Overall, they found limited reliable evidence of associations between alcohol exposure in pregnancy and these effects.

In their discussion, the authors commented on a systematic review and meta-analysis undertaken in the U.K. by Mamluk et al. (2017), which was designed specifically to determine the effects of low to moderate levels of maternal alcohol consumption on both pregnancy outcomes and longer-term offspring outcomes, published after the term of the Australian search. They concluded, with that addition, that there were 1) mixed effects of low-level consumption on child behavioural problems and 2) no effects of low-level alcohol consumption on birth defects.

The systematic review of alcohol consumption while breastfeeding identified one study. The results suggested that infants of mothers who drank alcohol had more favourable personal-social development at 12-months (measured by the Ages and Stages Questionnaires) compared to those whose mothers abstained while breastfeeding (Middleton et al., 2018). However, no other significant associations were reported.

The University of Sydney review examined all risks associated with alcohol, not only those related to pregnancy and breastfeeding (NHMRC Clinical Trials Centre, 2017). The authors considered the following outcomes: developmental delay, FASD, small for gestational age (SGA), low birth weight, birth defects, stillbirth, behavioural problems, neonatal withdrawal, spontaneous abortion and miscarriage, and premature birth. No systematic reviews were identified that addressed stillbirth, neonatal withdrawal, or spontaneous abortion and miscarriage. The authors stressed the inconsistency across studies of the measurement of maternal alcohol consumption and the methods used to quantify prenatal alcohol exposure, and the limited investigation of dose and response (NHMRC Clinical Trials Centre, 2017). However, the authors concluded that there was a dose-response relationship between increased levels of alcohol consumption and increased risk of preterm birth, low birthweight and SGA. Findings suggested a large effect of alcohol on low birthweight and that at less than 10 g of alcohol per day there was a dose-response relationship indicating increased levels of alcohol consumption were associated with increased risks of SGA.

The authors further described an association between alcohol consumption during pregnancy and child motor function, when compared with pregnant women who did not drink (with a caveat about the differing scales used to measure motor function). They noted that higher levels of alcohol consumption may confer an increased risk of poorer child motor function. The authors did not find any systematic reviews that addressed the health risks and benefits of varying levels or patterns of alcohol consumption for breastfeeding women and their children (NHMRC Clinical Trials Centre, 2017).

A systematic review and meta-analysis from the U.K. was noted in the discussion section of the Australian reviews, although it was published after the timeframe of their overall studies. This review explored the effects of low-to-moderate levels (≤32 g/week) of maternal alcohol consumption during pregnancy on pregnancy, and fetal, infant or child outcomes (Mamluk et al., 2017). They included 24 studies and reported on 30 outcomes including 1) pregnancy outcomes: miscarriage, gestational length and preterm delivery, hypertensive disorders of pregnancy, gestational diabetes, low amniotic fluid, placenta previa, placental abruption and congenital malformations; 2) delivery outcomes: SGA, stillbirth, assisted delivery, Apgar score at birth and admission to the neonatal unit; and 3) features of FASD: childhood growth restriction, cranium size and head circumference, developmental delays, behaviour problems, cognitive impairment and IQ, and facial malformations (Mamluk et al., 2017).

We built on these findings, examining systematic reviews identified from a supplemental search conducted by a CCSA information specialist on literature published between 2015 and 2021 to determine the impact of alcohol use on pregnancy and delivery outcomes, fetal outcomes and features of FASD, and breastfeeding. We included six (*n = 6)* systematic reviews and one (*n = 1)* scoping review related to pregnancy and delivery outcomes (Oostingh et al., 2019; Sundermann et al., 2019; Ng et al., 2021; Steane et al., 2021; Reijnders et al., 2019; Lagadec et al., 2018;

Pentecost et al., 2021); 50 (*n = 50*) related to fetal and child outcomes, including 14 (*n=14*) that addressed low exposure to some degree (Oostingh et al., 2019; Huang et al., 2019; Koning et al., 2017; du Plooy et al., 2016; Pyman et al., 2021; San Martin Porter et al., 2019; Easey et al., 2019; Hendricks et al., 2019; Kippin et al., 2021; Zhang et al., 2020; Reid et al., 2019; Caputo et al., 2016; Akison et al., 2019; Römer et al., 2020); and two (*n* = 2) systematic reviews and one (*n* = 1) literature review related to alcohol use and breastfeeding outcomes (Spahn et al., 2019; Jullien 2021; Brown et al., 2018).

Pregnancy and Delivery Outcomes

Most research on alcohol use in pregnancy has focused either on the prevalence of alcohol use in pregnancy or the effects of alcohol on fetal outcomes and the development of FASD. Fewer studies have explored the impacts of alcohol use on pregnancy outcomes. This was reflected in the systematic reviews used to inform this section, where most findings were related to fetal health outcomes. Here we consider six (*n = 6)* studies, including five (*n = 5)* systematic reviews and one (*n = 1)* scoping review.

Alcohol has been associated with a range of adverse health outcomes for pregnant women. Recent systematic reviews confirmed three of these: risk of miscarriage, hypertensive disorders of pregnancy, and placental abruption.

One systematic review explored the literature on the influence of maternal lifestyle factors (including alcohol) on fertility, preconception outcomes and first-trimester pregnancy outcomes, including miscarriage and embryonic growth. The systematic review included 17 (*n* = 17) studies that addressed alcohol as a factor of interest. Findings indicated a relationship between alcohol use and time to pregnancy, indicating that alcohol use was associated with lower conception rates (Oostingh et al., 2019). Two of the included studies found that women consuming more than seven units of alcohol per week (self-reported and not explicitly measured) reported a prolonged time to pregnancy compared to women consuming less than seven units per week or no alcohol. The authors found inconsistent findings related to maternal alcohol consumption and miscarriage. The highest quality study found no association between binge drinking in the first trimester and the risk of spontaneous miscarriage. These findings were supported by two other studies. However, other studies found an association between drinking more than three drinks per week and the risk of spontaneous miscarriage (Oostingh et al., 2019)

In the discussion, the authors note that perinatal complications may be related to hormonal fluctuations, including an alcohol-induced increase of aromatization of testosterone that results in an increase in estrogen and reduction of follicle stimulating hormone, thus suppressing ovulation and folliculogenesis. They also stressed that, despite inconclusive findings, alcohol is a teratogen and that the increasing prevalence of alcohol use in the reproductive years and the unknown implications of the dose-response relationship and differential effects of different types of alcohol use urgently require more research (Oostingh et al., 2019)

Another systematic review and meta-analysis of alcohol use in pregnancy and miscarriage explored *n* = 24 studies published between 1970 and 2019. Twelve (*n* = 12) studies found that alcohol exposure is associated with an increased risk of miscarriage. In a meta-analysis of the association between alcohol use and miscarriage, alcohol-exposed pregnancies were 19% more likely to end in a miscarriage (OR 1.19, 95% CI 1.12 to 1.28). Seventeen (*n* = 17) studies reported on dose-specific effects of alcohol on risk of miscarriage, and a pooled analysis indicated that for alcohol use in pregnancy of ≤5 drinks per week, each additional drink per week was associated with a 6% increase in miscarriage risk. The effect was lower among studies solely exploring first-trimester miscarriages (Sundermann et al., 2019). The authors note the challenges in capturing a representative sample

given that most miscarriages occur early in pregnancy and thus women need to be enrolled in studies soon after their pregnancy is confirmed.

A systematic review and meta-analysis explored the impact of lifestyle factors (including alcohol use) on recurrent pregnancy loss (RPL). Four (*n* = 4) studies explored the impact of alcohol on RPL. Findings indicated no significant effect of alcohol on the risk of RPL (Ng et al., 2021).

One systematic review explored the placental outcomes from alcohol exposure during pregnancy (Steane et al., 2021). The review identified one study that found a small but significant decrease in the likelihood of pre-eclampsia. Five of eight studies reporting on placental abruption found increased odds of placental abruption in alcohol-exposed pregnancies that increased with increasing levels of alcohol consumption in all but one study. In a meta-analysis of prenatal alcohol exposure and placenta previa no association was found. The authors report increased lesions among alcohol-exposed placentas but that placental weight was lower only in pregnancies where infants were diagnosed with fetal alcohol syndrome (Steane et al., 2021).

Another systematic review exploring lifestyle factors analyzed the evidence on the impact of periconception lifestyle factors on placental development and function during pregnancy. Five (*n* = 5) studies explored the impact of periconception alcohol use on placental development and function. The findings indicated increased placental growth factor levels and pre-eclampsia in the second and third trimesters among women who consumed ≥8 drinks per week in the periconception period and decreased placental weights among women who used alcohol (Reijnders et al., 2019).

One systematic review exploring the quality of life of pregnant women found that a history of alcohol dependence was associated with a poorer quality of life (Lagadec et al., 2018). Another scoping review evaluated the literature analyzing the connection of perinatal substance use, perinatal depression and anxiety with maternal-newborn outcomes. Women who used alcohol had significantly greater odds of reporting perinatal mental health concerns (OR 1.71, 95% CI 1.10 to 2.66). The authors discussed the underreporting of perinatal substance use due to stigma and possible legal consequences (Pentecost et al., 2021). Table 1 summarizes the key findings related to alcohol use and pregnancy and delivery outcomes based on the findings from seven reviews published between 2015–2021.

Table 1. Key findings related to alcohol use and pregnancy and delivery outcomes

Outcome of interest	Key findings
Miscarriage	Inconsistent findings on alcohol use in the first trimester; research indicating both no association between binge drinking in the first trimester and spontaneous miscarriage with other studies indicating an association between >3 drinks per week and risk of spontaneous miscarriage (Oostingh et al., 2019) Dose-dependent increase in risk, whereby in pregnancies with ≤5 drinks per week, each additional drink per week was associated with a 6% increased risk of miscarriage (Sundermann et al., 2019) No significant effect of alcohol on RPL (Ng et al., 2021)
Gestational length and preterm delivery (<37 weeks gestation)	No outcomes reported
Hypertensive disorders of pregnancy	Increased placental growth factor levels in the second and third trimesters with ≥8 drinks per week of alcohol in the periconception period (Reijnders et al., 2019) Decreased likelihood of pre-eclampsia (Steane et al., 2021)

Gestational diabetes	No outcomes reported
Low amniotic fluid (oligohydramnios)	No outcomes reported
Placenta previa	No association between prenatal alcohol exposure and placenta previa (Steane et al., 2021)
Placental abruption	Increased odds of placental abruption with a dose-response relationship (Steane et al., 2021)
Stillbirth (pregnancy loss after week 24)	No outcomes reported
Assisted delivery (including vacuum extraction, forceps delivery, caesarean section)	No outcomes reported
Apgar score at birth	No outcomes reported
Admission to neonatal unit	No outcomes reported

Fetal Outcomes and Features of FASD

The Canadian FASD diagnostic guidelines describe brain dysfunction related to prenatal alcohol exposure (PAE) in the following neurodevelopmental domains: motor skills, neuroanatomy and neurophysiology, cognition, language, academic achievement, memory, attention, executive function, including impulse control and hyperactivity, affect regulation, and adaptive behaviour, social skills or social communication (Cook et al., 2016). In the creation of the guidelines, the authors describe the threshold of alcohol exposure known to be associated with these adverse neurobehavioural effects to be seven or more standard drinks per week or any episode of drinking four or more drinks on the same occasion.

With a database of outcomes from Canadian diagnostic clinics now in place, our understanding of child outcomes related to alcohol use in pregnancy will increase (CanFASD Research Network, 2020). However, the challenge remains to have accurate data on quantity, frequency and timing of alcohol use in pregnancy, and capacity to estimate the effects of other substance use and related health and social influences. In the past five years, young adults with FASD have published survey results showing their significantly higher rates of many health conditions and diseases including autoimmune conditions, hypertension, scoliosis, sleep disorders, osteoarthritis, endocrine disorders, digestive and intestinal problems, cancer, reproductive health problems and mental health concerns. They have noted that this range of conditions makes FASD a “whole-body” diagnosis (Himmelreich et al., 2020). Some of these conditions are addressed below, but clearly many more areas of the effects of PAE are yet to be studied.

Fifty reviews published since 2015 were found that contribute to more comprehensively describing the effects of PAE on fetal and child health. Many authors noted limitations in the articles reviewed such as weaknesses in study designs and reporting. In addition to previously identified outcomes related to FASD, the following examples are of specific effects in offspring that were cited in this recent literature related to significant PAE:

- Metabolic and body composition outcomes including glucose intolerance and/or insulin resistance; dyslipidemia and/or hypercholesterolemia; and increased adiposity in offspring with PAE (Akison et al., 2019)
- Brain structure differences (e.g., smaller volumes in the left anterior cingulate cortex) and mental health symptom profiles in children with PAE with and without postnatal adversity (Andre et al., 2020)

- Abnormalities of the heart, kidney, liver, gastrointestinal tract and endocrine systems (Caputo et al., 2016)
- Somatic problems, high pain tolerance, destructive behaviour, hyperactivity and aggressiveness, as well as social problems with friendship, school attendance and maintenance of steady employment (Domeij et al., 2018)
- Impaired verbal and visual-spatial episodic memory performance, including impairments specific to the encoding stage (du Plooy et al., 2016)
- Diffusivity alterations in white matter brain structure in commissural, association and projection fibers causing a range of cognitive impairments (Ghazi Sherbaf et al., 2019)
- Significant decline in protein synthesis or enzyme activity in offspring fetal liver (Liu et al., 2016)
- 428 conditions co-morbid with FASD, with abnormal results in function studies of peripheral nervous system and special senses, conduct disorder, receptive language disorder, chronic serous otitis media (a middle ear condition) and expressive language disorder as the most prevalent (Popova et al., 2016)
- Aspects of cardiovascular and renal function, including blood pressure, heart rate control, heart function and urinary excretion (Reid et al., 2019)
- Receptive and expressive communication delays up to 36 months (Hendricks et al., 2019)
- Central auditory nervous system impairment symptoms (Simões et al., 2016)

Of particular interest are the findings from systematic reviews and meta-analyses published since 2017 that explore outcomes related to low or moderate PAE. These are important in determining if any change is required to the current precautionary principle recommendation that "zero alcohol use in pregnancy is safest."

The previously described systematic review and meta-analysis by Mamluk et al. (2017) explored the effects of low to moderate levels (≤32 g/week) of maternal alcohol consumption during pregnancy on pregnancy, fetal, infant and child outcomes (Mamluk et al., 2017). Their meta-analysis included 19 studies that examined the impacts of low to moderate PAE on outcomes. The findings yielded modest evidence for an increased risk of being small for gestational age (OR 1.08, 95% CI 1.02–1.14) and evidence of preterm delivery (OR 1.10, 95% CI 0.95–1.28). Compared to offspring of those who did not drink, the offspring of those who drank lightly had a lower birth weight than average (-13.49 g; 95% CI -30.28 – +3.31) and birth weight <2,500 g (OR 1.00, 95% CI 0.82–1.22) (Mamluk et al., 2017). Other pregnancy outcomes were not included in the meta-analysis due to heterogeneity across studies. There were limited studies eligible for inclusion due to the focus on low levels of alcohol use, thus prohibiting the authors from pooling the findings (Mamluk et al., 2017).

With respect to fetal outcomes, the same authors found "a surprisingly limited number of prospective studies specifically addressing the question of whether light maternal alcohol consumption has any causal effect … on infant and later offspring outcomes." They noted that there was some evidence that light PAE is associated with SGA and preterm delivery, but with the exception of birth size and gestational age, there were insufficient data to meta-analyze or make

There is a well-established risk for learning, health and social effects that have a lifelong impact, including brain injury, birth defects, health problems and diseases, in those exposed to alcohol prenatally.

Recent reviews that considered low levels of exposure have found some of these adverse effects, reinforcing the message that it is safest not to drink in pregnancy.

robust conclusions. Given the lack of evidence they recommended that the precautionary principle be applied (Mamluk et al., 2017).

Table 2 presents an overview of 14 systematic reviews identified in the current search on the topic of fetal and child outcomes that included some level of focus on dose response outcomes. The authors repeatedly noted inconsistencies across studies related to definitions of levels of PAE, lack of information on timing and dose of alcohol consumed during pregnancy, limitations related to comparison group characteristics and other limitations.

Table 2: Key findings related to fetal health and features of FASD

Outcome of interest	Key findings
Memory & attention	Three systematic reviews examined the effects of PAE on episodic memory (du Plooy et al., 2016), attention (Pyman et al., 2021) and ADHD symptoms (San Martin Porter, 2019). PAE was found to impair verbal and visual-spatial episodic memory, and (in one study) heavy PAE was found to result in significantly greater impairments in memory encoding not found for moderate levels of PAE (du Plooy et al., 2016). A significant adverse effect of any PAE was identified for shifting attention compared to controls; trends showed low to moderate PAE was associated with greater odds of behavioural attention problems. No increased risk of ADHD symptoms was identified in offspring PAE up to 70 g/week. Notably stratified analysis by sex showed for a PAE ≤ 50 g/week exposed less risk of ADHD symptoms in male compared to female offspring.
Mental health	In a systematic review that examined the association of PAE with offspring mental health at age 3+, it was found in over half of the 33 included studies that PAE is positively associated with offspring mental health problems (Easey 2019). All but four used varying measures of PAE and definitions of “low” or “moderate” use making comparison between studies challenging.
Communication	A systematic review studying oral and written communication skills that included young people with PAE or FASD age 10 -24 years found that oral and written communication skills were generally weaker among adolescents with PAE compared to those with low or no PAE (Kippen et al., 2021).
Congenital heart disease	One systematic review examined the association between parental alcohol consumption and the risk of congenital heart diseases. The review found that both maternal and paternal alcohol exposures were significantly associated with risk of congenital heart diseases in offspring; that with an increase in parental alcohol use, the risk of total congenital heart diseases in offspring gradually increases; and a statistically significant association between paternal binge drinking of alcohol and risk of total congenital heart diseases in offspring (Zhang et al., 2020).
Leukemia	One systematic review found a statistically significant dose-response association with any level of maternal alcohol consumption compared with no drinking during pregnancy for risk of acute myeloid leukemia in offspring age 0–14 (Karalexi et al., 2017).
Immune health	A systematic review investigated immune-related outcomes in offspring with PAE, who had a diagnosis of FASD or were suspected to have been exposed to moderate-to-heavy PAE (Reid et al. 2019). Again, the authors noted that information on timing and dose of alcohol consumed during pregnancy is lacking from many studies. In one study where dose was reported, high PAE (>7 drinks per week) was associated with three to four-fold increase in infections in children compared to moderate levels resulting in a 2.5-fold risk.
Organ function	In one systematic review on FASD the authors summarized the effects on organ systems from studies published between 2009 and 2016 (Caputo et al., 2016). They found all organ systems impacted with the brain most severely impacted, and reduced brain volume and malformations to corpus callosum most common. In two studies, women’s drinking was classified as moderate, heavy or binge (by grams or units of alcohol) and “both heavy and binge drinking were found to exert an effect on the stability of organ functions … and consequences for the individuals starting in utero through early childhood.”

Outcome of interest	Key findings
Offspring reproductive outcomes	One systematic review reported on the impacts of PAE on the reproductive system, including clinical and preclinical studies published up until October 2018 (Akison et al., 2019). Limited female reproductive outcomes were studied and findings were mixed, but both female and male reproductive function outcomes were described. For males with PAE, increase in testosterone levels, delayed pubertal development and decreased Sertoli cell function and sperm concentration were reported. For females, increased salivary testosterone levels and possible delay in age of first menarche (in a study where mothers drank >2 drinks/day during pregnancy) were mentioned.
Overall child development & behaviour	One systematic review examined the influence of low and moderate amounts of prenatal alcohol and nicotine exposure on early child development (up to two years) using literature published January 2009 to December 2019 (Römer et al., 2020). To be included, degree of exposure needed to be described as low or moderate, or distinguished from heavy, high and binge exposure. This systematic review included n = 17 papers; of these, n = 13 studies on PAE. Individual studies reported: • No association between low PAE and neurobehavioural deficits among six-month-old infants; • Decreased sensory regulatory responses in nine-month-old infants compared to non-PAE; • Increased cognitive capacities among 12-month-old-infants with PAE; however, authors note that cognition more impacted by social and environmental factors of family; • No impact on gross motor development at 12 months with low PAE; • 18-month-olds exposed to low and moderate amounts of alcohol were less cautious when approaching strangers and had smaller body sizes than controls; • Disrupted cortisol in 19-month-old boys exposed to low PAE; and • Low-level PAE not associated with language delays or behavioural problems in 24-month-old toddlers.

The Mamluk et al. study discussed in this summary was entitled “Low alcohol consumption and pregnancy and childhood outcomes: Time to change guidelines indicating apparently ‘safe’ levels of alcohol during pregnancy?” (Mamluk et al., 2017). Given the lack of quality evidence found by those authors and throughout this review we cannot yet identify a safe level of PAE and therefore ought to continue to apply the precautionary principle.

Breastfeeding

Breastfeeding is the best and safest method for supporting infant growth and development, and supporting infant immune function (Giglia, 2020). Alcohol enters breast milk through passive diffusion within 30 to 60 minutes following ingestion (Spahn et al., 2019; Giglia, 2020). While the blood alcohol concentration (BAC) of the mother is influenced by body weight, adipose tissue, rate at which alcohol is consumed and the strength of the alcohol consumed, the level of alcohol exposure of breastfed infants is influenced by maternal body water, BAC and body weight (Giglia, 2020; Giglia & Binns, 2016). Breastfeeding infants are exposed to alcohol at the same BAC as maternal BAC (Wilson et al., 2017). However, they are unable to metabolize alcohol the same way, thus increasing the potential risk of alcohol-related harms.

Two (*n* = 2) systematic reviews and one (*n* = 1) literature review described alcohol use and breastfeeding. A systematic review exploring the relationship between maternal diet during lactation and flavour transfer to breastmilk, children’s behavioural response and dietary intake found that in eight of 10 studies, alcohol use by women who were lactating transferred alcohol into mothers’ breast milk. In exploring chemical and adult sensory analysis, the authors found that seven studies indicated a time-dependent relationship between maternal ingestion with the presence and peak

odour of alcohol in breastmilk 30 to 60 minutes following ingestion, with a decreased odour change following the 60-minute mark ($P < 0.001$). Further, the authors identified one U.S. study that found a small but significant change in odour of breastmilk following the consumption of non-alcoholic beer. While no ethanol was detected, changes in the ethanol content of milk paralleled the sensory changes in milk from alcohol consumption (Spahn et al., 2019).

Effects of alcohol consumption on breastfeeding include a decrease in milk production, early cessation of breastfeeding and effects on infant sleep patterns.

The authors further found that infants consumed less breast milk three hours following maternal alcohol consumption and the frequency of suckling increased. The authors did not find a difference in the feeding duration (including number of feeds and time attached to the nipple at each feed) or maternal perception of enjoyment. However, a more recent (2001) study found that while breast milk intake zero to four hours after alcohol ingestion was reduced, eight to 12 hours after ingestion, breast milk intake increased (Spahn et al., 2019). This may be a result of the impact of alcohol on the release of oxytocin and prolactin, the two pituitary hormones that control breastfeeding, that can result in a decrease in milk production and availability (Mennella et al., 2001; Haastrup et al., 2014).

Another systematic review examining the existing recommendations and successful strategies to prevent SIDS found an association between PAE and postnatal alcohol use with SIDS (Jullien, 2021). Alcohol use was more likely to increase the occurrence of bed-sharing, which has been associated with both an increased risk of SIDS while also promoting attachment and breastfeeding, thus acting as a protective factor for SIDS. The authors note that there is not enough information on the harms and benefits of bed-sharing when breastfeeding and alcohol use were taken into consideration. However, their findings suggest that for infants born preterm or with low-birth weight, or where parental alcohol consumption is present (no gender specified) there is an increased risk of SIDS (Jullien, 2021).

A 2018 literature review on alcohol and breastfeeding further emphasized the effects of alcohol on oxytocin. The review reported that doses as low as 0.3 g/kg body weight have been shown to have an inhibitory effect on oxytocin, thus decreasing milk intake. The authors found no association between motor skills and alcohol during lactation (Brown et al., 2018). While the findings from this review were consistent with previous research, the authors note challenges to the generalizability of the findings, given that there are the few authors conducting breastfeeding research thus increasing the risk of introducing recruitment bias (Brown et al., 2018; Haastrup et al., 2014).

There is a growing body of research demonstrating that high socioeconomic status is associated with alcohol consumption while breastfeeding. Several studies within this review indicated that older age and higher educational attainment were also associated with alcohol use during lactation. The authors note that maternal under-reporting and social desirability bias likely contribute the lower reported rates of alcohol consumption while breastfeeding. However, exposure to programs such as the Canada Prenatal Nutrition Program was associated with a reduction in alcohol use prenatally and during lactation, as well as prolonged lactation (Brown et al., 2018).

Table 3 summarizes the key findings related to alcohol use and the breastfeeding outcomes of interest based on the findings from three reviews published between 2015 and 2021.

Table 3. Key findings related to alcohol use and breastfeeding outcomes

Outcome of interest	Key findings
Cognitive impairment	No outcomes reported
Child neglect	No outcomes reported
SIDS/SIDU	Increased incidence of bed-sharing, which is an increased risk factor for SIDS (Jullien, 2021)
Sedation	Increased disruption of sleep patterns (Brown et al., 2018) Decreased activity during wakefulness (Brown et al., 2018)
Maternal bonding	Early cessation of breastfeeding, particularly among women drinking at high-risk levels (Brown et al., 2018)
Failure to thrive in babies and children	No effect on motor development (Brown et al., 2018)
Milk production	Decrease in breast milk yield (Brown et al., 2018) Increased suckling (Brown et al., 2018) No change in breastfeeding duration (Brown et al., 2018) Milk ejection reflux (Brown et al., 2018) Family history of alcoholism associated with magnitude, rapidity and length of prolactin response (Brown et al., 2018)

Gender-Related Factors Affecting the Impact of Alcohol Use Among Women

It is important to identify various gender-related factors affecting women's alcohol use and their impacts to improve health literacy, prevention and health promotion. Knowledge translation efforts of low-risk drinking guidelines can also take these factors into consideration, in combination with sex-related factors. Understanding gendered experiences in an intersectional context places the impact of alcohol on women in a real-world context and considers life experiences, thereby facilitating better uptake.

For several decades, key gender related factors affecting women's alcohol use have been highlighted in reports from varied sources. For example, the U.S. National Institute of Drug Abuse released *Drug Addiction Research and the Health of Women* in 1998. The United Nations Office of Drugs and Crime released *Substance Abuse Treatment and Care for Women: Case Studies and Lessons Learned* in 2004 (United Nations Office on Drugs and Crime, 2004). The U.S. Substance Abuse and Mental Health Services Administration released *Substance Abuse Treatment and the Care of Women: Addressing the Specific Needs of Women* in 2009 (Substance Abuse and Mental Health Services Administration, 2009). In Canada, the Centre for Addictions and Mental Health published *Highs and Lows: Canadian Perspectives on Women and Substance Use* in 2007 (Poole & Greaves, eds., 2007).

In these publications, gendered influences on women's alcohol and other substance use are identified including:

- The impact of physical and sexual abuse experienced by women as children or adults;
- Heterosexual partner influences affecting norms of heavy drinking for women;
- Higher rates of depression and anxiety for women as antecedents for substance use problems;
- Stigma associated with heavy alcohol use by women, especially for pregnant women and mothers, and its negative impact on access to systems of care;
- Stress related to women's roles of caregivers;
- Punitive child welfare policy for mothers who use alcohol and other substances; and
- Gendered intersectional influences such as lower income, poverty, Indigeneity, and intimate partner violence.

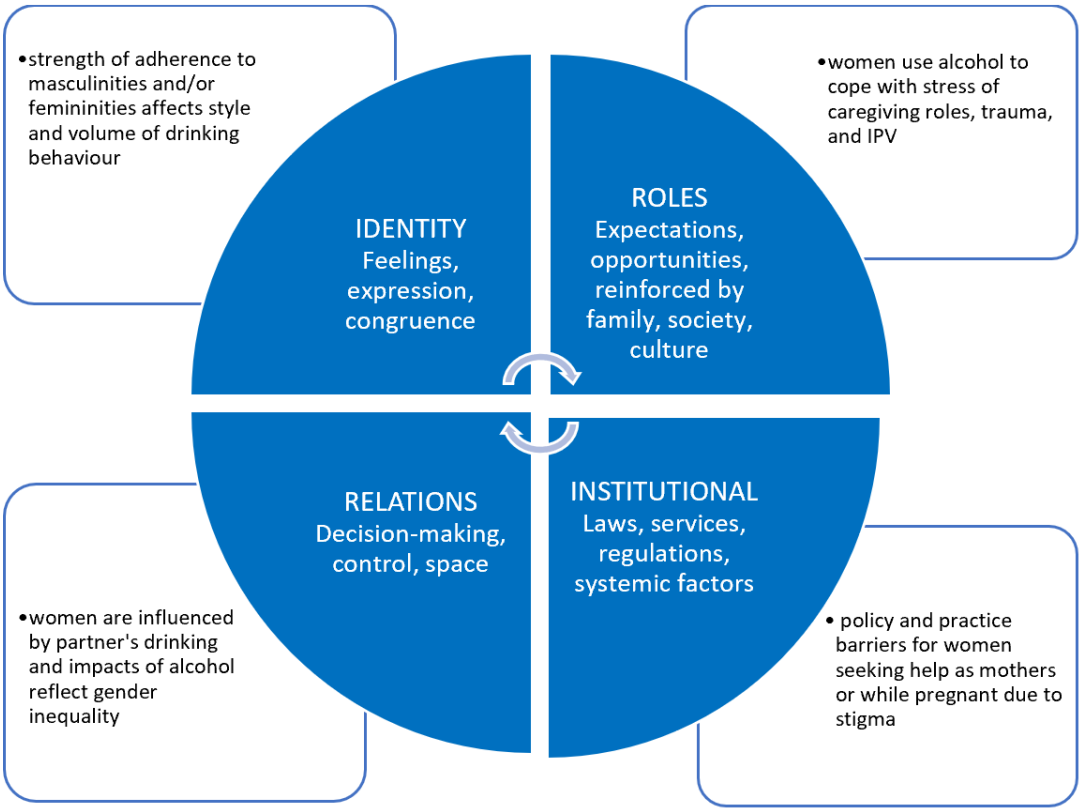
These factors directly affect the pathways, protective factors, progression and transition to alcohol problems, maintenance of use, and readiness for, access to, retention in and outcomes of treatment. Despite this longstanding knowledge, there is comparatively little research on gendered factors (Meyer et al., 2019), and surprisingly little gender- and sex-specific or tailored treatment and other services.

The impact of gender-related factors linked to alcohol use includes the various influences of roles, relations, identities and institutional practices. **Gender roles** reflect dominant and proscribed expectations of women and men such as jobs and caregiving, while **gendered relations** refer to the gendered dynamics of relationships in couples, work or friendship circles based on decision making, authority and access to resources. **Gendered identities** reflect the adherence to dominant and hegemonic femininities and masculinities for women, men and gender-diverse individuals, as well as

the congruence between such ascriptions and felt gender. Finally, **gendered institutional** factors reflect policies and practices that manifest in law, media or religions that affect people in gendered ways, such as child welfare policies, advertising or stigma.

Recognizing gender-related factors is to be distinguished from noting "gender differences" although the latter may inform the former. Gender-related factors are temporal and culturally specific and interact with sex-related factors to produce effects or impacts. These variabilities make measuring and assessing the impact of gender-related factors on health challenging. In short, understandings of gender are changeable, due to their links to cultural practices and time periods, and therefore merit continued examination to inform the LRDGs. Figure 2 presents the main categories of the gender concept, with an example of the impact of alcohol in each quadrant.

Figure 2: Gender-related factors



Adapted from Greaves & Hemsing, 2020

Our search for systematic reviews published since 2017 related to gendered influences on women's alcohol use identified 18 results, ten of which focused on the gender influences on pregnant women and mothers.

Gender Roles and Norms

Prevailing social roles are standard or normative behaviours expected of girls, boys, women and men, including norms and behaviours about use of alcohol, amount consumed or intoxication from alcohol use in a particular cultural or subgroup context. Roles and expectations about masculinities

and femininities are well established in most cultures and are reinforced through strong socialization processes and media. Gender diverse individuals may seek to conform with norms associated with a gender incongruent with their sex or non-binary individuals may reject all gendered norms. Prevailing norms, for example, may excuse or respond to intoxication among boys more than among girls. Stigma or negative attitudes about alcohol use may be applied to women more often than men and mothers more often than fathers, as another example. Further, these norms can shift over time, as, for example, tolerance for binge drinking among girls has increased, while social tolerance for alcohol use by pregnant women has decreased in recent decades.

Two systematic reviews focused on gender norms and roles. One review examined the evidence between conformity with gender norms and alcohol use and abuse in adults (Patró-Hernández et al., 2020). Conformity to norms associated with traditional masculine roles (dominance, womanizing, aggressiveness, risk behaviours) is related to greater alcohol use; conformity to norms associated with traditional feminine roles (interest in home life and family care) is related to lower alcohol use. These findings provide insight into the relationship between dimensions of gender and drinking. The possibilities of modifying gendered beliefs and patterns linked to risk behaviours is an important aspect of prevention. More precise development of gender measures is necessary to further deepen the study of these relationships.

Another review found norms related to mothering as influential in women's health behaviour during pregnancy, specifically related to dietary behaviour, physical activity, smoking and alcohol use (Rockliffe et al., 2021). Three overarching themes were noted: 1) a time to think about "me;" 2) adopting the "good mother" role; and 3) beyond mother and baby. These findings provide an improved understanding of the various dynamic changes in internal and external factors influencing women's health behaviour during the antenatal period.

Gender Relations

Relationships between people in romantic, sexual, household, work or friendship settings are typically gendered. In heterosexual relationships, there is often an imbalance in decision making power on issues such as freedom of movement or behaviour, including alcohol and drug use, spending money, driving vehicles or recreational pursuits. Members of any kind of couple relationship can and do influence each other to drink, drink more, drink less or not at all, with or without coercion. These couple dynamics have been shown to be important with respect to substance use patterns, and often mix with other factors or dynamics such as intimate partner violence (IPV), pregnancy and parenting, or addiction. Several of the recent reviews focused on the influence of IPV and coercive relationships. This long-standing gendered influence on women's alcohol use points to a need for tailored trauma- and gender-informed approaches in messaging about drinking guidelines.

One systematic review examined research in this area from 2012 through 2019 (Stubbs & Szoeke, 2021). Another systematic review described what is known about the prevalence, risk factors and health consequences associated with IPV among young pregnant women (Tipparat, et al., 2020). Risk factors associated with IPV during pregnancy included having a husband or partner with a low education level, a low level of family income, and partners' problem drinking. Protective factors included sex education for girls, youth services and reducing gender inequality. Without promoting gender equality, the problem of IPV is likely to continue. More culturally tailored intervention research addressing IPV among various populations is needed.

Gendered relations can be directly invoked in prevention efforts. For example, encouraging reciprocal partner support to reduce vulnerability to perinatal depression and anxiety can include

actions on becoming a parent, supporting each other through pregnancy and childbirth, communication, conflict, division of labor, practical support, emotional support, emotional closeness, sexual satisfaction, using alcohol and drugs, encouraging self-care, developing acceptance, and help-seeking (Pilkington et al., 2016).

Other gendered relational factors also matter in assessing risky alcohol use by women, such as vulnerability to sexual assault. One systematic review examined the evidence on the effects of alcohol intoxication on sexual assault risk information processing among young adult women (Melkonian & Ham, 2018). Thirteen of the 14 studies identified report at least partial support for intoxication impairing the attention to cues, interpretation of social information or intended behavioural response in a hypothetical sexual assault scenario. Another systematic review identified some psychosocial correlates of sexually transmitted and blood borne infection acquisition, unplanned pregnancy, abortion and risky sexual behaviours in general population samples of women of reproductive age (Edelman et al., 2015). Multiple partnerships were associated with intensity of marijuana and alcohol use, and smoking. These relational gender influences on women's alcohol use prompt consideration of settings such as schools, colleges and sexual health clinics as locations for sharing lower-risk alcohol guidelines. In short, gendered relations are not to be ignored in considering the content and impact of the messaging around drinking guidelines.

Gender Identity and Sexual Orientation

In general, people who are in either sexual minority or gender minority groups consume more alcohol than those in majority groups. However, reliance on non-representative samples and a range of other methodological limitations are drawbacks in this research (Hughes et al., 2020; Gilbert et al., 2018). The degree to which individuals conform to or resist prevailing femininities and masculinities, express gender in conforming or non-conforming ways, or claim or identify with a particular overarching gender identity such as woman, man, trans (masculine or feminine) or non-binary are all factors in how alcohol use might play out for groups of people. In addition, different sexual orientation groups such as heterosexual, homosexual (gay or lesbian) or bisexual may subscribe to different dimensions of femininity or masculinity along with experiencing sexual attraction to same sex persons.

No systematic reviews were found specifically related to alcohol and gender identity. However, several individual studies indicate potential gender influences on drinking for young people identifying as transgender, such as the links between alcohol use and risky sexual behaviour, and with identity formation as college students (Tupler et al., 2017; Emslie et al., 2017; Hotton et al., 2013). For example, one study found that high life stress was associated with an increased odds of sexual risk for young transgender women, and that this was further increased by alcohol and other substance use. They concluded that interventions aimed at reducing sexual risk behaviour in this population should address problems with alcohol and other substance use "as well as more distal factors that impact risk, such as homelessness, joblessness, and lack of access to medical care" (Hotton et al., 2013). Another study concluded that transgender compared with non-transgender first-year students engage in higher-risk drinking patterns and experience more alcohol-related blackouts and other negative alcohol-related consequences (Tupler et al., 2017). The authors note that male-to-female transgender students had higher levels of alcohol consumption and frequency of alcohol-related blackouts and consequences than female-to-male transgender students. While individual studies such as these do not permit comparisons or fully contextualize sexual and gender minority alcohol use patterns, they may offer insight into selected samples.

Gendered Institutional Impacts

Gendered applications of policies, laws, regulations and cultural prohibitions have an impact on different gender groups, particularly women. For example, the following practices all have differential impacts on men and women, boys and girls: warning signs about drinking during pregnancy in bar washrooms; stigma related to alcohol use for women, especially pregnant women and mothers; criminalization of pregnant women who drink in some jurisdictions; cultural and religious norms prohibiting alcohol use in women or men or both; and age guidelines for purchase. These policies and practices are all gendered in their impact or intent.

Stigma and trauma are gendered issues and important aspects to be considered in prevention, treatment and knowledge mobilization. These are particularly resonant when considering reproduction. One systematic review of qualitative studies involving pregnant and recently postpartum women was undertaken to understand the barriers and facilitators that influence alcohol use in pregnancy (Lyall et al., 2021). Five themes impacting women's alcohol use, abstention and reduction of use were identified: 1) social relationships and norms; 2) stigma; 3) trauma and other stressors; 4) alcohol information and messaging; and 5) access to trusted equitable care and essential resources. However, the impact of structural and systemic factors on prenatal alcohol use was largely absent in the included studies, instead focusing on individual choice (Lyall et al., 2021). This represents a missed opportunity.

Similarly, the availability of preconception health knowledge, messages, interventions and programming is a crucial gendered aspect of understanding alcohol use. One systematic review examined how preconception health knowledge has been measured in the existing literature and identified measurement gaps, biases and logistical challenges (Cairncross et al., 2019). The authors noted that preconception health knowledge tools focused on fertility, folic acid and alcohol, with few questions pertaining to men's health, mental health or the interconception period.

Another systematic review explored enablers and barriers to women's preconception lifestyle behaviours using several pre-established models and frameworks (Kandel et al., 2021). The presence or absence of knowledge on healthy behaviours was the most assessed enabler or barrier. Building opportunities for preconception interventions where alcohol guidelines can be routinely discussed, and giving support related to the importance of and confidence for change are important (Nathoo et al., 2018; Hemsing et al., 2017). However, in the current context of an overloaded healthcare system, online preconception interventions may be most feasible.

Interactions of Sex and Gender Factors and Intersectional Influences

Interactions of Sex and Gender Factors

Clearly, both sex and gender interact to determine impacts on alcohol use by women, and the consequences for women. Sex and gender interactions are enhanced when understood in an intersectional context, considering characteristics such as Indigeneity, low socioeconomic status, age, and other drug use. These processes result in internalized stigma for women and (re)trauma, often resulting in vicious circles of alcohol use and negative consequences.

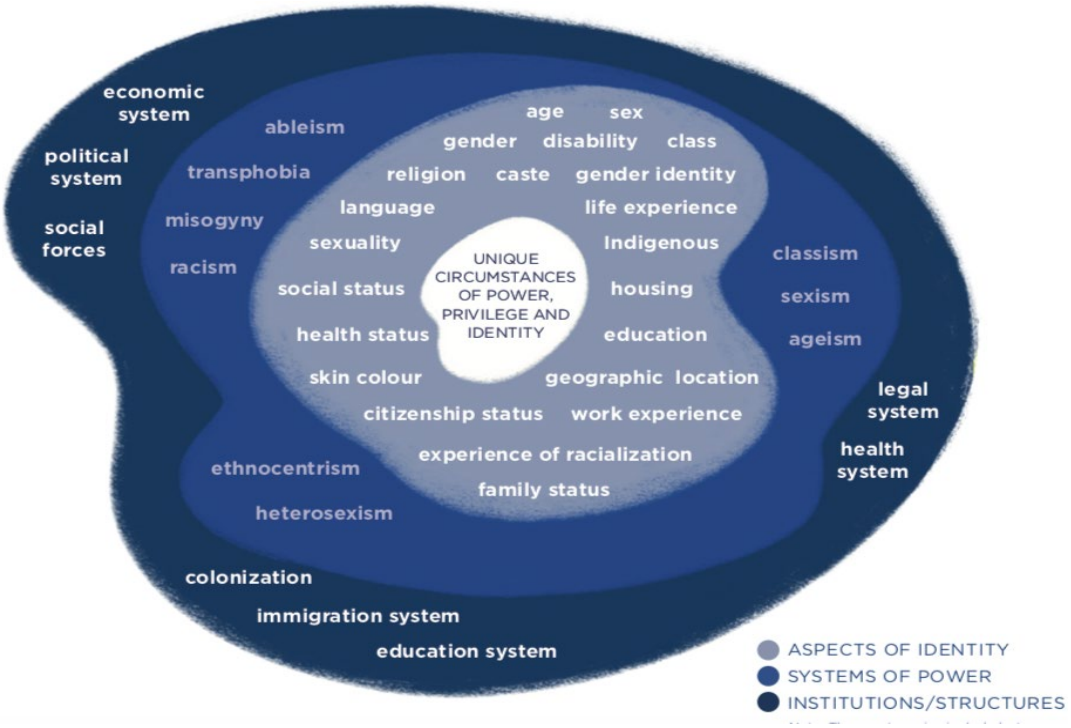
For example, pregnant women and mothers are subject to stigma regarding alcohol (and other substance) use (Lyall et al., 2021), especially for visibly pregnant women. This stigma is baked into a gendered institutionalized response, in the form of birth alerts, child custody and apprehension and welfare decisions that are state-specific and often punitive. Such experiences create long-term impacts on bonding, attachment processes, child development, and maternal and child mental health, and contribute to ongoing trauma. Other examples include the impact of advertising, posters and warnings in bars, public places, and washroom walls. These warnings rarely acknowledge the 6 weeks before pregnancy confirmation when women do not know they are pregnant, contributing to later anxiety and worry. Further, if contraception, pre-conception, and abortion services are missing in many settings or locales, there are disproportionate gendered impacts on women.

IPV and alcohol use are connected, illustrating another sex/gender interaction, as most victims of IPV are women. One systematic review described the negative effects of IPV on physical health outcomes for women, including worsening the symptoms of menopause, increasing the risk of diabetes, developing chronic diseases and pain, contracting sexually transmitted infections, and engaging in risk-taking behaviors including the abuse of drugs and alcohol (Stubbs & Szoeke, 2021). IPV also affects human immunodeficiency virus outcomes, worsening CD4+ cell depletion. This review highlights significant gaps in this field of research in relation to cardiovascular disease, endocrine dysfunction, and neurological symptoms and conditions and underlines the need for additional long-term studies to better inform the health care of women who have experienced IPV and to establish the physiological mediators of these outcomes (Stubbs & Szoeke, 2021). How alcohol may or may not be contributing to this range of health outcomes, as well as the association of alcohol use problems with IPV needs further study. A final example is IPV during pregnancy. The rates of IPV during pregnancy are higher than in other life phases, and IPV is often first experienced during pregnancy (Society of Obstetricians and Gynecologists of Canada, 2005). The provision of appropriate and timely services and messages during this period, regarding alcohol use, couple dynamics, help-seeking, first responders and gender equity remain rare, but are a key component of knowledge mobilization regarding the impacts of alcohol and pregnancy.

Intersectional Influences

Various factors and characteristics intersect with sex and gender to create outcomes for women. Figure 3 illustrates the complex interconnections that impact real-life experiences for women who use alcohol or who feel the impact of others' use of alcohol. The diagram, developed by the Canadian Research Institute for the Advancement of Women, provides an overview of these intersections (2021).

Figure 3. Feminist intersectionality framework



Source: Canadian Research Institute for the Advancement of Women, 2021
https://www.criaw-icref.ca/publications/feminist-intersectionality-poster

Three examples indicate the wide range of factors and issues that must be taken into account to tailor knowledge mobilization of low-risk drinking guidelines. One systematic review assessed the societal distribution of alcohol-attributable harm by investigating socioeconomic inequality and the related gender differences in alcohol-attributable mortality (Probst, 2015). They found alcohol-attributable mortality to be strongly distributed to the disadvantage of persons with a low socioeconomic status. Gender differences in this inequality were found with male-dominated occupations more strongly related to risky drinking cultures compared with female-dominated occupations of the same socioeconomic status.

Other studies assessed intersectional factors related to alcohol use in pregnancy. For example, analyses of the social determinants of health underpinning FASD in South Africa add critical insight from an intersectional feminist perspective (De Jong et al., 2021). The authors used an intersectionality wheel to conceptualize how the social and structural determinants of FASD identified in the literature are interconnected and indicative of broader inequalities shaping the lives of the affected women and children. Key intersecting social determinants that facilitate drinking during pregnancy among marginalized populations in South Africa include social norms and knowledge around drinking and drinking during pregnancy, alcohol addiction and biological dependence, gender-based violence, inadequate access to contraception and abortion services, trauma and mental health, moralization and stigma.

Most of the studies found were quantitative, so there was little representation of pregnant women's experiences and perspectives, and limited analyses of how these determinants intersect with one another and relate to the broader structural factors to influence pregnancy outcomes. Another systematic review identified demographic, health and psychosocial variables associated with alcohol

consumption during pregnancy, which may lead to FASD (Ward et al., 2021). This review identified the significance of prior mental illness, anxiety, depression, exposure to abuse and domestic violence, and alcohol consumption behaviours of partners and family members as strong predictors of risky alcohol consumption during pregnancy and associated risk of FASD. Studies such as these indicate another range of complex interconnecting factors that need consideration when trying to reach pregnant women with low-risk drinking guidelines.

Conclusions

Research on sex- and gender-related factors affecting women's use of alcohol and the impacts of others' alcohol use is lagging, as is most sex and gender science about health matters. Nevertheless, the recent evidence suggests that a range of sex-related factors affecting the ingestion of alcohol matter in determining the impact on women with specific impacts on female bodies. In short, females sustain more damage on lesser amounts of alcohol compared to males, and alcohol use is linked to numerous disease conditions. Women's reproductive health is also compromised by alcohol use, particularly during pregnancy and breastfeeding. Long-term damage to children can occur after being exposed to alcohol in the womb, and alcohol use during breastfeeding can reduce milk production. Gender also matters to understanding the impacts of alcohol use by women and by others that affect women in real-world situations. Relationship dynamics, drinking patterns and social expectations about alcohol use can have an impact on harms to women, such as binge drinking, IPV and sexual assault.

Further, sex and gender interact to produce singular patterns of impact on women, such as in response to childhood trauma, during pregnancy or in the context of state child welfare policies. Such situations are unique to women and reinforce a range of biological and social factors that operate together. Finally, sex and gender exist in the context of myriad intersectional factors, characteristics and processes that further delineate and describe lived experiences of women such as poverty and age; they operate in the context of wider processes such as sexism, racism and colonialism.

Taken together, the evidence suggests that approaches for improving knowledge mobilization must be informed by sex and gender and developed in recognition of social context. Some general approaches directly applicable to the development and distribution of low-risk drinking guidelines are for the development of:

- Sex, gender and trauma informed message content
- Destigmatizing approaches
- Women-centred messaging, especially in pregnancy
- Messages reflecting the real-world experiences of women
- Gender transformative messaging surrounding couple dynamics
- Precision in audience segmentation that reflects gender and sex

Knowledge Mobilization Messages

The statements below can be molded for various audiences and various formats. They can be developed into health promotion messages, videos, infographics, pamphlets or advertisements, ideally co-created and tested with intended audiences.

Sex-Related Themes and Messages

- Women and men process alcohol differently reflecting sex-related hormones and enzymes, water and fat ratios, body weight and organ size resulting in faster and more damaging effects for women. Women need to be aware of these differences when gauging how much they will drink.

- Women experience more bodily damage from alcohol, such as liver damage and injury, even when consuming lower amounts of alcohol.
- Alcohol use increases the risk of a range health conditions and cancers, including breast cancer. Women need to know that cancer is an alcohol-related risk and factor this into decision making about alcohol.

Pregnancy, Breastfeeding and Mothering Themes and Messages

- Alcohol use in pregnancy increases risks of short- and long-term effects, including miscarriage, brain injury, birth defects and health problems. There is no known safe level of alcohol use in pregnancy, so it is safest not to drink in pregnancy.
- Influences on pregnant women's drinking include the alcohol use and social pressure of their partners. Partners and care providers can be engaged to offer non-judgmental support in reducing or stopping alcohol use when pregnant, breastfeeding or planning a pregnancy.
- Stigma associated with alcohol use in pregnancy can result in avoidance of perinatal health and social care services. It is important that perinatal care providers and service systems proactively support pregnant women and new mothers by providing non-judgmental, trauma-informed, harm-reduction oriented, culturally safe and holistic care.

Gender-Related Themes and Messages

- Sex and gender interact to create more risk of faster intoxication among girls and women, especially in situations where social pressures encourage binge drinking.
- Alcohol use enhances risks of intimate partner violence and sexual assault when alcohol is involved in couple, dating or stranger situations, whether used by perpetrators, victims or both.
- Gender transformative messaging can be aimed at men and boys to increase awareness of sex- and gender-related impacts of alcohol and encourage attitudes and behaviours that prevent the exploitation of intoxicated girls and women.

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Appendix A: Search 1: Alcohol and Sex or Gender (2018–2021)

Search 1 identified research published between 2018 and 2021 that addressed sex- and/or gender-related factors and alcohol use.

Search 1 Terms:

("gender related" or "gender difference*" or "gender disparit*").ti,ab.
("sex related" or "sex difference*" or "sex disparit*").ti,ab.
"gender comparison*".ti,ab.
"sex comparison*".ti,ab.
"gender analys*".ti,ab
"sex analys*".ti,ab.
(transgender* or "trans gender*"). ti,ab.
("transsexual*" or "trans sexual*").ti,ab.
("non binar*" or nonbinar*).ti,ab.
exp Alcohol-Related Disorders/
exp Alcohol Drinking/
(binge drink* or underage drink* or under-age drink* or problem drink* or heavy drink* or harmful drink* or alcoholi* or inebriat* or intoxicat*).ti,ab.
("alcohol dependen*" or "alcohol misuse*" or "alcohol mis-use*" or "alcohol abuse*" or "alcohol overuse*" or "alcohol over-use*" or "alcohol addict*").ti,ab.
alcohol.ti,ab.
Alcohol Abstinence/
exp Risk Reduction Behavior/
("risk reduction" or "reducing risk" or "reducing risks" or "risk minimization" or "minimizing risk" or "minimizing risks" or "risk minimisation" or "minimising risk" or "minimising risks").ti,ab.

Inclusion Criteria

Study Design:

- Randomised controlled trials (RCTs) (not already covered in an included systematic review)
- Case-control studies
- Interrupted time series
- Cohort studies
- Cross sectional studies
- Observational studies

- Systematic reviews
- Qualitative studies
- Grey literature sources
- Case series

Note:

- Narrative reviews will not be included but saved as context.
- Case studies will be excluded.

The following types of literature will be included in the grey literature review:

- Book chapters
- Reports
- Practice guidelines
- Health policy documents
- Unpublished research, theses

Note:

- Magazines and books will be excluded from the grey literature.

Country of Studies:

Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, United States

Studies published in all other countries will be excluded, including animal studies.

Studies including data from multiple countries, that include an out-of-scope country, will be excluded if the data are not disaggregated.

Systematic reviews that include studies from multiple countries will be included if reporting on one or more studies published in an eligible country.

Language:

Only studies published in the English language will be included.

Appendix B: Search 2: Alcohol, Pregnancy, Delivery and Fetal Outcomes (2015–2021)

Search 2 identified literature published between 2015 and 2021 that addressed pregnancy, fetal and reproductive health. Medical Subject Headings (MeSH) were used where applicable and combined with appropriate keywords for each risk factor topic.

Search 2 Terms:

- Alcohol and pregnancy complications
- Alcohol and delivery outcomes
- Fetal alcohol
- Alcohol and pregnan* or perinatal or breast feeding or breastfeeding or postpartum or prenatal or preconception

Inclusion Criteria

Study Design:

- Randomised controlled trials (RCTs) (not already covered in an included systematic review)
- Case-control studies
- Interrupted time series
- Cohort studies
- Cross sectional studies
- Observational studies
- Systematic reviews
- Qualitative studies
- Grey literature sources
- Case series

Note:

- Narrative reviews will not be included but saved as context.
- Case studies will be excluded.

The following types of literature will be included in the grey literature review:

- Book chapters
- Reports
- Practice guidelines

- Health policy documents
- Unpublished research, theses

Note:

- Magazines and books will be excluded from the grey literature.

Country of Studies:

Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, United States

Studies published in all other countries will be excluded, including animal studies.

Studies including data from multiple countries, that include an out-of-scope country, will be excluded if the data are not disaggregated.

Systematic reviews that include studies from multiple countries will be included if reporting on one or more studies published in an eligible country.

Language:

Only studies published in the English language will be included.

Appendix C: Sex-Related Differences and Factors in Drug Processing

SEX-RELATED DIFFERENCES & FACTORS IN DRUG PROCESSING

In Females	Physiological Differences	In Males
• Slower processing of most drugs • More accumulation of lipophilic drugs • Different concentrations of hydrophilic drugs (also throughout the menstrual cycle)	BODY COMPOSITION ↑ FAT MASS ↓ ↓ LEAN MASS ↑ ↑ FREE WATER ↓	• Faster processing of most drugs • Less accumulation of lipophilic drugs • Different concentrations of hydrophilic drugs
• Higher resting heart rate • Longer Q-T intervals • Higher risk of arrhythmias	↑ HEART RATE VARIATION ↓	• Lower resting heart rate • Shorter Q-T intervals • Lower risk of arrhythmias
• Slower absorption of drugs	↓ GASTRIC MOBILITY ↑	• Faster absorption of drugs
• Different expression of cytochrome P450 (e.g., CYP3A4 more in women) • Estrogen and progesterone compete with drugs for degradation by CYP450	↓ STOMACH ACIDITY ↓	• Different expression of cytochrome P450 (e.g., CYP2D6 and CYP2E1 more in men)
• Slower excretion of drugs	↓ KIDNEY EXCRETION ↑	• Faster excretion of drugs
• Slower elimination of drugs	↓ COLON MOTILITY ↑	• Faster elimination of drugs

Females tend to have smaller body size and more fat tissue than males, which affects drug distribution, and smaller kidneys, which leads to slower drug elimination. Liver enzymes may behave differently because of oral contraception and some hormone therapy. Female heart rhythms are different than mails (i.e., longer Q-T interval) which makes women more susceptible to fatal heart disturbances, called arrhythmias.

Adapted from: https://genderedinnovations.stanford.edu/case-studies/drugs.html#tabs-2