Report for systematic reviews of the association between different levels and patterns of maternal alcohol consumption during pregnancy and while breastfeeding and selected health outcomes for fetuses and children (up to age five)

Prepared by

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Contents

In April 2018 the South Australian Health and Medical Research Institute (SAHMRI) and Cochrane Australia were contracted by the National Health and Medical Research Council (NHMRC) to design and undertake the systematic reviews described in this report. These systematic reviews are two of several independent contracted evidence evaluations being undertaken to update or inform new sections of the 2009 *Australian Guidelines to Reduce Health Risks from Drinking Alcohol (the Alcohol Guidelines)*. The design and conduct of the review was done in collaboration with the NHMRC's Alcohol Working Committee (AWC) and the Office of NHMRC (ONHMRC).

Authors and contributors to the report

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Declarations of interest

All authors declare they have no financial, personal or professional interests that could be construed to have influenced the conduct or results of this systematic review.

Summary: systematic review of alcohol consumption during pregnancy

What is the issue?

Maternal consumption of alcohol can harm the fetus, and there may also be effects on babies and children.

Why is this important?

In this systematic review we have reported associations between levels and patterns of alcohol consumption during pregnancy and behavioural problems in babies and children, and also associations with birth defects.

What evidence did we find?

We included five studies addressing alcohol exposure during pregnancy and behavioural outcomes, 21 studies of birth defect outcomes– and one study of breastfeeding.

Meta-analysis was only possible for two outcomes – cleft lip/cleft palate (from four case-control studies) and spina bifida (two case-control studies). The cleft lip/cleft palate meta-analysis did not show a difference between alcohol exposure, generally in the first trimester, and mostly binge drinking and outcomes (very low certainty evidence). When the two spina bifida studies were pooled, there was also no reliable evidence of an association between alcohol consumption and rates of spina bifida (very low certainty evidence).

For the rest of the birth defects studies, most birth defects were assessed by single studies only, except for two studies looking at neural tube defects and four studies looking at heart defects, none of which could be meta-analysed. In the five studies assessing behavioural outcomes, two studies looking at the same outcomes from the Strength and Difficulties Questionnaire could not be meta-analysed. The other three studies each assessed different behavioural outcomes.

These single study results generally found no reliable evidence of associations between alcohol exposure in pregnancy and birth defects, except for:

- increased rates of cryptorchidism, gastroschisis, neural tube defects, and omphalocele;
- and decreased rates of congenital limb deficiencies, spina bifida and strabismus.

No single study results for behavioural outcomes indicated associations between alcohol exposure and better outcomes. For two outcomes (total difficulties and conduct), one study showed no differences and one study showed worse scores. Another four outcomes (personal-social behaviour, difficult temperament, sleeping problems and infant being demanding/irritable), indicated worse results with higher, compared with lower, alcohol consumption.

Summary: systematic review of alcohol consumption while breastfeeding

What is the issue?

Consumption of alcohol while breastfeeding can harm the breastfed baby, and there may also be adverse effects on children.

Why is this important?

In this systematic review we have reported associations between alcohol consumption while breastfeeding at eight weeks postpartum and sedation in breastfed babies, and also associations with measures of infant development.

What evidence did we find?

We included only one study, reporting three infant sedation, and eleven infant development measures, for one comparison, any alcohol consumption while breastfeeding and abstinence. No significant associations were seen excepting for personal-social development. Infants of mothers who drank had more favourable results for personal-social development at 12 months compared with those whose mothers abstained.

The included study was judged as at high risk of bias. Most of the women who reported drinking in this study also reported using a strategy to minimise alcohol passing onto their infants via breastmilk and drank at low levels.

1. Background and rationale

The National Health and Medical Research Council (NHMRC), is updating the 2009 *Australian Guidelines to Reduce Health Risks from Drinking Alcohol (the Alcohol Guidelines)* to ensure the Guidelines are based on an evaluation of the latest and best scientific evidence on the health effects (risks and benefits) of alcohol consumption. The South Australian Health and Medical Research Institute (SAHMRI) and Cochrane Australia were contracted to undertake two independent systematic reviews to inform the updating of these guidelines:

1) systematic review of the association between levels and patterns of maternal alcohol consumption during pregnancy and birth defects and behavioural problems in fetuses, babies and children; and

2) systematic review of the association between levels and patterns of maternal alcohol consumption whilst breastfeeding and selected health outcomes in babies who are being breastfed/were breastfed (up to age 5).

These systematic reviews are two of several contracted evidence evaluations being undertaken to update or inform new sections of the *Alcohol Guidelines*. The Terms of Reference (TOR) specified separate review (and technical) reports for the two reviews. However, since only one study was identified for the breastfeeding review it was agreed with the AWC to combine the reviews for the purpose of reporting. Therefore, both systematic reviews are reported in this report and the technical report companion document.

1.1 The 2009 Alcohol Guidelines

The 2009 *Alcohol Guidelines* provide universal guidance to healthy adults aged 18 years and over (Guideline 1 and 2), in addition to guidance specific to children and young people (Guideline 3) and to pregnant and breastfeeding women (Guideline 4A and 4B respectively) (Commonwealth of Australia 2009).

The review considering the association between maternal alcohol consumption during pregnancy and birth defects and behavioural problems in fetuses, babies, and children (up to age five) was performed to inform updates to Guideline 4A (Commonwealth of Australia 2009, p67&78).

Guideline 4A recommends that "For women who are pregnant or planning a pregnancy, not drinking is the safest option." (p5)

The overall conclusions drawn in the 2009 *Alcohol Guidelines* from the assessment of evidence underpinning this recommendation were as follows.

- "Maternal alcohol consumption can harm the developing fetus". (p5)
- The risk of harm is "highest when there is high, frequent, maternal alcohol intake". (p5)
- The risk of harm is "likely to be low if a woman has consumed only small amounts of alcohol …before she knew she was pregnant or during pregnancy". (p5)
- The level of risk to the individual fetus is variable and hard to predict, as it is influenced by maternal and fetal characteristics.

From the evidence available at the time, it was "not clear whether the effects of alcohol are related to the dose of alcohol and whether there is a threshold above which adverse effects occur" (Commonwealth of Australia 2009, p67). Consequently, the 2009 *Alcohol Guideline* emphasised that a safe level of alcohol consumption during pregnancy could not be established. More specifically, there was an identified need for evidence on the effects of low to moderate alcohol consumption during pregnancy, and of different patterns and timing of consumption.

The review on the association between maternal alcohol consumption while breastfeeding and selected health outcomes in babies who are being breastfed/were breastfed was conducted to inform updates to Guideline 4B (Commonwealth of Australia 2009, p67&81):

- For women who are breastfeeding, not drinking is the safest option.
- Advice for breast feeding mothers:
    - Not drinking is the safest option.
    - Women should avoid alcohol in the first month after delivery until breastfeeding is well established.
    - After that: alcohol intake should be limited to no more than two standard drinks a day; women should avoid drinking immediately before breastfeeding; women who wish to drink alcohol could consider expressing milk in advance.

1.2 Why is it important to review evidence about associations between alcohol consumption during pregnancy and breastfeeding for the selected child outcomes?

1.2.1 Importance of evidence on alcohol consumption during pregnancy and selected child outcomes

Alcohol consumption patterns during pregnancy and perception of risk

Most women in Australia are aware of potential risks of alcohol consumption during pregnancy for their babies, and when aware of being pregnant, either reduce alcohol consumption or abstain from drinking (AIHW 2017). The *Australian Drug and Alcohol Survey* 2016 found that approximately 30% of women consumed some alcohol during their pregnancy; most of whom (81%) drank monthly or less (1-2 standard drinks per occasion) (AIHW 2017; 8.13 and Table 8.16). However, there is variation in the levels and patterns of alcohol consumption during pregnancy among Australian women, with higher rates and levels of consumption among some groups and communities (e.g. Fitzpatrick 2017).

Adverse effects potentially associated with fetal alcohol exposure

A plethora of terms, classifications and diagnostic tools have been used to describe and diagnose adverse effects in infants and children presumed to have resulted from fetal alcohol exposure (Cook 2016; FAS Diagnostic and Prevention Network 2004; NOFASD 2018; Popova 2016; Stratton 1996). In 2000 the term "fetal alcohol spectrum disorder" (FASD) emerged to describe the broad range of effects that may occur in utero due to alcohol exposure, including neurodevelopmental problems (Bower 2016; Bukiya 2018; Mamluk 2017; Popova 2018). FASD has recently been included in international guidelines for diagnosis of prenatal alcohol exposure effects (Bower 2016; Cook 2016; NOFASD 2018), and the Australian diagnostic subcategories for FASD have been updated (Bower 2016; Cook 2016; NOFASD 2018) – (see Appendix 1 for details). FASD is difficult to diagnose and conditions in this spectrum remain under-reported, internationally and in Australia (Cook 2016; NOFASD 2018; Oliver 2016). Aside from the specific sentinel facial and growth features, FASD symptoms are seldom diagnosed at birth, and are often noticed only at school age, when learning and behavioural difficulties become more evident (NOFASD 2018).

Better understanding of the risk of birth defects, and behavioural problems associated with different levels and patterns of alcohol consumption during pregnancy, may help prevent these adverse effects, providing more certain evidence on which to base guidance. The review undertaken to inform the 2009 *Alcohol Guidelines* identified three systematic reviews reporting on the association between alcohol consumption during pregnancy and birth defects (Henderson 2007a; Henderson 2007b; Polygenis 1998). One (Henderson 2007b) also reported on behavioural problems in children (Commonwealth of Australia 2009; Appendix 3, Table 6).

Several limitations of the scope and data quality of the primary studies included in these reviews were reported, including problems with the measurement of levels and patterns of alcohol consumption.

Since publication of the 2009 *Alcohol Guidelines* additional systematic reviews have examined the association between maternal alcohol consumption during pregnancy and FASD, including birth defects and behavioural problems in fetuses and children up to the age of five. This systematic review evidence was examined in an overview of reviews commissioned by the Office of NHMRC (ONHMRC) to evaluate the long and short-term health effects of alcohol consumption (NHMRC Clinical Trials Centre 2017). The overview identified 21 systematic reviews pertaining to the effects of maternal alcohol consumption during pregnancy and FASD, of which 11 examined birth defects and three examined behavioural problems in babies and children. Important limitations in this systematic review evidence were identified, resulting in exclusion of all 14 of the above reviews from the overview, mostly due to the reviews failing to meet minimum methodological eligibility criteria (NHMRC Clinical Trials Centre 2017).

The absence of adequate systematic review evidence on the effects of different levels and patterns of alcohol consumption on birth defects or behavioural problems prompted this review of alcohol consumption during pregnancy.

1.2.2 Importance of evidence on alcohol consumption while breastfeeding and selected child outcomes

Breastfeeding is the safest and best method for providing optimal infant immune function and supporting infant growth and development (ABA 2018; NHMRC 2013; WHO 2017). Breastfeeding has been linked to higher infant survival rates, and improved growth, cognitive and neurological outcomes in babies and children (Horta 2007; Horta 2015). The breastfeeding relationship facilitates a close bond between mother and child, that forms the basis of psychological health for the child's entire lifetime (ABA 2018; Perrelli 2014; WHO 2017). International and Australian guidelines recommend exclusive breastfeeding until a child reaches four to six months of age, with continued breastfeeding and complementary foods until two years of age (NHMRC 2013; WHO 2017).

Alcohol enters breast milk by passive diffusion and reflects levels in maternal blood within 30-60 minutes after ingestion (Giglia 2006). The blood alcohol concentration of the mother is influenced by body weight, amount of adipose tissue, stomach contents at the time of alcohol ingestion, rate at which alcohol beverages are consumed, and the amount and strength of alcohol in the drink (Giglia 2006). The level of alcohol exposure to the breastfed infants is influenced by maternal body water, blood alcohol concentration and body weight (Giglia 2010). Exposure of alcohol to the infant while breastfeeding can be reduced by timing of alcohol consumption and feeding (Ho 2001; Commonwealth of Australia 2009, Table 5, p80). Alcohol in the bloodstream suppresses the action of oxytocin in initiating the let-down reflex, resulting in greater time until milk let down, and a decrease in total breastmilk yield (Chien 2008; Giglia 2010; Mennella 2008). There is evidence from Australia and overseas suggesting an association between heavy alcohol use in the postpartum period, and sudden infant death (SIDS), as well as infant mortality not diagnosed as SIDS (O'Leary 2013).

Few studies have reported on the prevalence and patterns of alcohol consumption while breastfeeding in Australia. Available studies indicate that, as in other countries (May 2016), many women who abstained from alcohol during pregnancy resume drinking after giving birth (Tay 2017; Tearne 2017), with most drinking at low levels and infrequently (Giglia 2010). Two studies of alcohol consumption patterns among breastfeeding mothers in Australia observed that most breastfeeding women drank 14 or fewer standard drinks per week, with less than three drinks consumed per occasion (Tay 2017; Tearne 2017). In these studies, 45%, 47% and 51% of breastfeeding women reported alcohol us at 4, 6 and 12 months postpartum respectively (rural Western Australia cohort recruited 2010 to 2011), and 61% and 70%

reported alcohol use at 8 weeks and 12 months postpartum respectively (New South Wales cohort recruited 2009 to 2014) (Tay 2017; Tearne 2017). The limited data on alcohol use while breastfeeding suggest that most women who drink while breastfeeding in Australia employ strategies (e.g. timing of alcohol use) to minimise alcohol exposure to their infants (Giglia 2006; Tay 2017; Tearne 2017). Views differ about whether there are risks associated with alcohol use while breastfeeding (Giglia 2006; Logan 2016). For example, in some populations consumption of beer while breastfeeding has been encouraged to improve lactational performance (Giglia 2006; May 2016).

The evidence review conducted to inform the 2009 *Alcohol Guidelines* identified one systematic review (Giglia 2006). The reviewers identified limited research investigating the effects of alcohol intake on infants of lactating women, with most studies conducted in animals. They reported that results consistently show a decrease in lactational performance with alcohol intake while breastfeeding, and suggestive evidence of lower rates of early breastfeeding cessation in actively abstaining women compared with women who drink while breastfeeding. Additionally, Giglia and colleague reported that alcohol intake by lactating mothers in amounts recommended as 'safe' for non-lactating women may have negative effects on infant development and behaviour (Giglia 2006). The conclusions drawn in the 2009 *Alcohol Guidelines* from the research available at the time were that (Commonwealth of Australia, 2009, p79):

- there is a lack of high-quality evidence from human studies regarding the effects of maternal alcohol consumption on lactation, infant behaviour and development;
- as a result, it is not possible to set a 'safe' or 'no risk' drinking level for breastfeeding women and practical guidance regarding minimising the risk to lactation and to the breastfed infant was provided for mothers who choose to drink.

The overview of reviews commissioned by the Office of NHMRC (ONHMRC) to evaluate the long and short-term health effects of alcohol consumption to inform the *Alcohol Guidelines* 2009, sought systematic review evidence on the effects of varying levels and patterns of alcohol consumption (including no alcohol consumption) during the breastfeeding period on: cognitive impairment in breastfeeding babies; sudden infant death syndrome (SIDS); sedation in breastfeeding babies; child neglect/bonding and failure to thrive. No systematic review reporting associations between maternal alcohol use during breastfeeding and any of these outcomes was identified by the overview (NHMRC 2017 p107), prompting this evidence review of alcohol consumption while breastfeeding.

2. Objectives

2.1 Systematic review on alcohol consumption during pregnancy

The objectives of this review were to examine the effects of different levels and patterns of alcohol consumption during pregnancy on birth defects and behavioural problems in babies and young children, and to investigate any dose response for these two outcome domains.

1. What are the effects[1] of different **levels** of alcohol consumption during pregnancy compared to not drinking (either never drinking or not drinking during pregnancy) on birth defects and behavioural problems (identified up to age 5)? Where the levels of alcohol are defined as:
   i. ≥ 1 to < 10 g/week
   ii. ≥ 10 to < 20 g/week
   iii. ≥ 20 to < 30 g/week
   iv. ≥ 30 to < 40 g/week
   v. ≥ 40 to < 50 g/week
   vi. ≥ 50 to < 60 g/week
   vii. ≥ 60 g/week?

2. What are the effects[1] of **patterns**[2] of alcohol consumption during pregnancy compared to not drinking in pregnancy (or one pattern compared with another pattern) on birth defects and behavioural problems (identified up to age 5)?
   - Patterns of alcohol consumption captures the amount consumed on any single drinking occasion, in addition to the frequency and average level of consumption, comparing for example consumption of five standard drinks on a single occasion per week (i.e. 50g alcohol per occasion, 50g/week) to drinking one standard drink daily (i.e. 10g/occasion, 50g/week).

3. Is there a **dose response** relationship between levels of alcohol consumption during pregnancy and birth defects or / and behavioural problems?

4. Is any effect[1] between alcohol consumption during pregnancy and birth defects and behavioural problems modified by **timing** of consumption (periconception, early pregnancy, mid-late pregnancy, throughout pregnancy).

[1] effects refers here to associations where potential confounding has been taken into account.

[2] patterns includes combinations of consumption e.g. amounts per occasion and frequencies.

2.2 Systematic review on alcohol consumption while breastfeeding

The specific objectives of this review were to address the following questions.

1. What are the effects[2] of different **levels** of alcohol consumption while breastfeeding compared to not drinking while breastfeeding (which may include abstainers, abstainers during pregnancy and breastfeeding, or / and abstainers during breastfeeding only) on cognitive impairment in babies, SIDS/SUDI, sedation in breastfeeding babies, maternal bonding, child neglect and failure to thrive? Where the levels are defined as:

    - >0 g to <10 g/week
    - ≥ 10 to <20 g/week
    - ≥ 20 to <30 g/week
    - ≥ 30 to <40 g/week
    - ≥ 40 g/day to <50 g/week
    - ≥ 50 g/week

2. What are the effects[3] of **patterns**[4] of alcohol consumption while breastfeeding compared to not drinking while breastfeeding (or one pattern compared with another pattern) on cognitive impairment in babies, SIDS/SUDI, sedation in breastfeeding babies, maternal bonding, child neglect and failure to thrive?

    - Patterns of alcohol consumption captures the amount of alcohol consumed on any single occasion, in addition to the frequency and average level of consumption, comparing for example consumption of five standard drinks on a single occasion per week (i.e. 50 g alcohol per occasion, 50 g/week) to drinking one standard drink daily (i.e. 10 g / occasion, 50 g / week)
    - Patterns of alcohol consumption also includes altering the **timing** of drinking or breastfeeding to avoid or minimise exposure of the breastfeeding infant to alcohol.

3. Is there a **dose response** relationship between levels of alcohol consumption while breastfeeding and cognitive impairment in babies, SIDS/SUDI, and sedation in breastfeeding babies?

3. Methods

Methods for the reviews were pre-specified in two protocols (Middleton et al 2018 a & b) and are based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with modifications for undertaking a review of exposures. The GRADE approach was used to summarise and assess the certainty of evidence arising from the two reviews. GRADE methods are widely used in guideline development to ensure a systematic, transparent and common

[2] Effects refers here to associations where potential confounding has been taken into account.

[3] Effects refers here to associations where potential confounding has been taken into account.

[4] Patterns includes combinations of consumption e.g. amounts and frequencies.

approach to interpreting results (Schunemann 2013). The review methods are described in full in the protocols and companion technical report for the reviews. A summary of the methods used follows.

3.1 Criteria for considering studies for the reviews

3.1.1 Types of participants

3.1.1.1 For the alcohol consumption during pregnancy review

Women who are pregnant (or planning a pregnancy) and their fetuses, babies and children (up to age five).

Healthy women, or women with a medical or health condition (including, but not limited to, an alcohol use disorder) were eligible.

Studies with wider inclusion criteria were eligible if data and analyses were available separately for the criteria specified for this review.

Studies conducted with participants living in any country, and from all settings were eligible.

If available separately, data and analyses from studies that met other eligibility criteria were reported for the following subgroup:

- Timing of alcohol consumption during pregnancy (periconception, early pregnancy, mid-late pregnancy, throughout pregnancy)

3.1.1.2 For the alcohol consumption while breastfeeding review

Healthy breastfeeding women, or women with a medical or health condition, of any age were eligible. Age ranges for babies and children varied according to the outcome, as follows.

For cognitive impairment, child neglect and failure to thrive

- Breastfeeding women and their babies who are being breastfed/were breastfed (up to 5 years of age)

For SIDS/SUDI

- Breastfeeding women and their babies who were breastfed (up to 1 year of age)

For sedation

- Breastfeeding women and their babies during or up to three hours after breastfeeding

For maternal bonding

- Breastfeeding women and their babies who are being breastfed/were breastfed (up to 1 year of age)

Studies with wider inclusion criteria were eligible if data and analyses were available separately for the included ages specified for each outcome.

Studies conducted with participants living in any country, and all settings were eligible.

3.1.2 Types of exposure

For both reviews, eligible studies were those examining various levels of alcohol consumption, patterns of alcohol consumption, or both.

Studies must have reported alcohol consumption in units that allow quantification of the average amount of alcohol consumed (e.g. grams or millilitres of pure alcohol) over a period of time (e.g. per day, week, month).

Studies were eligible irrespective of the methods used to measure alcohol exposure. We anticipated that these methods would vary across studies but may include retrospective survey involving recall of alcohol consumption over different periods of life or intake diaries to measure current alcohol consumption. To account for differences in the methods used to measure alcohol exposure, we extracted data on the measurement methods and assessed potential biases and confounding that may arise through the method used.

3.1.3 Types of comparator exposure

For both reviews, the eligible comparator groups were those comprised of abstainers. More specifically, for the pregnancy review, abstainers could be either never drinkers or not drinkers during pregnancy, and for the breastfeeding review abstainers could include never drinkers, abstainers during pregnancy and breastfeeding or abstainers during breastfeeding only.

We anticipated diversity across studies in the definition and composition of potentially eligible comparator groups. Whilst the main (ideal) comparison for inclusion in the reviews were abstainers (during pregnancy and while breastfeeding respectively), we did not want to rule out consideration of studies that met all the review inclusion criteria except for having a comparison group that included some (or all) women who had consumed a very little amount of alcohol. Therefore, we planned to consider such studies and the implications of including them in the interpretation of the evidence for the affected outcome domain as per the GRADE approach.

3.1.4 Types of outcomes

3.1.4.1 For the pregnancy review

Eligible studies were those that reported at least one measure of birth defects or at least one measure of behavioural problems.

Studies reporting broader FASD outcomes were considered provided data were reported separately for any one or more specified review outcome(s).

We expected that definitions and diagnostic criteria would vary across studies, so planned to accept a range of definitions as noted under *Methods of outcome assessment*. Table 1 defines the outcomes for the review of alcohol consumption during pregnancy.

Table 1: Pregnancy review outcomes

Outcome domain	Definitions	Outcome measure examples

Birth defects/congenital malformations in infants and children (identified up to age 5)	"any abnormality, structural or functional, identified up to five years of age, provided that the condition had its origin before birth." (SA Birth Defects Register) Includes the following congenital malformations, deformations and chromosomal abnormalities domains in WHO International Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10) (WHO 2007): congenital malformations of: • the nervous system; • the eye, ear, face and neck; • the circulatory system; • the respiratory system; • cleft lip and cleft palate; • the digestive system; • genital organs; • urinary system; • congenital malformations and deformities of the musculoskeletal system; • other congenital malformations Excludes: inborn genetic diseases; newborn infant diseases; fetal diseases.	Nervous system: microcephaly; congenital hydrocephalus Eye, ear, face and neck: congenital ptosis; congenital corneal opacity; low set/seated ears; short palpebral fissure, smooth philtrum, thin upper lip (3 sentinel FASD features) Circulatory system: atrial septal defect; patent ductus arteriosus Respiratory system: choanal stenosis Cleft lip and palate: cleft soft palate Other digestive system: long/smooth/indistinct/poorly developed/hypoplastic philtrum; narrow vermillion border/thin upper lip Genital organs: doubling of vagina; small phallus Urinary system: renal agenesis; renal/kidney dysplasia; urinary tract malformation Musculoskeletal system: feet malformations/positional foot deformities; minor hand anomalies
Behavioural problems (identified up to age 5)	Disturbances considered to be pathological based on age and state appropriateness. Includes: attention deficit, conduct and disruptive behaviour disorders. Excludes: neurodevelopmental disorders such as child development disorders (including autism spectrum disorder); communication disorders; learning disorders; developmental disabilities; intellectual disabilities; motor skills disorders; reactive detachment disorder; mutism; separation anxiety; childhood schizophrenia; stereotypic movement disorder; and tic disorders.	BRS (Behaviour Rating Scale); NBAS (Neonatal Behavioral Assessment Scale); BSID (Bayleys Scale of Infant and Toddler Development) – social and emotional component; SDQ (Strengths and Difficulties Questionnaire); CBCL (Child Behavior Check List)

3.1.4.2 For the breastfeeding review

Eligible studies were those that reported at least one measure of one or more of the following outcomes: cognitive impairment in babies; SIDS/SUDI; sedation in breastfeeding babies; maternal bonding; child neglect; and failure to thrive. These outcomes are broadly defined in

Table 2 using definitions from the 2016 overview of evidence on the health effects of alcohol consumption in breastfeeding women (NHMRC 2017 technical report, p15, Table 10).

We expected that definitions of the review outcomes and diagnostic criteria would vary across studies and considered all definitions and diagnostic criteria for which an evidence-based rationale is provided, as noted under *Methods of outcome assessment*.

Table 2: Breastfeeding review outcomes

Outcome	Definition of outcome	Outcome measures (examples)
Cognitive impairment (in babies and children up to 5 years of age)	Disturbances in mental processes related to learning, thinking, reasoning, and judgment.	Bayley Scales of Infant Development or Griffiths Mental Development Scales assessments (scores) Griffiths Mental Development Scales Extended Revised: 2 to 8 years or Kaufman Assessment Battery for Children or Wechsler Preschool and Primary Scale of Intelligence (WPPSI) assessments (scores) Results may be reported as an overall test score that provides a composite measure across multiple areas of cognitive ability/impairment, sub-scales that provide a measure of domain-specific cognitive function or cognitive abilities, or both.
Sudden infant death syndrome (SIDS) or sudden unexplained death of an infant (SUDI)	SIDS: The abrupt and unexplained death of an apparently healthy infant under one year of age, remaining unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history. SUDI: Death of an infant younger than 1 year of age that occurs suddenly and unexpectedly, and where there may be a cause, e.g. suffocation, trauma.	SIDS: number of unexplained deaths of infants <1 years of age (confirmed after autopsy, thorough case investigation and review of infant clinical history) SUDI: number deaths of infants <1 years of age with confirmed cause (following autopsy, thorough case investigation and review of infant clinical history) possible trauma or suffocation
Sedation (in breastfed infants during/soon after breastfeeding)	Reduction of anxiety, stress, irritability, or excitement by administration of a sedative agent or drug (in this case alcohol in breast milk), which may interfere with feeding (e.g. poor sucking).	Sedation, drowsiness, change in sleep, change in feeding behaviour (including sucking)
Child neglect in babies and children (up to age 5)	Child neglect is the failure by parents or guardians to provide for the basic human needs of a child by physical or emotional deprivation that interferes with normal growth and development	Substantiated maltreatment (yes/no) Notification to authorities (yes/no) Removal of child (yes/no)

	or that places the child in jeopardy	
Maternal bonding (with babies up to 1 year of age)	Bond is the emotional and physical attachment occurring between a parent or parent figure, especially a mother, and offspring, that usually begins at birth and is the basis for further emotional affiliation.	Mother-Infant Bonding Scale (MIBS), Maternal Attachment Inventory (MAI), Postpartum Bonding Questionnaire (PBQ) or Parent-to-infant Attachment Questionnaire (PAQ) assessment (scores)
Failure to thrive in babies and children (up to age 5)	A condition of substandard growth or diminished capacity to maintain normal function.	Growth measures including: height/length (cm); head circumference (cm); weight (g/kg); body mass index (BMI)

The technical report includes the PECO tables summarising the definitions and eligibility criteria for the reviews (see section 1.3 for the pregnancy review, and 1.4 for the breastfeeding review).

3.1.5 Types of studies

For both reviews, cohort studies (concurrently controlled prospective and concurrently controlled retrospective), case-control studies and nested case-controlled studies were eligible for inclusion.

In line with current Cochrane guidance, decisions about study eligibility were based on assessment of the study design features rather than the study design labels or broad definitions of each type of study (see technical report, section 1.5 for the design features used to classify study design features and determine study design eligibility for the reviews).

3.2 Search for studies

For both reviews, we searched primary studies published since January 2007. The independent evidence evaluation on the health effects of alcohol consumption commissioned by NHMRC (NHMRC 2017) listed systematic reviews (published between 2009 and 2016) related to alcohol and pregnancy. We checked these reviews for primary studies that met the eligibility criteria. We searched Australian Indigenous Health*Info*Net and checked the reference lists of eligible studies for additional relevant publications.

3.2.1 Electronic database searches for the pregnancy review

Our search of electronic databases for the alcohol consumption during pregnancy review included MEDLINE, Embase and PsycINFO. No language or geographic limitations were applied. We ran the Embase and MEDLINE searches on 10 July 2018, across both databases, deduplicated first within Ovid, and removed additional duplicates when importing to EndNote. We ran the PsycINFO search on 10 July 2018 and removed duplicates on import to EndNote. The search strategies are presented in the Technical report, with deviations from the protocol (see technical report section 2.1).

To improve the precision of the search we made three changes to the MEDLINE search strategy that was published in the protocol: we added ‘periconception’ to the search terms for pregnancy; removed the MeSH terms 'Cross-Sectional Studies/' and 'Surveys/ and Questionnaires/' from the list of study design terms; and replaced AND with ‘ADJ10’ in the set (#20) that combined terms for abnormalities and birth. These changes were also applied to the

search strategies for Embase and PsycINFO. This had the effect of reducing screening by about 20 per cent but without adversely affecting sensitivity.

The Ovid MEDLINE search strategy for the pregnancy review was evaluated on the basis of an assessment of the 2017 systematic review by Mamluk (Mamluk 2017). This review included 24 studies, of which our revised search retrieved 22. Of the missing studies, one was from 1989 (and had a very broad study design without an abstract) and the other was a questionnaire survey from 1991. Neither of these two studies met our eligibility criteria.

3.2.2 Electronic database searches for the breastfeeding review

Our search of electronic databases for the review on alcohol consumption while breastfeeding included MEDLINE, Embase and PsycINFO. No language or geographic limitations were applied. We ran the searches in each of the three databases on 23 May 2018. We also set up a weekly email alert to capture research added to PubMed between 20 May and 31 August 2018. The search strategies are provided in the technical report (see section 2.2).

3.3 Selection of studies

3.3.1 Screening of titles and abstracts

For each of the reviews, a screening tool based on the PECO eligibility criteria was developed to guide the selection of studies and piloted on a 5% sample of the citations retrieved by the search. Three of the review authors conducted pilot screening of citations for the pregnancy review (PM, SB, JG) and for the breastfeeding review (SB, JG, JR). Using the pre-tested coding guidance JG screened the remaining titles and abstracts for the reviews, excluding records that did not meet the inclusion criteria.

3.3.2 Retrieval and screening of full text articles

For both reviews, full-texts of all potentially eligible studies were retrieved by one reviewer (JG). Two review authors (JG and JR) independently screened the full texts for the breastfeeding review, with PM moderating disagreements and assisting with complex cases. Two review authors (JG and PM) screened the full texts for the pregnancy review, with SB performing the role of third reviewer. Citations that did not meet the inclusion criteria were excluded and the reason for the exclusion documented. The citations excluded during full-text review are listed in the Technical report with the reasons for exclusion (see section 2.3 for the pregnancy review, and section 2.4 for breastfeeding review).

Cohort names, author names, and study titles, locations and dates were used to identify multiple reports arising from the same study during the screening.

3.4 Data collection and management

For both reviews, one reviewer extracted data relating to study characteristics and results, using a pre-tested data extraction and coding form, and a second author independently verified the data.

3.5 Assessment of risk of bias for included studies

One author (JG or PM) assessed risk of bias in each included study using the RTI Item Bank for Assessing Risk of Bias and Confounding for Observational Studies of Interventions or Exposures (Viswanathan 2013), and a second author (MP) independently verified the assessments. Discrepancies were resolved through discussion, with advice from a third reviewer (SB) if agreement could not be reached or for more complex scenarios. To ensure concordance, the assessment process was piloted by all assessors (JG, PM, MP, SB) on three included studies.

The RTI tool includes 13 items (see Technical report section 3 for list of items). We divided one of the items (item 6) into three sub-items, that assessed whether the study authors used valid and reliable measures of: (a) confounders; (b) exposures; or (c) benefits and harms. We also changed the order of the items so that the three items focusing on confounding (item 6a, 12 and 13) were answered first. If the study was considered not to have addressed confounding adequately (based on responses to these three items), we rated the study at *critical risk of bias* and ceased assessment and data extraction of the study. If responses to the remaining items suggested:

- the study was free of methodological flaws, we rated the overall risk of bias in the study as *low risk*;
- the study had a minor methodological flaw, we rated the overall risk of bias in the study as *moderate risk*;
- the study had a major methodological flaw or multiple minor methodological flaws, we rated the overall risk of bias in the study as *serious risk*.

We had planned to use ROBINS-I tool to assess the studies included, for both reviews. Instead, we used the RTI tool because the pregnancy review included case control studies, a study design that ROBINS-I is not appropriate for.

3.6 Data analysis and synthesis methods

3.6.1 Measures of association

For reporting the results from the primary studies, we reported the metrics presented in the studies. For binary outcomes, this was adjusted odds ratios, and for continuous outcomes, this included regression analyses. For the meta-analyses of binary outcomes, we combined adjusted odds ratios. The adjusted odds ratios arose from logistic regression models that had adjusted for potential confounding factors.

3.6.2 Assessment of heterogeneity

We assessed heterogeneity visually by inspecting the overlap of confidence intervals on the forest plots, formally tested for heterogeneity using the χ^2 test (using a significance level of $\alpha=0.1$), and quantified heterogeneity using the I^2 statistic (Higgins 2002).

3.6.3 Unit of analysis issues

In this evidence review, the unit of analysis issue that arose was from studies contributing multiple effect estimates per comparison. These estimates were correlated since they compared against the same group of participants. Methods were used to adjust for the correlation between the estimated effects as described in the *Data synthesis* section.

3.6.4 Assessment of reporting biases

We did not investigate the potential for small study effects since there were fewer than 10 studies included in any of the meta-analyses.

3.6.5 Investigation of effects of levels and patterns of alcohol consumption (pairwise comparisons)

Meta-analyses were undertaken investigating the effects of binge drinking during pregnancy versus no drinking during pregnancy on 'cleft palate (isolated)', `cleft lip with or without cleft palate (isolated)' and 'spina bifida'. Estimates of effects were combined using a random effects

model with inverse-variance weighting. The restricted maximum likelihood between-study variance estimator was used (Raudenbush 2009), with the Knapp and Hartung adjustment (Knapp 2003).

If a study contributed multiple estimates per comparison (e.g. multiple estimates for different types of binge drinking [e.g. ≥5 drinks/≥3 sittings, ≥5 drinks/1-2 sittings]), the estimates and their variances were averaged (Lopez-Lopez, in press). Or, if estimates were presented separately for non-overlapping subgroups, these would first be combined using a fixed effect meta-analysis. However, no instance of the latter occurred. Analyses were undertaken using the `metafor` package in the statistical program R (Viechtbauer 2010).

We were unable to conduct planned meta-analysis investigating the effects of different *levels* of alcohol consumption during pregnancy due to lack of data (i.e. no included studies reporting on identical outcomes for identical exposure comparisons). When studies contributed results that could not be meta-analysed, the available effects (95% confidence intervals, p-values) were reported.

We were unable to conduct all planned meta-analysis for the breastfeeding review due to a lack of data (only one include study, which reported associations for qualitative descriptors of alcohol consumption while breastfeeding only).

3.6.6 Subgroup analyses

We did not investigate if the effects of binge drinking versus no drinking were modified by timing of alcohol consumption during pregnancy (e.g. never during pregnancy, periconception, first trimester, second trimester, third trimester, throughout pregnancy), for the 'birth defect' outcomes, since there were few studies (i.e. a maximum of four) contributing to any meta-analysis.

3.7 Evidence quality assessment and summary of findings using GRADE approach

We assessed the certainty of the evidence for meta-analytic results using the GRADE approach. In accordance with the detailed GRADE guidance (Schunemann 2013, Schunemann 2018), the following domains were assessed and a judgement made about whether there are serious, very serious or no concerns for each domain.

1. Risk of bias. Based on the summary assessment across studies for each outcome reported for a comparison (see 'Risk of bias' section).

2. Inconsistency. We assessed (1) whether there was heterogeneity in the observed effects across studies that suggested important differences in the effect of the exposure (based on visual inspection of data and statistical tests of heterogeneity), and (2) whether this could be explained (e.g. by study characteristics or design).

3. Imprecision. We assessed whether interpretation of the upper and lower confidence limits led to conflicting interpretations about whether the exposure has an important effect (e.g. consistent with both appreciable harm and benefit).

4. Indirectness. We assessed whether any differences between the PECO of included studies and the review PECO were likely to lead to important differences in the effects of alcohol exposure (i.e. the applicability of the evidence). This information was used to interpret results, rather than downgrade.

5. Publication bias. Our judgement of suspected publication bias was based on assessment of reporting bias. Evidence of small study effects and the absence of a plausible alternative explanation for these effects indicates that publication bias should be suspected.

6. Upgrading domains: large effect size, dose-response gradient, opposing plausible residual confounding.

GRADEpro GDT software (www.gradepro.org) was used to record decisions and derive an overall GRADE (high, moderate, low or very low) for the certainty of evidence for each outcome, using the GRADE rules in which observation studies begin as 'low' certainty evidence (score=2) and can be downgraded by -1 for each domain with serious concerns or -2 for very serious concerns and upgraded for any of the upgrading domains. A summary of findings table was prepared using the GRADEpro GDT software.

For each meta-analytic result, the evidence profile includes estimates of the effects of alcohol exposure, and the overall GRADE (rating of certainty). The evidence profile also includes the study design(s), number of studies contributing data (the type and size of the evidence base), and the assessment of each GRADE domain (risk of bias, inconsistency, indirectness, imprecision, publication bias, upgrading factors). Footnotes are included to explain judgements made about downgrading the rating of the certainty of the evidence.

Evidence statements were written for all outcomes, irrespective of whether results were meta-analysed. Formulation of the statements was based on the following decision-rules, as developed for the NHMRC. Where the direction of association varied across studies (i.e. harmful, beneficial or unclear), the effects were described as 'mixed'.

Statement	Decision rule (based on GRADE ratings)
Consistent evidence of an association	High certainty evidence from two or more studies
Evidence of an association	High certainty evidence from one study
Consistent evidence of no association	High certainty evidence from two or more studies
Limited evidence of an association	Low certainty evidence OR moderate certainty evidence from one study
No reliable evidence of an association	Very low certainty evidence

4. Results

4.1 Search results

4.1.1 Systematic review on alcohol consumption during pregnancy

The searches of MEDLINE, Embase and PsycINFO for primary studies retrieved 6326 records. After removing duplicates and conference abstracts, we screened 3427 records (see Figure 1). The full- text of 118 papers were screened, from which 87 were excluded (see Technical report section 2.3 for list of articles and reasons), leaving 31 articles (reporting 28 studies) for inclusion in the review (Alvik 2011, Benedum 2013, Bille 2007, Bitsko 2007, Caspers 2010, Caspers 2014, Davies 2017, Damgaard 2007, DeRoo 2008, Grewal 2008, Halliday 2017, Han 2012, Kelly 2009, Lundsberg 2015, Mateja 2012, Miller 2009, Muggli 2017, Mullally 2011, O'Leary 2010, Richardson 2011, Romitti 2007, Sayal 2007, Slickers 2008, Strandberg-Larsen 2011, Suarez 2008, Torp-Pederson 2010, Werler 2015, Zhu 2013). Two studies (Bitsko 2007 and Han 2012) were excluded during risk of bias assessment for being at critical risk of bias (lack of adjustment for confounders). Due to differences across studies in outcomes and

exposures assessed and reported, five studies (Benedum 2013, Bille 2008, de Roo 2008, Grewal 2008, Romitti 2007) only were included in quantitative synthesis (meta-analysis) (Figure 1).

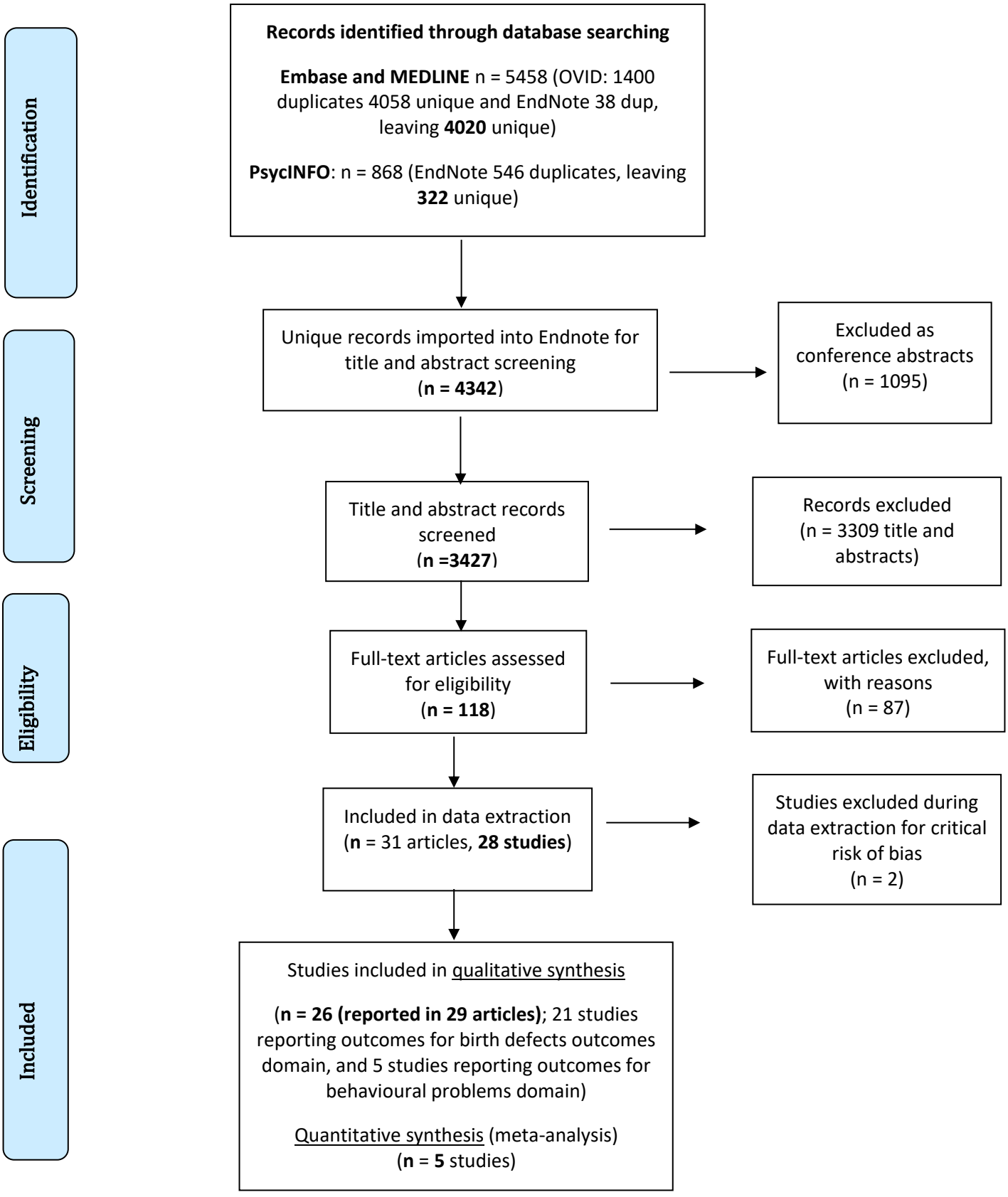


Figure 1: Study flow chart for systematic review on alcohol consumption during pregnancy

4.1.2 Systematic review on alcohol consumption while breastfeeding

A total of 2477 references were imported into EndNote after duplicates were removed for the breastfeeding review. Two additional articles were identified through screening the reference

lists of eligible studies and 110 additional records were identified from the PubMed weekly alerts. Therefore, 2589 unique references were screened, from which 2562 were excluded, leaving 27 articles for full text retrieval (see Figure 2). Of the 27 full-text articles assessed against the eligibility criteria, 26 were excluded (see Technical report section 2.4 for list and reasons), leaving only one study for inclusion (Tay 2017).

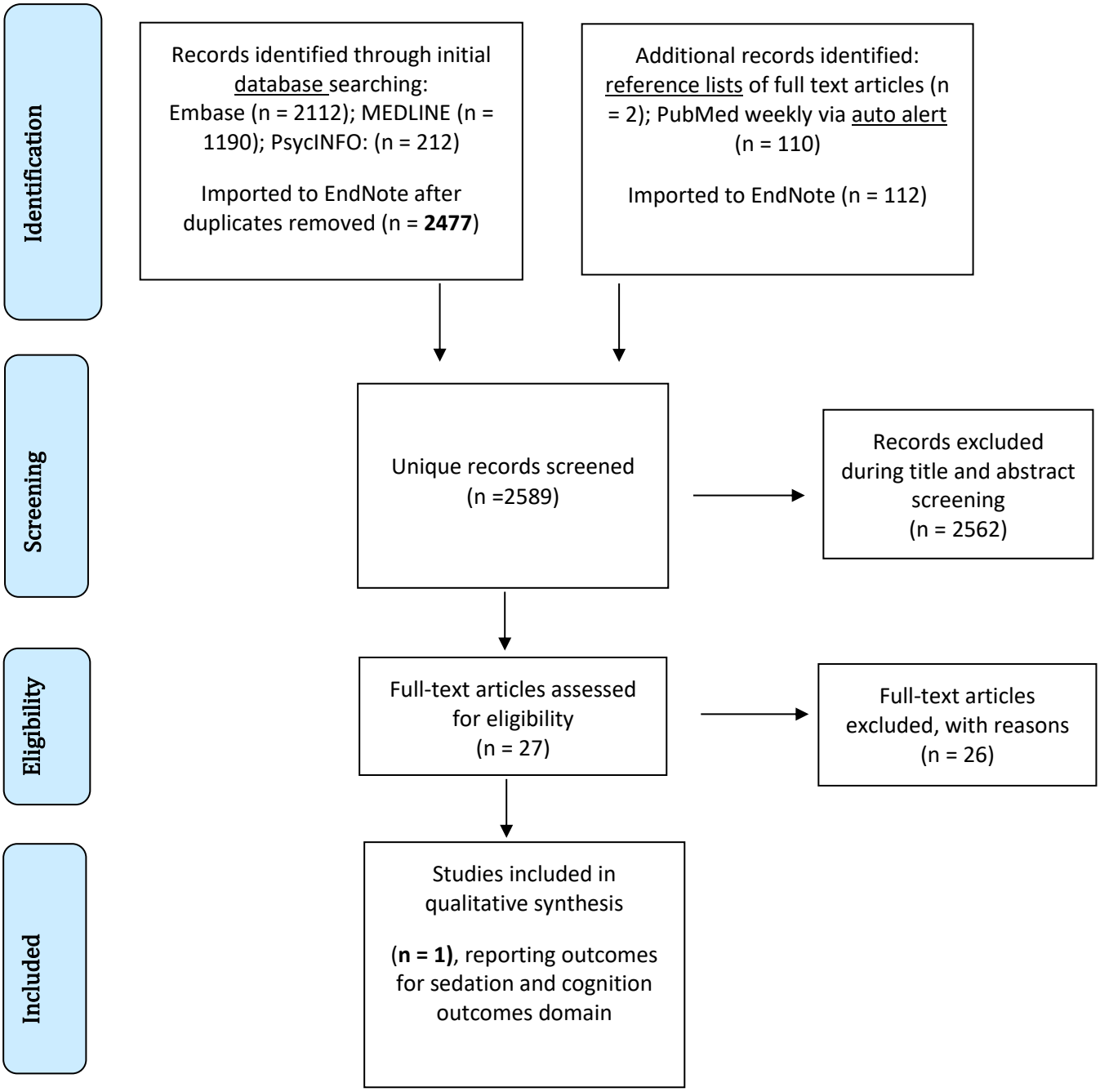


*Figure 2: Study flow chart for review on alcohol consumption while breastfeeding

4.2 Description of included studies: characteristics

4.2.1 Systematic review on alcohol consumption during pregnancy

Considering study design, **11** of the 26 included studies were identified using the study design identification criteria as **cohort studies** (Alvik 2011, Damgaard 2007, Halliday 2017, Kelly 2009, Lundsberg 2015, Muggli 2017, Mullally 2011, O'Leary 2010, Sayal 2007, Strandberg-Larsen 2011 Torp-Pederson 2010), **three** as **nested case control studies** (Bille 2007, Davies 2017, Richardson 2011) and the remaining **12** as **case control studies** (Benedum 2013, Caspers 2010, Caspers 2014, De Roo 2008, Grewal 2008, Mateja 2012, Miller 2009, Romitti 2007, Slickers 2008, Suarez 2008, Werler 2015, Zhu 2013).

Considering the **population and setting**, all were conducted in high income countries with the exception of one study from South Africa (Davies 2017). Twelve studies were undertaken in the USA (Caspers 2010, Caspers 2014, Grewal 2008, Lundsberg 2015, Mateja 2012, Miller 2009, Richardson 2011, Romitti 2007, Slickers 2008, Suarez 2008, Werler 2015, Zhu 2013). Three studies were performed in Australia (Halliday 2017, Muggli 2017, O'Leary 2011), and three in Denmark (Bille 2007, Strandberg-Larsen 2011, Torp3-Pederson 2010). Two studies were undertaken in Norway (Alvik 2017, De Roo 2008). One study was performed in Ireland (Mullally 2011), and one in England (Sayal 2007). The remaining three were performed in more than one country: Benedum 2013 in Canada and the USA; Damgaard 2007 in Denmark and Finland; and Kelly 2009 in England, Wales, Scotland and Ireland. Most of the studies included populations of mixed ethnicity. However, two of the studies conducted in Australia, Muggli 2017 and O'Leary 2010 included only non-Indigenous participants, and Suarez 2008 included only Mexican-Americans. Most of the studies were conducted in urban or mixed urban/rural locations. Davies 2017 and Suarez 2008 are the only studies that included mostly socio-economically disadvantaged participants. In the remaining studies, participants were either of mixed socio-economic status or relatively socio-economically advantaged. Maternal nutritional status and illicit/licit drug use were poorly reported across the included studies. Time periods covered by the studies ranged from 1976 to 2014.

Alcohol exposures assessed across the set of studies included **varied greatly** and only a few assessed drinking throughout the pregnancy period for the birth defect outcomes. There was a different focus seen between behavioural and birth defects outcomes.

Regarding the outcome domains **five studies** (Alvik 2011, Davies 2017, Halliday 2017, Kelly 2009, Sayal 2007) reported results for the **behavioural problem outcomes** domain and **21 studies** for the **birth defects outcomes** domain (Benedum 2013, Bille 2013, Caspers 2011, Caspers 2014, Damgaard 2007, DeRoo 2008, Grewal 2008, Lundsberg 2015, Mateja 2012, Miller 2009, Muggli 2017, Mullally 2011, O'Leary 2010, Richardson 2011, Romitti 2007, Slickers 2008, Strandberg-Larsen 2011, Suarez 2008, Torp-Pederson 2010, Werler 2015, Zhu 2013). No study reported outcomes for both domains.

Characteristics of the included studies are summarised in Table 3 below. Authors declarations of interest for the studies included in the pregnancy review are provided in the technical report (see section 4.1).

Table 3: Summary of characteristics of studies included in the synthesis of evidence on associations between alcohol consumption during pregnancy and birth defects and behavioural problems in children (up to age five)

Study ID	Study design, data sources and name (if reported)	Setting and population	Alcohol exposure (levels and/or patterns) reported in review: timing, measures and comparison(s); [*referent]	Review outcome domain(s) and measures reported
1. Alvik 2011	Cohort study Longitudinal population-based questionnaire study of pregnant women (items about alcohol use were identical with Norwegian Mother and Child Cohort Study (MoBa) where possible)) Birth data collected from the Medical Birth Registry of Norway	Setting: **Norway**, Oslo, mothers recruited from Ulleval University (data collection June 2000 to May 2001) Population: Pregnant women (n = 1873) and their live infants; representative sample of pregnant women in Oslo Special characteristics **: none reported	Exposure time: 0-6 weeks of pregnancy *Reported*: • 5 or more SU per occasion (never*; more seldom than once a week; once a week or more) *In grams*: • 60g or more per occasion (never*; more seldom than once a week; once a week or more)	Behavioural problems: • difficult temperament; • sleeping problems; • eating problems (assessed using Difficult Temperament Scale of the Infant and Infant Toddler Symptom Checklist, at 6 months of age)
2. Benedum 2013	Case control study Boston University Slone Epidemiology Center Birth Defects Study Birth data from birth hospitals, tertiary care centres and birth defects registries in USA and Canada (births 1976-2005) Alcohol exposure data from interviews with mothers	Setting: **North America** (USA and Canada (Massachusetts, Philadelphia, Pennsylvania, Toronto, Ontario, San Dieago, California and New York State)) (data collection 1976 to 2012 for overall sample; this study restricted to infants of subjects interviewed 1988 to 2012) Population: case group: infants and fetuses with spina bifida (n = 777) and their mothers; control group infants and fetuses without spina bifida (n = 8756) and their mothers Special characteristics **: none reported	Exposure time: first lunar month of pregnancy *Reported:* • < 1 drink/day*; 1 drink/day; 2 drinks/day; 3+ drinks/day *In grams*: • <14g/day*; 14g/day; 28g/day; ≥42g/day	Birth defects: • spina bifida (single study and meta-analysis results
3. Bille 2007***	Nested case control study	Setting: **Denmark** (pregnant women recruited 1996-2002)	Exposure time: 1st trimester (binge) [MA]	Birth defects:

	Case control study nested in the Danish National Birth Cohort Study	Population: singleton live, and stillborn infants born to women who attended their first antenatal clinic visit at any Danish hospital between 1996 and 2002; case group births with cleft (n = 220) and their mothers; control group births without cleft (n = 828) and their mothers Special characteristics **: none reported	*Reported:* • 0 units /week*; 3+ units/week *In grams*: • 0g/week*; ≥36g/week	• cleft lip, cleft palate
4. Caspers 2010	Case control study Birth data from the National Birth Prevention Defects Study (NBPDS), a multicentre, population-based case control study designed to investigate genetic and environmental risk factors for more than 30 birth defects Alcohol exposure data from interviews with mothers	Setting: **USA**, 10 states with population-based birth defects surveillance systems (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Georgia, North Carolina and Utah) Population: pregnancies with EDD October 1, 1997 through 31 December 2005 (varied across states); case group live births and fetuses (limited number) with congenital diaphragmatic hernia (n = 503 infants); control group: live births without congenital diaphragmatic hernia (n = 6703); controls randomly selected from either hospital delivery logs or birth certificate data. Special characteristics **: infants of mothers who spoke English or Spanish only	Exposure time: month prior to pregnancy to 3rd month of pregnancy *Reported:* • 0*; 1-15; 16-30; > 30 drinks a month • 0*; drinking but no binge; 1 or more binge episode (≥ 4 or ≥ 5 drinks/day) *In grams*: • 0g*/month; 14-210g/month; 224-420g/month • 0g/day*; drinking but no binge; 1 or more binge episode (≥56g or 70g/day)	**Birth defects**: • congenital diaphragmatic hernia
5. Caspers 2014	Case control study Birth data from the NBPDS Alcohol exposure data from interviews with mothers	Setting: **USA**, 10 states with population-based birth defects surveillance systems ((Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Georgia; North Carolina; Utah) Population: pregnancies with EDD 1 October 1997 through 31 December 2007 (varied across states); case group births with limb deficiencies (n=906); control group non-malformed births (n=8352);	Exposure time 1: Month prior to pregnancy (proxy for first three months) • *Reported*: 0*; 1-4; 5-15; 16-30; > 30 drinks/month • *In grams*: 0g/month; 1-56g/month; 70-210g/month; 224-420g/month;> 420g/month Exposure time 2: Month prior to pregnancy	**Birth defects**: • congenital limb deficiencies

		Special characteristics **: English and Spanish speaking women only	• *Reported*: No drinking, no binge*; drinking but no binge (<4 drinks on any occasions); ≥4 drinks on any occasion • *In grams:* no drinking, no binge *(≥56g/any occasion); drinking but no binge (<56g) on any occasion; ≥56g on any occasion	
6. Damgaard 2007	Cohort study Joint prospective birth cohort study in Denmark and Finland Births at the University Hospital of Copenhagen (Rigshospitalet and Hvidore Hospital) in Denmark (1997-2001) and at Turku University Central Hospital in Finland (1997-1999) (mostly prospective data collection)	Setting: **Denmark** and **Finland** (interviews with mothers conducted between 1988 and 2012) Population: pregnant women attending first antenatal visit in Denmark (n=2229) and Finland (n=2728) and their infants (boys). Boys assessed at birth and 3 years of age Special characteristics **: all mothers raised in Denmark or Finland (maximum residence abroad of 3 years for the mother and 10 years for the father and grandparents); no others reported	Exposure time: throughout pregnancy *Reported:* • *0; ≥ 1; ≥ 2; ≥ 3; ≥ 4; ≥ 5; ≥ 6; ≥ 7; ≥ 8; ≥ 9 drinks/week • *No binge episodes; binge episodes (≥ 5 drinks/occasion) *In grams*: • *0g; ≥12g; ≥24g; ≥36g; ≥48g; ≥60g; ≥72g; ≥84g; ≥96g; ≥108g / week • *No binge episodes; binge episodes (≥ 60g/occasion)	**Birth defects**: • Cryptorchidism at 3 months of age
7. Davies 2017	Nested case control study Data from the study were drawn from a FASD study in the Northern Cape South Africa	Setting: **South Africa**, Northern Cape Province, upper Karoo region (study conducted 2003 to 2008) Population: pregnant mothers (n=121) and their infants/children, born between 2002 and 2003 in the local hopsital Special characteristics **: rural population; socio-economically disadvantaged population	Exposure time: prior to pregnancy: *Reported:* • *No alcohol; alcohol exposed (median 13 drinks/week); FAS/PFAS (median 31 drinks week) *In grams*: • *No alcohol; exposed (median 156g/week); FAS/PFAS (median 372g/week)	**Behavioural problems**: • social development (assessed using Griffiths Mental Development Scales – Extended, Revised - personal social scale), at 7-12 months

8. DeRoo 2008	Case control study Population based case control study of oral facial clefts in Norway Birth data from the Medical Birth Registry of Norway Alcohol exposure data from interviews with mothers	Setting: **Norway** (study recruitment period May 1996-October 2001) Population: case group live births with orofacial clefts (May 1996 to October 2001) referred for surgical treatment (n = 377 cleft lip with or without cleft palate, n = 196 cleft palate only) and their mothers; control group livebirths September 1996 to April 2001 (n =763) randomly selected from the registry Special characteristics **: 8% of case infants (cleft lip with or without cleft palate) and 1% of control infants respectively had a parent or a grandparent with an oral cleft; over 75% of includes mothers were employed and most had at least a high school education; Norwegian speaking mothers only.	Exposure time: first trimester (binge) [MA}: Reported exposures: • *No drinking; ≥ 5 drinks/1-2 sittings combined with ≥ 5 drinks/≥ 3 sittings *In grams* • *No drinking; ≥ 60g/1-2 sittings combined with ≥ 60g/≥ 3 sittings First trimester linear trend also reported, for: no drinks to ≥ 5 drinks (60g)/≥ 3 sittings	**Birth defects**: • cleft lip and cleft palate
9. Grewal 2008	Case control study Birth data from hospital records of all live-born, still-born and prenatally diagnosed electively terminated cases that occurred between July 1999 and June 2003 Alcohol exposure data: interviews with mothers	Setting: **USA**, California (Los Angeles, San Francisco, Santa Clara counties) Population: eligible case group (n=1355) fetuses or infants and their mothers with conotruncal heart defects (n=323), neural tube defects (n=337) or orofacial cleft (n=701); control group nonmalformed live infants (n=901), randomly selected from the same hospitals as cases; information on maternal alcohol consumption and included case group (n= 1355) and control (n = 700) Special characteristics **: English or Spanish speaking mothers only; similar proportions of mothers in control and cases groups consumed folic acid during preconception period	Exposure time: First month of pregnancy [MA] *Reported*: • *0 drinking days/week versus binge drinking (5+ drinks/occasion) *In grams*: • *0 drinking days/week versus binge drinking (≥70g/occasion)	**Birth defects**: • conotruncal heart defects; • neural tube defects; • anencephaly; • spina bifida; • cleft palate
10. Halliday 2017	Cohort study Data from the Asking Questions About Alcohol in Pregnancy (AQUA) study	Setting: **Australia**, Melbourne (pregnant women recruited 1 January 2011 to 30 December 2014) Population: sample of pregnant women: n = 1570 total in AQUA; 948 children included in the behavioural outcome assessment at 2 years.	Exposure time: throughout pregnancy • Low in Trimester 1 (T1), abstinent in T2&3; • Moderate/high in T1, abstinent in T2&3 • Binge pre-aware, abstinent in T2&3	**Behavioural problems**: • sensory processing behaviours • social emotional (assessed using Infant/Toddler Sensory Profile 48-item in daily experiences); and Brief

		Special characteristics **: no particular unique characteristics (representative of the general antenatal population in the study area)	• Low in T1, low/moderate in T2 and/or T3 • Moderate in T1, any level in T2 and/or T3 • Binge pre-aware, low-moderate in T2 and/or T3	Infant Toddler Social Emotional Assessment (BITSEA), at 2 years of age
11. Kelly 2009***	Cohort study Data from the first two sweeps of the prospective UK Millennium Cohort study	Setting: **UK** (England, Wales, Scotland and Ireland) (enrolment 2000-2003) Population: n = 11,983 mothers and infants (for behavioural outcomes); child mean age 3.13 years (95% CI 3.12 to 3.13) when outcome assessed; households identified through the Department of Work and Pensions child benefit system and selected on the basis of where the family was resident shortly after the time of birth; probability design with clustering at the electoral ward level such that disadvantaged residential areas were over-represented. Special characteristics **: only white participants (in this study); 19.3% of mothers smoked; slightly more disadvantaged than background population	Exposure time: throughout pregnancy *Reported* • *Never • Light, not more than 1-2 units per week or per occasion • Moderate, not more than 3-6 unit per week or 3-5 units per occasion • Heavy/binge, 7 or more units per week or 6 or more units per occasion *In grams* • 0 g • Not more than 8 – 16 g per week or occasion • Not more than 24-48 g per week or32-40g per occasion • ≥ 56 g per week or 48 g or more per occasion	**Behavioural problems**: • total difficulties; • conduct problems; • hyperactivity; • emotional symptoms; • peer problems (assessed using strengths and difficulties questionnaire (SDQ) at 3 years of age))
12. Lundsberg 2015***	Cohort study Birth data from two related and almost concurrent longitudinal cohorts that examined 1) caffeine exposure during pregnancy; and 2) asthma in pregnancy Alcohol exposure data from interviews with mothers	Setting: **USA**, Connecticut (pregnant women recruited from 56 obstetric practices and 15 clinics associated with six hospitals, September 1996 through June 2000) Population: pregnant mothers and singleton infants from caffeine exposure cohort (n=2288); pregnant mothers and singleton infants from asthma cohort study (n=2008); total cohort (n = 4496) Special characteristics **: none reported	Exposure time: first month pregnancy *Reported*: • *None; < 0.10; 0.10 to < 0.25; ≥ 0.25 oz alcohol/day *In grams:* • *None; < 2.83g; 2.83g to <7.09g; ≥ 7.09g alcohol/day	**Birth defects**: • major congenital malformations

13. Mateja 2012	Case control study Pregnancy Risk Assessment Monitoring Survey (PRAMS)1996-2005 for alcohol exposure data Linked to state Birth Certificate Data for outcomes data	Setting: **USA**, nine states including Rhode Island, Nebraska, Alaska, Illinois, South Carolina, Utah, Maine, Colorado, and Arkansas (data collection 1996-2005) Population: n = 129,153 linked PRAMS surveys and birth certificates; cases infants with congenital cardiac defect on birth certificate; controls healthy infants without a congenital abnormality on birth certificate Special characteristics **: none reported (data presented show mixed ethnicity, maternal age, socio-economic status, drug use not reported, maternal health status poorly reported (similar to other study reports).	Exposure time: three months prior to pregnancy *Reported:* • *No binge drinking versus binge drinking (5 or more drinks in one sitting) *In grams*: • *No binge drinking versus binge drinking (≥60g in one sitting)	**Birth defects**: • congenital heart defects
14. Miller 2009	Case control study Birth data from the NBDPS Alcohol exposure data from interviews with mothers	Setting: **USA**, 10 states with population-based birth defects surveillance systems ((Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Georgia; North Carolina; Utah) Population: Cases live born infants with anorectal atresia and no strongly suspected single-gene condition(s) or chromosomal abnormalities (n = 464); controls a random sample of live born infants with no major birth defect (n= 4940) from same geographical region as cases; all with an EDD 1 October 1997 to 31 December 2003 Special characteristics **: none reported	Exposure time: month prior to pregnancy to third month of pregnancy *Reported:* • *None; av ≤ 1.5 drinks/day; > 1.5 drinks/day; drank any alcohol; ≥ 5 alcoholic drinks on at least one occasion *In grams*: • *None; av ≤7.5g/day; >7.5g/day; drank any alcohol; ≥ 70g on at least one occasion	**Birth defects**: • anorectal atresia
15. Muggli 2017	Cohort study Data from AQUA	Setting: **Australia**, Melbourne (pregnant women recruited 1 January 2011 to 30 December 2014) Population: total AQUA sample of pregnant women: n = 1570; recruited in first trimester at first appointment for antenatal care, from lo w-risk, public maternity hospitals; total infants included in this study: n = 415 (195 boys; n = 220 girls)	Exposure times: first trimester; throughout pregnancy • *Abstinent; • Low ≤ 20 g Absolute Alcohol/occasion and ≤ 70 g Absolute Alcohol/week; • Moderate 21-49 g Absolute Alcohol/occasion and ≤ 70 g Absolute Alcohol/week; • High > 70 g Absolute Alcohol/week;	Birth defects: • cranial facial shape

		Special characteristics **: "included in this analysis are the images of 415 white children whose mothers were not lifetime abstainers"; urban population	• Binge ≥ 50 g Absolute Alcohol per occasion	
16. Mullally 2011	Cohort study Cohort of pregnant women who delivered in a large Dublin maternity hospital	Setting: **Ireland** (births between 2000 and 2007) Population: complete geographical cohort of pregnant women attending a large urban maternity hospital over the eight-year study period (n = 61,241 women); demographic characteristics of the women similar to other urban populations in Ireland Special characteristics **: mostly urban population	Exposure time: periconception (booking visit) *Reported:* • *No alcohol; low (0-5 units); moderate (6-20 units); high (> 20 units) per week *In grams*: • *No drinking (0g); low (0g-50g); moderate (60-200g); high (>200g) per week	Birth defects: • suspected congenital malformations
17. O'Leary 2010	Cohort study Population based cohort of non-Indigenous women who gave birth between 1995 and 1997 Data linkage to WA Midwives Notification System and WA Birth Defects Registry Data for birth data Retrospective collection of alcohol exposure data	Setting: **Australia**, Western Australia (pregnant women recruited) Population: pregnant women and their live infants (n = 4714); births between 1995 and 1997 Special characteristics **: non-Indigenous Australians; prevalence of low birth weight infants and teen mothers slightly lower than those of the whole population in Western Australia	Exposure time: before pregnancy; first trimester; late pregnancy • *Abstinent • Low (≤ 70 g/week; no more than two standard drinks/occasion) • moderate (≤ 70 g/week; < 5 standard drinks/occasion) • high (> 70 g/week; <5 standard drinks/occasion)	Birth defects: • any birth defect; and • birth defects classified as Alcohol Related Birth Defects (IOM) (by clinicians)
18. Richardson 2011	Nested case control study Birth data from the NBDPS Alcohol exposure data from interviews with mothers	Setting: **USA**, 10 states (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Georgia; North Carolina; Utah), selected for their population-based surveillance systems and willingness to participate in the study (data collected for births 1 October 1997 through December 2005) Population: cases 1 768 infants and their mothers with birth defects (796 craniosynostosis, 254 with omphalocele, 720 with gastroschisis); controls 6622 non-malformed live	Exposure time: one month prior to pregnancy to third month of pregnancy *Reported:* • *0, 1-4, 5-15, 16-30, > 30 drinks a month • *0; Binge (≥ 4 drinks/occasion) *In grams*:	Birth defects: • craniosynostosis; • omphalocele • gastroschisis

		infants and their mothers; all birth with EDD 1 October 1997 through December 2005 Special characteristics **: none	• *0; 14-56g; 70-210g; 224-420g; >420g per month • *0; Binge (≥56g/occasion) [Also reports duration of drinking in months and type of alcohol consumed]	
19. Romitti 2007	Case control study Birth data from the NBDPS Alcohol exposure data from interviews with mothers	Setting: **USA**, births in the centres and states specified for the NBDPS, EDD October 1 1997 to December 31 2002 Population: case group n = 1749 births (liveborn, fetal deaths or elective terminations) with oral clefts and their mothers; control group n = 4094 live births and their mothers; cases with defects of known aetiology (single-gene disorders and chromosome abnormalities) were excluded, as well as non-co-resident infants and mothers Special characteristics **: women who spoke English and Spanish only; no others reported	Exposure time: month before conception to first 3 months of pregnancy *Reported:* • *0; 1-4; 5-15; 16-30; > 30 drinks a month • *No drinking versus binge (1 or more episodes of ≥5 drinks per episode) [MA] *In grams*: • *0; 14-56g; 70-210g; 224-420g; >420g per month • *No drinking versus binge (1 or more episodes of ≥70g per episodes)	Birth defects: • cleft lip and cleft palate
20. Sayal 2007***	Cohort study Avon Longitudinal Study of Parents and Children (ALSPAC)	Setting: **England**, South West (recruitment dates: pregnant women with EDD between April 1991 and December 1992) Population: cohort of n = 14, 541 pregnancies and their singleton infants included; n = 9086 children included for the 47 months of age outcome assessment Special characteristics **: maternal cannabis use 2%; maternal illicit drug use 0.4%; maternal smoking 19%	Exposure time: first trimester *Reported:* • *0; <1; ≥1 drink/week *In grams:* • *0g; <8g; ≥8g/week	Behavioural problems: • hyperactivity/inattention; • conduct problems; • emotional symptoms; and • peer relationship scores (assessed using the Strength and Difficulties Questionnaire (SDQ) at 47 months of age)
21. Slickers 2008	Case control study Birth data from the National Birth Defects Prevention Study	Setting: **USA**, 10 states (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Georgia; North Carolina; Utah), selected for their population-based surveillance systems and willingness to participate in the study (EDD 1997-2003)	Exposure time: month prior to pregnancy to third month of pregnancy *Reported:*	Birth defects: • kidney defect (including bilateral renal agenesis or hypoplasia)

	Alcohol exposure data from interviews with mothers	Population: case group n = 75 live born infants, stillborn infants or fetuses (elective terminations) with bilateral renal agenesis or hypoplasia and their mothers; control group n = 868 liveborn nonmalformed infants and their mothers; Special characteristics **: infants of mothers diagnosed with diabetes before pregnancy excluded; 2/75 mothers of cases and 19/868 mothers of control infants used vasoactive substances during first trimester; 4/75 and 56/868 mothers of cases and controls respectively diagnosed with GDM	• *no exposure; non-binge exposure (never an occasion of ≥ 5 drinks per episode); binge exposure (≥ 5 drinks per episode) *In grams*: • *no exposure; non-binge exposure (never and occasion of ≥70g per episode); binge exposure (≥70g per episode)	
22. Strandberg-Larsen 2011	Cohort study Data from the Danish National Birth Cohort Study	Setting: **Denmark** (pregnant women were enrolled in the cohort between 1996 and 2002) Population: n = 80, 346 pregnant women and their infants Special characteristics **: authors report that "few (if any) women with an excessive/abusive intake of alcohol were enrolled"	Exposure time: preconception/early pregnancy (up to10 weeks gestation) *Reported*: • 0*; 0.5 to 1.5; 2; 3+ drinks/week • 0* binge episodes; 1; 2, 3+ binge episodes • 0* binge episodes; binged at least once in week 1-2; week 3-4; week 5-10 *In grams:* • 0*; 7-21g; 28g; ≥42g/week • 0* binge episodes (≥70g/single occasion); 1; 2, 3+ binge episodes • 0* binge episodes (≥70g/single occasion); binged at least once in week 1-2; week 3-4; week 5-10	Birth defects: • congenital heart defects
23. Suarez 2008	Case control study Study subjects identified through the Texas Department of Health's Neural Tube Defect Project conducted along the Texas-	Setting: **USA**, 14 Texas counties bordering Mexico Population: cases infants and fetuses with neural tube defects (n = 175) born between March 1995 and May 2000 in hospitals, birthing centres, genetic clinics, ultrasound centres, abortion centres, or at home with the assistance of midwives; controls liveborn infants (n = 221) born during the same	Exposure time: first trimester pregnancy *Reported:* • *no drinking; < 1 drink daily; ≥ 1 drink daily	Birth defects: • neural tube defects

	Mexico border. Birth data from hospital and other birthing centre records (born 1995-2000) Alcohol exposure data from interviews with mothers	years and facilities, without a congenital malformation (randomly selected). Neural tube defect cases associated with anomalies Special characteristics **: all included women and infants/fetuses Mexican American; most participants likely living in low resource settings	• *no drinking; 3 or fewer drinks on any occasion; > 3 drinks on any occasion *In grams*: • *no drinking; <14g daily; ≥14g daily • *no drinking; ≤ 42g on any occasion; > 42g on any occasion	
24. Torp-Pederson 2010	Cohort study Data from Danish National Birth Cohort Births identified through national registries Mostly prospective alcohol data (pregnant women enrolled early in their pregnancy, at 12-14 weeks gestational age)	Setting: **Denmark** Population: pregnant women and their live born infants (n = 98, 842) born alive between 1996 and 2003 (30% of all deliveries in Denmark during this period) Special characteristics **: authors state than women in the cohort had slightly better health than the background population	Exposure time: throughout pregnancy • 12 g units/week: *0; > 0-1; > 1-3; > 3-5; > 5 • *no binge; binge drinking (≥ 5 drinks, or 50g/occasion)	**Birth defects**: • strabismus
25. Werler 2015	Case control study Birth data from birth defects registries during (years 2007-2011) Alcohol exposure data from interviews with mothers of included infants (interviewed 12 months after delivery)	Setting: **USA**, Massachusetts, New York, North Carolina Population: cases infants <11 months of age with a diagnosis of talipes equinovarus or clubfoot without a known chromosomal anomaly, inherited syndrome, bilateral renal agenesis, Potter syndrome, or neural tube deft (n = 646); controls infants born in the sae years as cases but without known malformations, sampled from birth certificates (Massachusetts and North Carolina) or the same birth hospital as cases (New York) Special characteristics **: none reported	Exposure time: early pregnancy (2nd to 4th lunar months) *Reported:* • *0, ≤ 3, > 3 drinks/day • Anytime • 2nd month quitters • 3rd month quitters • drinking throughout period *In grams*: • *0g/day; ≤ 42g/day; >42g /day • Anytime • 2nd month quitters • 3rd month quitters • drinking throughout period	**Birth defects**: • club foot

26. Zhu 2013	Case control study Birth data from the NBDPS Alcohol exposure data from interviews with mothers	Setting: **USA**, births in 10 states (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Georgia, North Carolina and Utah) Population: pregnancies with EDD between 1997 and 2007 included (EDD varied across study sites); case group included n = 7076 births (fetal deaths, elective terminations and live) with congenital heart defects and their mothers; control group: n = 7927 unaffected live births and their mothers Special characteristics **: none reported	Exposure time: 1 month prior to pregnancy through trimester 1 *Reported:* • *No alcohol; 1-4; 5-15; 16-30; > 30 drinks a month • *No alcohol; drinking (no binge); drinking with 1 or more binge episodes *In grams*: • *no alcohol; 14g-56g; 70g-210g; 224-420g; >420g / month • *no alcohol; drinking (no binge /<56g/occasion); drinking with 1 or more binge episodes (≥56g/occasion)	**Birth defects**: • congenital heart defects

Notes: * Referent;

**As per the protocol, we extracted data on participants' ages, ethnicity, health/co-morbidities, socio-economic status (including education), maternal smoking, maternal use of licit or/and illicit drugs, and family history of alcohol use. We noted when the study population included only (or no): maternal smokers, illicit or licit drug users, heavy alcohol users, or had a history of alcohol use; infants and mothers living in low resource settings, young mothers (<18 years) or old mothers (>40 years); one ethnic or language group(s); mothers with poor nutrition as these characteristics are important for appropriate interpretation of the study results, and GRADE evidence quality assessment. These notes reported as 'special characteristics' of the study population and setting;

***Included in the Mamluk (2017) systematic review on associations between low alcohol consumption and pregnancy and childhood outcomes.

[MA] denotes that this study and outcome has been included in a meta-analysis.

Where authors have not defined alcohol exposure categories in grams, we have accessed the definitions in grams for the conversions from a 2015 review of standard drink definitions in Europe (Mongran & Long 2015) funded by the Health Research Board and Health Programme of the European Union, and the definitions supplied by Wikipedia **https://en.wikipedia.org/wiki/Standard_drink#Definitions_in_various_countries)**

Abbreviations: AQUA (Asking Questions about Pregnancy study); Av (average); EDD (estimated delivery date); FASD (Fetal Alcohol Spectrum Disorders); SU (standard units); IOM (Institute of Medicine; USA (United States of America); MoBa (Norwegian Mother and Child Cohort Study); SDQ (Strengths and Difficulties Questionnaire); (NBPDS) National Birth Prevention Defects Study

4.2.2 Systematic review on alcohol consumption while breastfeeding

Characteristics of the one study included in the breastfeeding review are summarised in Table 4. The author declarations for the included study are provided in the Technical report (section 4.2).

Table 4: Characteristics of study reporting associations between alcohol consumption while breastfeeding and child outcomes in breastfed infants and children

Study ID	Study design, data sources and name (if reported)	Setting and population	Alcohol exposure (levels and/or patterns) reported in review: timing, measures and comparison(s); *referent	Review outcome domain(s) and measures reported
Tay 2017	Cohort study Data from the Australian Triple B Pregnancy Cohort Study (Triple B) Alcohol exposure data gathered via two interviews, at 8 and 12 weeks postpartum	Setting: **Australia**, New South Wales (women recruited 2009 to 2013 from general antenatal clinics and specialist drug and alcohol antenatal clinics in public hospitals, and area health service hospitals) Population: pregnant women (n-=457) attending public hospitals in New South Wales and their singleton infants (opportunistic sample) Special characteristics: most of the women in the sample were socio-economically advantaged; note also that almost all women reported employing a strategy to minimise potential effects of exposure on breastfeeding infant.	Time of exposure: 8 weeks postpartum *Reported*: • *any alcohol consumption (referent) • abstinence Any alcohol consumption included the categories: low (≤ 14 standard drinks (or 140g) per week, and < 3 drinks (30g) per occasion); moderate (≤ 14 standard drinks (or 140g) per week, ≥ 3 to < 5 standard drinks (or 30-50g) per occasion); risky drinking (≤ 14 standard drinks (140g) per week, ≥ 5 standard drinks (50g) per occasion); and heavy (> 14 standard drinks (140g) per week)).	**Sedation (in breastfed infants during/soon after breastfeeding)**: 1) infant feeding, number of milk feeds in a day ≥ 7, at 8 weeks; 2) infant sleeping: frequency (sleeps/day), at 8 weeks; and 3) mother's rating of the child's feeding behaviour, sale of 1 (poor) to 10 (excellent), at 8 weeks **Cognitive impairment (development)**: 4) ages and states questionnaire (ASQ), at 8 weeks 5) ASQ and 12 months

Notes: 1. This study was included even though the alcohol consumption level was not quantifiable because the authors reported the pattern of consumption in the sample, which showed that most women were consuming low or moderate levels of alcohol (see results section of report).

Abbreviations: ASQ (Ages and States Questionnaire)

4.3 Description of included studies: risk of bias

4.3.1 Systematic review on alcohol consumption during pregnancy

Most (19) studies included for the evidence evaluation on associations between alcohol consumption during pregnancy and birth defects and behavioural problems in fetuses and children (up to age 5) were assessed as at serious risk of bias overall (Alvik 2011, Benedum 2013, , Caspers 2011, Caspers 2014, Davies 2017, , DeRoo 2008, Grewal 2008, Halliday 2017, Kelly 2009, Mateja 2012, Miller 2009, O'Leary 2010, Richardson 2011, Romitti 2007, Sayal 2007, Slickers 2008, Suarez 2008, Werler 2015, Zhu 2013). Seven studies included for this review were assessed as at moderate risk of bias overall (Bille 2007, Damgaard 2007, Lundsberg 2015, Mullally 2011, Muggli 2017, Strandberg-Larsen 2011, Torp-Pederson 2010). As explained above, we judged the remaining two (Bitsko 2007, Han 2012) as critical risk of bias due to failure to adjust for confounding, and therefore excluded these from further consideration in the review (see Table 5 for risk of bias assessments for each study).

Table 5: ROB assessment overall for studies included in the pregnancy review

Study ID/Bias	Overall ROB	Rationale
Alvik 2011	Serious risk of bias	There is a high risk of bias in measurement of the outcome, as mothers' awareness of their prior alcohol consumption may have influenced their self-report of the outcome (child temperament). It was unclear if the proportion of missing data (30% in total) differed between exposure groups. At least one important confounding variable was not taken into account in the analysis.
Benedum 2013	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Bille 2007	Moderate risk of bias	At least one important confounding variable was not taken into account in the analysis.
Bitsko 2007	Critical risk of bias	No confounding variables were taken into account in the analysis.
Caspers 2011	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Caspers 2014	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. At least one important confounding variable was not taken into account in the analysis.
Damgaard 2007	Moderate risk of bias	Alcohol consumption was self-reported, but before the outcome (birth defect) occurred. The amount of missing data was low overall (10%) but it is unclear if the proportion differed between exposure groups. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Davies 2017	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (behavioural problems) had occurred. There was a high amount of missing data (34%), whose potential impact was not addressed. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
DeRoo 2008	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Grewal 2008	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Halliday 2017	Serious risk of bias	There was a high amount of missing outcome data (49%) that was differential across the exposure groups. At least one important confounding variable was not taken into account in the analysis.
Han 2012	Critical risk of bias	No confounding variables were taken into account in the analysis.

Kelly 2009	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (behavioural problems) had occurred. There is a high risk of bias in measurement of the outcome, as mothers' awareness of their prior alcohol consumption may have influenced their self-report of their child's behaviour. It was unclear if the proportion of missing data (~30%) differed between exposure groups. At least one important confounding variable was not taken into account in the analysis.
Lundsberg 2015	Moderate risk of bias	Alcohol consumption was self-reported, but before the outcome (birth defect) occurred, which reduces the risk of differential misclassification of exposure. The amount of missing data was low overall (10%) but it is unclear if the proportion differed between exposure groups. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Mateja 2012	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Miller 2009	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Muggli 2017	Moderate risk of bias	Alcohol consumption was self-reported, but before the outcome (birth defect) occurred, which reduces the risk of differential misclassification of exposure. The amount of missing data, and whether it differed across exposure groups, is unclear. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Mullally 2011	Moderate risk of bias	Alcohol consumption was self-reported, but before the outcome (birth defect) occurred, which reduces the risk of differential misclassification of exposure. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
O'Leary 2011	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Richardson 2011	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Romitti 2007	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Sayal 2007	Serious risk of bias	There is a high risk of bias in measurement of the outcome, as mothers' awareness of their prior alcohol consumption may have influenced their self-report of their child's behaviour. There was a high amount of missing outcome data (>25%) that was differential across the exposure groups. At least one important confounding variable was not taken into account in the analysis.
Slickers 2008	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.
Strandberg-Larsen 2011	Moderate risk of bias	Alcohol consumption was self-reported, but before the outcome (birth defect) occurred, which reduces the risk of differential misclassification of exposure. At least one important confounding variable was not taken into account in the analysis.

Suarez 2008	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. At least one important confounding variable was not taken into account in the analysis.
Torp-Pederson 2010	Moderate risk of bias	Alcohol consumption was self-reported, but before the outcome (birth defect) occurred, which reduces the risk of differential misclassification of exposure. At least one important confounding variable was not taken into account in the analysis.
Werler 2015	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. At least one important confounding variable was not taken into account in the analysis.
Zhu 2013	Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (birth defect) had occurred. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.

Table 6: Summary RoB assessments by criterion for studies included in the pregnancy review

Study ID/Bias	Valid and reliable measures implemented consistently across study participants used to assess confounding?	Attempt to balance allocation between groups or match groups?	Important confounding variables taken into account in design and / or analysis?	Inclusion / exclusion criteria vary across comparison groups?	Strategy for recruiting participants into the study differs across groups?	Is the selection of the comparison group in-appropriate, after considering feasibility and ethics?	Outcome assessor not blinded to the exposure status of the participants?	Valid and reliable measures implemented consistently across all study participants used to assess exposure?	Valid and reliable measures implemented consistently across all participants used to assess health benefits and harms)?	Length of follow-up different across study groups?	In cases of high loss to follow-up (or differential loss), was impact not assessed?	Are any important primary outcomes missing from the results?
Alvik 2011	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	yes, not blinded or blinding not reported	yes, used	yes, used	no, not different or remedied	no, impact not assessed	no important outcomes missing
Benedum 2013	yes	Yes	Partially	yes, varies	no, does not differ	no, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Bille 2007	yes	Yes	Partially	yes, varies	no, does not differ	no, not inappropriate	no, blinded	yes, used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Bitsko 2007	no, not used	no, or cannot determine	no, not taken into account	Not assessed as study excluded due to high risk of confounding.								
Caspers 2011	yes	Yes	Partially	yes, varies	no, does not differ	no, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Caspers 2014	yes	Yes	Partially	yes, varies	no, does not differ	no, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Damgaard 2007	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	yes, not blinded or	yes, used	yes, used	no, not different	no, impact not assessed	no important outcomes missing

Study ID/Bias	Valid and reliable measures implemented consistently across study participants used to assess confounding?	Attempt to balance allocation between groups or match groups?	Important confounding variables taken into account in design and / or analysis?	Inclusion / exclusion criteria vary across comparison groups?	Strategy for recruiting participants into the study differs across groups?	Is the selection of the comparison group in-appropriate, after considering feasibility and ethics?	Outcome assessor not blinded to the exposure status of the participants?	Valid and reliable measures implemented consistently across all study participants used to assess exposure?	Valid and reliable measures implemented consistently across all participants used to assess health benefits and harms)?	Length of follow-up different across study groups?	In cases of high loss to follow-up (or differential loss), was impact not assessed?	Are any important primary outcomes missing from the results?
							blinding not reported			or remedied		
Davies 2017	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	yes, not blinded or not reported	no, not used	yes, used	no, not different or remedied	no, impact not assessed	no important outcomes missing
DeRoo 2008	yes	Yes	Partially	yes, varies	no, does not differ	No, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Grewal 2008	yes	Yes	Partially	yes, varies	no, does not differ	yes, inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	No important outcomes missing
Halliday 2017	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	no, blinded	yes, used	yes, used	no, not different or remedied	no, impact not assessed	no important outcomes missing
Han 2012	no, not used	no, or cannot determine	no, not taken into account	Not assessed as study excluded due to high risk of confounding.								
Kelly 2009	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	no, impact not assessed	no important outcomes missing

Study ID/Bias	Valid and reliable measures implemented consistently across study participants used to assess confounding?	Attempt to balance allocation between groups or match groups?	Important confounding variables taken into account in design and / or analysis?	Inclusion / exclusion criteria vary across comparison groups?	Strategy for recruiting participants into the study differs across groups?	Is the selection of the comparison group in-appropriate, after considering feasibility and ethics?	Outcome assessor not blinded to the exposure status of the participants?	Valid and reliable measures implemented consistently across all study participants used to assess exposure?	Valid and reliable measures implemented consistently across all participants used to assess health benefits and harms)?	Length of follow-up different across study groups?	In cases of high loss to follow-up (or differential loss), was impact not assessed?	Are any important primary outcomes missing from the results?
Lundsberg 2015	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	yes, not blinded or not reported	no, not used	yes, used	no, not different or remedied	no, impact not assessed	no important outcomes missing
Mateja 2012	yes	Yes	Partially	yes, varies	no, does not differ	no, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	cannot determine
Miller 2009	yes	Yes	Partially	yes, varies	no, does not differ	no, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Muggli 2017	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	no, blinded	yes, used	yes, used	no, not different or remedied	cannot determine	no important outcomes missing
Mullally 2011	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	yes, not blinded or not reported	yes, used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
O'Leary 2010	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Richardson 2011	yes	Yes	Partially	yes, varies	no, does not differ	no, not inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing

Study ID/Bias	Valid and reliable measures implemented consistently across study participants used to assess confounding?	Attempt to balance allocation between groups or match groups?	Important confounding variables taken into account in design and / or analysis?	Inclusion / exclusion criteria vary across comparison groups?	Strategy for recruiting participants into the study differs across groups?	Is the selection of the comparison group in-appropriate, after considering feasibility and ethics?	Outcome assessor not blinded to the exposure status of the participants?	Valid and reliable measures implemented consistently across all study participants used to assess exposure?	Valid and reliable measures implemented consistently across all participants used to assess health benefits and harms)?	Length of follow-up different across study groups?	In cases of high loss to follow-up (or differential loss), was impact not assessed?	Are any important primary outcomes missing from the results?
Romitti 2007	yes	Yes	Partially	yes, varies	no, does not differ	yes, inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Sayal 2007	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	yes, not blinded	yes, used	yes, used	no, not different or remedied	no, not assessed	no important outcomes missing
Slickers 2008	yes	Yes	Partially	yes, varies	no, does not differ	yes, inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Strandberg-Larsen 2011	yes	Yes	Partially	no, does not vary	no, does not differ	no, not inappropriate	yes, not blinded	yes, used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Suarez 2008	yes	Yes	Partially	yes, varies	no, does not differ	yes, inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing
Torp-Pederson 2010	yes	Yes	Partially	no, does vary	no, does not differ	no, not 9inappropriate	yes, not blinded	yes, used	yes, used	no, not different or remedied	yes, impact assessed	no important outcomes missing
Werler 2015	yes	Yes	Partially	yes, varies	no, does not differ	no, not inappropriate	no, blinded	no, not used	no, not used	no, not different or remedied	not applicable	no important outcomes missing

Study ID/Bias	Valid and reliable measures implemented consistently across study participants used to assess confounding?	Attempt to balance allocation between groups or match groups?	Important confounding variables taken into account in design and / or analysis?	Inclusion / exclusion criteria vary across comparison groups?	Strategy for recruiting participants into the study differs across groups?	Is the selection of the comparison group in-appropriate, after considering feasibility and ethics?	Outcome assessor not blinded to the exposure status of the participants?	Valid and reliable measures implemented consistently across all study participants used to assess exposure?	Valid and reliable measures implemented consistently across all participants used to assess health benefits and harms)?	Length of follow-up different across study groups?	In cases of high loss to follow-up (or differential loss), was impact not assessed?	Are any important primary outcomes missing from the results?
Zhu 2013	yes	Yes	Partially	yes, varies	no, does not differ	yes, inappropriate	no, blinded	no, not used	yes, used	no, not different or remedied	not applicable	no important outcomes missing

We do not report, here in Table 6, the results of the assessments of studies included in the review of alcohol consumption during pregnancy, for one of the assessment criteria: Does the study fail to account for important variations in the execution of study from the proposed protocol? This is because we did not search for study protocols, unless this was essential for accessing comprehensive results, and therefore for all except one study the assessment was the same, and more specifically, "cannot determine: no access to study protocol" (refer to full assessments in technical report).

The complete ROB assessment form for each study that contributed results (associations) for the pregnancy review, which includes the rationale for the judgements for all 13 assessment criteria, are provided in the Technical report (see section 5).

4.3.2 Systematic review on alcohol consumption while breastfeeding

The one study included in the review of associations between alcohol consumption while breastfeeding and selected outcomes in breastfed infants and children (up to age 5) was assessed as at serious risk of bias overall (see Table 7 for rationale and criterion specific assessment; the technical report includes the complete ROB assessment for this study (see section 5).

Table 7: RoB assessment by criterion for study included in the breastfeeding review

Study ID/Bias	Valid and reliable measures implemented consistently across all study participants used to assess confounding?	Attempt to balance allocation between groups or match groups?	Important confounding variables not taken into account in the design and/or analysis?	Inclusion / exclusion criteria vary across comparison groups of study?	Strategy for recruiting participants into the study differs across groups?	Is the selection of the comparison group in-appropriate, after considering feasibility and ethical considerations?	Does study fail to account for important variations in the execution of study from the proposed protocol?	Outcome assessor not blinded to the exposure status of the participants?	Valid and reliable measures implemented consistently across all study participants used to assess exposure?	Valid and reliable measures implemented consistently across all participants used to assess participant health benefits and harms)?	Length of follow-up different across study groups?	In cases of high loss to follow-up (or differential loss), was impact not assessed?	Are any important primary outcomes missing from the results?
Tay 2017	Yes	Yes	Partially	No, does not vary	No, does not differ	No, not inappropriate	Cannot determine (without access to study protocol)	Yes, not blinded	No	Yes	No, not different or remedied	Not applicable	No
Overall assessment: Serious risk of bias	There is a high risk of recall bias as mothers self-reported their prior alcohol consumption after the outcome (behavioural problems) had occurred. There is a high risk of bias in measurement of the outcome, as mothers' awareness of their prior alcohol consumption may have influenced their self-report of their child's behaviour. All important confounding variables were taken into account in the analysis but there is a risk of residual confounding.												

4.4 Associations between alcohol exposures and the selected child outcomes

4.4.1 Systematic review on alcohol consumption during pregnancy

Results are structured by domain (behaviour and birth defects) and then by individual outcomes. Within outcomes, meta-analysis results (when available) are presented first, followed by results from each study. The majority of studies reported levels and frequency of alcohol consumption, for various time periods, few for throughout pregnancy, and most studies reported consumption levels considered to be binge drinking (usually defined as ≥5 drinks per episode).

Note: significant outcomes are highlighted in bold text.

Behaviour outcomes

Total difficulties, Strength and Difficulties Questionnaire

In Kelly 2008, there were very few associations seen between alcohol consumption and high behavioural difficulties scores in children at 3 years of age (separately reported for boys and girls).

High behavioural difficulties scores – Boys

Total difficulties: n = 4753	High score
No drinking (9.5%)	referent (1.00)
Light drinking (6.5%)	aOR 0.77 95% CI 0.56 to 1.07
Moderate drinking (7.5%)	aOR 0.65 95% CI 0.35 to 1.23
Heavy/binge (17.1%)	aOR 1.76 95% 0.83 to 3.73

Conduct problems: n = 4813	
No drinking (10.4%)	referent (1.00)
Light drinking (6.3%)	**aOR 0.59 95% CI 0.44 to 0.81**
Moderate drinking (10.3%)	aOR 0.68 95% CI 0.39 to 1.21
Heavy/binge (10.8%)	aOR 0.53 95% CI 0.22 to 1.27

Hyperactivity: n= 4799	
No drinking (10.1%)	referent (1.00)
Light drinking (7.3%%)	**aOR 0.69 95% CI 0.50 to 0.95**
Moderate drinking (8.7%)	aOR 0.71 95% CI 0.41 to 1.23
Heavy/binge (12.8%)	aOR 1.02 95% CI 0.52 to 1.99

High behavioural difficulties scores – Girls

Total difficulties: n = 4593	
No drinking (6.2%)	referent (1.00)
Light drinking (3.9%)	aOR 0.70 95% CI 0.43 to 1.14
Moderate drinking (8.2%)	aOR 1.18 95% CI 0.63 to 2.19
Heavy/binge (7.2%)	aOR 0.83 95% CI 0.30 to 2.28

Conduct problems: n = 4813	
No drinking (7.3%)	referent (1.00)
Light drinking (6.1%)	aOR 0.72 95% 0.52 to 1.00
Moderate drinking (14.6%)	aOR 1.60 95% CI 0.92 to 2.78
Heavy/binge (1.15%)	aOR 1.18 95% CI 0.49 to 2.83

Hyperactivity: n= 4799

No drinking (4.9%)	referent (1.00)
Light drinking (4.8%)	aOR 1.18 95% CI 0.78 to 1.77
Moderate drinking (5.3%)	aOR 1.03 95% CI 0.52 to 2.06
Heavy/binge (2.1%)	aOR 0.32 95% CI 0.08 to 1.19

These results were adjusted for child's age, birthweight, mother's age at the time of birth, number of children in the household, mother smoked during pregnancy, pregnancy planned, household income, mother's highest educational qualification, mother's occupational class, mother's K6 score, warmth of relationship between mother and child, parental discipline, mother's current drinking.

In Sayal 2007, overall total problems and hyperactivity/inattention scores in the Strengths and Difficulties Questionnaire were higher (worse) in children at 47 months of age; with no clear difference seen for conduct problems.

SDQ at 47 months (n=6355)

Total problems (0-40)	**aMD 0.46 (95% CI 0.17 to 0.74)**	**p = 0.002**
Hyperactivity/inattention (0-10)	**aMD 0.25 (95% CI 0.11 to 0.40)**	**p = 0.001**
Conduct problems (0-10)	aMD 0.06 (95% CI -0.03 to 0.15)	

These results were adjusted for maternal age, parity, highest level of maternal education, daily frequency of smoking during the second trimester, use of cannabis and/or other illicit drugs in pregnancy, home ownership, whether currently married, high scores (> 12) on the Edinburgh Postnatal Depression Scale, and child gestational age, birthweight, gender and ethnicity.

Personal-social subscale of Griffiths Mental Developmental Scales

In Davies 2017, compared with a mean personal-social rating of 100.9 for a 1 year old, the alcohol exposed group of children had a mean rating of 108.9 (p=0.974); and the FAS/PFAS group had a lower score (mean 103.1; p=0.198). When infants were 5 years old, the comparisons were:

- mean 116.8 for the unexposed group,
- 113.4 for the alcohol-exposed group (p=0.357) and
- **101.5 for the FAS/PFAS group (p=0.001)**.

Difficult temperament; sleeping problem; demanding/irritable

In Alvik 2011, binge drinking ≥ once a week was associated with higher rates of behavioural problems in infants at six months of age (using selected measures from the Difficult Temperament Scale of the Infant Characteristics Questionnaire, the Infant Toddler Symptom Checklist and the Ages and Stages Questionnaire).

No binge drinking in week 0-6 (referent) was compared with binge drinking < once a week and binge drinking ≥ once a week. Binge drinking was defined as ≥ 5 drinks (60 g) per occasion.

Difficult temperament: 167/1179 infants

Referent: no binge drinking in week 0-6	aOR 1.00	
Binge drinking < once a week	aOR 0.7 95% CI 0.7 to 1.2	
Binge drinking ≥ once a week	**aOR 3.3 95% 1.4 to 7.9**	**p < 0.01**

Sleeping problem: 168/1207 infants

Referent: no binge drinking in week 0-6	aOR 1.00

Binge drinking < once a week	aOR 0.7 95% CI 0.5 to 1.3	
Binge drinking ≥ once a week	**aOR 6.0 95% CI 2.7 to 13.7**	**p < 0.001**

Demanding, irritable, uneasy: 174/1234 infants

Referent: no binge drinking in week 0-6	aOR 1.00	
Binge drinking < once a week	aOR 0.7 95% CI 0.4 to 1.1	
Binge drinking ≥ once a week	**aOR 4.5 95% CI 1.9 to 10.4**	**p < 0.001**

Results were adjusted for mother's age, income, education, and civil status; father's income and education; mother's smoking status; and pregnancy recognition before or after beginning of week 5.

Infant/Toddler Sensory Profile (ITSP) and Brief Infant-Toddler Social and Emotional Assessment (BITSEA) – (Halliday 2017)

In Halliday 2017, few differences were seen in the ITSP and BITSEA between different patterns alcohol exposure during pregnancy. In the low alcohol in T1, abstinent in T2/3 group, compared with no alcohol, there was less likelihood of sensation-seeking. In the binge pre-aware, low moderate consumption in trimester 2 and/or trimester 3 group, children at 24 months of age were more likely to be sensation-avoiding. Binge drinking was defined as ≥ 50 g absolute alcohol per occasion.

ITSP: Low registration	**N=868**	**Referent (no alcohol) OR 1.00**	**p value**
Low alcohol in T1, abstinent in T2/3		aOR 0.68 95% CI 0.33 to 1.39	0.29
Moderate/high in T1/abstinent in T2/3		aOR 1.21 95% CI 0.65 to 2.26	0.55
Binge pre-aware, abstinent T2/T3		aOR 1.07 95% CI 0.52 to 2.19	0.85
Low T1, low/moderate T2 and/or T3		aOR 0.75 95% CI 0.36 to 1.58	0.45
Moderate T1, any level T2 and/or T3		aOR 1.68 95% CI 0.94 to 2.98	0.08
Binge pre-aware, low/moderate T2 and/or T3		aOR 1.29 95% CI 0.71 to 2.36	0.40
ITSP: Sensation seeking	**N=823**		
Low alcohol in T1, abstinent in T2/3		**aOR 0.38 95% CI 0.15 to 0.94**	**0.04**
Moderate/high in T1/abstinent in T2/3		aOR 0.52 95% CI 0.25 to 1.11	0.09
Binge pre-aware, abstinent T2/T3		aOR 1.14 95% CI 0.56 to 2.34	0.72
Low T1, low/moderate T2 and/or T3		aOR 0.44 95% CI 0.16 to 1.18	0.10
Moderate T1, any level T2 and/or T3		aOR 0.83 95% CI 0.44 to 1.58	0.58
Binge pre-aware, low/moderate T2 and/or T3		aOR 0.74 95% CI 0.38 to 1.45	0.38
ITSP: Sensory sensitivity	**N=801**		
Low alcohol in T1, abstinent in T2/3		aOR 1.20 95% CI 0.61 to 2.33	0.60
Moderate/high in T1/abstinent in T2/3		aOR 1.36 95% CI 0.72 to 2.60	0.34
Binge pre-aware, abstinent T2/T3		aOR 0.88 95% CI 0.38 to 2.02	0.76
Low T1, low/moderate T2 and/or T3		aOR 0.86 95% CI 0.40 to 1.85	0.70
Moderate T1, any level T2 and/or T3		aOR 0.81 95% CI 0.42 to 1.56	0.52
Binge pre-aware, low/moderate T2 and/or T3		aOR 1.25 95% CI 0.67 to 2.32	0.49
ITSP: Sensation avoiding	**N=789**		
Low alcohol in T1, abstinent in T2/3		aOR 1.09 95% CI 0.55 to 2.18	0.79

Moderate/high in T1/abstinent in T2/3	aOR 1.32 95% CI 0.70 to 2.49	0.39
Binge pre-aware, abstinent T2/T3	aOR 1.22 95% CI 0.58 to 2.59	0.60
Low T1, low/moderate T2 and/or T3	aOR 1.36 95% CI 0.66 to 2.78	0.41
Moderate T1, any level T2 and/or T3	aOR 1.18 95% CI 0.63 to 2.20	0.61
Binge pre-aware, low/moderate T2 and/or T	**aOR 1.88 95% CI 1.03 to 3.41**	**0.04**

Low registration: adjusted for ethnicity, maternal education, parity, folate supplements in T1, socioeconomic index, child sex, general family functioning, maternal mental health, parental warmth, hostile parenting and maternal rating of self-efficacy.
Sensation seeking: adjusted for maternal age, parity, prepregnancy BMI, folate supplements in T1, breastfeeding, parental warmth.
Sensory sensitivity adjusted for maternal age, ethnicity, maternal education, parity, prepregnancy BMI, exercise in T1, breastfeeding, child sex, general family functioning, maternal mental health, parental warmth, hostile parenting, and maternal rating of self-efficacy.
Sensation avoiding: adjusted for ethnicity, maternal education, parity, prepregnancy BMI, folate supplements in T1, household income, socioeconomic index, breastfeeding, child sex, general family functioning, maternal mental health, parental warmth, hostile parenting and maternal rating of self-efficacy.

BITSEA: possible problem N=879	**Referent (no alcohol) OR 1.00**	**p value**
Low alcohol in T1, abstinent in T2/3	aOR 1.09 95% CI 0.47 to 2.53	0.85
Moderate/high in T1/abstinent in T2/3	aOR 0.59 95% CI 0.23 to 1.53	0.28
Binge pre-aware, abstinent T2/T3	aOR 0.67 95% CI 0.24 to 1.87	0.45
Low T1, low/moderate T2 and/or T3	aOR 0.72 95% CI 0.27 to 1.94	0.52
Moderate T1, any level T2 and/or T3	aOR 0.42 95% CI 0.16 to 1.13	0.09
Binge pre-aware, low/moderate T2 and/or T3	aOR 1.11 95% CI 0.48 to 2.58	0.81

BITSEA: possible competence deficit N=855	**Referent (no alcohol) OR 1.00**	**p value**
Low alcohol in T1, abstinent in T2/3	aOR 1.28 95% CI 0.51 to 3.23	0.60
Moderate/high in T1/abstinent in T2/3	aOR 1.17 95% CI 0.47 to 2.90	0.74
Binge pre-aware, abstinent T2/T3	aOR 0.55 95% CI 0.15 to 2.06	0.38
Low T1, low/moderate T2 and/or T3	aOR 0.56 95% CI 0.17 to 1.85	0.34
Moderate T1, any level T2 and/or T3	aOR 0.88 95% CI 0.35 to 2.21	0.78
Binge pre-aware, low/moderate T2 and/or T3	aOR 0.60 95% CI 0.21 to 1.71	0.34

Possible problem: adjusted for maternal age, ethnicity, parity, folate supplements in T1, household income, general family functioning, maternal mental health, hostile parenting, and maternal rating of self-efficacy.
Possible competence deficit: adjusted for ethnicity, parity, folate supplements in T1, folate supplements in T2/3, healthy diet, breastfeeding, general family functioning, maternal mental health, parental warmth, hostile parenting, and maternal rating of self-efficacy.

T1=trimester 1; T2 = trimester 2; T3 = trimester 3

Birth defects outcomes

Major congenital malformations (Lundsberg 2015)

In Lundsberg 2015, no drinking in the first month of pregnancy was compared with < 0.10; 0.10 to < 0.25; and ≥ 0.25 ounces of absolute alcohol for the outcome of major congenital malformations (n=190; 4.4%).

<0.10	OR 0.78 95% CI 0.40 to 1.50
0.10 to 0.25	OR 1.20 95% CI 0.65 to 2.22
≥ 0.25	OR 1.15 95% CI 0.77 to 1.71

These results were adjusted for parity, maternal age, education, BMI, marital status, ethnicity, caffeine, smoking, exercise, work, prenatal vitamin use, passive smoke exposure, marijuana use, cocaine use, study cohort, preterm labour, respiratory problem, infant gender, bleeding, nausea/vomiting, hypertension, state of cervix, placental problems, sexually transmitted disease, induction/augmentation, maternal asthma, gestational diabetes.

Suspected congenital malformations (Mullally 2011)

In Mullally 2011, various levels of alcohol intake periconceptionally showed the following associations with congenital malformations.

Referent: alcohol 'never'

Low (0-5 units/week)	OR 1.01 95% CI 0.71 to 1.44
Moderate (6-20 units/week)	OR 1.01 95% CI 0.82 to 1.27
High (> 20 units/week)	OR 0.56 95% CI 0.17 to 1.88

These results were adjusted for maternal age, single maternal status, socio-economic status, nationality, private health insurance, nulliparity, unplanned pregnancy, late booking, smoking and history of illicit drug use.

Any birth defect and birth defects classified as alcohol related birth defects (O'Leary 2010)

In O'Leary 2010, the associations between alcohol exposure and both overall birth defects and alcohol-related birth defects were explored

(Note: the outcome alcohol related birth defects refers to birth defects classified by health professionals in the WA Birth Defects Registry (WABDR) because they could not be attributed to another syndrome or a genetic or congenital condition, as per the IOM definitions and classifications) (O'Leary 2010; pg.845).

<u>Any birth defect</u>
Referent: abstinent
Before pregnancy

Low (≤ 70 g/week; no more than 2 standard drinks/occasion) OR 1.00 95% CI 0.72 to 1.40

moderate (≤ 70 g/week; < 5 standard drinks/occasion) OR 0.81 95% CI 0.57 to 1.14

high (> 70 g/week; <5 standard drinks) OR 1.21 95% CI 0.82 to 1.80

First trimester

Low	OR 0.84 95% CI 0.62 to 1.13
moderate	OR 0.85 95% CI 0.55 to 1.29
high	OR 1.28 95% CI 0.69 to 2.38

Late pregnancy

Low	OR 0.87 95% CI 0.67 to 1.14
moderate	OR 1.05 95% CI 0.70 to 1.56
high	OR 1.27 95% CI 0.59 to 2.72

Birth defects classified (by health professionals) as alcohol related birth defects
Referent: abstinent

Before pregnancy

Low ((≤ 70 g/week)	OR 0.97 95% CI 0.44 to 2.17
moderate (≤ 70 g/week; binge)	OR 0.80 95% CI 0.34 to 1.85
high (> 70 g/week; binge)	OR 1.54 95% CI 0.63 to 3.75

First trimester

Low	OR 1.11 95% CI 0.52 to 35
moderate	OR na
high	**OR 4.57 95% 1.46 to 14.26**

Late pregnancy

Low	OR 1.25 95% CI 0.63 to 2.48
moderate	OR 2.28 95% CI 0.98 to 5.30
high	OR na

These results were adjusted for maternal age, marital status, parity, income, smoking during pregnancy and drug use during pregnancy.

Anencephaly (Grewal 2008)

In the Grewal 2008 case control study (116 cases), the OR of anencephaly for binge drinking (5+ drinks per occasion) was 0.5 95% CI 0.1 to 1.7, compared with a referent of zero consumption.

None of the measured variables met the criteria for confounding, so the unadjusted odds ratios as reported in the study have been presented here.

Anorectal atresia (Miller 2008)

In the Miller 2008 case control study (all cases: n = 464; isolated defect: n = 216), non-drinkers (referent) were compared with women who reported drinking alcohol in the month before pregnancy to the third month of pregnancy, specifically:

All cases of anorecta atresia			
Non-drinkers (referent)	OR 1.00		
Average ≤ 1.5 drinks/day	OR 0.9 95% CI 0.7 to 1.2		687 controls; 57 cases
Average > 1.5 drinks/day	OR 1.0 95% CI 0.8 to 1.2		1180 controls; 113 cases
Drank any alcohol	OR 0.9 95% CI 0.8 to 1.1		1861 controls; 167 cases
≥5 alcoholic drinks	OR 1.0 95% CI 0.7 to 1.4		420 controls; 40 cases
Isolated defect			
Non-drinkers (referent)	OR 1.00		
Average ≤ 1.5 drinks/day	OR 1.0 95% CI 0.7 to 1.5	6	87 controls; 29 cases

Average > 1.5 drinks/day	OR 1.2 9% CI 0.9 to 1.6	1180 controls; 60 cases
Drank any alcohol	OR 0.9 95% CI 0.7 to 1.2	1861 controls; 87 cases
≥5 alcoholic drinks	OR 0.9 95% CI 0.6 to 1.6	420 controls; 17 cases

None of the measured variables met the criteria for confounding, so the unadjusted odds ratios have been presented.

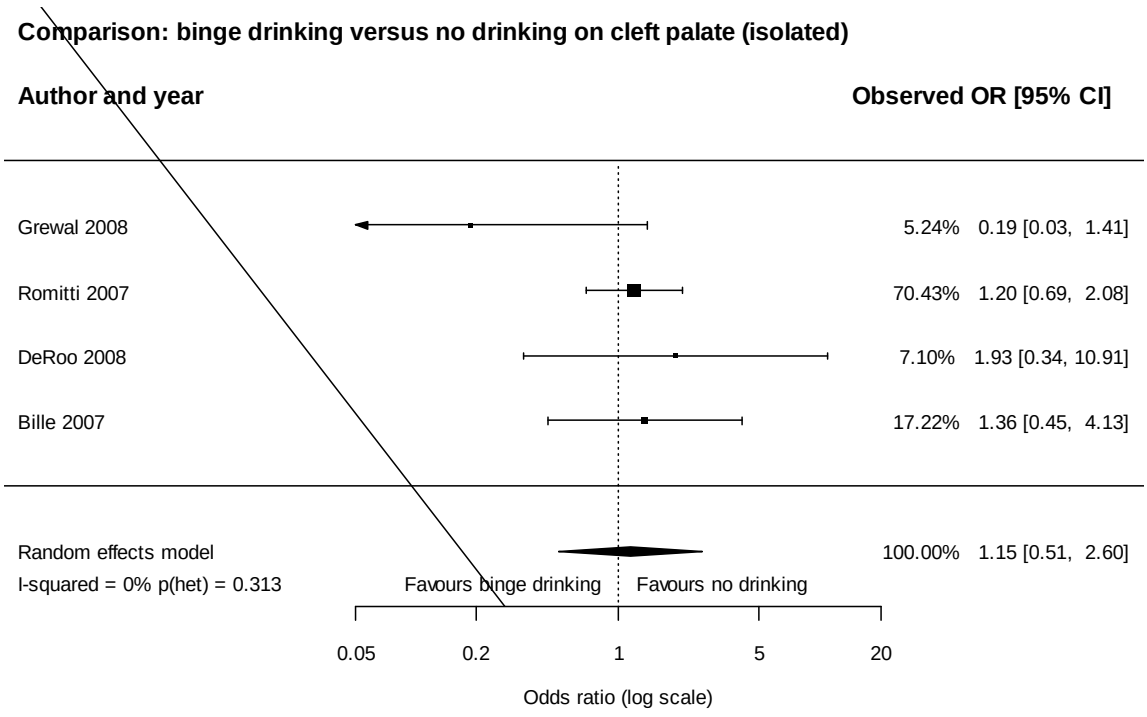
Bilateral renal agenesis or hypoplasia (Slickers 2008)

In the Slickers 2008 case-control study, compared with no alcohol (from one month prior to pregnancy to the third month of pregnancy), the OR for non-binge exposure (< 5 drinks per episode) and for binge exposure (≥5 drinks) was 1.35 95% CI 0.73 to 2.51 and for binge exposure, OR 1.94 95% CI 0.90 to 4.18.

These results were adjusted for prepregnancy BMI, periconceptual smoke exposure, study centre, maternal education, maternal ethnicity, maternal age, hypothyroidism, gestational diabetes, subfertility, pregnancy identification after 12 weeks, substance use and folate use.

Cleft (Bille 2007, De Roo 2008, Grewal 2008, Romitti 2007)

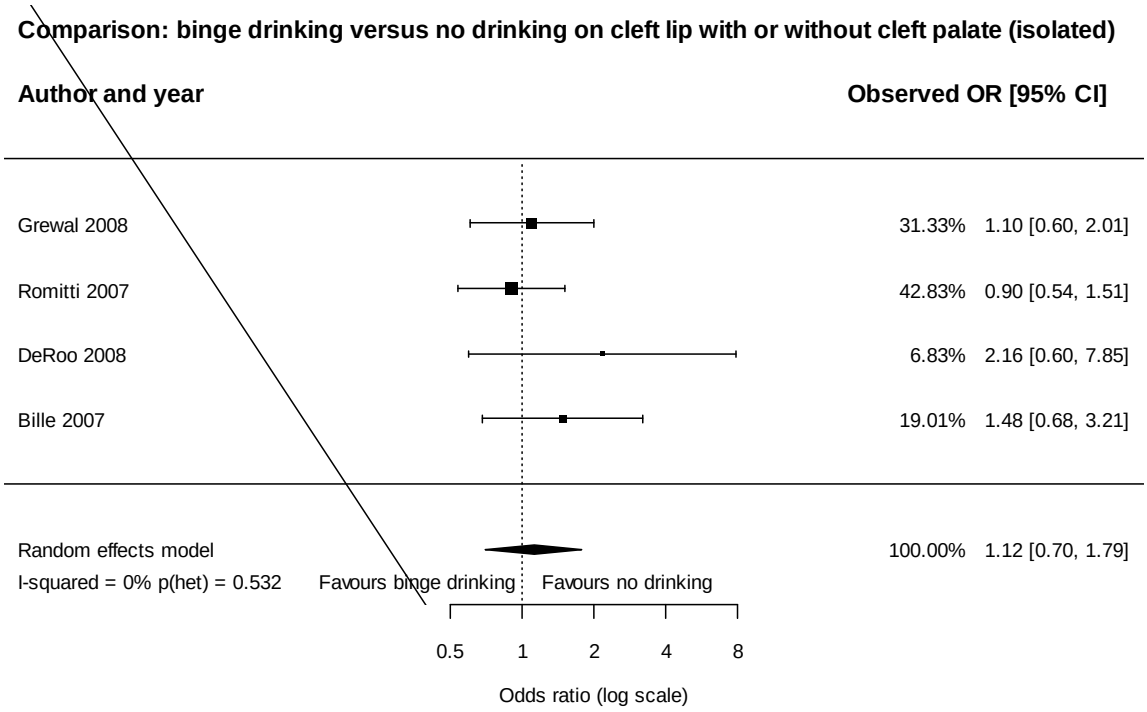
Meta-analysis:
For **isolated cleft palate**, results from four studies were able to be meta-analysed (Bille 2007; De Roo 2008; Grewal 2008 and Romitti 2007). The odds of isolated cleft palate was 15% higher for binge drinking versus no binge drinking (OR 1.15; 95% CI 0.51 to 2.60). There was no evidence of inconsistency in the odds ratios ($I^2 = 0\%$, p-value = 0.313).



Notes: DeRoo 2008: The DeRoo adjusted OR and variance included in the meta-analysis was calculated as the average of the OR and variance estimates from the comparisons 1) ≥ 5 drinks/1-2 sittings versus no drinking, and 2) ≥ 5 drinks/≥ 3 sittings (9 cases; 16 controls) versus no drinking (26 cases; 65 controls).

Bille 2007: The exposure for this study is ≥ 3 units per week. While the exposure measure differs to the other studies, this study has been included in this meta-analysis for two reasons. First, the 3 units could be consumed on one occasion, and second, regardless of this, this consumption per week would be considered heavy drinking.

For cleft lip with or without cleft palate, results from four studies were able to be meta-analysed (Bille 2007; De Roo 2008; Grewal 2008 and Romitti 2007). The odds of cleft lip with or without cleft palate was 12% higher for binge drinking versus no drinking (OR 1.12; 95%CI 0.70 to 1.79; p-value = 0.502;). There was no evidence of inconsistency in the odds ratios (I2 = 0%, p-value = 0.532).



Notes: The same notes apply as above, note that the outcome in Romitti 2007 is 'cleft lip and cleft palate'.

Single study results

In the DeRoo 2008 case control study, the linear trend (adjusted) over no drinking to ≥ 5 drinks/≥ 3 sittings had a p-value of 0.06 and 0.26 for cleft lip with/without cleft palate (n = 377) and cleft palate (n = 196) respectively. The results were adjusted for child's year of birth, mother's age, prenatal smoking, education, household income, and family history of clefts.

In the Romitti 2007 case control study, categories of alcohol consumption were compared with no drinking. The results for all cases of cleft lip/palate are:

1-4 drinks/month	OR 1.2 95% CI 0.9 to 1.5	726 controls; 347 cases
5-15 drinks/month	OR 1.0 95% CI 0.7 to 1.3	503 controls; 207 cases
16-30 drinks/month	OR 0.9 95% CI 0.6 to 1.3	221 controls; 81 cases

> 30 drinks/month	OR 1.0 95% CI 0.6 to 1.5	119 controls; 54 cases

These results were adjusted for family history, maternal ethnicity, smoking, centre, and duration of alcohol exposure.

Club foot (Werler 2014)

In the Werler 2014 case control study, associations between clubfoot and drinking any time in lunar months 2-4 were reported.

Referent: no alcohol consumption (554 cases)

≤ 3 drinks/day	OR 1.09 95% CI 0.77 to 1.54	56 cases
3+ drinks/day	OR 1.25 95% CI 0.80 to 1.95	36 cases

For women who quit during these months and for women who drank throughout the two months, the results were similar to the findings above.

Results were adjusted for cigarette smoke exposure, coffee drinking, study centre, child sex, maternal ethnicity, primiparity, obesity, fertility treatment, and lunar month 2-4 use of opioids, selective serotonin reuptake inhibitors, phenergan, ondansetron, pseudoephedrine, diphenhydramine, amoxicillin and salicylates.

Congenital diaphragmatic hernia (Caspers 2010)

In the Caspers 2010 case control study, associations between congenital diaphragmatic hernia and drinks per month, as well as binge drinking, were reported.

Referent: no alcohol consumption (325 cases)

1-15 drinks/month	OR 0.9 95% CI 0.7 to 1.1	131 cases
16-30 drinks/month	OR 1.1 95% CI 0.7 to 1.7	30 cases
> 30 drinks/month	OR 0.7 95% CI 0.4 to 1.4	10 cases

Referent: no alcohol consumption (325 cases)

drinking but no binge episode	OR 0.9 95% CI 0.6 to 1.3	134 cases
1 or more binge episode	OR 0.9 95% CI 0.7 to 1.1	37 cases

These results were adjusted for infant sex, gestational age, maternal age, ethnicity, periconceptional smoking, family history and study centre.

Congenital limb deficiencies (Caspers 2014)

In the Caspers 2014 case control study, associations between congenital limb deficiencies and drinks per month, as well as binge drinking, were reported.

Referent: no alcohol consumption (610 cases)

1-4 drinks/month	**OR 0.74 95% CI 0.60 to 0.92**	124 cases
5-15 drinks/month	OR 0.78 95% CI 0.61 to 1.00	90 cases
16-30 drinks/month	OR 0.76 95% CI 0.53 to 1.07	44 cases
30+ drinks/month	OR 0.70 95% CI 0.43 to 1.12	22 cases

Referent: no alcohol consumption (610 cases)

Drinking without bingeing	**OR 0.71 95% CI 0.58 to 0.85**	174 cases
Binge (≥ 4 drinks/occasion)	OR 0.84 95% CI 0.66 to 1.06	107 cases

These results were adjusted for infant sex, maternal pre-pregnancy BMI, maternal education; chorionic villis sampling, periconceptional vasoactive medication use, cigarette smoke exposure.

Craniosynostosis (Richardson 2011)

In Richardson 2011, associations between craniosynostosis and drinks per month, as well as binge drinking, were reported.

Drinks per month:

Referent: 0 drinks/month (500 cases; 63.1%)

1-4 drinks/month	OR 1.00 95% CI 0.82 to 1.22	148 cases; 18.8%
5-15 drinks/month	OR 0.89 95% CI 0.69 to 1.14	88 cases; 11.1%
16-30 drinks/month	OR 0.79 95% CI 0.56 to 1.14	38 cases; 5.2%
30+ drinks/month	OR 0.76 95% CI 0.46 to 1.25	18 cases; 3.0%

Binge drinking:

Referent: no drinking (500 cases; 63.1%)

Drinking, not binge	OR 0.89 95% CI 0.74 to 1.07	196 cases; 24.5%
Binge ≥ 4/occasion	OR 0.99 95% CI 0.78 to 1.25	97 cases; 12.3%

These results were adjusted for race, age and state of residence at time of infant's birth.

Craniofacial shape (Muggli 2017)

Craniofacial shape at the global level

Muggli 2017 compared several different patterns of alcohol exposure with controls of abstinent during pregnancy, using partial least squares regression analysis, using the R2 statistic. No significant association between alcohol exposure and craniofacial shape at the global level was shown, for any of the comparisons:

	R2	p value	N	
• Low (≤ 20 g AA/occasion and ≤ 70 g AA/week) in trimester 1, abstinent in trimester 2&3)	0.8	0.31	49	
• Moderate to high (≥ 21 g AA/occasion in trimester 1), abstinent in trimester 2&3	1.4	0.06	46	
• Binge (≥ 50 g AA per occasion) before pregnancy awareness, abstinent in trimester 2&3	0.5	0.72	38	
• Low in trimester 1, low to moderate (≤ 20 to 49 g AA/occasion) in trimester 2&3	0.8	0.41	29	
• Moderate to high in trimester 1, any level in trimester 2&3		0.6	0.37	84
• Binge before pregnancy awareness, low to moderate in trimester 2 and/or 3	0.4	0.70	70	

Each result was adjusted for maternal age, prepregnancy BMI, smoking during pregnancy, child's sex and birthweight.

Craniofacial shape regions

The authors reported "reginal mean differences in craniofacial shape of children exposed to any alcohol, regardless of whether PAE occurred in the first trimester only or throughout pregnancy" shown a Figure (1). The figure showed that "regions of difference were concentrated around the midface, nose, lips, and eyes. Directional visualisation showed that these differences correspond to a general recession around the midface and a superior

displacement of points of the nose, especially the tip of the nose, indicating a shortening of the nose and upturning of the nose tip" (Muggli 2017, pg. 773).

Cryptorchidism (Damgaard 2007)

Compared with consumption of '0 alcoholic drinks/week' throughout pregnancy (n=1719), the following associations were seen with cryptorchidism in infants at three months of age:

• ≥ 1 drink/week	OR 0.94 95% CI 0.58 to 1.51	n=579 cases
• ≥ 2 drinks/week	OR 1.28 95% CI 0.72 to 2.27	n=274
• ≥ 3 drinks/week	OR 1.21 95% CI 0.55 to 2.66	n=126
• ≥ 4 drinks/week	OR 1.77 95% CI 0.67 to 4.69	n=62
• ≥ 5 drinks/week	**OR 3.10 95% CI 1.05 to 4.69**	n=34
• ≥ 6 drinks/week	**OR 5.47 95% CI 1.59 to 18.88**	n=20
• ≥ 7 drinks/week	**OR 6.54 95% CI 1.56 to 27.43**	n=13
• ≥ 8 drinks/week	**OR 16.78 95% CI 3.48 to 81.02**	n=9
• ≥ 9 drinks/week	**OR 31.89 95% CI 3.96 to 256.93**	n=5

These results were adjusted for country, smoking, caffeine intake, maternal age, social class, parity, maturity, birthweight, and binge episodes and alcoholic drinks mutually. (Binge drinkers without a regular intake were included in the '0 alcoholic drinks/week' category although they were not total abstainers.)
Pattern: Compared with 'no binge episodes' throughout pregnancy (n=1708), the following associations were seen with cryptorchidism in infants at three months of age:

• Binge episodes	OR 1.18 95% CI 0.77 to 1.83	n=736

These results were adjusted for country, smoking, caffeine intake, maternal age, social class, parity, maturity, and birthweight.

Gastroschisis (Richardson 2011)

In the Richardson 2011 case-control study, associations between gastroschisis and drinks per month, as well as binge drinking, were reported.

Drinks per month:
Referent: 0 drinks/month (425 cases; 59.8%)

1-4 drinks/month	**OR 1.30 95% CI 1.02 to 1.64**	113 cases; 15.8%
5-15 drinks/month	**OR 1.51 95% CI 1.15 to 1.97**	91 cases; 12.8%
16-30 drinks/month	OR 1.12 95% CI 0.75 to 1.66	36 cases; 5.1%
30+ drinks/month	**OR 1.89 95% CI 1.29 to 2.75**	48 cases; 6.7%

Binge drinking:
Referent: no drinking (425 cases; 59.8%)

Drinking, not binge	**OR 1.27 95% CI 1.01 to 1.59**	134 cases; 18.9%
Binge ≥ 4/occasion	**OR 1.53 95% CI 1.21 to 1.92**	152 cases; 21.4%

These results were adjusted for race, age, state of residence at time of infant's birth, and periconceptional smoking.

Heart defects (Grewal 2008, Mateja 2012, Strandberg-Larsen 2011, Zhu 2015)

In the Grewal 2008 case control study (247 cases of conotruncal heart defects), the OR for binge drinking (5+ drinks per occasion), compared with '0' drinking days/week during the first

month of pregnancy, was 1.0 95% CI 0.5 to 2.0. (These are unadjusted results but study authors state that findings did not change in adjusted models.)

In the Mateja 2012 case control study, the OR for any binge drinking in the three months prior to pregnancy, compared with no binge drinking, was 1.71 95% CI 0.75 to 3.88, adjusted for smoking, maternal age, maternal race, maternal ethnicity, maternal marital status, insurance and stress. For binge drinking more than once in the same period, the OR was **2.99 95% CI 1.19 to 7.51**, (adjusted for the same factors as above).

In Strandberg-Larsen 2011 (cohort of 80,346), associations between several different alcohol exposure patterns and ventral septal defects (VSD) and isolated atrial septal defects (ASD) were assessed.

VSD: Drinks per week		
Referent: 0 drinks/week (98 cases)		
0.5 to 1.5 drinks/week	OR 1.22 95% CI 0.90 to 1.66	73 cases
2 drinks/week	OR 1.38 95% CI 0.83 to 2.28	18 cases
3+ drinks/week	OR 1.10 95% CI 0.54 to 2.23	9 cases
	p-value for trend: 0.29	
VSD: Number of binge episodes		
Referent: 0 (146 cases)		
1 binge episode	OR 0.86 95% CI 0.57 to 1.29	28 cases
2 binge episodes	OR 1.08 95% CI 0.61 to 1.91	13 cases
3+ binge episodes	OR 1.33 95% CI 0.72 to 2.46	11 cases
VSD: Binged at least once		
Referent: no binge		
Week 1-2	OR 1.13 95% CI 0.71 to 1.79	19 cases
Week 3-4	OR 1.02 95% CI 0.69 to 1.50	31 cases
Week 5-10	OR 0.98 95% CI 0.57 to 1.71	14 cases
ASD: Drinks per week		
Referent: 0 drinks/week (84 cases)		
0.5 to 1.5 drinks/week	OR 1.03 95% CI 0.73 to 1.47	51 cases
2 drinks/week	OR 0.45 95% CI 0.18 to 1.11	5 cases
3+ drinks/week	OR 0.66 95% CI 0.27 to 1.62	5 cases
	p-value for trend: 0.11	
ASD: Number of binge episodes		
Referent: 0 (113 cases)		
1 binge episode	OR 0.59 95% CI 0.34 to 1.02	15 cases
2 binge episodes	OR 0.94 95% CI 0.47 to 1.89	9 cases
3+ binge episodes	OR 1.15 95% CI 0.57 to 2.35	8 cases
ASD: Binged at least once		
Referent: no		
Week 1-2	OR 0.83 95% CI 0.44 to 1.56	10 cases
Week 3-4	OR 0.96 95% CI 0.59 to 1.56	20 cases
Week 5-10	OR 0.83 95% CI 0.42 to 1.65	9 cases

All results were adjusted for maternal age, parity, smoking, household occupational status and time to pregnancy.

Zhu 2015 did not find clear increased risks between measures of alcohol consumption and most of the many congenital heart effects examined.

Isolated simple conotruncal
Referent (no alcohol)

1-4 drinks/month	OR 1.1 95% CI 0.9 to 1.3
5-15 drinks/month	OR 1.1 95% CI 0.9 to 1.3
16-30 drinks/month	OR 1.0 95% CI 0.8 to 1.3
> 30 drinks/month	OR 0.9 95% CI 0.6 to 1.3

(Unadjusted because no covariate altered the OR by at least 10%)

Isolated simple septal
Referent (no alcohol)

1-4 drinks/month	OR 1.0 95% CI 0.8 to 1.1
5-15 drinks/month	**OR 0.7 95% CI 0.6 to 0.9**
16-30 drinks/month	**OR 0.7 95% CI 0.5 to 0.9**
> 30 drinks/month	OR 0.9 95% CI 0.7 to 1.2

(Adjusted for periconceptional active or passive smoking exposure)

Neural tube defects (Grewal 2008, Suarez 2008)

In the Grewal 2008 case control study, the odds of neural tube defects were 1.6 times higher (95% CI 0.9 to 2.6) and 2.1 times higher (95% CI 1.1 to 4.0) in women who consumed alcohol < once/week and more than once per week, respectively, compared with non-drinkers. (This is an unadjusted association, however, the authors' note that adjustment for covariates did not change the association such that the interpretation would differ for this outcome.)

In the Suarez 2008 case control study (175 cases), the OR for no alcohol use in the first trimester compared with ≥ 1 drink daily was 1.5 95% CI 0.4 to 6.1; and for no drinking compared with > 3 drinks on any occasion the OR was 1.7 95% CI 0.8 to 3.6. Both results were adjusted for maternal age, education, body mass index and folate intake.

Omphalocele (Richardson 2011)

In Richardson 2011, associations between omphalocele and drinks per month, as well as binge drinking, were reported.

Drinks per month:
Referent: 0 drinks/month (137 cases; 53.9%)

1-4 drinks/month	**OR 1.55 95% CI 1.12 to 2.14**
5-15 drinks/month	OR 1.39 95% CI 0.93 to 2.09
16-30 drinks/month	**OR 1.73 95% CI 1.05 to 2.87**
30+ drinks/month	OR 1.41 95% CI 0.70 to 2.82

Binge drinking:
Referent: no drinking (137 cases; 53.9%)

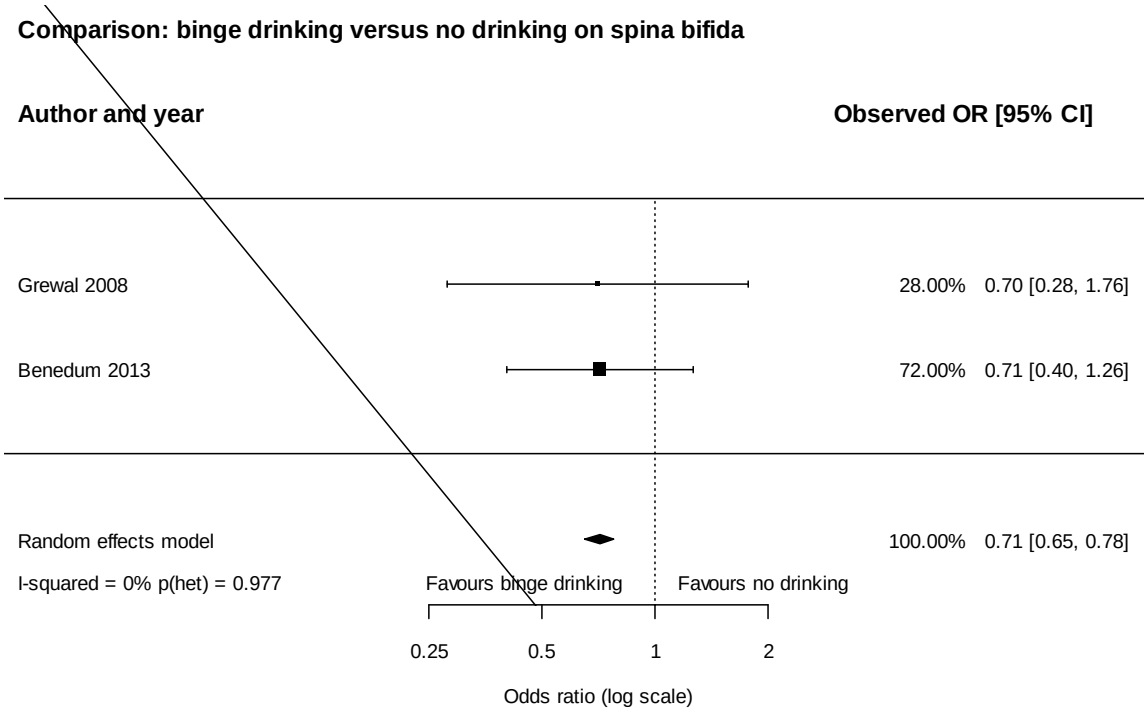
Drinking, not binge	**OR 1.43 95% CI 1.06 to 1.93**	74 cases; 29.1%
Binge ≥ 4/occasion	**OR 1.71 95% CI 1.19 to 2.45**	43 cases; 16.9%

These results were adjusted for race, age and state of residence at time of infant's birth.

Spina Bifida (Benedum 2013, Grewal 2008)

Meta-analysis:

For **spina bifida**, results from two studies were able to be meta-analysed (Benedum 2013; and Grewal 2008). The combined OR for binge drinking versus no binge drinking was **0.71 (95%CI 0.65 to 0.78)** p-value = 0.0134 (I^2 = 0%, p-value = 0.977).



Notes: Benedum 2013: The adjusted OR and variance included in the meta-analysis was calculated as the average of the OR and variance estimates from the comparisons 1) ≥ 3 drinks/ ≥ 3 days per week versus no drinking, 2) ≥ 3 drinks/2 days per week versus no drinking, and 3) ≥ 3 drinks/1 day per week versus no drinking.

Single study results

In the Benedum 2013 case control study (424 cases, 4886 controls) the associations with spina bifida and drinks per drinking day in the first month of pregnancy were:

Referent: < 1 drink/day		
1 drink/day	**OR 0.7 95% CI 0.5 to 0.9**	114 cases, 1174 controls
2 drinks/day	OR 0.8 95% CI 0.6 to 1.1	113 cases, 1493 controls
3 drinks/day	OR 0.7 95% CI 0.6 to 1.0	125 cases, 1201 controls

Results were adjusted for folic acid intake, study centre by year, and maternal education.

Strabismus (Torp-Pederson 2010)

In Torp-Pederson 2010, the following associations between 12 g units of alcohol consumption during pregnancy and strabismus were seen:

Referent: 0 units/week (587 cases)		
> 0-1	**OR 0.86 95% CI 0.76 to 0.98**	455 cases
> 1-3	**OR 0.77 95% CI 0.65 to 0.91**	208 cases
> 3-5	**OR 0.64 95% CI 0.43 to 0.95**	30 cases

> 5	OR 1.22 95% CI 0.73 to 2.04 p value < 0.004	16 cases

For any binge drinking, compared with no binge drinking, the OR for strabismus was 1.99 95% CI 0.87 to 1.12.

Both analyses were adjusted for year of birth, social class, maternal age, maternal smoking does and maternal tea and coffee consumption.

4.4.2 Systematic review on alcohol consumption while breastfeeding

Tay 2017

Tay and colleagues (2017) examined: 1) frequency of alcohol consumption while breastfeeding; 2) associations between alcohol consumption by breastfeeding mothers and a range of infant outcomes in a sample of mothers.

Note that this is a unique sample in that almost all the women who reported drinking while breastfeeding employed a strategy to minimise potential effects of their consumption on their breastfed infants. Most of the women who consumed alcohol during breastfeeding at 8 weeks and 12 months postpartum (83% and 88% respectively) said they delayed consumption until after breastfeeding.

Frequency of alcohol consumption while breastfeeding: results (Tay 2017)

Frequency of alcohol consumption by breastfeeding mothers was reported for the drinking categories: abstinent; low (≤ 14 standard drinks per week, and < 3 drinks per occasion); moderate (≤ 14 standard drinks per week, ≥ 3 to < 5 standard drinks per occasion); risky drinking (≤ 14 standard drinks per week, ≥ 5 standard drinks per occasion); and heavy (> 14 standard drinks per week). Most women were either low alcohol users or abstinent at 8 weeks postpartum (49.5% and 39.3% respectively), as well as at 12 months postpartum (42.4% and 30.4% respectively).

As summarised in Table 4, Tay 2017 reported measures of association for *any alcohol consumed (referent)* versus alcohol *abstinence while breastfeeding at eight weeks postpartum* for the two review domains reported, namely **sedation** and **cognitive impairment**. The sedation outcome measures were assessed at 8 weeks postpartum only, whereas the cognition outcomes were reported at 8 weeks and 12 months postpartum.

Associations for alcohol consumption while breastfeeding: results

Sedation outcomes (Tay 2017)

Milk feeds per day ≥7, at 8 weeks (162 participants)

**Any alcohol consumption while breastfeeding at 8 weeks postpartum (referent) versus abstinence:* OR 0.85 (95% CI 0.55 to 1.32) (adjusted for maternal education).

Sleep duration (hours per day), at 8 weeks

**Any alcohol consumption at 8 weeks postpartum (referent) versus a*bstinence: adjusted comparison p = 0.46 η = 0.00; mean (SD) abstainers 14.09 (3.27), alcohol consumers 14.33 (2.24)

Results were adjusted for maternal employment, maternal anxiety score at 8 weeks, household income, other children under mother's care, maternal education.

Sleep frequency (sleeps per day), at 8 weeks

**Any alcohol consumption at 8 weeks postpartum versus a*bstinence: adjusted comparison p = 0.54 η2 = 0.00; mean (SD) abstainers 6.46 (1.85), alcohol consumers 6.39 (1.61)

Results were adjusted for maternal employment, infant gestation at birth, maternal country of birth, maternal education.

Mothers' rating of infant feeding, at 8 weeks

**Any alcohol consumption at 8 weeks postpartum versus abstinence:* adjusted comparison: p = 0.08 2 η= 0.02; mean (SD) abstainers 6.46 (1.85), alcohol consumers 6.39 (1.61)

Results were adjusted for maternal depression score at 8 weeks, risky drinking during pregnancy, presence of breastfeeding difficulties at 8 weeks, and whether mother smoked during pregnancy.

Cognitive impairment outcomes (Tay 2017)

8-week ASQ – monitoring zone/below cut-off, communication (66 participants)

Any alcohol consumption at 8 weeks postpartum versus abstinence: OR 0.74 (95% CI 0.41 to 1.31) (adjusted for infant gestation at birth)

8-week ASQ – monitoring zone/below cut-off, gross motor (45 participants)

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 1.16 (95% CI 0.59 to 2.28) (adjusted for risky drinking during pregnancy)

8-week ASQ – monitoring zone/below cut-off, fine motor (65 participants)

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 1.09 (95% CI 0.63 to 1.88) (adjusted for other children under mother's care)

8-week ASQ – monitoring zone/below cut-off, problem solving (75 participants)

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 0.92 (95% CI 0.54 to 1.54) (unadjusted as no confounders found to be significant in exploratory analysis)

8-week ASQ – monitoring zone/below cut-off, personal-social interactions (46 participants)

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 1.32 (95% CI 0.69 to 2.55) (adjusted for maternal employment, infant gestation at birth, maternal age)

12-month ASQ – monitoring zone/below cut-off, communication (50 participants)

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 0.97 (95% CI 0.53 to 1.79 (unadjusted as no confounders were found to be significant in exploratory analysis)

12-month ASQ – monitoring zone/below cut-off, gross motor (98 participants)

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 0.87 (95% CI 0.53 to 1.42) (adjusted for maternal employment and infant birth weight).

12-month ASQ – monitoring zone/below cut-off, fine motor (58 participants)

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 1.24 (95% CI 0.67 to 2.27) (adjusted for other children under mothers' care, maternal health problems at 12 months, household income).

12-month ASQ – monitoring zone/below cut-off, problem solving (54 participants):

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 0.70 (95% CI 0.37 to 1.32), p = 0.27; 54 participants) (adjusted for household income).

12-month ASQ – monitoring zone/below cut-off, personal-social interactions (74 participants)

Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* **OR 2.43 (95% CI 1.43 to 4.13 (adjusted for infant gestation at birth, and child health problems at 12 months)

This significant positive association showed that infants of mothers who drank at 8 weeks postpartum while breastfeeding (most of whom employed a strategy to minimise the transfer of alcohol to their babies through breastfeeding, see above) had *more favourable* results for personal-social development at 12 months compared to those whose mothers abstained.

12-month ASQ – monitoring zone/below cut-off, social emotional (14 participants)

**Any alcohol consumption at 8 weeks postpartum (referent) versus abstinence:* OR 1.11 (95% CI 0.32 to 3.90) (adjusted for maternal country of birth, maternal education, maternal anxiety score at 8 weeks).

5. GRADE evidence quality assessment and evidence statements

Table 8 provides a GRADE evidence profile assessing certainty of evidence and summarising the findings for the outcomes included in meta-analysis for the review of evidence on alcohol consumption during pregnancy. Evidence statements for all the outcomes reported in this review are provided in Table 9

Table 8: Evidence profile for meta-analysed outcomes

Certainty assessment		Summary of findings		Certainty (GRADE level of confidence in result)
		No of participants (studies)	Summary of effect (based on single study)	
Binge drinking versus no drinking during early pregnancy				
Outcome domain: **birth defects** outcome measure: s**pina bifida** Studies (n=2): Benedum 2013 and Grewal 2008 Outcome importance: critical in decision making				
Case control studies	Risk of bias: serious (-2) [1] Inconsistency: not serious [2] Indirectness: no concern(s) Imprecision: not serious [3] Other considerations: none	6588 (n=2)	The association between binge drinking during early pregnancy and **spina bifida** is **uncertain** due to very low-quality evidence. Maternal binge drinking during early pregnancy lowered the odds of spina bifida by 29% compared to no drinking during early pregnancy: OR 0. 71 (95% CI: 065 to 0.78).	⊕◯◯◯ **VERY LOW** due to serious design limitations and imprecision CRITICAL outcome
Outcome domain: **birth defects** outcome measure: **cleft palate** Studies (n= 4): Billie 2007, De Roo 2008, Grewal 2008 and Romitti 2007 Outcome importance: critical in decision making				
Case control studies	Risk of bias (-2): serious [4] Inconsistency: not serious [5] Indirectness: no concern(s) Imprecision: serious (-2) [6] Other considerations: none	3733 (n=4)	The association between binge drinking during early pregnancy and **cleft palate** is **uncertain** due to very low-quality evidence. Maternal binge drinking during early pregnancy increased the odds of cleft palate by 15% compared to no drinking during early pregnancy: OR 1.15 (95% CI 0.51 to 2.60). However, the confidence interval includes the possibility of decreased odds (by 49%) or increased (by 160%).	⊕◯◯◯ **VERY LOW** due to serious design limitations and imprecision CRITICAL outcome
Outcome domain: **birth defects** outcome measures: **cleft lip** (with or without cleft palate) Studies (n = 4): Billie 2007, De Roo 2008, Grewal 2008 and Romitti 2007 Outcome importance: critical in decision making				
Case control studies	Risk of bias: serious (-2) [4] Inconsistency: not serious [5] Indirectness: no concern(s) Imprecision: serious) (-2) [6] Other considerations: none	3817 (n=4)	The association between binge drinking during early pregnancy and **cleft lip** (with or without cleft palate) is **uncertain** due to very low-quality evidence. Maternal binge drinking during early pregnancy increased the odds of cleft lip (with or without cleft palate) by 12% compared to no drinking during early pregnancy: OR 1.12 (95% CI 0.70 to 1.79). However, the confidence interval includes the possibility of decreased	⊕◯◯◯ **VERY LOW** due to serious design limitations and imprecision CRITICAL outcome

			odds (by 30%) or increased odds (by 79%).	

Reasons for downgrading

1. **ROB (-2)**: 2 case control studies at high risk of recall bias, one with potentially inappropriate control, usual concern about self-reported alcohol exposure data (possible under-reporting) and may be residual confounding;
2. **Inconsistency** (no downgrade): no heterogeneity, $I^2 = 0$
3. **Imprecision** (no downgrade): narrow confidence interval; only 2 studies, however not few participants
4. **ROB** (-2): 4 case control studies (1 nested) at high risk of recall bias, 2 with potential concern about inappropriate controls, 1 with some attrition. Additionally, potential under-reporting of alcohol exposure due to self-report and may be residual confounding
5. **Inconsistency** (no downgrade): no heterogeneity, $I^2 = 0$
6. **Imprecision** (-2): wide confidence interval crossing line of no effect signalling uncertainty about direction of association (appreciable harm or benefit)

Table 9: Evidence statements

BEHAVIOUR	
Total difficulties (SDQ)	There is **mixed evidence** of associations between alcohol consumption (in the first trimester or throughout pregnancy) and high behavioural difficulties scores in infants; 2 cohort studies, N=21,069 – with one study showing **no clear differences** and the other study showing **worse scores**.
Conduct (SDQ)	There is **no reliable evidence** of associations between alcohol consumption (in the first trimester or throughout pregnancy) and conduct problems and hyperactivity in infants; 2 cohort studies, N=21,069.
Hyperactivity (SDQ)	There is **mixed evidence** of associations between alcohol consumption (in the first trimester or throughout pregnancy) and hyperactivity in infants: 2 cohort studies, N=21,069 – with one study showing **no clear differences** and the other study showing **worse scores**.
Personal-social (GMDS)	The evidence shows a **limited association** between higher alcohol consumption (prior to pregnancy) and worse personal-social behaviour in infants, but **no reliable evidence** of an association between lower alcohol consumption (prior to pregnancy) and personal-social behaviour in infants; 1 nested case control study, N=121.
Difficult Temperament Scale of the Infant and Infant Toddler Symptom Checklist	The evidence shows **a limited association** between one or more binge episodes a week (in weeks 0-6 of pregnancy) and worse behavioural outcomes in infants (difficult temperament, sleeping problems and being demanding and/or irritable) but **no reliable evidence** of an association for these outcomes for binge drinking less than once a week in this period and these outcomes; 1 cohort study, N=1873.
ITSP and BITSEA	There is **no reliable evidence** of an association between alcohol consumption (throughout pregnancy) and ITSP or BITSEA scores in infants; 1 cohort study, N=948.
BIRTH DEFECTS	
Major congenital malformations	There is **no reliable evidence** of an association between alcohol consumption (in the first month of pregnancy) and major congenital malformations; 1 cohort study, N=190.
Suspected congenital malformations	There is **no reliable evidence** of an association between periconceptional alcohol consumption and suspected congenital malformations; 1 cohort study, N=61,241.

Any birth defects	There is **no reliable evidence** of an association between alcohol consumption prior to pregnancy, in the first trimester or in late pregnancy and any birth defect; 1 cohort study, N=4714.
Alcohol-related birth defects	There is **no reliable evidence** of an association between alcohol consumption prior to pregnancy, in the first trimester or in late pregnancy and alcohol-related birth defects, except for **a limited association** between high alcohol consumption in the first trimester and an increase in alcohol-related birth defects; 1 cohort study, N=4714.
Anencephaly	There is **no reliable evidence** of an association between alcohol consumption in the first month of pregnancy and anencephaly; 1 case-control study; N=116 cases; 507 controls.
Anorectal atresia	There is **no reliable evidence** of an association between alcohol consumption from the month prior, through to the third month of pregnancy, and anorectal atresia; I case-control study; N=464 cases for any defect; N=216 for isolated defect; N = 4940 controls
Bilateral renal agenesis or hypoplasia	There is **no reliable evidence** of an association between alcohol consumption from the month prior, through to the third month of pregnancy, and bilateral renal agenesis or hypoplasia; 1 case-control study, N=75 cases; 868 controls.
Cleft lip/cleft palate [meta-analysis]	There is **no reliable evidence** of an association between alcohol consumption spanning the month prior to pregnancy to the first trimester and cleft lip/cleft palate; meta-analysis of 4 case-control studies, N=3817 (*VERY LOW certainty evidence*).
Club foot	There is **no reliable evidence** of an association between alcohol consumption from the second to the fourth month of pregnancy and club foot; 1 case-control study, N=646 cases; 2037 controls.
Congenital diaphragmatic hernia	There is **no reliable evidence** of an association between alcohol consumption from the month prior, through to the third month of pregnancy, and congenital diaphragmatic hernia; 1 case-control study, N=503 cases, 6703 controls.
Congenital limb deficiencies	The evidence shows **a limited association** between low alcohol consumption (and drinking without bingeing) in the month prior to pregnancy, and a **decrease** in congenital limb deficiencies, compared with no alcohol consumption; 1 case-control study, N=906 cases; 8352 controls.
Craniosynostosis	There is **no reliable evidence** of an association between alcohol consumption from the month prior, through to the third month of pregnancy, and craniosyntosis; 1 nested case-control study, N=796 cases; 6622 controls.
Craniofacial shape	There is **no reliable evidence** of an overall association between alcohol consumption, in the first trimester or throughout pregnancy, and craniofacial shape; 1 cohort study, N=415 infants.
Cryptorchidism	The evidence shows **a limited association** between consumption of more than 5 alcoholic drinks a week and **increased rates** of cryptorchidism; 1 cohort study; N=4957
Gastroschisis	The evidence shows **a limited association** between alcohol consumption from the month prior, through to the third month of pregnancy, and **increased rates** of gastroschisis; 1 nested case-control study; 720 cases, 6622 controls.

Heart defects	There is **no reliable evidence** of an overall association between alcohol consumption • in the first month of pregnancy and conotruncal heart defects; 1 case control study; N=323 cases • in early pregnancy and septal defects; 1 cohort study; N=80,346 • in the three months prior to pregnancy and generally for congenital heart defects; 1 case control study; N=668 cases However • for more than one binge episode in the three months prior to pregnancy, there was **limited evidence of increased rates** of congenital heart effects; 1 case control study; N=668 cases • for 5 to 30 drinks a month, compared with no alcohol consumption, there was **limited evidence of lower rates** of congenital heart defects; 1 case control study; N=7076 cases.
Neural tube defects	There is **mixed evidence** of associations between alcohol consumption and neural tube defects: • for alcohol consumption in the first month of pregnancy, there was **limited evidence of increased rates of neural tube defects**; 1 case control study; N=337 cases • for alcohol consumption in the first trimester of pregnancy, control, there was **no reliable evidence** of an association with neural tube defects; 1 case control study; N=175 cases.
Omphalocele	There is evidence of a **limited association** between alcohol consumption one month prior to pregnancy and the first three months of pregnancy, and increased rates of omphalocele; 1 case control study; N=254 cases; 6622 controls.
Spina bifida [meta-analysis]	There is **no reliable evidence** of an association between alcohol consumption in the first month of pregnancy and **decreased rates of spina bifida;** meta-analysis of 2 case-control studies; N=6588 (*VERY LOW certainty evidence*).
Strabismus	There is evidence of a **limited association** between alcohol consumption throughout pregnancy and **decreased rates of strabismus**; 1 cohort study; N=98,482

6. Discussion

6.1 Summary of main findings

6.1.1 Systematic review of alcohol consumption during pregnancy

We were able to include five studies addressing alcohol exposure during pregnancy and behavioural outcomes (Alvik 2011, Davies 2017, Halliday 2017, Kelly 2009 and Sayal 2007); and 21 studies of birth defect outcomes (Benedum 2013, Bille 2007, Caspers 2010, Caspers 2014, Damgaard 2007, DeRoo 2008, Grewal 2008, Lundsberg 2015, Mateja 2012, Miller 2009, Muggli 2017, Mullally 2011, O'Leary 2011, Richardson 2011, Romitti 2007, Slickers 2008, Strandberg-Larsen 2011, Suarez 2008, Torp-Pedersen 2010, Werler 2015 and Zhu 2015).

Meta-analysis was only possible for two outcomes – cleft lip/cleft palate (from four case-control studies) and spina bifida (two case-control studies). The cleft lip/cleft palate meta-analysis did not show a difference between alcohol exposure, generally in the first trimester, and mostly binge drinking and outcomes (*very low certainty evidence*). When the two spina bifida studies were pooled, there was also no reliable evidence of an association between alcohol consumption and rates of spina bifida (*very low certainty evidence*).

For the rest of the birth defects studies, most birth defects were assessed by single studies only, except for two studies looking at neural tube defects and four studies looking at heart defects, none of which could be meta-analysed. In the five studies assessing behavioural outcomes, two studies looking at the same outcomes from the Strength and Difficulties Questionnaire could not be meta-analysed. The other three studies each assessed different behavioural outcomes.

These single study results generally found no reliable evidence of associations between alcohol exposure in pregnancy and birth defects, except for:

- increased rates of cryptorchidism, gastroschisis, neural tube defects, and omphalocele;
- and decreased rates of congenital limb deficiencies, spina bifida and strabismus.

No single study results for behavioural outcomes indicated associations between alcohol exposure and better outcomes. For two outcomes (total difficulties and conduct), one study showed no differences and one study showed worse scores. Another four outcomes (personal-social behaviour, difficult temperament, sleeping problems and infant being demanding/irritable), indicated worse results with higher, compared with lower, alcohol consumption.

Of the 26 included studies, 19 were judged to be at serious risk of bias and the remaining seven at moderate risk of bias. The main contributors to potential bias were measurement of exposures and outcomes; recall bias, residual confounding and losses to follow-up.

For two outcomes (cleft lip/palate and heart defects), studies at both moderate and serious risk of bias contributed data, with studies at moderate risk of bias showing similar findings to studies at high risk of bias.

6.1.2 Systematic review of alcohol consumption while breastfeeding

Only one study was identified for inclusion in the review of alcohol consumption while breastfeeding (Tay 2017). This study reported outcome measures for one comparison only: any alcohol consumption at 8 weeks postpartum, versus abstinence, for only two of the outcome domains included in this review: sedation in breastfed infants; and cognition/child development.

No difference between alcohol exposure was seen in the three sedation outcomes reported, including milk feeds per day ≥7, sleep duration of infants, and sleep frequency (all assessed at eight weeks). Of the eleven child development outcomes reported (all measured by the ASQ), the only significant association showed that infants of mothers who drank (at 8 weeks postpartum), had more favourable results for personal-social development at 12 months compared with those whose mothers abstained.

Most of the women included in this study reported drinking drank at low levels and employed strategies to minimise potential effects of their consumption on their breastfed infants.

The study included for the breastfeeding review was judged to be at serious risk of bias. Possible residual confounding, recall bias (mothers self-reported their prior alcohol consumption after the outcomes had occurred), and risk of bias in measurement of the outcomes (self-report by mothers) were identified as the main sources of potential bias.

6.2 Summary of how these review results compare with previous reviews

6.2.1 Systematic review of alcohol consumption during pregnancy

On systematic review (Mamluk 2017) has been published since the conduct of the NHMRC commissioned overview. The objective of this review, by Mamluk (2017) and colleagues was to conduct a comprehensive systematic review and meta-analysis of the literature to determine the effects of low-to-moderate levels of maternal alcohol consumption on pregnancy and longer-term offspring outcomes". The review reported on alcohol consumption of up to two UK units of alcohol up to twice a week (the equivalent of ~32g/week)… as this was the cut-off specified by the UK guidelines at the time of writing this review as being an implicitly 'safe' threshold… our original protocol included studies exploring the effects of alcohol consumption (the commonly used threshold for moderate consumption) versus abstinence…Here we focused specifically on low alcohol consumption , that is up to ~32g/week".

The Mamluk review identified and included two studies (three articles) (Kelly 2009; Sayal 2007; Sayal 2009) reporting associations for behavioural problems in children up to age 5, and three studies reporting associations for birth defects in children (up to age 5) (Bille 2007; Ernhart 1989; Lundsberg 2015). Four of the five studies included in the Mamluk review, published between 2007 and 2017, are included in this NHMRC commissioned review of associations between alcohol consumption during pregnancy and selected child outcomes. No meta-analyses were conducted by Mamluk and colleagues for the birth defect and behavioural problem outcomes, due to different outcome definitions and insufficient data (Mamluk 2017, pg. 6).

Considering findings of the review by Mamluk and colleagues, the little evidence presented by these reviewers showed: 1) mixed effects of low-level consumption on child behavioural problems; and 2) no effects of low-level alcohol consumption on birth defects (Mamluk 2017, pg. 6 main text and Table 2). (Section 5 of the technical report presents further details on the differences in scope, method and findings between this review of alcohol consumption and pregnancy, and the Mamluk 2017 review).

6.2.2 Systematic review of alcohol consumption while breastfeeding

A "companion article" to the systematic review conducted to inform the 2009 Alcohol Guidelines (Giglia & Binns (2006) was published in 2010 (Giglia 2010). Giglia states that the purpose of the companion publication was to provide a systematic review of the literature regarding breastfeeding and maternal alcohol consumption published since the first review (Giglia 2010, pg. 237). More specifically, the objective was to provide a critical review of literature from 2005 onwards on the effect of alcohol intake during lactation on the hormonal

control of lactogenesis; breastmilk alcohol concentration; the breastfeeding infant; and on the breastfeeding outcomes of the mother and infant dyad. Providing an update on policy guiding alcohol consumption during lactation and internationally was a secondary objective of this review update.

In the 2010 Giglia study, the databases PubMed, CINAHL, Proquest Health and Medical Complete, ScienceDirect, Medline and ISI Web of knowledge were searched for literature published 2005 to 2010 using the appropriately broad terms "breastfeeding", "breast feeding", "breast milk", breastmilk", "lactation", "alcohol" and "ethanol". The study inclusion criteria for the review were broader than those of this review commissioned by NHMRC to inform the 2018 updating of the *Alcohol Guidelines* and included the PECO and study design specified for this current NHMRC review of the evidence on alcohol consumption while breastfeeding.

No evidence on associations between alcohol consumption while breastfeeding and any one of the six outcomes domains included in this review was identified by the Giglia (2010) study.

6.3 Limitations

Two limitations of the pregnancy review are important to note:

1) It was not feasible to look at potential differences in effects of consumption of different types of alcohol (e.g. wine versus spirits) during pregnancy on birth defects. Literature reviewed during this review raised this question as important to address for some of the birth defect outcomes.

2) We limited our child age to five and younger, for both the birth defect and behavioural outcomes. However, the literature suggests that some behavioural problems may only become evident when the child is at school age (and later).

7. References

7.1. Included studies

7.1.1 Systematic review of alcohol consumption during pregnancy

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