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

Prepared by

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Declarations of interest

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

1. Review questions and eligibility criteria

1.1 Questions of systematic review on alcohol consumption during pregnancy

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 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.

1.2 Questions of systematic review on alcohol consumption while breastfeeding

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?

[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.

1.3 PECO table for systematic review on alcohol consumption during pregnancy

Population	Exposure	Comparator	Outcomes
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 analysis were reported separately for the age criteria specified for the 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).	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 methods used to measure alcohol exposure. We anticipated that these methods would vary across studies and may include retrospective survey involving recall of alcohol consumption over different periods. 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.	Comparator groups were those comprised of abstainers. Abstainers could be either never drinkers or not drinkers during pregnancy. Whilst the main (ideal) comparison for inclusion was abstainers, 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 have consumed a very little amount of alcohol. Therefore, we considered such studies, and the implications of including them in the interpretation of the evidence for the affected outcome domain, as per the GRADE approach.	1) Birth defects/congenital malformations: "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). Included malformations, deformations and chromosomal abnormalities domains in WHO (ICD-10) (WHO 2007). Excluded*:* inborn genetic diseases; newborn infant diseases; fetal diseases. 2) Behavioural problems: "Disturbances considered to be pathological based on age and state appropriateness" Included: attention deficit, conduct and disruptive behaviour disorders. Excluded: 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. We expected measures and diagnostic criteria would vary and were inclusive, accepting a range of measure types with evidence of validation (see Table 1 in main review report for examples of measures eligible for the two included outcomes domains).

1.4 PECO table for systematic review on alcohol consumption while breastfeeding

Population	Exposure	Comparator	Outcomes
Healthy breastfeeding women, or women with a medical or health condition, of any age were eligible. Age ranges for babies and children varied: For cognitive impairment, child neglect and failure to thrive • Babies who are being breastfed/were breastfed (up to 5 years of age) For SIDS/SUDI • Babies who were breastfed (up to 1 year of age) For sedation • Babies during or up to three hours after breastfeeding For maternal bonding • Babies who are being breastfed/were breastfed (up to 1 year of age) Studies conducted in all settings, and with wider inclusion criteria if reported separately for ages specified were eligible.	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 over a period of time Studies were eligible irrespective of methods used to measure alcohol exposure. We anticipated that these methods would vary across studies and may include retrospective survey involving recall of alcohol consumption over different periods. 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.	Comparator groups were abstainers. Abstainers could include never drinkers, or abstainers during pregnancy and breastfeeding or abstainers during breastfeeding only. Whilst the main (ideal) comparison in the reviews was abstainers 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 considered such studies, and the implications of including them in the interpretation of the evidence for the affected outcome domain, as per the GRADE approach.	1)Cognitive impairment: "Disturbances in mental processes related to learning, thinking, reasoning, and judgment" 2)Sudden infant death syndrome (SIDS): number of unexplained deaths of infants <1 year of age (confirmed after autopsy, thorough case investigation and clinical history review); sudden unexplained death of an infant (SUDI): number of infant deaths <1 year of age with confirmed cause (following autopsy, case investigation and review of history) possible trauma or suffocation 3)Sedation (in breastfed infants): 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 and/or sleeping. 4)Child neglect in babies and children: "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 or that places the child in jeopardy" 5)Maternal bonding: "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" 6)Failure to thrive in babies and children: "A condition of substandard growth or diminished capacity to maintain normal function" We expected measures would vary and were inclusive, accepting all measures with evidence of validation (see Table 1 in main review report for examples of eligible measures for the six outcomes domains).

1.5 Design features used to determine study design eligibility for these reviews

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 Collaboration 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. The design features we used to classify study design features and determine study design eligibility for the reviews were as follows:

Study design feature	Prospective cohort	Retrospective cohort	Nested case-control	Case-control
A comparison between two or more groups of participants with different levels or patterns of alcohol exposure (ideal one of which is no exposure, i.e. 'abstainers')	Yes	Yes	Yes	Yes
Participants were allocated to groups based on different levels or patterns of alcohol exposure	Yes	Yes	No (based on outcome)	No (based on outcome)
The following parts of the study were prospective:				
• identification of participants	Yes	No	Yes	No
• assessment of baseline and allocation to exposure group	Yes	No	Yes	No
• assessment of outcomes	Yes	Possibly	Yes	No
• generation of hypotheses	Yes	Yes	Yes	Possibly
Assessment of comparability of groups was based on:				
• potential confounders	Possibly	Possibly	Probably	Possibly
• outcome variables at baseline	Possibly	Possibly	No	No

2. Search and study selection

2.1 Search for review of alcohol consumption during pregnancy

We ran the Embase and MEDLINE searches (10 July 2018) across both databases (5458) and deduplicated within Ovid (1400 dups; 4058 unique). We removed additional duplicates when importing to EndNote (38 dups; 4020 unique). We ran PsycINFO search (868) on the same date, however, removed all duplicates on import to EndNote (546 dups; 322 unique).

Total to screen = 4342, of which 1095 were Conference Abstracts.

Changes from protocol:

MEDLINE Embase and PsycINFO

- #14 add 'periconception'

- #20 replace AND with adjacency within 10 words (adj10)

- #20 added newborn$

- #24 remove the MeSH terms (exp Surveys/ and Questionnaires/) or Cross-Sectional Studies/ [MEDLINE only]

- limited to English language

2.1.1 MEDLINE and Embase search terms

Search conducted on 10 July 2018

Embase Classic+Embase 1947 to 2018 July 06
Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid MEDLINE and Versions 1946 to July 05, 2018

Embase, Ovid MEDLINE(R)			
#	**Search Statement**	**Results**	**Annotation**
1	exp Alcohol drinking/	109251	
2	exp Alcohol-Related Disorders/	232516	
3	exp Alcoholic Beverages/	46844	
4	Ethanol/	315413	
5	Temperance/	8509	
6	Alcohol abstinence/	6465	
7	(alcohol$ or drinking).ti.	343215	
8	((alcohol or alcoholic) adj3 (drink$ or exposure or consumption or consume$ or consuming or low or light or moderate$ or abstin$ or abstain$ or pattern$ or behavio?r$)).tw.	159157	

9	(drink$ adj3 (low or light or moderate$ or abstin$ or abstain$ or pattern$ or behavio?r$)).tw.	31576	
10	or/1-9	766227	
11	Pregnant Women/	64289	
12	exp Pregnancy/	1581318	
13	exp Pregnancy Complications/	528136	
14	(prepregnan$ or pre-pregnan$ or periconception or conception or preconception or pregnan$ or prenatal$ or pre-natal$ f?etus or f?etal or in utero).tw.	1592483	
15	exp Maternal Behavior/	24093	
16	Maternal Exposure/	8885	
17	Fetal Alcohol Spectrum Disorders/	7906	
18	Prenatal Exposure Delayed Effects/	46795	
19	(FASD or "f?etal alcohol spectrum disorder$" or "f?etal alcohol exposure" or "f?etal alcohol syndrome" or "prenatal alcohol exposure" or "prenatal exposure to alcohol" or "alcohol exposed" or "alcohol related birth defects" or "alcohol related neurodevelopment disorder$" or "f?etal effects" or "alcoholic embryopathy").tw.	13508	
20	((defect$ or abnormalit$ or cognit$ or impair$ or conduct or neglect or behavio?r$ or bonding or "attention deficit" or ADHD) adj10 (f?etal or f?etus$ or birth or newborn$ or baby or babies or infant$ or child$)).tw.	385406	
21	or/11-20	2613424	
22	exp Cohort Studies/	2139523	
23	exp Case-Control Studies/	1069826	
24	Risk Factors/	1267667	
25	((cohort$ or "follow up" or observational or longitudinal$ or prospectiv$ or retrospectiv$) adj3 (study or studies or analys$)).tw.	2226369	
26	((case$ adj3 control$) or (negative$ adj3 control)).tw.	393055	
27	or/22-26	4913442	
28	10 and 21 and 27	8428	
29	Animals/ not Humans/	5790558	
30	28 not 29	8374	
31	limit 30 to yr="2007 -Current"	4921	
32	exp drinking behavior/	115480	
33	exp alcoholism/	197096	
34	exp alcoholic beverage/	46844	

35	alcohol/	254724	
36	alcohol abstinence/	6465	
37	(alcohol$ or drinking).ti.	343215	
38	((alcohol or alcoholic) adj3 (drink$ or exposure or consumption or consume$ or consuming or low or light or moderate$ or abstin$ or abstain$ or pattern$ or behavio?r$)).tw.	159157	
39	(drink$ adj3 (low or light or moderate$ or abstin$ or abstain$ or pattern$ or behavio?r$)).tw.	31576	
40	or/32-39	722181	
41	pregnant woman/	76302	
42	exp pregnancy/	1581318	
43	(prepregnan$ or pre-pregnan$ or periconception or conception or preconception or pregnan$ or prenatal$ or pre-natal$ f?etus or f?etal or in utero).tw.	1592483	
44	maternal behavior/	23287	
45	maternal exposure/	8885	
46	Fetal Alcohol Spectrum Disorders/	7906	
47	prenatal exposure/	47701	
48	(FASD or "f?etal alcohol spectrum disorder$" or "f?etal alcohol exposure" or "f?etal alcohol syndrome" or "prenatal alcohol exposure" or "prenatal exposure to alcohol" or "alcohol exposed" or "alcohol related birth defects" or "alcohol related neurodevelopment disorder$" or "f?etal effects" or "alcoholic embryopathy").tw.	13508	
49	((defect$ or abnormalit$ or cognit$ or impair$ or conduct or neglect or behavio?r$ or bonding or "attention deficit" or ADHD) adj10 (f?etal or f?etus$ or birth or newborn$ or baby or babies or infant$ or child$)).tw.	385406	
50	or/41-49	2576230	
51	exp cohort analysis/	2139523	
52	exp case control study/	1069826	
53	exp risk factor/	1611494	
54	exp longitudinal study/	231655	
55	((cohort$ or "follow up" or observational or longitudinal$ or prospectiv$ or retrospectiv$) adj3 (study or studies or analys$)).tw.	2226369	
56	((case$ adj3 control$) or (negative$ adj3 control)).tw.	393055	
57	or/51-56	5202245	
58	40 and 50 and 57	9142	

59	exp animal/ not human/	9693256	
60	58 not 59	8997	
61	limit 60 to yr="2007 -Current"	5638	
62	limit 61 to english language	5458	
63	remove duplicates from 62	4058	

Execute Searches in Ovid

2.1.2 PsycINFO search terms

Search conducted 10 July 2018

PsycINFO <1806 to July Week 1 2018>			
#	**Search Statement**	**Results**	**Annotation**
1	exp alcoholism/	29506	
2	exp alcohol drinking patterns/	63417	
3	exp drinking behavior/	68914	
4	exp binge drinking/	2112	
5	exp alcohol abuse/	46198	
6	exp alcoholic beverages/	2662	
7	exp alcohols/	17309	
8	(alcohol$ or drinking).ti.	64765	
9	((alcohol or alcoholic) adj3 (drink$ or exposure or consumption or consume$ or consuming or low or light or moderate$ or abstin$ or abstain$ or pattern$ or behavio?r$)).tw.	36884	
10	(drink$ adj3 (low or light or moderate$ or abstin$ or abstain$ or pattern$ or behavio?r$)).tw.	12638	
11	or/1-10	99073	
12	exp pregnancy/	23128	
13	exp prenatal care/	1895	
14	(prepregnan$ or pre-pregnan$ or periconception or conception or preconception or pregnan$ or prenatal$ or pre-natal$ f?etus or f?etal or in utero).tw.	80358	
15	fetal alcohol syndrome/	1653	
16	(FASD or "f?etal alcohol spectrum disorder$" or "f?etal alcohol exposure" or "f?etal alcohol syndrome" or "prenatal alcohol exposure" or "prenatal exposure to alcohol" or "alcohol exposed" or "alcohol related birth defects" or "alcohol related neurodevelopment disorder$" or "f?etal effects" or "alcoholic embryopathy").tw.	2831	

17	((defect$ or abnormalit$ or cognit$ or impair$ or conduct or neglect or behavio?r$ or bonding or "attention deficit" or ADHD) adj10 (f?etal or f?etus$ or newborn$ or birth or baby or babies or infant$ or child$)).tw.	168161	
18	or/12-17	241460	
19	exp risk factors/	71066	
20	exp longitudinal studies/	15946	
21	exp followup studies/	12363	
22	((cohort$ or "follow up" or observational or longitudinal$ or prospectiv$ or retrospectiv$) and (study or studies or analys$)).tw.	264775	
23	((case$ adj3 control$) or (negative$ adj3 control)).tw.	16251	
24	or/19-23	340793	
25	11 and 18 and 24	1370	
26	limit 25 to yr="2007 -Current"	911	
27	limit 26 to english language	868	

Execute Searches in Ovid

2.2 Search terms for review of alcohol consumption while breastfeeding

2.2.1 MEDLINE search terms

The three databases searched for potentially relevant studies on associations between alcohol while breastfeeding and the selected outcomes in breastfed infants and children (up to age 5) were searched on 23 May 2018. The search terms used are provided below.

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to May 16, 2018>			
#	**Search Statement**	**Results**	**Annotation**
1	exp Alcohol drinking/	62921	
2	exp Alcohol-Related Disorders/	107417	
3	exp Alcoholic Beverages/	17963	
4	(alcohol$ or drinking or wine).tw.	371871	
5	or/1-4	410778	
6	exp Breast Feeding/	34428	
7	Milk, Human/	17737	
8	exp Lactation/	38166	
9	(breastfe?d* or breast-fe?d* or lactat* or breast-milk).tw.	180988	

10	or/6-9	206989	
11	5 and 10	4108	
12	Animals/ not Humans/	4430502	
13	11 not 12	2450	
14	limit 13 to yr="2007 -Current"	1190	

Execute Searches in Ovid

2.2.2 Embase search terms

Embase Classic+Embase <1947 to 2018 May 22>			
#	Search Statement	Results	Annotation
1	exp drinking behavior/	45927	
2	exp alcoholism/	124151	
3	exp alcoholic beverage/	28585	
4	(alcohol$ or drinking or wine).tw.	523009	
5	or/1-4	562804	
6	exp breast feeding/	47500	
7	lactation/	50115	
8	breast milk/	26715	
9	(breastfe?d* or breast-fe?d* or lactat* or breast-milk).tw.	228065	
10	or/6-9	261210	
11	5 and 10	5662	
12	exp animal/ not human/	5196836	
13	11 not 12	3559	
14	limit 13 to yr="2007 -Current"	2112	

Execute Searches in Ovid

2.2.3 PsycINFO search terms

PsycINFO <1806 to May Week 2 2018>			
#	Search Statement	Results	Annotation
1	exp alcoholism/	29390	
2	exp alcohol drinking patterns/	63059	
3	exp drinking behavior/	68542	
4	exp binge drinking/	2081	

5	exp alcohol abuse/	45952	
6	exp alcoholic beverages/	2648	
7	(alcohol$ or drinking or wine).tw.	134210	
8	or/1-7	137588	
9	breast feeding/	3281	
10	lactation/	1422	
11	(breastfe?d* or breast-fe?d* or lactat* or breast-milk).tw.	10616	
12	or/9-11	10919	
13	8 and 12	427	
14	limit 13 to yr="2007 -Current"	212	

Execute Searches in Ovid

For the breastfeeding review, we also searched PubMed weekly via auto alert results (26 May to 1 September 2018), using the search terms:
(((alcohol drinking[MH] OR alcohol-related disorders[MH] OR alcoholic beverages[MH] OR alcohol[TIAB] OR alcoholic[TIAB] OR drinking[TIAB] OR wine[TIAB]) AND (breast feeding[MH] OR lactation[MH] OR milk, human[MH] OR breastfeed*[TIAB] OR breastfed[TIAB] OR breast-feed*[TIAB] OR breast-fed[TIAB] OR lactat*[TIAB] OR breast-milk[TIAB])) NOT (animals[MH] NOT humans[MH]))

2.3 Records excluded during full text review with reasons: pregnancy review

Reference for this source [from endnote]	Reason for exclusion
1. Anonymous (2013). "Papers Presented at the Annual Meeting of the Blair Bell Research Society 2012." BJOG: An International Journal of Obstetrics and Gynaecology Conference: Annual Meeting of the Blair Bell Research Society 2012. London United Kingdom. Conference Publication: (var.pagings). 2120 (2019) (no pagination).	Design – Abstracts (no data)
2. Bakker, R., et al. (2010). "Associations of light and moderate maternal alcohol consumption with fetal growth characteristics in different periods of pregnancy: the Generation R Study." International Journal of Epidemiology 39(3): 777-789.	Exclude as review outcomes not reported
3. Boyles, A. L., et al. (2011). "Maternal alcohol consumption, alcohol metabolism genes, and the risk of oral clefts: A population-based case-control study in Norway, 1996-2001."	Duplicate that was not identified as duplicate citation by Endnote (different dates).

Reference for this source [from endnote]	Reason for exclusion
Obstetrical and Gynecological Survey 66(2): 85-87.	
4. Ceccanti, M., et al. (2007). "Clinical delineation of fetal alcohol spectrum disorders (FASD) in Italian children: Comparison and contrast with other racial/ethnic groups and implications for diagnosis and prevention." Neuroscience and Biobehavioral Reviews 31(2): 270-277.	Alcohol exposure not quantifiable
5. Chen, J.-H. (2013). "Early childhood health and inequalities in children's academic and behavioural outcomes." Dissertation Abstracts International Section A: Humanities and Social Sciences 73(7-A(E).	Alcohol consumption not quantifiable
6. Chen, J. H. (2012). "Maternal alcohol use during pregnancy, birth weight and early behavioural outcomes." Alcohol & Alcoholism 47(6): 649-656.Cheng, D. T., et al. (2017). "Functional MRI of Human Eyeblink Classical Conditioning in Children with Fetal Alcohol Spectrum Disorders." Cerebral Cortex 27(7): 3752-3767.	Alcohol consumption not quantifiable
7. Cheng, D. T., et al. (2017). "Functional MRI of Human Eyeblink Classical Conditioning in Children with Fetal Alcohol Spectrum Disorders." Cerebral Cortex 27(7): 3752-3767.	Population: outcomes reported for children at age 10 and eyeblink not a birth defect outcome.
8. Cheng, D. T., et al. (2018). ""Functional MRI of human eyeblink classical conditioning in children with fetal alcohol spectrum disorders": Erratum." Cerebral Cortex 28(2): 688.	No relevant study outcome reported.
9. Chiodo, L. M., et al. (2009). "A metric of maternal prenatal risk drinking predicts neurobehavioral outcomes in preschool children." Alcoholism: Clinical & Experimental Research 33(4): 634-644.	Population - outcomes reported for children age 4 and 5 (no separate reporting for age 4)
10. Conradt, E., et al. (2013). "Prenatal substance exposure: neurobiologic organization at 1 month." Journal of Pediatrics 163(4): 989-994.e981.	Alcohol exposure - study assessed alcohol and other exposures, including cocaine, does not report results for alcohol exposure separately
11. Davies, L., et al. (2011). "Developmental delay of infants and young children with and without fetal alcohol spectrum disorder in the Northern Cape Province,	Exposure - No results reported on alcohol consumption levels or patterns for the review outcome (behaviour problems)

Reference for this source [from endnote]	Reason for exclusion
South Africa." African Journal of Psychiatry 14(4): 298-305.	
12. De Marco, P., et al. (2011). "Maternal periconceptional factors affect the risk of spina bifida-affected pregnancies: an Italian case-control study." Childs Nervous System 27(7): 1073-1081.	Exposure - Alcohol consumption exposure not quantifiable
13. D'Onofrio, B. M., et al. (2007). "Causal inferences regarding prenatal alcohol exposure and childhood externalizing problems." Archives of General Psychiatry 64(11): 1296-1304.	Population - Children age 4 to 11 years were assessed for behaviour problems (child behaviour checklist) and results for 4-year-old children not reported separately
14. Eiden, R. D., et al. (2011). "Child behavior problems among cocaine-exposed toddlers: indirect and interactive effects." Development & Psychopathology 23(2): 539-550.	Outcomes - Cannot identify data linking quantity of alcohol consumed (dose per occasion or average level) to relevant review outcome (behaviour)
15. Eilertsen, E. M., et al. (2017). "Maternal alcohol use during pregnancy and offspring attention-deficit hyperactivity disorder (ADHD): a prospective sibling control study." International Journal of Epidemiology 46(5): 1633-1640.	Population - Children assessed at age 5, and review inclusion criteria specify that only children younger than 5 to be included
16. Elliott, E. J., et al. (2008). "Fetal alcohol syndrome: a prospective national surveillance study." Archives of Disease in Childhood 93(9): 732-737.	Population - children not age 0-5 and ineligible design (clearly not cohort or case control study)
17. Feldman, H. S., et al. (2011). "Patterns of prenatal alcohol exposure and associated non-characteristic minor structural malformations: a prospective study." American Journal of Medical Genetics. Part A 155A(12): 2949-2955.	Secondary report of the Sawada study (reported in the dissertation, 2011), which was excluded for no low-level alcohol exposure comparator
18. Feldman, H. S., et al. (2012). "Prenatal alcohol exposure patterns and alcohol-related birth defects and growth deficiencies: a prospective study." Alcoholism: Clinical & Experimental Research 36(4): 670-676.	Secondary report of the Sawada study (reported in the dissertation, 2011) (excluded for no low-level alcohol exposure comparator)
19. Fitzpatrick, J. P., et al. (2012). "The Lililwan Project: study protocol for a population-based active case ascertainment study of the prevalence of fetal alcohol spectrum disorders (FASD) in remote Australian Aboriginal communities." BMJ Open 2(3).	Protocol for a study on FASD prevalence (Australian, in Fitzroy Valley)
20. Flanigan, E. Y., et al. (2008). "Eye malformations in children with heavy alcohol exposure in utero." Journal of Pediatrics 153(3): 391-395.	Population - Children age 4 to 9 years were assessed for eye malformations associated with heavy alcohol exposure and no alcohol exposure,

Reference for this source [from endnote]	Reason for exclusion
	and no results were reported separately for children up to age 5
21. Fuglestad, A. J., et al. (2015). "Executive functioning deficits in preschool children with Fetal Alcohol Spectrum Disorders." Child Neuropsychology 21(6): 716-731.	Population and outcomes - This study included children who were mean age 4.1, but some were 5 years (age 3 to 5 included), also measured executive functioning, not behavioural problems, in children with FASD, and alcohol exposure not quantifiable
22. Hao, Y., et al. (2015). "Association of Parental Environmental Exposures and Supplementation Intake with Risk of Nonsyndromic Orofacial Clefts: A Case-Control Study in Heilongjiang Province, China." Nutrients 7(9): 7172-7184.	Excluded as alcohol consumption reported is not quantifiable
23. Jensen, M. S., et al. (2007). "Prenatal alcohol exposure and cryptorchidism." Acta Paediatrica 96(11): 1681-1685.	Exposure - No low level or zero alcohol consumption during pregnancy comparator.
24. Kendler, K. S., et al. (2013). "Dimensions of parental alcohol use/problems and offspring temperament, externalizing behaviors, and alcohol use/problems." Alcoholism: Clinical & Experimental Research 37(12): 2118-2127.	Exposure – Alcohol consumption not quantifiable
25. Kesmodel, U. S., et al. (2012). "The effect of different alcohol drinking patterns in early to mid-pregnancy on the child's intelligence, attention, and executive function." BJOG: An International Journal of Obstetrics & Gynaecology 119(10): 1180-1190.	Population - outcomes measured at child age 5
26. Kesmodel, U. S., et al. (2012). "The effect of alcohol binge drinking in early pregnancy on general intelligence in children.[Erratum appears in BJOG. 2012 Dec;119(13):1683]." BJOG: An International Journal of Obstetrics & Gynaecology 119(10): 1222-1231.	Population - outcomes measured at child age 5
27. Knudsen, A. K., et al. (2014). "Maternal pre-pregnancy risk drinking and toddler behavior problems: the Norwegian Mother and Child Cohort Study." European Child & Adolescent Psychiatry 23(10): 901-911.	Alcohol exposure - no low-level alcohol comparator

Reference for this source [from endnote]	Reason for exclusion
28. Kuciene, R. and V. Dulskiene (2009). "Maternal socioeconomic and lifestyle factors during pregnancy and the risk of congenital heart defects." Medicina (Kaunas, Lithuania) 45(11): 904-909.	Alcohol exposure - Alcohol consumption during pregnancy not quantifiable, qualitative descriptors of alcohol use only (none, several times a week, several times a month, no data)
29. Kuehn, D., et al. (2012). "A prospective cohort study of the prevalence of growth, facial, and central nervous system abnormalities in children with heavy prenatal alcohol exposure." Alcoholism: Clinical & Experimental Research 36(10): 1811-1819.	Population - outcomes only reported across 3-8 years.
30. Kummet, C. M., et al. (2016). "Passive Smoke Exposure as a Risk Factor for Oral Clefts-A Large International Population-Based Study." American Journal of Epidemiology 183(9): 834-841.	Design - this citation is a study report for a meta-analysis. Needs to be checked to ensure that the studies it analysed have been considered in this review for inclusion.
31. LaGasse, L. L., et al. (2012). "Prenatal methamphetamine exposure and childhood behavior problems at 3 and 5 years of age." Pediatrics 129(4): 681-688.	Exposure - multiple exposures; no separate outcome data reported for alcohol exposure
32. Leite, I. C. and S. Koifman (2009). "Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil." Pesquisa Odontologica Brasileira = Brazilian Oral Research 23(1): 31-37.	Exposure_ alcohol consumption pattern exposure not presented in a way that allows quantification of amount, and one average level is reported, but without any comparator level
33. Lemola, S., et al. (2009). "Infant irritability: The impact of fetal alcohol exposure, maternal depressive symptoms, and low emotional support from the husband." Infant Mental Health Journal 30(1): 57-81.	Design_not a case control or cohort study, see design inclusion criteria in protocol, this study did not compare two different groups of participants but same participants over time
34. Liu, X., et al. (2018). "Does maternal environmental tobacco smoke interact with social-demographics and environmental factors on congenital heart defects?" Environmental Pollution 234: 214-222.	Exclude_alcohol consumption levels during pregnancy not quantifiable (only yes or no consumption prior to and during pregnancy)
35. Lowe, J., et al. (2017). "The effect of prenatal substance use and maternal contingent responsiveness on infant affect." Early Human Development 115(pp 51-59).	Exposure – outcomes not reported separately for different exposure levels or patterns.

Reference for this source [from endnote]	Reason for exclusion
36. Luquetti, D. V., et al. (2013). "Risk factors and demographics for microtia in South America: a case-control analysis." Birth Defects Research 97(11): 736-743.	Exposure (alcohol) _ not quantifiable (binge drinking without definition of number of drinks/units of alcohol per binge occasion)
37. May, P. A., et al. (2016). "Maternal nutritional status as a contributing factor for the risk of fetal alcohol spectrum disorders." Reproductive Toxicology 59: 101-108.	Exposure - no results reported (summary data or comparisons) for different patterns or levels of alcohol consumption during pregnancy (any period).
38. McAteer, J. P., et al. (2014). "Maternal medical and behavioral risk factors for congenital diaphragmatic hernia." Journal of Pediatric Surgery 49(1): 34-38; discussion 38.	Exposure - alcohol consumption during pregnancy not quantifiable (no, any or unknown)
39. Medwick, H. and A. E. Chudley (2018). "A global research collaboration on fetal alcohol spectrum disorder." Biochemistry and Cell Biology 96(2).	Design - Editorial, excluded based on no data to extract
40. Mongraw-Chaffin, M. L., et al. (2008). "Maternal smoking, alcohol consumption, and caffeine consumption during pregnancy in relation to a son's risk of persistent cryptorchidism: a prospective study in the Child Health and Development Studies cohort, 1959-1967." American Journal of Epidemiology 167(3): 257-261.	Exposure - This study did not report a no or very low-level alcohol consumption comparator for the included review outcome and has no data for inclusion in pattern analysis
41. Morales-Munoz, I., et al. (2018). "The effects of maternal risk factors during pregnancy on the onset of sleep difficulties in infants at 3 months old." Journal of Sleep Research.	Alcohol consumption exposure not quantifiable and no low or no level comparator group
42. Murphy, D. J., et al. (2014). "A prospective cohort study of alcohol exposure in early and late pregnancy within an urban population in Ireland." International Journal of Environmental Research & Public Health [Electronic Resource] 11(2): 2049-2063.	Outcomes – no data reported
43. Murray, J., et al. (2016). "Moderate alcohol drinking in pregnancy increases risk for children's persistent conduct problems: causal effects in a Mendelian randomisation study." Journal of Child Psychology & Psychiatry & Allied Disciplines 57(5): 575-584.	Population - assessed behavioural outcomes in children from 4 years through to adolescence and does not report the outcomes of children at age 4 separately

Reference for this source [from endnote]	Reason for exclusion
44. Myers, B., et al. (2018). "Effect of Hazardous Alcohol Use During Pregnancy on Growth Outcomes at Birth: Findings from a South African Cohort Study." Alcoholism: Clinical & Experimental Research 42(2): 369-377.	Outcomes - study assessed infant growth and other birth outcomes and did not include the two outcomes of this review.
45. Nash, K., et al. (2011). "A differential approach for examining the behavioural phenotype of fetal alcohol spectrum disorders." Journal of Population Therapeutics & Clinical Pharmacology 18(3): e440-453.	Population – children aged 6 to 18 years old when outcomes assessed
46. Nayak, R., et al. (2012). "Fetal alcohol spectrum disorders--a case-control study from India." Journal of Tropical Pediatrics 58(1): 19-24.	Exposure - exposed to alcohol during pregnancy, and not exposed only.
47. Nothling, J., et al. (2013). "Maternal post-traumatic stress disorder, depression and alcohol dependence and child behaviour outcomes in mother-child dyads infected with HIV: a longitudinal study." BMJ Open 3(12): e003638.	Outcomes - This study assessed effects of postnatal depression and alcohol consumption, among other postpartum risk factors on behaviour in young children.
48. Oberlander, T. F., et al. (2010). "Prenatal alcohol exposure alters biobehavioral reactivity to pain in newborns." Alcoholism: Clinical & Experimental Research 34(4): 681-692	Alcohol exposure not well defined ("heavily" exposed compared to abstainers/light), Analyses not adjusted for our prespecified factors (although Table 1 indicates no clear differences for most maternal and infant characteristics), raw data not reported (for Facial Action Pain Responses and NBAS)
49. O'Leary, C., et al. (2013). "Intellectual disability: population-based estimates of the proportion attributable to maternal alcohol use disorder during pregnancy." Developmental Medicine & Child Neurology 55(3): 271-277.	Outcomes - This study assessed intellectual disability in children exposed to alcohol prenatally, and whilst the abstract suggests that congenital anomalies may have been reported, intellectual disability was the only outcome reported
50. O'Leary, C., et al. (2009). "Prenatal alcohol exposure and language delay in 2-year-old children: the importance of dose and timing on risk." Pediatrics 123(2): 547-554.	This is a report of an included study, that reports an outcome not included in this review (language delay) in children at age 2.
51. O'Leary, C. M., et al. (2010). "A new method of prenatal alcohol classification accounting for dose, pattern and timing of exposure: improving our ability to examine fetal effects from low to moderate alcohol." Journal of Epidemiology & Community Health 64(11): 956-962.	Outcomes _ Behavioural problems assessed in children at age 2, 5 and 8 (repeat measures), and no separate reporting for children at 2 (younger than 5 years)

Reference for this source [from endnote]	Reason for exclusion
52. O'Leary, C. M., et al. (2013). "Exploring the potential to use data linkage for investigating the relationship between birth defects and prenatal alcohol exposure." Birth Defects Research 97(7): 497-504.	Alcohol exposure - not quantifiable categories of alcohol exposure (qualitative descriptors)
53. O'Leary, C. M., et al. (2010). "Evidence of a complex association between dose, pattern and timing of prenatal alcohol exposure and child behaviour problems." Addiction 105(1): 74-86.	Population - adjusted analyses only reported by 2, 5 and 8 years combined (Tables 5 and 6) (raw data reported for 2 years, but not adjusted (Table 4)).
54. Omo-Aghoja, V. W., et al. (2010). "Antenatal determinants of oro-facial clefts in Southern Nigeria." African Health Sciences 10(1): 31-39.	Exposure - cleft palate association with pre-natal and other drug exposures and qualitative alcohol exposure descriptor only (i.e. alcohol exposure level and/or pattern not quantifiable)
55. Ortega-Garcia, J. A., et al. (2012). "Head circumference at birth and exposure to tobacco, alcohol and illegal drugs during early pregnancy." Childs Nervous System 28(3): 433-439.	Outcomes - head circumference of infants at birth (not a birth defect but growth outcome (examined in overview)
56. Palmer, S. R., et al. (2013). "The role of maternal stress in early pregnancy in the aetiology of gastroschisis: an incident case control study." PLoS ONE [Electronic Resource] 8(11): e80103.	Exposure - study assessed association between various risk factors for gastroschisis, including two patterns of alcohol consumption, however does not include a low level (no consumption or low consumption) comparator
57. Paranaiba, L. M., et al. (2010). "Cleft lip and palate: series of unusual clinical cases." Revista Brasileira de Otorrinolaringologia 76(5): 649-653.	Exposure - study reported birth defects associated with alcohol and other prenatal exposures, and did not report alcohol in a way that allows quantification of the prenatal alcohol exposure
58. Pfinder, M., et al. (2012). "Explanation of social inequalities in hyperactivity/inattention in children with prenatal alcohol exposure." Klinische Padiatrie 224(5): 303-308.	Design (language)
59. Prakalapakorn, S. G., et al. (1500). "Assessment of risk factors for infantile cataracts using a case-control study: National birth defects prevention study, 2000-2004." Ophthalmology 117(8): 1500-1505.	Exposure - alcohol exposure not quantifiable
60. Reynolds, J. N., et al. (2015). "Proceedings of the 2014 Annual Meeting of the Fetal Alcohol Spectrum Disorders Study Group." Alcohol 49(5): 453-460.	Design (no data) _ This citation reports the proceedings of a conference about effects of prenatal alcohol exposure. Useful for background, and checking for potential study inclusions, but no data reported

Reference for this source [from endnote]	Reason for exclusion
61. Robinson, M., et al. (2010). "Low-moderate prenatal alcohol exposure and risk to child behavioural development: a prospective cohort study." BJOG: An International Journal of Obstetrics & Gynaecology 117(9): 1139-1150.	Population: Table 5 and 6 adjusted, but only report years 2-14 overall. Table 3 not adjusted for confounders. Table 4 gives frequency data for confounders but cannot use (have not specified in the protocol that we would recalculate)
62. Ruchkin, V., et al. (2008). "Developmental pathway modeling in considering behavior problems in young Russian children." Child Psychiatry and Human Development 39(1): 49-66.	Exposure _ Data not reported in a 'raw' form that enables inclusion in our specified comparisons
63. Sawada, G. H. (2011). "Prenatal alcohol exposure pattern and timing and minor structural malformations and growth deficiencies." Dissertation Abstracts International: Section B: The Sciences and Engineering 72(5-B).	Alcohol exposure - no low-level comparator
64. Schuetze, P., et al. (2014). "Empathic responsivity at 3 years of age in a sample of cocaine-exposed children." Neurotoxicology & Teratology 42: 1-8.	Exposure _ This study focused on assessing prenatal exposure and behaviour of very young infants. Whilst alcohol consumption (drinks per week) is reported for the cocaine and non-cocaine exposed infant's data on alcohol consumption is not presented for the behavioural outcomes.
65. Sen, B. and S. Swaminathan (2007). "Maternal prenatal substance use and behavior problems among children in the U.S." Journal of Mental Health Policy and Economics 10(4): 189-206.	Population _ This study assessed behavioural outcomes in children in children age 4 and older and did not report separately for children age 4
66. Silva, H., et al. (2018). "Risk factors and comorbidities in Brazilian patients with orofacial clefts." Pesquisa Odontologica Brasileira = Brazilian Oral Research 32: e24.	Population _ This case control study assessed association between cleft palate and various risk factors, including prenatal alcohol exposure. It is excluded as the participants were age 1 to 21 years and the alcohol consumption levels and patterns are not quantifiable (yes / no only)
67. Singer, L. T., et al. (2012). "Neurobehavioral outcomes of infants exposed to MDMA (Ecstasy) and other recreational drugs during pregnancy." Neurotoxicology and Teratology 34(3): 303-310.	Exposure _ unable to quantify exposure.
68. Skare, O., et al. (2012). "Application of a novel hybrid study design to explore gene-environment interactions in orofacial clefts." Annals of Human Genetics 76(3): 221-236.	Exposure _ This study focused on pathways through which a range of risk factors, including prenatal alcohol exposure and genetic factors affect risk of orofacial clefts. Whilst average number of drinks per setting was collected, results for different levels of alcohol consumption and the birth defect are not reported in the paper. Do we contact authors? Probably not for these guidelines?

Reference for this source [from endnote]	Reason for exclusion
69. Slickers, J. E., et al. (2008). "Maternal body mass index and lifestyle exposures and the risk of bilateral renal agenesis or hypoplasia: the National Birth Defects Prevention Study." American Journal of Epidemiology 168(11): 1259-1267.	Duplicate
70. Souza, L. T., et al. (2012). "TGFA/Taq I polymorphism and environmental factors in non-syndromic oral clefts in Southern Brazil." Pesquisa Odontologica Brasileira = Brazilian Oral Research 26(5): 431-435.	Exclude as case control study examining oral cleft risk factors, including alcohol consumption during pregnancy without quantifiable reporting of alcohol exposure.
71. Spiegler, J., et al. (2013). "Influence of smoking and alcohol during pregnancy on outcome of VLBW infants." Zeitschrift fur Geburtshilfe und Neonatologie 217(6): 215-219.	Design (language)
72. Stephen, J. M., et al. (2018). "Hypersynchrony in MEG spectral amplitude in prospectively-identified 6-month-old infants prenatally exposed to alcohol." NeuroImage Clinical 17: 826-834.	Outcomes _ surrogate
73. Strandberg-Larsen, K., et al. (2009). "Alcohol binge drinking during pregnancy and cryptorchidism." Human Reproduction 24(12): 3211-3219.	Population _ reported for children age 3-9 and no separate reports for children age 3 and 4.
74. Streissguth, A. (2007). "Offspring effects of prenatal alcohol exposure from birth to 25 years: The Seattle prospective longitudinal study." Journal of Clinical Psychology in Medical Settings 14(2): 81-101.	Design - This is a report of a longitudinal study that will have provided useful data for inclusion the review. This report should be excluded based on type of report - descriptive report of study - however it should be checked to identify potentially missed citations.
75. Sundelin-Wahlsten, V., et al. (2017). "Higher alcohol consumption in early pregnancy or low-to-moderate drinking during pregnancy may affect children's behaviour and development at one year and six months." Acta Paediatrica 106(3): 446-453.	Exposure _ Alcohol consumption not quantifiable.
76. Taye, M., et al. (2018). "Factors associated with congenital anomalies in Addis Ababa and the Amhara Region, Ethiopia: a case-control study." BMC Pediatrics 18(1): 142.	Exposure _ Alcohol consumption levels and patterns not quantifiable, qualitative descriptor only (daily, occasionally, and 1-3 times a week)
77. Thern, E., et al. (2018). "The effect of increased alcohol availability on alcohol-related health problems up to the age of 42 among children exposed in utero: a natural experiment." Alcohol & Alcoholism 53(1): 104-111.	Exposure _ Not quantifiable (This study examined the effects of a policy change relating to access to alcohol (natural experiment) on health outcomes of children who were in utero at the time of the change. The alcohol consumption patterns and level of women in the exposed group are not

Reference for this source [from endnote]	Reason for exclusion
	quantifiable, the outcome is a composite health outcome of children who were born to exposed mothers, and the health outcome is not for children younger than 5)
78. Troese, M., et al. (2008). "Sleep fragmentation and evidence for sleep debt in alcohol-exposed infants." Early Human Development 84(9): 577-585.	Alcohol exposure not quantifiable
79. Underbjerg, M., et al. (2012). "The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on selective and sustained attention in 5-year-old children [Erratum appears in BJOG. 2012 Dec;119(13):1683]." BJOG: An International Journal of Obstetrics & Gynaecology 119(10): 1211-1221.	Population _ Study measured effects of low to moderate alcohol consumption and binge drinking in early pregnancy on child behaviour at age 5
80. van Beynum, I. M., et al. (2010). "Protective effect of periconceptional folic acid supplements on the risk of congenital heart defects: a registry-based case-control study in the northern Netherlands." European Heart Journal 31(4): 464-471.	Exposure _ alcohol consumption not quantifiable, qualitative descriptors only
81. Vereczkey, A., et al. (2012). "Ventricular septal defects in function of maternal sociodemographic aspects." Central European Journal of Medicine 7(4): 511-522.	Exposure _ no quantifiable alcohol consumption data
82. Williams Brown, C., et al. (2010). "Maternal alcohol consumption during pregnancy and infant social, mental, and motor development." Journal of Early Intervention 32(2): 110-126.	Exposure (and outcomes) _ Numbers of individuals per group are not specified in tables 3 and 4 and cannot quantify alcohol consumption (only frequency reported). NOTE: does report 4+ drinks a week – could use a binge category but the two behavioural outcomes are reported only as adjusted mean differences and p-value categories (and no n's)
83. Wong-Gibbons, D. L., et al. (2008). "Maternal periconceptional exposure to cigarette smoking and alcohol and esophageal atresia +/- tracheo-esophageal fistula." Birth Defects Research 82(11): 776-784.	Exposure _ No low-level comparator.
84. Wozniak, J. R., et al. (2018). "Proceedings of the 2017 annual meeting of the Fetal Alcohol Spectrum Disorders study group." Alcohol 69(pp 7-14).	Design conference abstract (no data)
85. Yang, W., et al. (2012). "The Effects of Periconceptional Risk Factor Exposure and Micronutrient Supplementation on Birth Defects in Shaanxi Province in	Exposure _ No quantification of alcohol consumption levels or patterns (qualitative descriptor)

Reference for this source [from endnote]	Reason for exclusion
Western China." PLoS ONE [Electronic Resource] 7(12).	
86. Zaheri, F., et al. (2017). "Risk factors associated with neural tube defects in infants referred to western Iranian obstetrical centers; 2013-2014." Electronic Physician [Electronic Resource] 9(6): 4636-4642.	Exposure _ No quantification of alcohol consumption levels or patterns (qualitative descriptor)
87. Zuccolo, L., et al. (2016). "Pre-conception and prenatal alcohol exposure from mothers and fathers drinking and head circumference: results from the Norwegian Mother-Child Study (MoBa)." Scientific Reports 7: 39535.	Outcomes – growth (not a birth defect or behavioural problem)

2.4 Records excluded during full text review with reasons: breastfeeding review

Reference for this source [from endnote]	Reason for exclusion
1. Bonfig, J. (2014). "[Inquiry]." Nachgefragt. 33(6): 229-230.	Design_Abstract (no data)
2. Carpenter, R., et al. (2013). "Bed sharing when parents do not smoke: is there a risk of SIDS? An individual level analysis of five major case-control studies." BMJ open 3(5).	Exposure _ not alcohol consumption while breastfeedinge, examines association between maternal alcohol consumption and review outcome (SIDS/SUDI)
3. Chien, Y.-C., et al. (2009). "Maternal lactation characteristics after consumption of an alcoholic soup during the postpartum 'doing-the-month' ritual." Public health nutrition 12(3): 382-388.	Not population of interest (for outcomes)- no infants included in the study, only breastfeeding women

Reference for this source [from endnote]	Reason for exclusion
4. Christensen, L. H., et al. (2013). "Prenatal smoking exposure and children's motor development: A follow-up study." European Journal of Epidemiology 28(1 SUPPL. 1): S190-S191.	Not population - pregnant women, not breastfeeding women (i.e. in uterine exposure, not exposure while breastfeeding)
5. Connelly, R. and L. Platt (2014). "Cohort profile: UK Millennium Cohort Study (MCS)." International journal of epidemiology 43(6): 1719-1725.	Not population of interest - pregnant women, not breastfeeding women included
6. De Kroon, M. L. A., et al. (2011). "The Terneuzen Birth Cohort. Longer exclusive breastfeeding duration is associated with leaner body mass and a healthier diet in young adulthood." BMC pediatrics 11: 33.	Not alcohol exposure (while breastfeeding) - study examined association between exclusive breastfeeding and outcomes of children age 18 (BMI and diet), not association between alcohol exposure when breastfeeding and outcomes of very young children
7. Giglia, R. C., et al. (2008). "The effect of alcohol intake on breastfeeding duration in Australian women." Acta paediatrica (Oslo, Norway: 1992) 97(5): 624-629.	Outcomes - study assesses association between alcohol consumption while breastfeeding and breastfeeding initiation and duration, and does not assess any of this review's outcomes
8. Giglia R, Symons M, and Shaw T. (2018). "The provision of alcohol and breastfeeding information by maternal health practitioners in the Australian setting". Aust N Z J Obstet Gynaecol 2018; 1-7.	Exposure - study examines implementation of the 2009 Alcohol Guideline (4B) relating to risk of consuming alcohol while breastfeeding, in a selected sample of General Practitioner practices, it does not examine levels and/or patterns of alcohol consumption in breastfeeding women and their effects on child health outcomes
9. Halliday, J., et al. (2017). "The relationship between common patterns of prenatal alcohol exposure and neurodevelopment in two-year old children." Journal of paediatrics and child health 53(Supplement 2): 70-71.	Population - alcohol consumption in pregnant women, not while breastfeeding
10. Hallit, S., et al. (2017). "Association between Caregiver Exposure to Toxics during Pregnancy and Childhood-onset Asthma: A Case-control Study." Iranian journal of allergy, asthma, and immunology 16(6): 488-500.	Outcomes - reports effects of alcohol consumption (and other toxins) during breastfeeding on respiratory disease (childhood-onset Asthma)

Reference for this source [from endnote]	Reason for exclusion
11. Ko, J. Y., et al. (2018). "Marijuana use during and after pregnancy and association of prenatal use on birth outcomes: A population-based study." Drug and alcohol dependence 187: 72-78.	Exposure - study assessed association between marijuana use during pregnancy and breastfeeding period on child
12. Magnus, M. C., et al. (2014). "Prospective study of maternal alcohol intake during pregnancy or lactation and risk of childhood asthma: the Norwegian Mother and Child Cohort Study." Alcoholism, clinical and experimental research 38(4): 1002-1011.	Outcome - study assessed effects of alcohol consumption during pregnancy and lactation on childhood asthma and other respiratory diseases and did not report any of the outcomes included in this review
13. May, P. A., et al. (2014). "Breastfeeding while consuming alcohol: Prevalence and effects on fetal alcohol spectrum disorders and child outcomes in communities of South Africa." Alcoholism: Clinical and Experimental Research 38(SUPPL. 1): 252A.	Design _abstract and same study as reported by exclude May 2016 (below).
14. May, P. A., et al. (2016). "Breastfeeding and maternal alcohol use: Prevalence and effects on child outcomes and fetal alcohol spectrum disorders." Reproductive toxicology (Elmsford, N.Y.) 63: 13-21.	Population - children age 6-7, also alcohol consumption reported as yes/no (though data on consumption levels collected), do we contact authors?
15. Mennella, J. A. and M. Y. Pepino (2008). "Biphasic effects of moderate drinking on prolactin during lactation." Alcoholism, clinical and experimental research 32(11): 1899-1908.	Outcome - Study examines the effects of alcohol consumption on lactation parameters and did not include assessment of any of the outcomes included in this review
16. Mennella, J. A. and M. Y. Pepino (2010). "Breast pumping and lactational state exert differential effects on ethanol pharmacokinetics." Alcohol (Fayetteville, N.Y.) 44(2): 141-148.	Outcome - Study examines the effects of breast pumping on ethanol pharmacokinetics and does not report on any of the included child outcomes
17. Mennella, J. A. and M. Y. Pepino (2010). "Breastfeeding and prolactin levels in lactating women with a family history of	Outcome - Study examines effects of alcoholic consumption in lactating women with and without a family history of alcoholism on lactation performance (including magnitude, rapidity and duration of the

Reference for this source [from endnote]	Reason for exclusion
alcoholism." Pediatrics 125(5): e1162-1170.	prolactin response to breast stimulation and milk volume), when women used a beast pump. None of the outcomes included in this review were included.
18. Mennella, J. A., et al. (2007). "Breastfeeding and smoking: Short-term effects on infant feeding and sleep." Pediatrics 120(3): 497-502.	Exposure - Study examines smoking while breastfeeding and infant outcomes (sleep patterns)
19. Mgongo, M., et al. (2013). "Prevalence and predictors of exclusive breastfeeding among women in Kilimanjaro region, Northern Tanzania: a population based cross-sectional study." International breastfeeding journal 8(1): 12.	Exposure - Alcohol consumption not quantifiable, also study examines breastfeeding at 6 months, and not any one or more of the review outcomes
20. Muhajarine, N., et al. (2012). "Understanding the impact of the Canada Prenatal Nutrition Program: a quantitative evaluation." Canadian journal of public health = Revue canadienne de sante publique 103(7 Suppl 1): eS26-31.	Exposure - Study examined the effects of a prenatal nutrition program, which included the goal of reducing consumption of alcohol while pregnant, it did not also examine effects of alcohol while breastfeeding
21. Pepino, M. Y. and J. A. Mennella (2008). "Effects of breast pumping on the pharmacokinetics and pharmacodynamics of ethanol during lactation." Clinical pharmacology and therapeutics 84(6): 710-714.	Outcome - Study examines effects of alcohol consumption when breastfeeding on lactation-related changes in ethanol pharmacokinetics/pharmacodynamics, and how these effects of pumping change when ethanol is consumed after a meal compared with before. None of the review outcomes were assessed in the study.
22. Pepino, M. Y., et al. (2007). "Lactational state modifies alcohol pharmacokinetics in women." Alcohol Clin Exp Res 2007(31): 909-918.	Outcome - study examined effects of alcohol consumption on alcohol pharmacokinetics in breastfeeding women, and did not include assessment of any outcomes included in this review
23. Peyre, H., et al. (2014). "Predicting changes in language skills between 2 and 3 years in the EDEN mother-child cohort." PeerJ 2: e335.	Exposure (and population) - Study assessed effects of alcohol consumption while pregnant on relevant review outcome (cognition in children age 0-2)
24. Pirila, S., et al. (2014). "Breast-fed infants and their later cardiovascular health: a prospective study from birth to	Exposure (and population and outcome) - Study assessed factors for cardiovascular risk including breastfeeding, consumption of alcohol during breastfeeding not

Reference for this source [from endnote]	Reason for exclusion
age 32 years." The British journal of nutrition 111(6): 1069-1076.	examined, and outcome reported not one of review outcomes
25. Richiardi, L., et al. (2018). "[Communicating data of the Italian NINFEA birth cohort]." Comunicare i dati della coorte italiana di nuovi nati NINFEA. 42(2): 121-126.	Design _ not study data and language (written in Italian)
26. Rossouw, M. E., et al. (2016). "Feeding practices and nutritional status of HIV-exposed and HIV-unexposed infants in the Western Cape." Southern African journal of HIV medicine 17(1): 398.	Exposure - study examined HIV-exposure (versus HIV unexposed) in infancy and feeding practices and nutritional status of infants, while percentage of mothers of the two groups who drank alcohol is reported, alcohol consumption as an exposure while breastfeeding (compared to not consuming alcohol while breastfeeding, or various levels/patterns) is not considered.

3. Modified RTI tool used to assess included study ROB

Risk of bias assessment: Study ID					
Domain	**Assessment**				**Explanation**
Were valid and reliable measures, implemented consistently across all study participants used to assess confounding?	☒ yes, valid and reliable measures used	☐ no, valid and reliable measure not used	☐ cannot determine or measurement approach not reported		
Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores)	☐ yes, or study accounts for imbalance through a post hoc approach such as multivariate analysis	☐ no or cannot determine			
Were important confounding variables (age, smoking, drugs, socio-economic status, co-morbidities) not taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	☐ yes, not accounted for or identified	☐ partially, some variables taken into account or adjustment achieved to some extent	☐ no, taken into account	☐ cannot determine	
If you have serious concerns based on responses to the above questions (e.g. no adjustment for any confounders), stop assessment					
Do the inclusion/exclusion criteria vary across the comparison groups of the study?	☐ yes, varies	☐ partially: some but not all applied to all groups or not	☐ no, does not vary	☐ cannot determine, article does not specify	

		clear if all criterial applied equally			
Does the strategy for recruiting participants into the study differ across groups?	☐ yes, differs	☐ no, does not differ	☐ cannot determine		
Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	☐ yes, inappropriate	☐ no, not inappropriate	☐ cannot determine or no description of the derivation of the comparison group		
Does the study fail to account for important variations in the execution of the study from the proposed protocol?	☐ yes, fails to account	☐ partially, fails to account	☐ no, does not fail to account	☐ cannot determine	
Was the outcome assessor not blinded to the exposure status of the participants?	☐ yes, not blinded	☐ no, blinded	☐ not applicable: assessor cannot be blinded		
Were valid and reliable measures implemented consistently across all study participants used to assess exposure?	☐ yes, valid and reliable measure used	☐ no, valid and reliable measure not used	☐ cannot determine or measurement approach not reported		
Were valid and reliable measures, implemented consistently across all study participants used to assess participant health benefits and harms (in this case birth defects or behavioural problems)?	☐ yes, valid and reliable measure used	☐ no, valid and reliable measure not used	☐ cannot determine or measurement approach not reported		
Was the length of follow-up different across study groups?	☐ yes, different or cannot determine		☐ not applicable		

		☐ no, not different or remedied through analysis			
In cases of high loss to follow-up (or differential loss to follow-up), was the impact not assessed (e.g. through sensitivity analysis or adjustment method)?	☐ yes, impact assessed	☐ no, impact not assessed	☐ cannot determine	☐ not applicable: no loss to follow-up or not considered to be high, or case control study selected outcome	
Are any important primary outcomes missing from the results?	☐ yes, important outcome(s) missing from the results	☐ no important outcomes missing	☐ cannot determine		
Are results believable taking study limitations into consideration?	☐ yes, believable		☐ no, not believable		

4. Author declarations for included studies

4.1 Author declarations for studies included in the pregnancy review

Study ID	Author declarations: none declared, not reported or reported (specified)
1. Alvik 2011	None declared
2. Benedum 2013	Reported: "Martha Werler owns less than $5,000 in Starbucks Corporation stock. Investigators have no other conflicts to report" (pg. 3277).
3. Bille 2007	Not reported
4. Caspers 2010	Not reported
5. Caspers 2014	None declared: "There are no stated conflicts of interest" (Acknowledgements pg. 9).
6. Damgaard 2007	None declared
7. Davies 2017	None declared
8. DeRoo 2008	None declared
9. Grewal 2008	Not reported
10. Halliday 2017	None declared
11. Kelly 2009	None declared
12. Lundsberg 2015**	None declared
13. Mateja 2012	None declared: "No competing financial interests exist" (pg. 32).
14. Miller 2009	Not reported
15. Muggli 2017	None declared (pg. 779).
16. Mullally 2011	None declared
17. O'Leary 2011	None declared
18. Richardson 2011	Not reported
19. Romitti 2007	None declared
20. Sayal 2007**	Not reported
21. Slickers 2008	None declared
22. Strandberg-Larsen 2011	Not reported

23. Suarez 2008	Not reported
24. Torp-Pederson 2010	None declared
25. Werler 2015	Not reported
26. Zhu 2013	Not reported

4.2 Author declarations for studies included in the breastfeeding review

Study ID	Author declarations
1. Tay 2017	Not reported

5. Differences between Mamluk (2017) and NHMRC review of alcohol consumption during pregnancy

5.1 Findings of Mamluk (2017) review for the relevant outcomes

The Mamluk (2017) review identified and included two studies (reported in three articles) (Kelly 2009; Sayal 2007; Sayal 2009) reporting associations between low level alcohol consumption during pregnancy and behavioural problems in children up to age 5. Three studies reporting associations between low level alcohol consumption during pregnancy and birth defects in children (up to age 5) were identified by this review: (Bille 2007; Ernhart 1989; Lundsberg 2015). No meta-analysis was conducted for these outcomes, due to different outcome definitions and insufficient data (Mamluk 2017, pg. 6).

The narrative and tabular summary of the study results for the behavioural outcomes by Mamluk and colleagues suggested:

mixed findings on the effects of **low-level alcohol consumption** (consumption of up to ~32g/week) on child **behavioural problems**; and

no effects of **low-level alcohol consumption** (consumption of up to ~32g/week) on **birth defects** (Mamluk 2017, pg. 6 main text and Table 2).

The four studies included in the Mamluk review published between 2007 and 2017, are included in this NHMRC (2018) commissioned review of alcohol consumption during pregnancy (in the qualitative synthesis

5.2 Tabular summary of scope and methods of the Mamluk 2017 and NHMRC alcohol during pregnancy reviews

Review objective / questions	Population included	Alcohol exposure assessed	Comparator considered	Outcomes included	Study designs included	Search	Data analysis and evidence quality assessment
Mamluk review (2017)							
"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" Authors report: "*here* we report 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".	Included: Pregnant women or women trying to conceive Excluded: Women with alcohol abuse / dependency	Included: Prenatal maternal alcohol consumption of up to ~32g/week Excluded: • Retrospective assessment. • Measures that could not be converted to grams of alcohol consumed per week. • Insufficient data to estimate effect size of the association of predefined low-consumption categories versus abstinence (e.g. studies that analysed alcohol as a continuous variable).	Abstinence from alcohol consumption (during pregnancy or while trying to conceive)	Range of outcomes included: stillbirth; miscarriage; gestational length and preterm delivery (<37 w gestation); hypertensive disorders of pregnancy; gestational diabetes; small for gestational age (<10th percentile in weight or <-2SD scores, and birth size (weight (including low birth weight defined as <2500 g), length and head circumference; low amniotic	Studies using standard analytical approaches (e.g., multivariable regression), and that used innovative analytical methods, such as i) quasi-experimental studies (for example comparing outcomes before and after implementation of new guidelines on alcohol consumption), ii) negative control studies (e.g. Comparing the association of offspring outcomes with maternal alcohol consumption among fathers, under the assumption that confounding is likely to be similar but that if there was a direct	Comprehensive search for studies published in English from database inception up to 11 July 2016.	Meta-analysis and tabular reporting of results, prioritising measures adjusted for the key confounders (maternal smoking, maternal age, socioeconomic status and ethnicity). Note that due to insufficient data, no meta-analysis was performed for the two review outcomes defined for the NHMRC review in the Mamluk review. Subgroup analysis by gestational age (first vs second vs third pregnancy) planned. However

Review objective / questions	Population included	Alcohol exposure assessed	Comparator considered	Outcomes included	Study designs included	Search	Data analysis and evidence quality assessment
		• Lowest exposure category had an upper bound exceeding 32 g/week or was unspecified).		fluid; placenta previa; placental abruption; assisted delivery; Apgar score at birth; admission to neonatal care unit; congenital malformations (birth defects); childhood growth restriction; cranium size and head circumference; developmental delays; behaviour problems; cognitive impairment and IQ; facial malformations Study specific definitions used for all outcomes.	causal effect of maternal consumption on outcomes, maternal associations would be stronger) and iii) Mendelian randomisation studies (using genetic variants associated with alcohol consumption and metabolism).		not conducted due to insufficient data. No dose response analysis. ROB assessment using Newcastle-Ottawa Scale. No evidence quality assessment for each outcome using GRADE. No summary of findings (SOF) tables.
NHMRC review							

Review objective / questions	Population included	Alcohol exposure assessed	Comparator considered	Outcomes included	Study designs included	Search	Data analysis and evidence quality assessment
1.What are the effects[5] 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 are defined as: ≥ 1 to < 10 g/week ≥ 10 to < 20 g/week ≥ 20 to < 30 g/week ≥ 30 to < 40 g/week ≥ 40 to < 50 g/week ≥ 50 to < 60 g/week ≥ 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 may include	Women who are pregnant or planning a pregnancy and their offspring (up to age five). Healthy women, or women with a medical or health condition (including, but not limited to, an alcohol abuse/dependency diagnosis) eligible.	Only 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). May include retrospective survey involving recall of alcohol consumption over different periods of life (preconception or pregnancy period) or intake diaries to	Abstainers from alcohol consumption while pregnant (either never drinkers or not drinking during pregnancy).	Two review outcomes for inclusion: • Birth defects/congenital malformations (in infants and children up to age 5) • Behavioural problems (identified up to age 5) All reported measures to be considered for the two outcome domains provided a rationale for the measure is	Cohort and case control study designs	Comprehensive search for studies published in English from database inception up to end July or August 2018.	Meta-analysis, and tabular analysis where data do not permit pooling. Estimates adjusted for key confounders (see below), to be prioritised for inclusion in analysis and reporting. Dose response analysis. Subgroup analysis, if data available: timing of exposure (periconception, early pregnancy, mid-late pregnancy,

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

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

Review objective / questions	Population included	Alcohol exposure assessed	Comparator considered	Outcomes included	Study designs included	Search	Data analysis and evidence quality assessment
irregular heavy drinking (episodic or 'binge' drinking) or daily drinking at low levels. 3.Is there a dose response relationship between levels of alcohol consumption during pregnancy and birth defects? 4.Is there a dose response relationship between levels of alcohol consumption during pregnancy and behavioural problems? 5.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)?		measure current alcohol See specification of average consumption levels included, and patterns, in questions 2) and 3) left (column 1).		provided in the study report. Trustworthiness of the measure is to be considered in the ROB assessment and evidence quality assessment using the GRADE approach.			throughout pregnancy) ROB assessment using ROBINS-I GRADE evidence quality assessment and reporting of outcomes in Summary of Findings (SOF) tables. Confounders for consideration in ROB assessment: maternal age; maternal co-morbidities; maternal smoking; socio-economic status.

6. Response to reviewer comments

Comment	Response
Comments from the Alcohol Working Committee (AWC) (videoconference on 13 11 2018 and summarised in report and email dated 16 November 2018)	
1. Only the global results of altered craniofacial shape from the Muggli 2017 study were considered, consider adding the two additional sub-outcomes for altered craniofacial shape.	We have added a narrative report in the results section (see Craniofacial shape: Muggli 2017)
2. Review investigates outcomes for children ≤5 as per the protocol, which is highlighted as a limitation in the report. SAHMRI to forward the list of studies excluded on the basis of age.	List provided (e-mailed to Rebecca Reece at alcohol@nhmrc.gov.au on 23 November 2018).
3. Moderate to high quality studies revealed both significant and nonsignificant results. Recommend noting this in the executive summary.	Noted and done (moderate and low – no high quality studies).
4. Protective effects of alcohol noted for several outcomes, e.g. congenital limb defects and strabismus. Consider including these effects in the executive summary.	Considered and done.
5. Different approaches to measuring alcohol intake (e.g. grams v standard drinks vs ounces). Standardize the alcohol exposure categories by converting to grams, noting the assumptions that were necessary to make the conversions. (The reviewers comment on reluctance to make assumptions where studies do not specify the exposure level was noted, and AWC members were satisfied with assumptions based on the study location and the standard drink in that country)	We have standardised the reporting of exposures assessed by providing the definitions in grams, see Table 3 (for pregnancy review, and Table 4 (for breastfeeding review).
6. Results of Davies 2017 (pg. 45) using Griffiths Mental Development Scales: unclear if higher or lower score desirable. Edit to improve clarity.	Edited.
7. Avoid use of the acronyms AA and ARBD as they are both ambiguous: AA = alcoholic anonymous or absolute	We have removed these ambiguous acronyms.

Comment	Response
alcohol; ARBD – alcohol related brain damage or alcohol related birth defect	
8. Heavy drinkers not captured in these studies and not specified in the protocol. Include this as a limitation of the review.	Heavy drinkers were not excluded from this review (see population and exposure inclusion criteria). Therefore, we have not added this limitation.
9. Inconsistency noted in some bolded results details. Ensure all significant outcomes are bolded, and that some explanatory text be added notifying the reader that significant outcomes are bolded.	Done; see results section of main text.
10. Tay 2017 study (page 55): AWC considered this to include an atypical cohort as almost all women reported employing a strategy to minimise potential effects of exposure on breastfeeding infant. Note this in the report.	We have made the requested note: see Table 4 summarising characteristics of the study included the breastfeeding review; and the main text reporting results for this review (section 4.4.2, paragraph two).
11. Risk of Bias tables reported O'Leary 2011 (page 37) as serious risk of recall bias. Queried by ONHMRC as other factors not identified that might support this assessment. Review team have reviewed and reported inaccurate assessment. Revise report according to reviewer's assessment.	We have not changed the risk of bias assessment for this study, as having reconsidered the study, we are convinced that our initial assessment was correct and consistent with other studies. In this study, at 3 months after giving birth, mothers were asked to recall their alcohol intake 3 months prior to pregnancy, and during each of the 3 trimesters of pregnancy. Therefore, the maximum recall period is 15 months. This is a serious concern as it is in all other studies with retrospective exposure measurement, in which mothers were asked to self-report their prior alcohol consumption when they knew whether their child had a birth defect (that is, there is a high risk of recall bias). Also, as with all other studies included in the review, there is a risk of residual confounding in O'Leary, which should have been noted in the overall risk of bias judgement. We have added these concerns to the overall assessment for this study (see Table 5).
12. Figure 1 (page 20): final figures for included studies queried as numbers appear inaccurate. Review team reported some studies have supplementary papers that have been included. Edit to clarify numbers	We have made the distinction between the number of included studies for the pregnancy review, and the number of articles reporting the included studies clearer, see Figure 1.

Comment	Response
13. Request to modify Summary of Findings table (page 58) to include quality assessment.	Done, see Table 8 main report, in which we have replaced the SOF table with an Evidence Profile table, informed by the two templates provided by the AWC (Rebecca Reece, via emails).
14. Request to include evidence statements for study outcomes for both meta-analyses and single studies. ONHMRC to provide the categories of association utilised in the evidence statements developed for a previous systematic review.	Provided, see section 5 of main report.
15. Mamluk and Giglia reviews (pages 59 & 60): could benefit from improved reporting of their conclusions and the review team's assessment of these. Include conclusions and the review team's assessment in the context of the systematic review (where reported in the discussion).	See discussion.
16. Table 5: Inconsistency identified with self-reporting. Single scale applied for determining bias on length of recall involved. Consider this comment.	We have edited the rationale for the risk of bias judgement for all studies listed in Table 5, using standardised sentences to describe our concerns about particular methodological flaws. We hope that this makes it clearer why some studies have been rated at "moderate", others at "serious" and others at "critical" risk of bias.
17. Check that single day consumption is not confused with a non-defined measure (binge)	We have checked reporting of exposures in Tables 3 & 4 as well as in the main text (results sections) and adjusted where necessary to avoid such confusion.
18. Summary, 6.2.1 (should this be 6.3.1?) The first paragraph states that for the birth defect outcomes domain: 'no consideration of how different types of alcohol consumption influences associations between PAE and birth defects'. I am assuming that by 'different types of alcohol consumption' you are referring to the dose, pattern, and timing of alcohol consumption. This is an important issue and one of the key issues in alcohol and pregnancy research that has masked the relationship between PAE and fetal effects and makes comparing results across	Should this be 6.3.1? Yes, thank you for spotting this error. We have changed 6.2.1 and 6.3.1 (as well as 6.2.2 to 6.3.2) Definition of 'different types of alcohol consumption': here we are referring to different types of liquor, for example spirits versus wine, versus beer. We have made this clearer in the updated discussion section of the report.

Comment	Response
studies so difficult. It would be good if this point could be elaborated in the limitations section to inform readers unfamiliar with this area of research.	
19. Page 38 Error in Summary Table for Halliday et al 2017: The outcome assessor was blinded to the exposure status of participants in the study by Halliday et al 2017.	Error corrected. The assessment in the summary table now aligns with the reporting of the full assessment for this study in the Technical Report, and what was done in the study).
20. Reference O'Leary 2011, page 61, the reference for Prenatal Alcohol Exposure and Risk of Birth Defects is incorrect and should be: Paediatrics 2010; 126, (4) e843	Corrected, and we have changed the date of this included study to 2010, throughout the review.
21. Page 45 O'Leary 2010: Error in definition of 'Low' PAE – it should read <70g/week and no more than two standard drinks per occasion. Moderate exposure did not include binge drinkers but included <5 standard drinks per occasion.	Corrected, both in the text (section referred to here), and in Table 3 (in the description of exposures considered in this included study).
Comments from the methodological reviewers (received in report on 13 11 2018)	
22. Adjust the description of the search for literature in the technical report by "presenting the MEDLINE search first" to make it clearer for readers to understand which databases the deviation from the protocol applied to.	Technical report adjusted as requested.
23. A second change from the approved protocol was the use of the RTI tool for Risk of Bias (RoB) assessment rather than the ROBINS-I tool. This was justified on the basis that "the pregnancy review included case control studies, which is a study design for ROBINS-I yet to be developed (p18 EER)." This is not strictly correct according the guidance for the ROBINS-I tool which states: *"This document relates most closely to NRSIs with cohort-like designs, such as cohort studies, quasi-randomized trials and other concurrently controlled studies. Much of the*	One of us (MJP) has been closely involved in the extension of the ROBINS-I tool to study designs other than cohort studies. From this involvement it has become clear that there are some important considerations for assessing risk of bias in case-control studies that are not yet covered by ROBINS-I. Therefore, we considered it inappropriate to use the tool to assess the case-control studies in our review. Given that the RTI tool can be used to assess cohort and case-control studies, we considered it prudent to apply it to all studies in our review.

Comment	Response
material is also relevant to designs such as case-control studies, cross-sectional studies, interrupted time series and controlled before-after studies, although we are currently considering whether modifications to the signalling questions are required for these other types of studies (Sterne et al. 2016).” The protocol notes that “if infeasible to apply ROBINS-I due to inclusion of a large number of studies, we will assess studies using the Agency for Health Research and Quality Item Bank for Assessing Risk of Bias and Confounding for Observational Studies of Interventions or Exposures (p16, protocol).” Although we do not consider the use of the RTI tool to be a major deviation from the protocol, the justification for it appears inconsistent.	
24. “Account for risk of bias” in the discussion of the findings from the reviews	The inclusion of evidence statements summarising the results for all outcomes, and addition of an evidence profile for the meta-analysed results (replaces the SOF table) has improved the results presentation and ensured that risk of bias is more transparently and comprehensively included in the interpretation of the results.
25. “The presentation of the results could be improved, predominantly by improving the formatting. There might be some value in presenting some of the results in tables rather than tabbed text”	
26. Provide clarity on the interpretation of the results could be improved, for example, Griffiths Mental Development Scale (EER, p45) where a statement clarifying whether a higher or lower score indicates a better rating would be helpful.	Provided.
27. Further explanation of ‘alcohol related birth defect’ is also warranted (EER, p46) as this implies causation is already known.	We have added the following as an explanation (in the reporting of the results from this study): “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)”.

Comment	Response
28. Insert a statement that makes explicit that it was not possible to do any meta-analysis for the question about levels of alcohol consumption.	Done; see methods, data analysis and synthesis, section 3.5.6
29. Add the search date restriction – 2007 forward – as a limitation of the review.	We have not added this as a limitation of the review as the start date for the search was specified by the committee and was informed by search dates covered in previous review that are relevant for the formulation of the alcohol guidelines.
30. Minor comments: P13, last line. Change 'pregnancy' to 'pregnant' P31, second line of table. Denmark should be in bold font. P32, last line of table. USA should be in bold font. P32, Notes. The single asterisk notes do not clearly relate to the single asterisk locations in the table (no alcohol). P33, ASU is defined as standard units. Remove the 'A' to be consistent with the table (line 1)? P34, Notes. Remove the note with a double asterisk, not relevant for this table. P43, last line. Missing close of bracket. P53. 'Isolated simple septal' heading – missing data? P55, last paragraph. Missing cross reference for 'Table X' P59, first line, last paragraph. Remove 'performed' P60, last heading and second last paragraph. To be completed? P62, Romitti (2007). Title of the reference is missing 'Maternal periconceptional alcohol consumption and risk of orofacial clefts.'	Thank you for highlighting these errors, which we have corrected.