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Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses.

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Systematic Review & Meta-analysis

Title: Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses.

Running tittle: Low alcohol consumption and pregnancy and childhood outcomes.

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What this paper adds

What is already known on this subject

Until recently UK guidelines advised women to avoid drinking alcohol while trying to conceive, and in the first trimester, but at the same time indicated that consumption should be restricted to within "1 to 2 UK units, once or twice a week.

Despite the guidance on light drinking versus abstinence being the point of confusion for health professionals and pregnant women and contributing to inconsistent guidance and advice, previous reviews have reported on a range of "low/moderate" alcohol consumption levels in pregnancy and have not focused specifically on the threshold that current UK guidelines refer to.

Additionally, they did not specifically seek out study designs that reduce the impact of confounding and other forms of bias on the effect estimates.

What this study adds

We examined the effects of light alcohol consumption during pregnancy using the best quality evidence by only including studies with prospective assessment of exposure and prioritising results adjusted for main confounders.

We uniquely sought to include alternative study designs to further improve causal inference alongside standard analytical approaches.

We found very few studies employing either standard or alternative analytical approaches that answered the research question focussed on the specific range of exposure. Pooled estimates from these studies provided some evidence that even light alcohol consumption in pregnancy is associated with risk of preterm delivery and small for gestational age.

We found very little evidence to support recommendations of a 32g alcohol/week limit with respect to most outcomes.

Abstract:

Objectives: To determine the effects of low-to-moderate levels of maternal alcohol consumption in pregnancy on pregnancy and longer-term offspring outcomes.

Search Strategy: Medline, Embase, Web of Science, and Psychinfo from inception to 11-07-2016.

Selection Criteria: Prospective observational studies, negative control and quasi-experimental studies of pregnant women estimating effects of light drinking in pregnancy (≤32g/week) versus abstaining. Pregnancy outcomes such as birth weight, and features of fetal alcohol syndrome were examined.

Data Collection and Analysis: One reviewer extracted data and another checked extracted data. Random effects meta-analyses were performed where applicable, and a narrative summary of findings was carried out otherwise.

Main Results: 24 cohort and two quasi-experimental studies were included. With the exception of birth size and gestational age, there was insufficient data to meta-analyse or make robust conclusions. Being small-for-gestational-age (SGA) and preterm birth odds were higher for babies whose mothers consumed up to 32g/week versus none, but estimates for preterm birth included the null value: summary odd ratios (OR) 1·08, 95% confidence intervals (CI) (1·02 to 1·14), I^2 0%, OR 1·10, 95%CI (0·95 to1·28), I^2 60.2%, respectively.

Conclusion: Evidence of the effects of drinking <=32g/w in pregnancy is sparse. As there was some evidence that even light prenatal alcohol consumption is associated with being SGA and preterm delivery, guidance could advise abstention as a precautionary principle, but should explain the paucity of evidence.

Keywords: Alcohol, pregnancy, systematic review.

Strengths and Limitations of this study:

Strengths

- Completeness of searches with a focused research question aimed at informing alcohol in pregnancy guidelines.
- Biases minimised by only including those with prospective assessment of exposure and prioritising results adjusted for main confounders.
- Unique effort to include alternative study designs to further improve causal inference alongside standard analytical approaches.

Limitations

- Limitation of results on the effects of light drinking in pregnancy from standard analytical approaches is bias due to residual confounding.
- The inclusion of only English language studies may have led to missing some studies, however there is little evidence that exclusion of non-English language studies leads to systematic bias in systematic reviews of conventional medicine.
- We could not pool eligible studies for various reasons (e.g. too few studies, lack of standard errors)

Introduction

Alcohol is a known teratogen[1] and the evidence about the risks of heavy alcohol consumption during pregnancy on intellectual ability, birth defects, behaviour, fine motor skills, and mental health (comprising fetal alcohol spectrum disorder – FASD)[2] is clear and compelling.[3] Internationally, clinical guidelines recommend that pregnant women should abstain from heavy or "binge" drinking.[4] However, until recently UK guidelines advised women to avoid drinking alcohol while trying to conceive, and in the first trimester, but at the same time indicated that consumption should be restricted to within "1 to 2 UK units, once or twice a week".[5] The UK Chief Medical Officer (CMO) commissioned a review of guidelines on alcohol consumption during pregnancy. Based on a review of reviews, the Guidelines Development Expert Group has recently proposed a change to guidelines such that women should be advised to abstain from alcohol when pregnant and/or trying to conceive,[6] based on the precautionary principle (i.e. "better safe than sorry"), in the absence of robust evidence.

Our aim 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 in pregnancy on pregnancy and longer term offspring outcomes. Here we report on alcohol consumption of up to two UK units of alcohol up to twice a week (the equivalent of ~ 32g/week), compared to no alcohol. In the absence of evidence from randomised controlled trials, we examine observational studies of pregnant women from the general population with prospective assessment of alcohol exposure, to reduce recall bias. In particular, we specifically seek out quasi-experimental studies, negative control comparisons, and Mendelian randomisation analyses in order to reduce the impact of confounding and measurement error on the effect estimates.

Methods

Selection strategy and selection criteria

A full protocol of this systematic review carried out using PRISMA guidelines[7] is available from the PROSPERO systematic review register (registration number CRD4201501594; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015941).

In brief, eligible studies were defined as epidemiological studies of pregnant women or women trying to conceive with prospective assessment of prenatal alcohol exposure (i.e. before birth), sampled from general population. The protocol specifically included studies using standard analytical approaches (e.g. multivariable regression analysis), as well as studies that used innovative analytical methods to improve causal inference, 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 to the association of the same outcomes with consumption among fathers, under the assumption that confounding is likely to be similar but that if there was a direct causal effect of maternal consumption on outcomes, maternal associations would be stronger); and Mendelian randomisation studies (using genetic variants associated with alcohol consumption and metabolism). We considered these analytical approaches to be the most appropriate in terms of their ability to minimise bias from confounding and other sources. Our original protocol included studies exploring the effects of prenatal alcohol consumption up to 83g/week (the commonly used threshold for moderate consumption [8-10]) versus abstinence. Here we have focused specifically on low alcohol consumption, i.e. up to 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.[5] This specific cut off value has not been reviewed and is the main point of discussion as the guideline change from low consumption (equating to 1 to 2 UK units, once or twice a week or 32g/week) to abstinence.

Outcomes included: 1) pregnancy outcomes: still birth; miscarriage; gestational length and preterm delivery; hypertensive disorders of pregnancy; gestational diabetes; small for gestational age (SGA) and birth size (weight, length, and head circumference); low amniotic fluid (oligohydramnios); placenta previa; placental abruption; assisted delivery (including vacuum extraction, forceps delivery, Caesarean section); Apgar score at birth; admission to neonatal unit; congenital malformations. 2) Features of foetal alcohol spectrum disorder (FASD): childhood growth restriction; cranium size and head circumference; developmental delays; behaviour problems; cognitive impairment and intelligent quotient (IQ); facial malformations.

Studies were excluded if: there was no quantitative measure of alcohol consumption that could be converted to grams of alcohol/week; there was insufficient data to estimate the effect size of the association of our pre-defined low consumption categories versus abstinence with any outcome, including studies that analysed alcohol as a continuous variable (i.e. assuming the same linear or log linear effect across the entire alcohol distribution); the lowest exposure category (compared to non-drinkers) had an upper bound exceeding 32g/week, or was unspecified; they were cohort studies of pregnant women with alcohol abuse/dependency; they were case-control studies or cohort studies with retrospective alcohol consumption assessment (e.g. after birth).

The following databases were searched: MEDLINE, PsycINFO, EMBASE on Ovid; the Cochrane Library including CENTRAL (the Cochrane Central Database of Controlled Trials) on Wiley Interscience; and Science Citation Index, Social Science Citation Index, on Web of Science from inception to 11 July 2016 (supplementary Table 1). We limited the search to English language papers and excluded animal studies, letters, editorials, and conference proceedings for which there were no full-text papers. Searches were tailored to each database by investigators. The search focused on published medical literature and did not include grey literature. We additionally performed manual searches of the reference lists of:

(i) all papers included in recent systematic reviews of the effects of prenatal alcohol exposure on the outcomes of interest; and (ii) all recent papers citing those reviews. Titles and abstracts, and full texts if necessary, were screened independently by two reviewers. Discrepancies were discussed and disagreements resolved through consensus. We assessed potential for bias in included studies by assessing how well the study adjusted for known confounders known to impact on the exposure-outcome associations (namely: socioeconomic positioning, smoking during pregnancy, maternal age, and ethnicity. We considered the potential for confounding and bias across studies included in the analyses and described it narratively alongside summary results.

Data extraction

Data were extracted into a custom built Microsoft Access database. We extracted the following information from each study: title, authors, publication year, country/region, study design, population characteristics (sample size, methods of sampling, age distribution, and ethnicity), measures of exposure (assessment method; including timing and quantification of alcohol consumption, reference group, categories of exposure, and information on unit equivalence if stated), outcome assessment methods (including whether this was abstracted from medical records, obtained via a research interview and the person reporting the outcome e.g. parent, teacher, health professional, researcher or child), model adjustments, and study results. If a study reported more than one result for each outcome, we extracted all of them (e.g. relative to different timing of exposure, model adjustments, etc.). Information from each included paper was extracted by one reviewer (LM) and subsequently checked for accuracy and completeness by another reviewer (HE).[11] Extraction errors were minimal and were resolved through discussion between extractor and checker.

Alcohol unit conversion

Alcohol consumption in drinks/week was converted into grams/week based on the pure ethanol equivalent of one drink, as stated in each individual article, or otherwise inferred based on the definition of standard drinks in the country where the study took place.

Data analysis

The association of low alcohol use with pregnancy and related outcomes was investigated comparing the highest category within the range of 0-32g/week to abstention (during pregnancy). In studies providing data across several categories of intake within the 0-32g/week range, we used the effect estimate for the highest category of intake. If studies reported on exposure to alcohol during different trimesters, we included estimates relative to the earliest exposure. Similarly, if results were available from both unadjusted and adjusted regressions, we prioritised fully adjusted results, as a way of minimising the impact of confounding by important factors such as maternal smoking, age, socio-economic position and ethnicity. In case of multiple results from the same cohort (relative to the same outcome), we analysed those pertaining to the largest population size (i.e. conducted on the least 'selected' population as result of exclusions, to minimise selection bias). Results from all studies that fulfilled our inclusion criteria were summarised, together with information about the study. Where appropriate, we additionally pooled results for each outcome. Authors were not contacted for extra data.

Individual study estimates were pooled using random effects meta-analysis. When continuous outcomes were measured using different scales, we derived and pooled Cohen's d statistics (representing standardised differences in means by level of exposure). Where only two studies were available to meta-analyse, results were pooled unless they were very different from each other ($I^2 \geq 50\%$).[12] In this case, a narrative summary of findings was carried out and results were reported in Table 2. Where a study only reported unadjusted results, we kept these separate in the forest plots (sub-group analysis) but then also showed overall pooled estimates combining all results.

Planned sub-group analyses by trimester could not be performed due to insufficient number of included studies with this information.

The likelihood of small study bias deriving from publication bias was assessed through visual inspection of funnel plots for pooled analyses including ≥4 studies.

Statistical analyses were carried out using Stata version 13.1 (StataCorp, College Station, TX, USA).[13]

Results

A flowchart of the article review process is shown in Figure 1. A total of 4680 citation records were identified from searching the four relevant databases. A manual search of recent systematic reviews identified 33 additional articles. After exclusions, 24 prospective studies analysed using standard approaches and two quasi-experimental studies were included, reporting on 30 outcomes in total.

Standard analytical approaches

Pooled estimates for continuous and binary outcomes are presented in Figure 2 and 3 respectively.

The outcome reported by the largest number of studies was preterm delivery (9 studies, for a total of 318832 participants, Figure 3A), followed by birthweight and SGA (7 studies each, Figures 2 and 3B), and low birthweight (5 studies, Figure 3C).

The meta-analysis yielded a summary OR of 1·10 (95% CI 0·95; 1·28) for preterm delivery, but there was substantial statistical heterogeneity between studies (I^2=60·2%), due to a large Danish study reporting a protective effect (Figure 3A). There was also modest evidence for an increased risk of being SGA (OR 1·08, 95% CI 1·02; 1·14) for a total of 288512 participants, although this was almost entirely driven by a single US study contributing 95% of the participants to this meta-analysis (Figure 3B). The birthweight meta-analysis yielded a summary effect of -13·9g (95% CI -13·49g; +3·31g) for offspring of light drinkers versus non-drinkers (Figure 2).

Other outcomes were typically reported by a limited number of studies and mostly could not be meta-analysed due to clinical heterogeneity in outcome assessment or incompleteness of published data (supplementary Figure 1, and Table 2). Based on two studies with data on behavioural outcomes, there was little evidence of any effect for internalising symptoms but a suggestion that light drinking in pregnancy protected against high externalising behaviour scores (OR 0·97, (95%CI 0·93; 1·01, supplementary Figure 1)). However, an additional study assessing conduct problems and hyperactivity (in the same externalising domain) reported results in the opposite direction, which could not be meta-analysed due to different outcome definitions.

Table 2 presents results of included studies that did not contribute to the meta-analyses for various reasons. There was no strong evidence of association between consuming up to 32 g/week of alcohol and any of the remaining outcomes excluded from meta-analyses, with three exceptions: a very large US study showing increased risk of placental abruption and decreased risk of pre-eclampsia (OR 1·24, 95%CI 1·05; 1·46 and OR 0·82, 95% CI 0·74; 0·90, respectively)[14], and a single British study reporting better cognitive outcomes in children exposed to light maternal drinking in pregnancy.[15]

For outcomes with a sufficient number of studies (≥4 studies), there was little evidence of small study effect based on inspection of funnel plots (supplemental Figures 2-5), with only preterm birth showing some asymmetry due to the three smallest studies showing point estimates in the direction of increased risk (supplementary Figure 2).

Of all included results, only two were unadjusted[16 17], and most of the others were adjusted for maternal smoking, age and socio-economic position (supplementary Table 2). Studies that did not adjust for ethnicity were generally conducted in homogenous populations. Due to the small number of studies for each outcome, we could not further investigate the effect of adjusting for all or some of these confounders. Similarly, there was insufficient data to examine the effect of timing of exposure on outcomes.

Alternative analytical approaches

Two negative control publications[18] based on the same UK cohort met our inclusion criteria.[17 19] They investigated the effects of maternal alcohol consumption on childhood educational achievement[19] and IQ.[17] Offspring exposed to maternal consumption of <12g/week of alcohol in the first trimester did not have worse outcomes compared to those of mothers who abstaining from alcohol, and a similar pattern was found for paternal alcohol consumption.

One further quasi-experimental study, one natural experiment and five Mendelian randomisation studies were excluded from the present review because they did not specifically test the effect of consuming up to 32g/week in pregnancy versus abstaining. These will be included in a forthcoming review focused on estimating the causal effects of prenatal alcohol exposure based on alternative study designs and analytical approaches to strengthen causal evidence.

Table 1. Prospective studies examining the effects of prenatal alcohol exposure on pregnancy outcomes (studies included in the meta-analysis)

Study (year)	Country	Number in analysis	Outcomes	Age at outcome assessment (child)	Adjusted (yes/no)
[20] Lundsberg (2015)	USA	3,916	Birth weight (<2500g) SGA (< 10th percentile)	Birth	Yes
[21] Nykjaer (2014)	UK	535	Birth weight (g) Customised birth centile SGA (< 10th centile) Low birth weight <2500g Preterm birth	Birth	Yes
[22] Niclasen (2014)	Denmark	5,710	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ), Parent report Boys Internalising behaviour Girls Internalising behaviour Boys Externalising behaviour Girls Externalising behaviour	7 years	Yes
[23] Miyake (2014)	Japan	1,493	Preterm birth SGA (< 10th percentile) Adjusted mean birth weight Low birth weight	0-11 months	Yes
[14] Salihu (2011)	USA	276,288	Preterm birth SGA (< 10th percentile)	Birth	Yes
[24] Robinson (2010)	Australia	1849	Clinically significant problems (T score ≥60), Child Behaviour Checklist (CBCL) Parent report Internalising behaviour Externalising behaviour	2-14 years inclusive	Yes
[25] Jaddoe (2007)	Holland; UK	4,132	Low birth weight SGA (weight < −2 standard deviation scores) Preterm birth Birth weight	Birth	Yes
[26] Sayal (2007)	UK	720	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Hyperactivity* - Externalising	7.75 years	Yes
[26] Sayal (2007)	UK	700	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report C*onduct problems*- Externalising	7.75 years	Yes
[27] Albertsen (2004)	Denmark	29,463	Preterm birth (<37 weeks) Moderate preterm birth (32-37 weeks) Very preterm birth (<32 weeks)	Birth	Yes
[28] Lundsberg (1997)	USA	2,063	SGA (lowest 10th percentile) Low birth weight Preterm delivery	Birth	Yes
[29] Passaro (1996)	UK	7,052	Birth weight (g)	Birth	Yes
[30] Shu (1995)	USA	398	Birth weight (g)	Birth	Yes
[16] Peacock (1995)	UK	901	Preterm birth <37 weeks	Birth	No
[31] Olsen (1991)	Denmark	11,698	Birth weight (<2500g)	Birth	yes
[32] Brooke (1989)	UK	1,140	Birthweight	Birth	yes

SGA :small for gestation age

Table 2. Prospective studies examining the effects of prenatal alcohol exposure on pregnancy outcomes (results not included in the meta-analysis)

Outcome	Study (year)	Country (sample size)	Outcome details	Reason not included in meta-analysis	Age at outcome assessment (child)	Results [1]	Adjusted (yes/no)
Malformations	[20] Lundsberg (2015)	USA (4,496)	Major malformations	Only study with this outcome	Birth	OR 0·78 (95% CI 0·40 – 1·50)	Yes
	[33] Bille (2007)	Denmark (1020)	Oral clefts	Only study with this outcome	Birth	OR 1·06 (95% CI 0·74 – 1·50)	Yes
	[34] Ernhart (1989)	USA (873)	Craniofacial anomalies	SE/SD not reported	Birth	Mean craniofacial anomalies was 1·92 for those exposed, compared to 1·85 for those unexposed (p=0·26)	Yes
	[34] Ernhart (1989)	USA (873)	Total anomalies	SE/SD not reported	Birth	Mean total anomalies was 2·60 for those exposed, compared to 2·53 for those unexposed (p=0·28)	Yes
Gestational age and preterm birth	[29] Passaro (1996)	UK (10,539)	Gestational age	Only study with this outcome	Birth	Mean gestational age 40·1 (SD 1·9) for those exposed, compared to 40·1 (SD 2·0) for those unexposed.	Yes
	[35] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Per cent of infants with gestational age <37 weeks			3·7% in those exposed compared to 3·9% in those unexposed.	Yes
Birthweight	[35] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mean birthweight (g) in non-smokers	SE/SD not reported	Birth	3414g in those exposed, compared to 3363g in those unexposed.	Yes
	[35] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mean birthweight (g) in smokers	SE/SD not reported	Birth	3225g in those exposed, compared to 3225g in those unexposed.	Yes
Height	[20] Lundsberg (2015)	USA (4,496)	Lowest 10th percentile of birth length	Only study with this outcome	Birth	OR 1·10 (95% CI 0·78 – 1·54)	Yes
Head circumference	[20] Lundsberg (2015)	USA (4,496)	Lowest 10th percentile of head circumference	Only study with this outcome	Birth	OR 1·08 (95% CI 0·83 – 1·42)	Yes
Apgar score	[20] Lundsberg (2015)	USA (4,496)	Apgar <7 at 5 minutes	Only study with this outcome	Birth	OR 1·61 (95% CI 0·67 – 3·84)	Yes
Admission to Neonatal Intensive Care Unit (NICU)	[20] Lundsberg (2015)	USA (4,496)	Admission to NICU	Only study with this outcome	Birth	OR 1·12 (95% CI 0·86 – 1·46)	Yes
Miscarriage	[36] Andersen (2012)	Denmark (89,322)	Miscarriage in first trimester	Only study with this outcome	(Outcome confirmed via National / Hospital Registries, or from maternal report)	OR 1·05 (95% CI 0·94 – 1·18)	Yes
	[37] Windham (1997)	USA (5,324)	Spontaneous abortion occurring ≤20 weeks gestation	Only study with this outcome	(Outcome confirmed via medical records)	OR 1·0 (95% CI 0·7 – 1·5)	Yes
Stillbirth	[36] Andersen (2012)	Denmark (89,322)	Stillbirth	Estimates are in different directions	(Outcome confirmed via National / Hospital Registries, or from maternal report)	OR 0·90 (95% CI 0·73 – 1·12)	Yes
	[14] Salihu (2011)	USA (1,226,685)	Stillbirth	Estimates are in different directions	Birth	OR 1·10 (95% CI 0·88 – 1·39)	Yes

Placenta-related	[14] Salihu (2011)	USA (1,226,685)	Placental abruption	Only study with this outcome	Birth	OR 1·24 (95% CI 1·05 – 1·46)	Yes
	[14] Salihu (2011)	USA (1,226,685)	Placenta previa	Only study with this outcome	Birth	OR 1·11 (95% CI 0·87 – 1·43)	Yes
Pre-eclampsia	[14] Salihu (2011)	USA (1,226,685)	Pre-eclampsia	Only two studies with this outcome	Birth	OR 0·82 (95% CI 0·74 – 0·90)	Yes
	[38] McCarthy (2013)	New Zealand, Australia, Ireland, UK	Pre-eclampsia	Only two studies with this outcome	Birth	OR 0·59 (95% CI 0·35 – 0·99)	Yes
Motor development	[39] Faebo Larsen (2013)	Denmark (32,097)	Developmental Coordination Disorder (DCD)	Only study with this outcome	7 years	OR 0·85 (95% CI 0·70 – 1·03)	Yes
Behaviour /development	[26] Sayal (2007)	UK (967)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Conduct problems*	Later age used in analysis	3.9 years	OR 1·14 (95% CI 0·98 – 1·32)	Yes
	[26] Sayal (2007)	UK (1077)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Hyperactivity*	Later age used in analysis	3.9 years	OR 0·99 (95% CI 0·86 – 1·16)	Yes
	[26] Sayal (2007)	UK (257)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) teacher report *Conduct problems*	Parent report used in analysis instead	7.75- 9 years	OR 1·41 (95% CI 1·02– 1·94)	Yes
	[26] Sayal (2007)	UK (525)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) teacher report *Hyperactivity*	Parent report used in analysis instead	7.75- 9 years	OR 1·20 (95% CI 0·96– 1·51)	Yes
	[40] Parry (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mental Development Index, Bayley Scales of Infant Development	No SE/SD reported for reference group	18 months	Mean increase of 1·80 points (SE 1·1) for those exposed compared to unexposed.	Yes
	[40] Parry (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Psychomotor Development Index, Bayley Scales of Infant Development	No SE/SD reported for reference group	18 months	Mean increase of 0·81 points (se 0·8) for those exposed compared to unexposed.	Yes
Cognition	[15] Sayal (2013)	UK (10,558)	Key Stage 2 scores	Only study with this outcome	11 years	Mean increase of 0·38 (95% CI -0·02 – 0·78) on KS2 score for those exposed compared to unexposed.	Yes
	[17] Alati (2008)	UK (4,332)	IQ, Weschler Intelligence Scale for Children (WISC-III)	Only study with this outcome	8 years	Mean IQ score 106·4 (SD 16·3) in those exposed, compared to 105·7 (SD 16·2) in those unexposed, p=0·10.	No

[1] Odds Ratio results compare the odds of outcome in those exposed to ≤32g AA per week. SE: Standard error SD: standard deviation SGA :small for gestation age IQ: intelligence quotient.

Table 3. Quasi-experimental studies examining the effects of prenatal alcohol exposure on pregnancy outcomes.

Study (year)	Country	Sample size	Study type	Gene	SNP-rs number	Age at outcome assessment (child)	Outcomes	Summary of results & conclusions as presented in the paper	Limitations
[19] Alati (2013)	UK	7,062	Maternal-paternal comparison	na	na	11 years	Academic achievement: Key Stage 2 scores (standardised)	Maternal alcohol consumption abstainers: mean 102·0 (SD 9·1); <1 glass/week: mean 102·8 (SD 8·7) Paternal alcohol consumption abstainers: mean 98·9 (SD 11); <1 glass/week: mean 101·1 (SD 9·1)	Different confounding structures for the association of maternal vs. paternal alcohol with the outcome
[17] Alati (2008)	UK	4,332	Maternal-paternal comparison	na	na	8 years	IQ: Wechsler Intelligence Scale for Children (WISC)	Maternal alcohol consumption abstainers: mean 105·7 (SD 16·2); <1 glass/week: mean 106·4 (SD 16·3) Paternal alcohol consumption abstainers: mean 102·2 (SD 16·8); <1 glass/week: mean 104·0 (SD 16·7)	Different confounding structures for the association of maternal vs. paternal alcohol with the outcome

Abbreviations: OR: Odds ratio CI: Confidence intervals MD: Mean difference SD: standard deviation IQ: Intelligence quotient.

Discussion

Main findings: We conducted a comprehensive systematic review of the literature aimed at examining whether low levels of alcohol drinking in pregnancy have a causal detrimental effect on pregnancy and offspring outcomes. Our two main findings are: i) a surprisingly limited number of prospective studies specifically addressing the question of whether light maternal alcohol consumption (i.e. up to 32g/week (or 4 UK units) has any causal effect (adverse or beneficial) on infant and later offspring outcomes and pregnancy outcomes, and, as a result, ii) a paucity of evidence demonstrating a clear detrimental effect, or safe limit, of light alcohol consumption on outcomes. The upper limit that we chose to examine here is that of the current version of the UK National Institute for Health and Care Excellence (NICE) guidelines.[41] The question we have attempted to address is very important given the mixed advice that women are given with regards to whether they should abstain completely or be allowed light alcohol consumption in pregnancy. The lack of research evidence to address this question is notable.

Strengths and limitations: Strengths of this review include the completeness of searches with a focused research question aimed at informing alcohol in pregnancy guidelines. In addition to observational studies' biases minimised by only including those with prospective assessment of exposure and prioritising results adjusted for main confounders. Another strength of this review is the unique effort to include alternative study designs to further improve causal inference alongside standard analytical approaches. The main limitation of results on the effects of light drinking in pregnancy from standard analytical approaches is bias due to residual confounding. Women who drink low amounts of alcohol may be more likely to be of higher socio-economic position, compared to abstainers, at least in developed settings in recent years,[42] and both of these characteristics are associated with better pregnancy and cognitive outcomes.[43] Maternal smoking and ethnicity are also known correlates of maternal alcohol use, and risk factors for e.g. low birth weight.[44] Most studies included in this review adjusted for at least some of these factors. However, due to the small

number of studies included for any given outcome, it was impossible to formally investigate the effect of incomplete adjustment for some (or all) of these confounders. Additionally, for most outcomes, we could not pool eligible studies for various reasons (e.g. too few studies, lack of standard errors) and that we limited our review to a number of pre-specified outcomes including the most common pregnancy-related outcomes and childhood outcomes related to FASD. The inclusion of only English language studies may have led to missing some studies, however there is little evidence that exclusion of non-English language studies leads to systematic bias in systematic reviews of conventional medicine.[45-48]

Interpretation: This review demonstrates the paucity and poor quality of evidence addressing this important public health question, and the difficulty of designing studies that can effectively evaluate the causal impact of low alcohol consumption whilst minimising bias and confounding. It also shows the value of reporting measures of effect for meaningful categories of the exposure. Whilst many studies reported that associations did not differ from linearity prior to providing a single coefficient for the dose-response association, it is possible that statistical power limited the ability to detect non-linear associations in single studies. Such detail is especially important when there are controversies about the shape of the association of interest (linear, U or J-shaped) and/or the existence of safe thresholds. Outstanding questions also remain about the effects of maternal alcohol consumption at different stages of conception and pregnancy. Alternative analytical approaches such as sibling comparisons[49] and the use of instrumental variable approaches[50] as well as triangulating the totality of evidence from multiple study types[51] (formally or informally) are needed in order to strengthen confidence in the direction and size of any potential causal relationships.

The recently proposed change in the guidelines for alcohol use in pregnancy in the UK to complete abstinence, would be an application of the precautionary principle. This review confirmed some increased risk of babies being born SGA but little direct evidence of any

other detrimental effect for maternal drinking up to 32g/week. However, there have been few well-conducted studies examining this specific category of exposure. This issue remains of great public health importance, with alcohol consumption during pregnancy prevalent in the UK, Ireland, New Zealand and Australia and reaching up to 80% of pregnant women.[52] For some, the evidence of the potential for harm – mostly coming from animal experiments and human studies of effects due to higher levels of exposure will be sufficient to advocate that guidelines should advise women to avoid all alcohol in pregnancy, while others will wish to retain the existing wording of guidelines.[53]

In conclusion, we found limited evidence for a causal role of light drinking in pregnancy, compared to abstaining, on most of the outcomes examined. Despite the distinction between light drinking and abstinence being the point of most tension and confusion for health professionals and pregnant women and contributing to inconsistent guidance and advice now and in the past, our extensive review shows that this specific question is not being researched thoroughly enough, if at all. In addition, there has been no evidence regarding possible benefits of light alcohol consumption versus absence. Further studies, including those using designs that improve causal inference, are required to provide further evidence and a better estimation of the likely effects, in particular to inform expectant women who choose not to follow the new recommendation for abstinence or are anxious about their drinking in the very early stages before pregnancy recognition. Formulating guidance on the basis of the current evidence is challenging. However, describing the paucity of current research and explaining that “absence of evidence is not evidence of absence”, appears warranted.

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Details of contributors

Loubaba Mamluk: Drafting the protocol, preparing the data extraction database, data screening and collection (lead reviewer), data analysis, figures, tables, data interpretation, and drafting the manuscript. Hannah B Edwards: screening, data collection, data quality checking, data interpretation, and preparation of final manuscript. Theresa HM Moore: Advising on the protocol, preparing the protocol, screening title and abstract. Timothy Jones: Data extraction and full text screening. Sharea Ijaz: Abstract and full text screening. Jelena Savović: protocol development/study design (including the development of searching, article screening and data collection strategies), oversaw and managed the review process and the review team, provided methodological advice for the review and meta-analysis conduct, and critically revised the manuscript. George Davey Smith: Obtained funding, formulation of project plan, review of progress and of the manuscript. Jenny L. Donovan: Obtained funding and contributed to drafting the manuscript, and approved the final version. Verity Leach: Data extraction. Deborah A. Lawlor: contributed to the study design, data interpretation and review of earlier manuscript drafts; she approved the final version that has been submitted. Sarah J. Lewis: contributed to the study design, data interpretation and review of earlier manuscript drafts; she approved the final version that has been submitted. Abigail Fraser: Contributed to the study design, data analysis and interpretation and drafting of manuscript. Luisa Zuccolo: Contributed to the study design, data analysis and interpretation and drafting of manuscript. I, Loubaba Mamluk, the corresponding author of this manuscript, certify that I have full access to all the data in the study and had final responsibility for the decision to submit for publication.

Transparency declaration

I, Loubaba Mamluk, the corresponding author of this manuscript, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflict of interest:

The authors have nothing to disclose.

This work has not been submitted for publication elsewhere.

Disclosure

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Transparency declaration

The lead author (Loubaba Mamluk) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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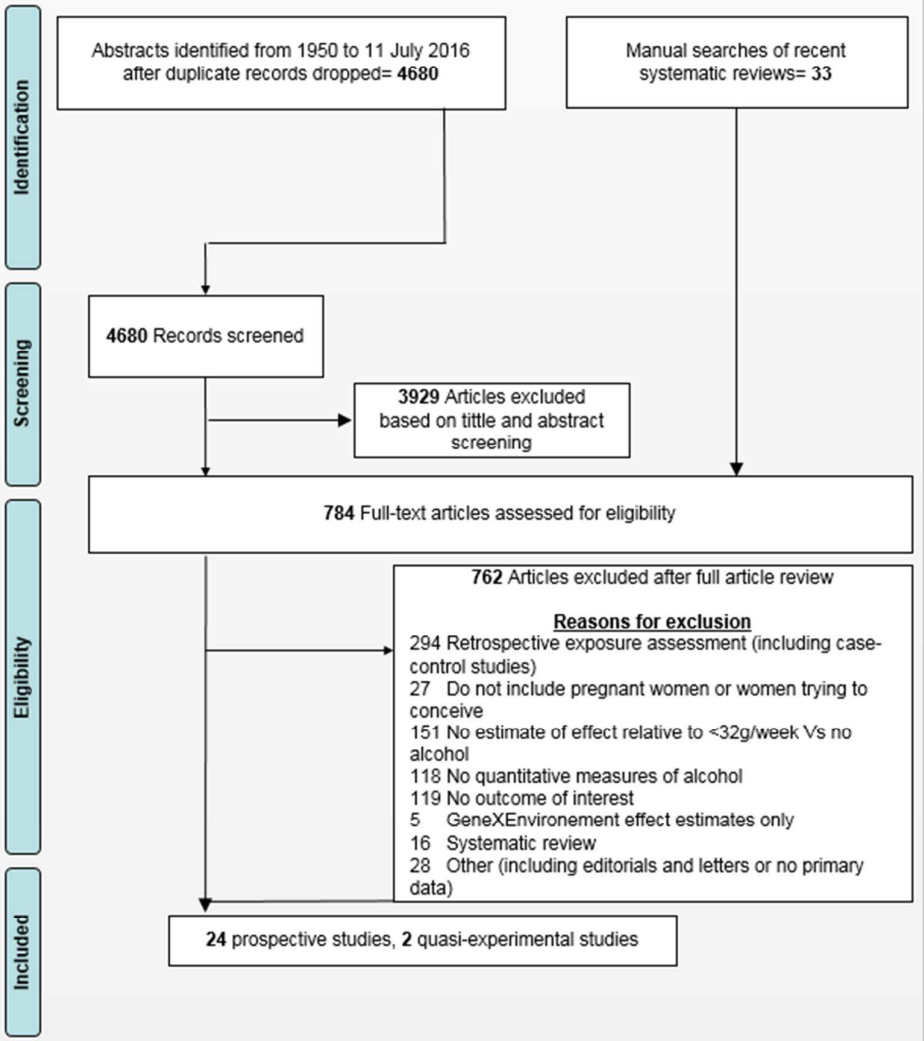


Figure 1. Flowchart of search strategy including primary reasons for article exclusion.

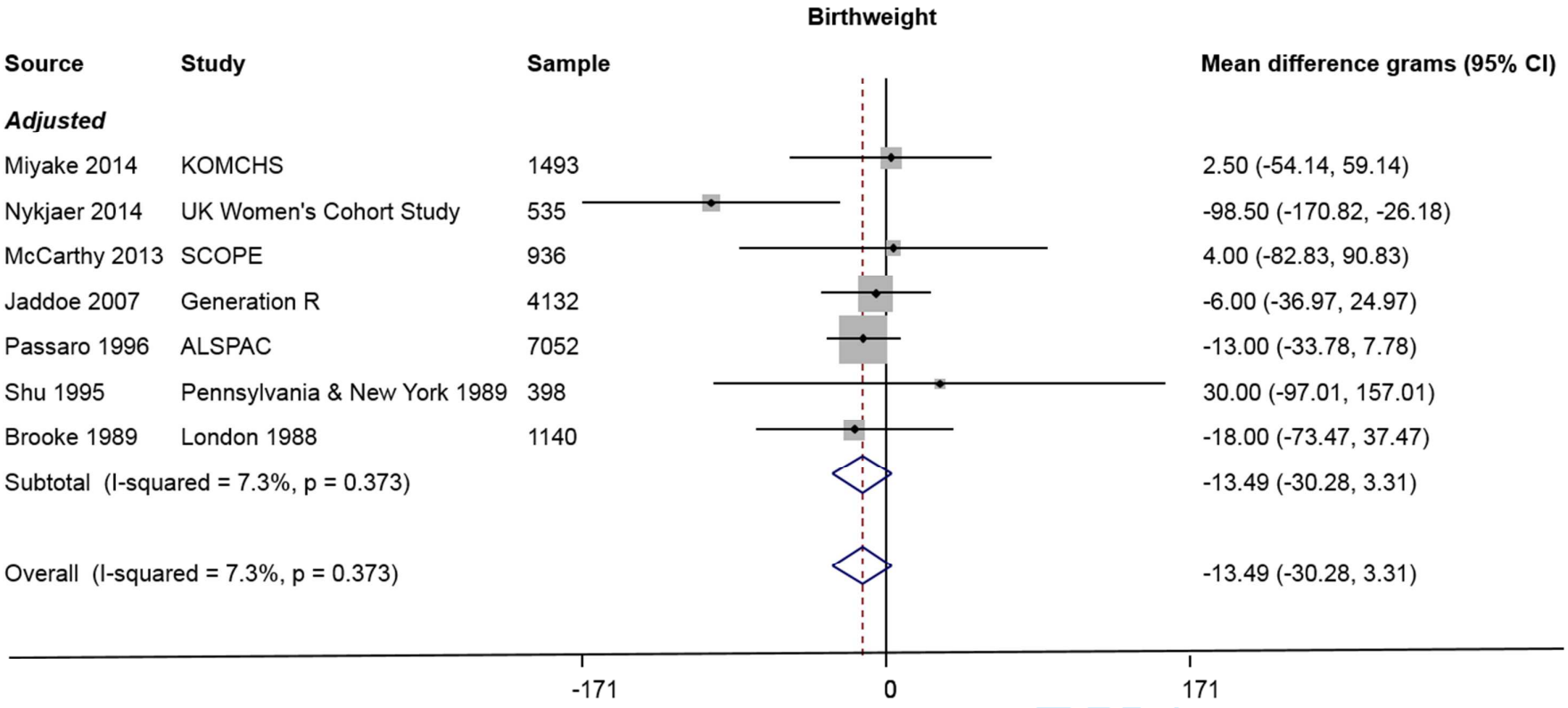
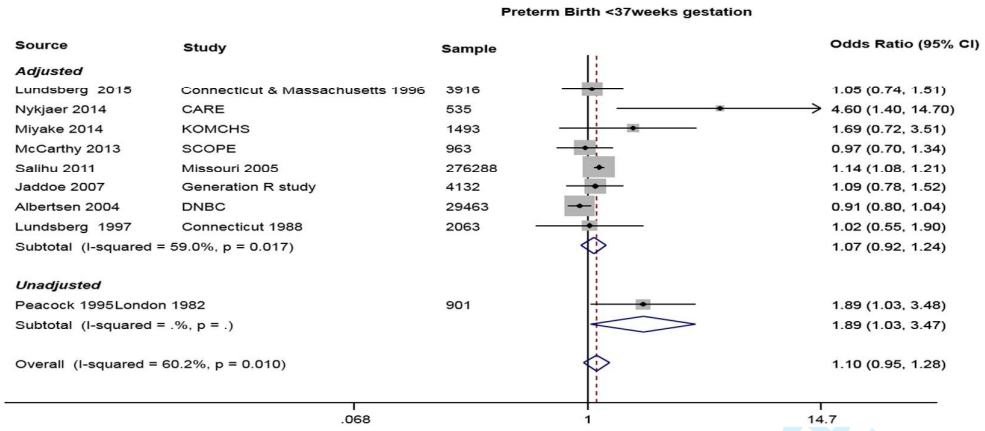
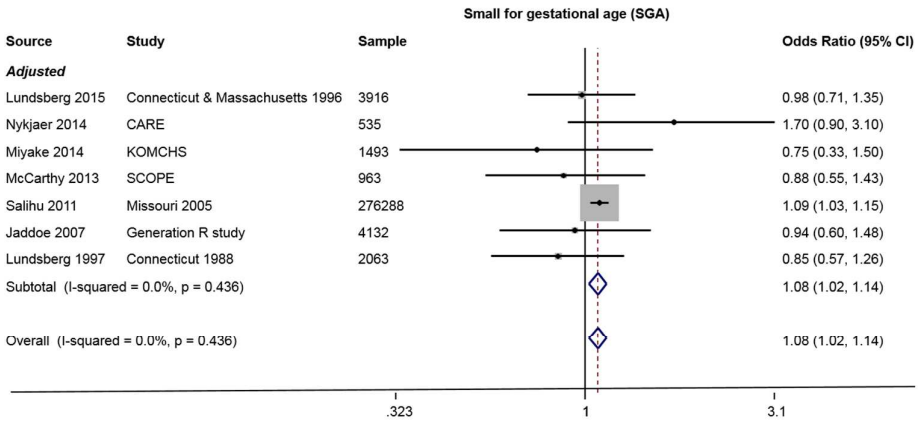


Figure 2. Pooled mean difference for birthweight comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (7 studies). 'Adjusted' refers to adjusted for both smoking and a measure of socio-economic status. CI: Confidence intervals.

a)

b)





c)

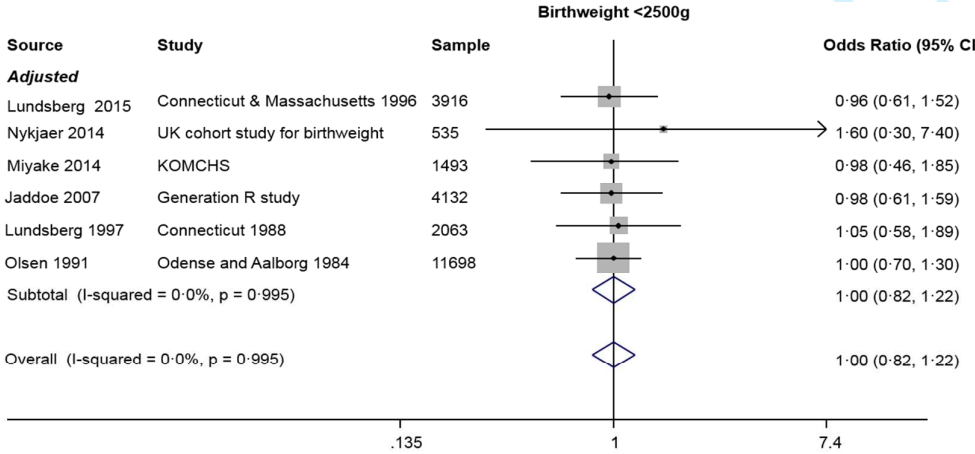
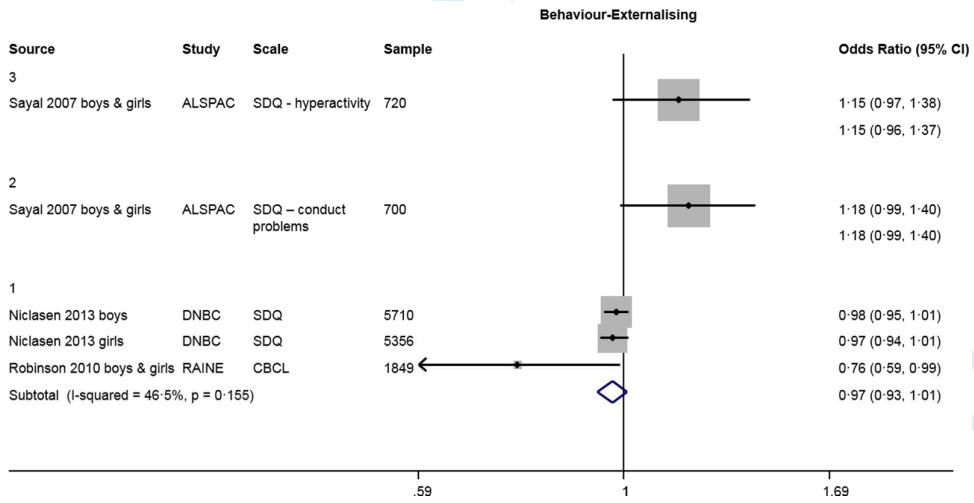


Figure 3a) Odd Ratios for preterm birth comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (8 studies); **3b)** Odd Ratios for small for gestational age comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (7 studies) **3c)** Odd Ratios for low birthweight comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (6 studies). OR: Odds ratio, CI: Confidence intervals. Pooled OR includes both adjusted and unadjusted estimates from studies, 'Adjusted' refers to adjusted for both smoking and a measure of socio-economic status.

Supplementary material

a)



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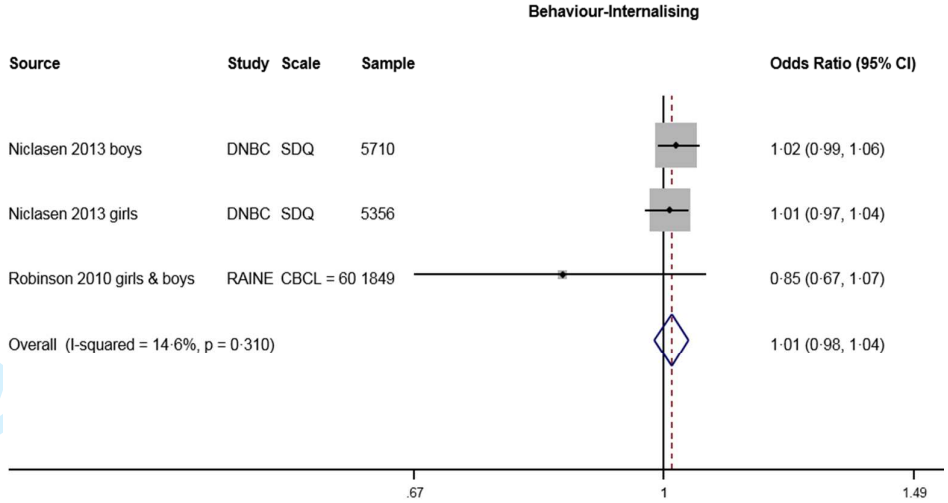
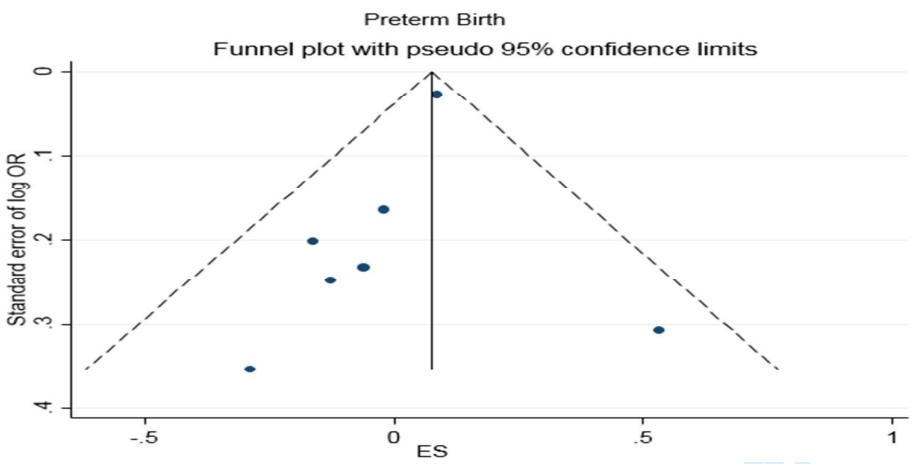


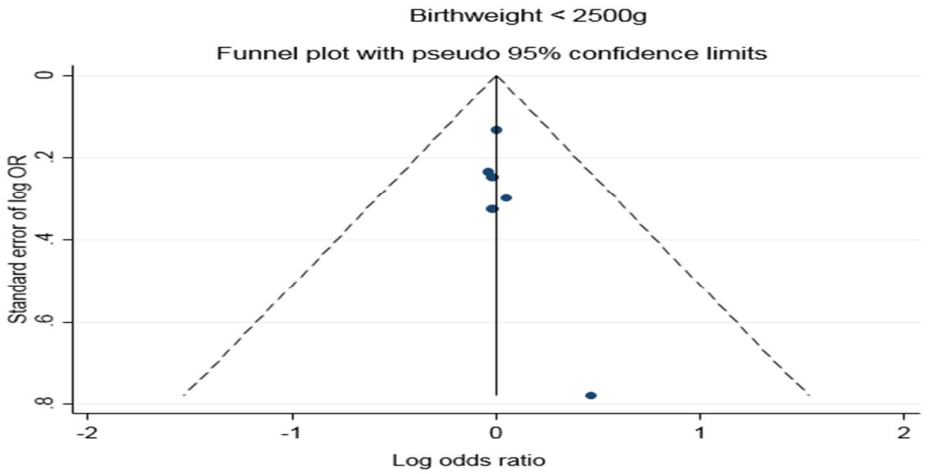
Supplementary figure 1a) Odds ratios for externalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (3 studies); **1b)** Odds ratios for internalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (2 studies); OR: Odds ratio, CI: Confidence intervals.

a)



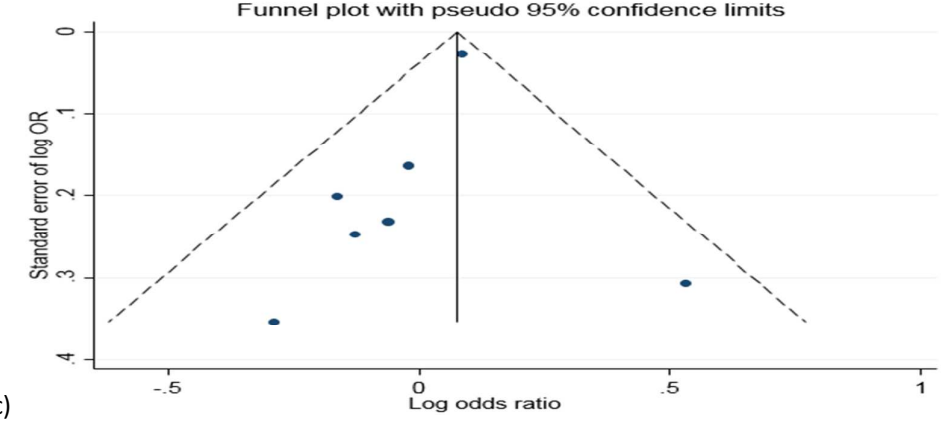
Supplementary figure 2a. Funnel plot of studies included in the meta-analysis for preterm birth.

b)



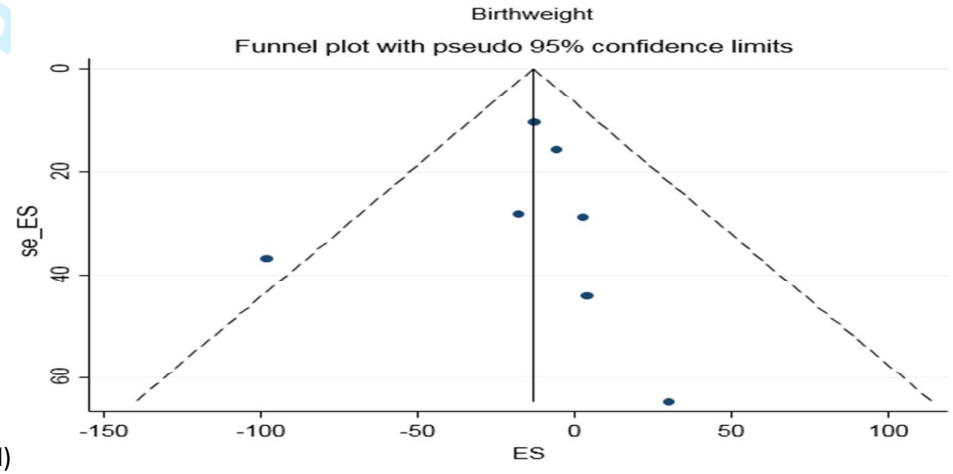
Supplementary figure 2b. Funnel plot of studies included in the meta-analysis for birthweight <2500g.

c)



Supplementary figure 2c. Funnel plot of studies included in the meta-analysis for small for gestational age.

d)



Supplementary figure 2d. Funnel plot of studies included in the meta-analysis for birthweight in grams.

Supplementary Table 1. Search Strategy 1950 to 11·07·2016. MEDLINE, PsycINFO, EMBASE on Ovid; the Cochrane Library including CENTRAL (the Cochrane Central Database of Controlled

Trials) on Wiley Interscience; and Science Citation Index, Social Science Citation Index, on Web of Science.

1 exp pregnancy/ (719661)

2 Pregnant Women/ (5199)

3 preconception care/ or prenatal care/ (21644)

4 exp "embryonic and fetal development"/ (212127)

5 Fetus/ (68424)

6 exp Pregnancy Complications/ (343999)

7 (prepregnan$ or conception or preconception or pregnan$ or prenatal$ or pre-natal$ or f?etal or f?etus or in utero).ti,ab. (588557)

8 Maternal exposure/ (5534)

9 or/1-8 (1079283)

10 Ethanol/ (73449)

11 Alcohol dehydrogenase/ (5809)

12 Aldehyde Oxidoreductases/ (3672)

13 exp Drinking Behavior/ (57821)

14 Temperance/ (2430)

15 alcohol$.ti. (106954)

16 (alcohol dehydrogenase or acetaldehyde dehydogenase).ti,ab. (8557)

17 ((alcohol or alcoholic) adj3 (drink$ or exposure or consumption or consume$ or consuming or low or light or moderat$ or abstin$ or abstain$)).ti,ab. (49470)

18 ((low or light or moderate or abstin$ or abstain$ or pattern$ or behavio?r$) adj3 drink$).ti,ab. (10558)

19 (ADH1B$ or teetotal$ or temperance or nondrink$ or non-drink$).ti,ab. (3093)

20 Genome-Wide Association Study/ or Linkage Disequilibrium/ or genotype/ or phenotype/ or polymorphism, genetic/ or (polymorphism$ or ((gene or genes or genetic or genotyp$) adj3 (instrument$ or variant$ or variable$ or variability or variabilities or variance$))).ti,ab. (494904)

21 *Alcohols/ or exp *Alcohol-Related Disorders/ or (alcohol adj3 (misuse or "use" or abuse or addict$ or dependence or response$ or susceptibility)).ti,ab. (110843)

22 20 and 21 (3108)

23 or/10-19,22 (213050)

24 9 and 23 (11403)
25 letter/ (861500)
26 editorial/ (368458)
27 news/ (166329)
28 exp historical article/ (325965)
29 Anecdotes as topic/ (4586)
30 comment/ (610211)
31 case report/ (1708277)
32 (letter or comment$).ti. (100442)
33 or/25-32 (3417468)
34 randomized controlled trial/ or Randomized Controlled Trials as Topic/ or random$.ti,ab. (888907)
35 33 not 34 (3386180)
36 animals/ not humans/ (3889478)
37 exp Animals, Laboratory/ (730783)
38 exp Animal Experimentation/ (6477)
39 exp Models, Animal/ not humans/ (310115)
40 exp rodentia/ (2688128)
41 (rat or rats or mouse or mice).ti. (1123907)
42 or/35-41 (7849766)
43 24 not 42 (6498)
44 meta-analysis/ (52850)
45 meta-analysis as topic/ (13933)
46 (meta analy$ or metaanaly$ or metanaly$ or meta regression).ti,ab. (72390)
47 ((systematic$ or evidence$ or realist or narrative or literature) adj2 (review$ or overview$)).ti,ab. (171877)
48 "review of reviews".ti,ab. (211)
49 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab. (27094)
50 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (28877)
51 (search$ adj4 literature).ab. (30686)

52 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or cinahl or science Citation index or bids or cancerlit).ab. (95294)

53 cochrane.jw. (11053)

54 ((multiple treatment$ or indirect or mixed) adj2 comparison).ti,ab. (991)

55 or/44-54 (293491)

56 43 and 55 (201)

57 epidemiologic studies/ (6077)

58 ep.fs. (1223653)

59 exp case control studies/ (691899)

60 exp cohort studies/ (1394149)

61 cross-sectional studies/ (185407)

62 Mendelian Randomization Analysis/ (229)

63 (case control or negative control).ti,ab. (93097)

64 (cohort adj (study or studies or analys$)).ti,ab. (98537)

65 ((follow up or observational) adj (study or studies)).ti,ab. (87771)

66 ((longitudinal$ or retrospectiv$ or prospectiv$) and (study or studies or studied or review$ or analys$ or cohort$)).ti,ab. (870699)

67 cross sectional.ti,ab. (183479)

68 (mendel$ or natural experiment$).ti,ab. (11082)

69 ((family or sibling or population) adj3 (study or studies)).ti,ab. (115245)

70 or/57-69 (2937160)

71 exp guideline/ (25834)

72 guidelines as topic/ or practice guidelines as topic/ (114690)

73 guideline$.mp. (291621)

74 or/71-73 (291621)

75 55 or 70 or 74 (3362878)

76 43 and 75 (3349)

77 limit 76 to english language (3096)

78 ((smok$ or drug$ or tobacco or nicotine or cigarette$ or substance$ or methamphetamine$ or amphetamine$ or cocaine$ or heroin or cannabis or marijuana) not (alcohol or alcoholic or drink$)).ti. (489662)

79 77 not 78 (2822)

Supplementary Table 2. Lists of confounders adjusted for by each study

Study (year)	Confounders
[20] Lundsberg (2015)	Parity, maternal age, education, BMI, marital status, ethnicity, caffeine, smoking, exercise, work, prenatal and multivitamin use, passive smoke exposure, marijuana use, cocaine use, study cohort, preterm labour, respiratory problem, infant gender, bleeding, nausea/vomiting, hypertension, incompetent cervix, placental problems, sexually transmitted disease, induction/augmentation, maternal asthma, gestational diabetes.
[21] Nykjaer (2014)	Maternal pre-pregnancy weight, height, age, parity, ethnicity, salivary cotinine levels, caffeine intake, education, energy intake, gestation and baby's sex
[22] Niclasen (2014)	Adjusted for the following confounders: parental smoking, parental education, parental pre-pregnancy psychiatric diagnoses, and maternal psychological well-being in pregnancy.
[23] Miyake (2014)	Low birth weight, preterm birth: maternal age; region of residence; number of children; family structure; maternal education; maternal employment; body mass index; maternal smoking during pregnancy; and baby's gender. Small for gestational age: maternal age; region of residence; number of children; family structure; maternal education; maternal employment; body mass index; maternal smoking during pregnancy; gestational age; and baby's gender.
[39] Faebo Larsen (2013)	Sex, gestational age, intrauterine growth restriction, maternal age, mother's occupational status, maternal smoking (ever) in first trimester, amount of maternal smoking and alcohol consumption in first trimester.
[15] Sayal (2013)	Maternal age, parity, highest level of maternal education, daily frequency of smoking, use of cannabis and/or other illicit drugs during the first trimester, homeownership, whether currently married, high scores (>12) on the Edinburgh Postnatal Depression Scale, and child gestational age, birth weight and gender.
[38] McCarthy (2013)	Maternal age, smoking, years of schooling, ethnicity, body mass index, infant sex, maternal status, family income, and drug use during pregnancy. Adjusted for clustering. Birthweight adjusted for gestational age at delivery.
[36] Andersen (2012)	Number of previous abortions, coffee consumption, changes in alcohol consumption since prior to pregnancy and smoking. Effect of coffee consumption and smoking was stratified according to period. The model is stratified according to maternal age and parity.
[14] Salihu (2011)	Maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, maternal height, gender of the infant, and year of birth
[24] Robinson (2010)	Maternal age, maternal education, presence of the biological father in the family home, family income, stress in pregnancy, child's age at follow up (and child's age at follow-up squared), and maternal cigarette smoking.
[25] Jaddoe (2007)	Controlled for maternal body mass index, smoking, educational level, height, ethnicity, parity and age and infant gender; birth weight and low birth weight models also controlled for gestational age.
[33] Bille (2007)	Parental age and social class
[26] Sayal (2007)	Gender, smoking, cannabis use and use of illicit drugs in the first trimester; highest level of maternal education; home ownership; marital status; parity; maternal age group; high EPDS score; child ethnicity; gestational age group; and birth weight
[27] Albertsen (2004)	Type 1 diabetes, age, previous preterm delivery, smoking during pregnancy, coffee consumption during pregnancy, occupational status in the household, parity, and total alcohol consumption during pregnancy.
[28] Lundsberg (1997)	Small for gestational age: smoking in month 7, ethnicity, weight, height, infant sex, parity, bleeding during pregnancy, high blood pressure, and preeclampsia/eclampsia. Low birthweight: smoking in month 7, height, weight, ethnicity, infant sex, parity, coffee use in month 7, exercise in third trimester, employment, bleeding during pregnancy, high blood pressure, pre-eclampsia/eclampsia, anomalies, and placental problems. Preterm delivery: smoking in month 7, height, parity, age, caffeine use in month 7, exercise first 16 weeks, bleeding during pregnancy, high blood pressure, pre-eclampsia/eclampsia, anomalies, and placental problems.
[37] Windham (1997)	Maternal age, prior spontaneous abortion, gestational age at interview, and cigarette and caffeine consumption in week before interview.
[29] Passaro (1996)	Gestational age, infant sex, parity, maternal smoking, and maternal body mass index.
[30] Shu (1995)	Gestational age, parity, smoking and income.
[16] Peacock (1995)	Unadjusted
[31] Olsen (1991)	Age, school education and parity, alcohol and smoking entered the model as "dummy variables".
[35] Ogston (1992)	Gestational age at birth, sex, mother's age, parity and smoking.
[40] Parry (1992)	Gestational age at birth, sex, mother's age, parity and smoking.
[32] Brooke (1989)	Gestational age, sex, maternal height, and parity

[34] Ernhart (1989)	Parity, smoking, race and year of study.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6 & 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	33-39
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7 & 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6 & 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8 & 9
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MOOSE Checklist for Meta-analyses of Observational Studies

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3	Description of study outcome(s)	6&7
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	supplementary table 1
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	7
11	Search software used, name and version, including special features used (eg, explosion)	supplementary table 1
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	NA
15	Method of handling abstracts and unpublished studies	supplementary table 1
16	Description of any contact with authors	NA
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the	6

	hypothesis to be tested	
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	NA
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	supplementary table 2 & 8
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8
22	Assessment of heterogeneity	Figures 2&3
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	9&10
24	Provision of appropriate tables and graphics	27-36
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BMJ Open

Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-015410.R1
Article Type:	Research
Date Submitted by the Author:	24-Apr-2017
Complete List of Authors:	Mamluk, Loubaba; University of Bristol School of Social and Community Medicine, IEU Edwards, Hannah; University of Bristol, School of Social and Community Medicine Savovic, Jelena; University of Bristol, NIHR CLAHRC West Leach, Verity; University of Bristol Jones, Tim; NIHR CLAHRC West, Moore, Theresa; NIHR CLAHRC West Ijaz , Sharea ; NIHR CLAHRC West Lewis, Sarah; University of Bristol, School of Social and Community Medicine Donovan, Jenny; NIHR CLAHRC West Lawlor, Debbie; Department of Social Medicine, University of Bristol, MRC Integrative Epidemiology Unit Davey Smith, George; University of Bristol, Social Medicine Fraser, Abigail; University of Bristol, MRC Integrative Epidemiology Unit Zuccolo, Luisa; University of Bristol, School of Social and Community Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Reproductive medicine
Keywords:	PAEDIATRICS, EPIDEMIOLOGY, Maternal medicine < OBSTETRICS

Systematic Review & Meta-analysis

Title: Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses.

Running tittle: Low alcohol consumption and pregnancy and childhood outcomes.

Authors: Loubaba Mamluk PhD[1,2,3], Hannah B Edwards MSc[2,3], Jelena Savović PhD[2,3], Verity Leach PhD [2,3], Timothy Jones PhD [2,3], Theresa HM Moore MSc [2,3], Sharea Ijaz PhD [2,3], Sarah J. Lewis PhD [2], Jenny L. Donovan PhD [2,3], Debbie Lawlor PhD [1,2,3], George Davey Smith PhD [1,2], Abigail Fraser PhD*[1,2], Luisa Zuccolo PhD*[1,2]

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Word Count: 3802
Figures: 3
Tables: 3
Supplementary Tables: 3
Supplementary Figures:1
Supplementary Document:1
Number of references: 61

Abstract:

Objectives: To determine the effects of low-to-moderate levels of maternal alcohol consumption in pregnancy on pregnancy and longer-term offspring outcomes.

Search Strategy: Medline, Embase, Web of Science, and Psychinfo from inception to 11-07-2016.

Selection Criteria: Prospective observational studies, negative control and quasi-experimental studies of pregnant women estimating effects of light drinking in pregnancy (≤32g/week) versus abstaining. Pregnancy outcomes such as birth weight, and features of fetal alcohol syndrome were examined.

Data Collection and Analysis: One reviewer extracted data and another checked extracted data. Random effects meta-analyses were performed where applicable, and a narrative summary of findings was carried out otherwise.

Main Results: 24 cohort and two quasi-experimental studies were included. With the exception of birth size and gestational age, there was insufficient data to meta-analyse or make robust conclusions. Odds of small-for-gestational-age (SGA) and preterm birth were higher for babies whose mothers consumed up to 32g/week versus none, but estimates for preterm birth included the null value: summary odd ratios (OR) 1·08, 95% confidence intervals (CI) (1·02 to 1·14), I^2 0%, (7 studies, all estimates were adjusted) OR 1·10, 95%CI (0·95 to1·28), I^2 60%, (9 studies, includes one unadjusted estimates) respectively. The earliest time points of exposure were used in the analysis.

Conclusion: Evidence of the effects of drinking <=32g/w in pregnancy is sparse. As there was some evidence that even light prenatal alcohol consumption is associated with being SGA and preterm delivery, guidance could advise abstention as a precautionary principle, but should explain the paucity of evidence.

Keywords: Alcohol, pregnancy, systematic review.

Strengths and Limitations of this study:

Strengths

- Completeness of searches with a focused research question aimed at informing alcohol in pregnancy guidelines.
- Biases minimised by only including those with prospective assessment of exposure and prioritising results adjusted for main confounders.
- Unique effort to include alternative study designs to further improve causal inference alongside standard analytical approaches.

Limitations

- Limitation of results on the effects of light drinking in pregnancy from standard analytical approaches is bias due to residual confounding.
- The inclusion of only English language studies may have led to missing some studies, however there is little evidence that exclusion of non-English language studies leads to systematic bias in systematic reviews of conventional medicine.
- We could not pool eligible studies for various reasons (e.g. too few studies, lack of standard errors)

Keywords: Alcohol, pregnancy, systematic review.

Introduction

Alcohol is a known teratogen[1] and the evidence about the risks of heavy alcohol consumption during pregnancy on intellectual ability, birth defects, behaviour, fine motor skills, and mental health (comprising fetal alcohol spectrum disorder – FASD)[2] is clear and compelling.[3] Internationally, clinical guidelines recommend that pregnant women should abstain from heavy or "binge" drinking.[4] However, until recently UK guidelines advised women to avoid drinking alcohol while trying to conceive, and in the first trimester, but at the same time indicated that consumption should be restricted to within "1 to 2 UK units, once or twice a week".[5] The UK Chief Medical Officer (CMO) commissioned a review of guidelines on alcohol consumption during pregnancy. Based on a review of reviews, the Guidelines Development Expert Group has recently proposed a change to guidelines such that women should be advised to abstain from alcohol when pregnant and/or trying to conceive,[6] based on the precautionary principle (i.e. "better safe than sorry"), in the absence of robust evidence.

Our aim 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 in pregnancy on pregnancy and longer term offspring outcomes. Here we report on alcohol consumption of up to two UK units of alcohol up to twice a week (the equivalent of ~ 32g/week), compared to no alcohol. In the absence of evidence from randomised controlled trials, we examine observational studies of pregnant women from the general population with prospective assessment of alcohol exposure, to reduce recall bias. In particular, we specifically seek out quasi-experimental studies, negative control comparisons, and Mendelian randomisation analyses in order to reduce the impact of confounding and measurement error on the effect estimates.

Methods

Selection strategy and selection criteria

A full protocol of this systematic review carried out using PRISMA guidelines[7] is available from the PROSPERO systematic review register (registration number CRD4201501594); http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015941).

In brief, eligible studies were defined as epidemiological studies of pregnant women or women trying to conceive with prospective assessment of prenatal alcohol exposure (i.e. before birth), sampled from general population. The protocol specifically included studies using standard analytical approaches (e.g. multivariable regression analysis), as well as studies that used innovative analytical methods to improve causal inference, 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 to the association of the same outcomes with consumption among fathers, under the assumption that confounding is likely to be similar but that if there was a direct causal effect of maternal consumption on outcomes, maternal associations would be stronger); and Mendelian randomisation studies (using genetic variants associated with alcohol consumption and metabolism). We considered these analytical approaches to be the most appropriate in terms of their ability to minimise bias from confounding and other sources. Our original protocol included studies exploring the effects of prenatal alcohol consumption up to 83g/week (the commonly used threshold for moderate consumption [8-10]) versus abstinence. Here we have focused specifically on low alcohol consumption, i.e. up to 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.[5] This specific cut off value has not been reviewed and is the main point of discussion as the guideline change from low consumption (equating to 1 to 2 UK units, once or twice a week or 32g/week) to abstinence (reference group).

Outcomes included: 1) pregnancy outcomes: still birth (pregnancy loss after week 24; miscarriage; gestational length and preterm delivery (<37 weeks gestation); hypertensive disorders of pregnancy; gestational diabetes; small for gestational age (SGA), < 10th percentile in weight or <−2 standard deviation scores) and birth size (weight (including low birth weight defined as <2500g), length, and head circumference); low amniotic fluid (oligohydramnios); placenta previa; placental abruption; assisted delivery (including vacuum extraction, forceps delivery, Caesarean section); Apgar score at birth; admission to neonatal unit; congenital malformations. 2) Features of foetal alcohol spectrum disorder (FASD): childhood growth restriction; cranium size and head circumference; developmental delays; behaviour problems; cognitive impairment and intelligent quotient (IQ); facial malformations. We adopted study specific definitions for all outcomes.

Studies were excluded if: there was no quantitative measure of alcohol consumption that could be converted to grams of alcohol/week; there was insufficient data to estimate the effect size of the association of our pre-defined low consumption categories versus abstinence with any outcome, including studies that analysed alcohol as a continuous variable (i.e. assuming the same linear or log linear effect across the entire alcohol distribution); the lowest exposure category (compared to non-drinkers) had an upper bound exceeding 32g/week, or was unspecified; they were cohort studies of pregnant women with alcohol abuse/dependency; they were case-control studies or cohort studies with retrospective alcohol consumption assessment (e.g. after birth).

The following databases were searched: MEDLINE, PsycINFO, EMBASE on Ovid; the Cochrane Library including CENTRAL (the Cochrane Central Database of Controlled Trials) on Wiley Interscience; and Science Citation Index, Social Science Citation Index, on Web of Science from inception to 11 July 2016 (supplementary Table 1). We limited the search to English language papers and excluded animal studies, letters, editorials, and conference proceedings for which there were no full-text papers. Searches were tailored to each

database by investigators. The search focused on published medical literature and did not include grey literature. We additionally performed manual searches of the reference lists of: (i) all papers included in recent systematic reviews of the effects of prenatal alcohol exposure on the outcomes of interest; and (ii) all recent papers citing those reviews. Titles and abstracts, and full texts if necessary, were screened independently by two reviewers. Discrepancies were discussed and disagreements resolved through consensus. We assessed potential for bias in included studies by assessing how well the study adjusted for several main confounders known to impact on the exposure-outcome associations (socioeconomic positioning as measured by the individual study, smoking during pregnancy, maternal age, and ethnicity). We considered the potential for confounding and bias across studies included in the analyses and described it narratively alongside summary results.

Data extraction

Data were extracted into a custom-built Microsoft Access database. We extracted the following information from each study: title, authors, publication year, country/region, study design, population characteristics (sample size, methods of sampling, age distribution, and ethnicity), measures of exposure (assessment method; including timing and quantification of alcohol consumption, reference group (abstinence), exposure (e.g 1-2 units or 2-4 units), and information on unit equivalence if stated), outcome assessment methods (including whether this was abstracted from medical records, obtained via a research interview and the person reporting the outcome e.g. parent, teacher, health professional, researcher or child), model adjustments, and study results. If a study reported more than one result for each outcome, we extracted all of them (e.g. relative to different timing of exposure, model adjustments, etc.). Information from each included paper was extracted by one reviewer (LM) and subsequently checked for accuracy and completeness by another reviewer (HE).[11] Extraction errors were minimal and were resolved through discussion between extractor and checker.

Alcohol unit conversion

Alcohol consumption in drinks/week was converted into grams/week based on the pure ethanol equivalent of one drink, as stated in each individual article, or otherwise inferred based on the definition of standard drinks in the country where the study took place.

Data analysis

The association of low alcohol use with pregnancy and related outcomes was investigated comparing the highest category within the range of 0-32g/week to abstention (during pregnancy). In studies providing data across several categories of intake within the 0-32g/week range, we used the effect estimate for the highest category of intake. If studies reported on exposure to alcohol during different trimesters, we included estimates relative to the earliest exposure. This is because for some outcomes, the first trimester tends to be the most critical timing/window of exposure [12] [13] and because most studies that only reported on one time point reported on exposure in early gestation. Similarly, if results were available from both unadjusted and adjusted regressions, we prioritised fully adjusted results, as a way of minimising the impact of confounding by important factors such as maternal smoking, age, socio-economic position and ethnicity. In case of multiple results from the same cohort (relative to the same outcome), we analysed those pertaining to the largest population size (i.e. conducted on the least 'selected' population as result of exclusions, to minimise selection bias). Results from all studies that fulfilled our inclusion criteria were summarised, together with information about the study. Where appropriate, we additionally pooled results for each outcome. Authors were not contacted for extra data. Results from Different study designs have been reviewed separately. Individual study estimates were pooled using random effects meta-analysis. Where only two studies were available to meta-analyse, results were pooled unless they were very different from each other ($I^2 \geq 50\%$).[14] In this case, a narrative summary of findings was carried out and results were reported in Table 2. Where a study only reported unadjusted results, we kept

these separate in the forest plots (sub-group analysis) but then also showed overall pooled estimates combining all results.

Planned sub-group analyses by trimester could not be performed due to insufficient number of included studies with this information.

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) [15] was used to assess risk of bias for included reports. This is an eight-item questionnaire assessing the following: representativeness of the exposed cohort; selection of the non-exposed cohort; exposure assessment methods; absence of outcome (of interest) at the start of the study; comparability of exposed and non-exposed groups (with regard to confounding variables); blind assessment of exposure and outcome; and length and adequacy of follow up. NOS allocates 'stars' for adequate methods, but does not specifically advise calculating the sum of allocated stars to give an overall score. Scores for quality are not helpful in assessing the effect of risk of bias on a meta-analysis so we report each item separately in line with recommended methods [16 17]. To be assessed as adequate for comparability of cohorts (risk of confounding) a study had to control for the following four pre-specified potential confounding factors related to foetal development: maternal age, socio-economic status (SES), ethnicity, and smoking.

The likelihood of small study bias, such as publication bias, could not be assessed through visual inspection of funnel plots for pooled analyses as no outcome was assessed by 10+ studies [18]. Statistical analyses were carried out using Stata version 13.1 (StataCorp, College Station, TX, USA).[19]

Results

A flowchart of the article review process is shown in Figure 1. A total of 4680 citation records were identified from searching the four relevant databases. A manual search of recent systematic reviews identified 33 additional articles. After exclusions, 24 prospective studies

analysed using standard approaches and two quasi-experimental studies were included, reporting on 30 outcomes in total.

Risk of bias

Six studies (Albertson 2003; Anderson 2012; Bille 2007; Brooke 1989; Lundsberg 2015; McCarthy 2013) had low risk of bias for all eight NOS items and were therefore considered at low risk of bias overall. All studies were judged to be at a low risk of bias for the following three NOS items: selection of the non-exposed cohort (always from the same source population as the exposed cohort); the absence of outcome at the start of the study; and adequate length of follow up for outcome to have occurred. Fourteen studies had adequate ascertainment of exposure as these were all based on structured interviews or validated records. Objective outcome assessments (assessor unaware of the exposure status) were reported in 16 of the studies. For five others either parent self-report was used (high risk), and for the remaining three the method of outcome assessment was not reported (unclear risk). Eleven studies did not report enough detail to decide if cohorts were representative of the population, therefore only 10 could be judged as low risk. Only four studies did not control for the pre-specified potential confounding factors, and one did not report enough detail to permit judgement. Thus, in the majority of studies (19) the compared groups were similar. Nineteen studies had adequate follow up of the cohort (small loss to follow up). Only three were judged high risk for this item and two studies presented insufficient information to make a clear judgment. Standard analytical approaches

Pooled estimates for continuous and binary outcomes are presented in Figure 2 and 3 respectively.

Figure 2 presents results for birthweight (7 studies). Figure 3A presents results for preterm delivery (9 studies) Figure 3B, presents results for SGA (7 studies), and results for low birthweight (6 studies) are given in Figure 3C.

The meta-analysis yielded a summary OR of 1·10 (95% CI 0·95; 1·28) for preterm delivery, but there was substantial statistical heterogeneity between studies (I^2=60%), due to a large Danish study reporting a protective effect (Figure 3A). Additionally, most studies assessing preterm birth had corrected for main confounders know to be associated with preterm birth, with the exception of [20] that did not correct for any. There was also modest evidence for an increased risk of being SGA (OR 1·08, 95% CI 1·02; 1·14) for a total of 288512 participants, although this was almost entirely driven by a single US study contributing 95% of the participants to this meta-analysis (Figure 3B). The birthweight meta-analysis yielded a summary effect of -13·49g (95% CI -30·28g; +3·31g) for offspring of light drinkers versus non-drinkers (Figure 2). Summary effect for birthweight <2500g was, OR 1·00, 95% CI 0·82; 1·22 (Figure 3C).

Other outcomes were typically reported by a limited number of studies and mostly could not be meta-analysed due to clinical heterogeneity in outcome assessment or incompleteness of published data (supplementary Figure 1, and Table 2). Based on two studies with data on behavioural outcomes, there was little evidence of any effect for internalising symptoms but a suggestion that light drinking in pregnancy protected against high externalising behaviour scores (OR 0·97, (95%CI 0·93; 1·01, supplementary Figure 1)). However, an additional study assessing conduct problems and hyperactivity (in the same externalising domain) reported results in the opposite direction, which could not be meta-analysed due to different outcome definitions.

Table 2 presents results of included studies that did not contribute to the meta-analyses for various reasons. There was no strong evidence of association between consuming up to 32 g/week of alcohol and any of the remaining outcomes excluded from meta-analyses, with three exceptions: a very large US study showing increased risk of placental abruption and decreased risk of pre-eclampsia (OR 1·24, 95%CI 1·05; 1·46 and OR 0·82, 95% CI 0·74; 0·90, respectively)[21], and a single British study reporting better cognitive outcomes in children exposed to light maternal drinking in pregnancy.[22]

We did not include funnel plots as no outcome was assessed by 10+ studies.

Of all included results, only two were unadjusted[20 23], and most of the others were adjusted for maternal smoking, age and socio-economic position (supplementary Table 2). Studies that did not adjust for ethnicity were generally conducted in homogenous populations. Due to the small number of studies for each outcome, we could not further investigate the effect of adjusting for all or some of these confounders. Similarly, there was insufficient data to examine the effect of timing of exposure on outcomes.

Alternative analytical approaches

Two negative control publications[24] based on the same UK cohort met our inclusion criteria.[23 25] They investigated the effects of maternal alcohol consumption on childhood educational achievement[25] and IQ.[23] Offspring exposed to maternal consumption of <12g/week of alcohol in the first trimester did not have worse outcomes compared to those of mothers who abstaining from alcohol, and a similar pattern was found for paternal alcohol consumption.

One further quasi-experimental study, one natural experiment and five Mendelian randomisation studies were excluded from the present review because they did not specifically test the effect of consuming up to 32g/week in pregnancy versus abstaining. These will be included in a forthcoming review focused on estimating the causal effects of prenatal alcohol exposure based on alternative study designs and analytical approaches to strengthen causal evidence.

Table 1. Prospective studies examining the effects of prenatal alcohol exposure on pregnancy outcomes (studies included in the meta-analysis)

Study (year)	Country	Event	Total number	Outcomes	Timing of exposure	Age at outcome assessment (child)	Adjusted (yes/no)
[26] Lundsberg (2015)	USA	191 315 274	3,907	Birth weight (<2500g) SGA (< 10th percentile) Preterm birth (<37 weeks)	1st trimester	Birth	Yes
[27] Nykjaer (2014)	UK	- - - - 23	535	Birth weight (g) Customised birth centile SGA (< 10th centile) Low birth weight (<2500g) Preterm birth (<37 weeks)	1st trimester	Birth	Yes
[28] Niclasen (2014)	Denmark	-	10,649	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ), Parent report Boys Internalising behaviour Girls Internalising behaviour Boys Externalising behaviour Girls Externalising behaviour	Entire pregnancy	7 years	Yes
[29]Miyake (2014)	Japan	126 185 - 202	1,493	Preterm birth (<37 weeks) SGA (< 10th percentile) Adjusted mean birth weight Low birth weight (<2500g)	Between 5th and 39th weeks of pregnancy	0-11 months	Yes
[30] McCarthy (2013)	New Zealand, Australia, UK, and Ireland	- 325 150	3166	Birthweight SGA (< 10th percentile) Preterm birth (<37 weeks)	1st trimester	Birth	yes
[21] Salihu (2011)	USA	-	-	Preterm birth (<37 weeks) SGA (< 10th percentile)	Within the gestational age range 20-44 weeks	Birth	Yes
[31] Robinson (2010)	Australia	202	1335	Clinically significant problems (T score ≥60),Child Behaviour Checklist (CBCL) Parent report Internalising behaviour Externalising behaviour	2nd trimester	2-14 years inclusive	Yes
[32] Jaddoe (2007)	Holland; UK	- - -	4,132	Low birth weight SGA (weight < −2 standard deviation scores) Preterm birth (<37 weeks) Birth weight	Late pregnancy	Birth	Yes
[33] Sayal (2007)	UK	-	10,323	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Hyperactivity* - Externalising	1st trimester	7.75 years	Yes
[33] Sayal (2007)	UK	-	10,323	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report C*onduct problems*- Externalising	1st trimester	7.75 years	Yes
[34] Albertsen (2004)	Denmark	1488	29,463	Preterm birth (<37 weeks) Moderate preterm birth (32-37 weeks) Very preterm birth (<32 weeks)	During pregnancy	Birth	Yes
[35] Lundsberg (1997)	USA		2,062	SGA (lowest 10th percentile) Low birth weight Preterm delivery (<37 weeks)	1st trimester	Birth	Yes
[36] Passaro (1996)	UK		8,886	Birth weight (g)	At booking for antenatal care (before 24 weeks gestation)	Birth	Yes
[37] Shu (1995)	USA		638	Birth weight (g)	Throughout pregnancy (12.9, 28 & 36 weeks gestation)	Birth	Yes
[20] Peacock (1995)	UK	64	901	Preterm birth (<37 weeks)	At booking for antenatal care (before 24 weeks gestation)	Birth	No

[38] Olsen (1991)	Denmark	8772	Birth weight (<2500g)	During the first 36 weeks gestation	Birth	yes
[39] Brooke (1989)	UK	1,140	Birthweight (g)	Early pregnancy	Birth	yes

SGA: small for gestation age

Table 2. Prospective studies examining the effects of prenatal alcohol exposure on pregnancy outcomes (results not included in the meta-analysis)

Outcome	Study (year)	Country (Total number)	Outcome details	Reason not included in meta-analysis	Age at outcome assessment (child)	Results [1]	Adjusted (yes/no)
Pregnancy outcomes							
Stillbirth	[40] Andersen (2012)	Denmark (89,322)	Stillbirth	Estimates are in different directions	(Outcome confirmed via National / Hospital Registries, or from maternal report)	OR 0·90 (95% CI 0·73 – 1·12)	Yes
	[21] Salihu (2011)	USA (1,226,685)	Stillbirth	Estimates are in different directions	Birth	OR 1·10 (95% CI 0·88 – 1·39)	Yes
Miscarriage	[40] Andersen (2012)	Denmark (89,322)	Miscarriage in first trimester	Only study with this outcome	(Outcome confirmed via National / Hospital Registries, or from maternal report)	OR 1·05 (95% CI 0·94 – 1·18)	Yes
	[41] Windham (1997)	USA (5,324)	Spontaneous abortion occurring ≤20 weeks gestation	Only study with this outcome	(Outcome confirmed via medical records)	OR 1·0 (95% CI 0·7 – 1·5)	Yes
Gestational age and preterm birth	[36] Passaro (1996)	UK (10,539)	Gestational age	Only study with this outcome	Birth	Mean gestational age 40·1 (SD 1·9) for those exposed, compared to 40·1 (SD 2·0) for those unexposed.	Yes
	[42] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Per cent of infants with gestational age <37 weeks			3·7% in those exposed compared to 3·9% in those unexposed.	Yes
Birthweight	[42] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mean birthweight (g) in non-smokers	SE/SD not reported	Birth	3414g in those exposed, compared to 3363g in those unexposed.	Yes
	[42] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mean birthweight (g) in smokers	SE/SD not reported	Birth	3225g in those exposed, compared to 3225g in those unexposed.	Yes
Placenta-related	[21] Salihu (2011)	USA (1,226,685)	Placental abruption	Only study with this outcome	Birth	OR 1·24 (95% CI 1·05 – 1·46)	Yes
	[21] Salihu (2011)	USA (1,226,685)	Placenta previa	Only study with this outcome	Birth	OR 1·11 (95% CI 0·87 – 1·43)	Yes
Pre-eclampsia	[21] Salihu (2011)	USA (1,226,685)	Pre-eclampsia	Only two studies with this outcome	Birth	OR 0·82 (95% CI 0·74 – 0·90)	Yes
	[30] McCarthy (2013)	New Zealand, Australia, Ireland, UK	Pre-eclampsia	Only two studies with this outcome	Birth	OR 0·59 (95% CI 0·35 – 0·99)	Yes
Height	[26] Lundsberg (2015)	USA (4,496)	Lowest 10th percentile of birth length	Only study with this outcome	Birth	OR 1·10 (95% CI 0·78 – 1·54)	Yes
Head circumference	[26] Lundsberg (2015)	USA (4,496)	Lowest 10th percentile of head circumference	Only study with this outcome	Birth	OR 1·08 (95% CI 0·83 – 1·42)	Yes
Apgar score	[26] Lundsberg (2015)	USA (4,496)	Apgar <7 at 5 minutes	Only study with this outcome	Birth	OR 1·61 (95% CI 0·67 – 3·84)	Yes
Admission to Neonatal Intensive Care Unit (NICU)	[26] Lundsberg (2015)	USA (4,496)	Admission to NICU	Only study with this outcome	Birth	OR 1·12 (95% CI 0·86 – 1·46)	Yes
Features of foetal alcohol spectrum disorder (FASD)							
Malformations	[26] Lundsberg (2015)	USA (4,496)	Major malformations	Only study with this outcome	Birth	OR 0·78 (95% CI 0·40 – 1·50)	Yes

	[43] Bille (2007)	Denmark (1020)	Oral clefts	Only study with this outcome	Birth	OR 1·06 (95% CI 0·74 – 1·50)	Yes
	[44] Ernhart (1989)	USA (873)	Craniofacial anomalies	SE/SD not reported	Birth	Mean craniofacial anomalies was 1·92 for those exposed, compared to 1·85 for those unexposed (p=0·26)	Yes
	[44] Ernhart (1989)	USA (873)	Total anomalies	SE/SD not reported	Birth	Mean total anomalies was 2·60 for those exposed, compared to 2·53 for those unexposed (p=0·28)	Yes
Motor development	[45] Faebo Larsen (2013)	Denmark (32,097)	Developmental Coordination Disorder (DCD)	Only study with this outcome	7 years	OR 0·85 (95% CI 0·70 – 1·03)	Yes
Behaviour /development	[33] Sayal (2007)	UK (967)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Conduct problems*	Later age used in analysis	3.9 years	OR 1·14 (95% CI 0·98 – 1·32)	Yes
	[33] Sayal (2007)	UK (1077)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Hyperactivity*	Later age used in analysis	3.9 years	OR 0·99 (95% CI 0·86 – 1·16)	Yes
	[33] Sayal (2007)	UK (257)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) teacher report *Conduct problems*	Parent report used in analysis instead	7.75- 9 years	OR 1·41 (95% CI 1·02– 1·94)	Yes
	[33] Sayal (2007)	UK (525)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) teacher report *Hyperactivity*	Parent report used in analysis instead	7.75- 9 years	OR 1·20 (95% CI 0·96– 1·51)	Yes
	[46] Parry (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mental Development Index, Bayley Scales of Infant Development	No SE/SD reported for reference group	18 months	Mean increase of 1·80 points (SE 1·1) for those exposed compared to unexposed.	Yes
	[46] Parry (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Psychomotor Development Index, Bayley Scales of Infant Development	No SE/SD reported for reference group	18 months	Mean increase of 0·81 points (se 0·8) for those exposed compared to unexposed.	Yes
Cognition	[22] Sayal (2013)	UK (10,558)	Key Stage 2 scores	Only study with this outcome	11 years	Mean increase of 0·38 (95% CI -0·02 – 0·78) on KS2 score for those exposed compared to unexposed.	Yes
	[23] Alati (2008)	UK (4,332)	IQ, Weschler Intelligence Scale for Children (WISC-III)	Only study with this outcome	8 years	Mean IQ score 106·4 (SD 16·3) in those exposed, compared to 105·7 (SD 16·2) in those unexposed, p=0·10.	No

[1] Odds Ratio results compare the odds of outcome in those exposed to ≤32g AA per week. SE: Standard error SD: standard deviation SGA: small for gestation age IQ: intelligence quotient.

Table 3. Quasi-experimental studies examining the effects of prenatal alcohol exposure on pregnancy outcomes.

Study (year)	Country	Total Number	Study type	Gene	SNP-rs number	Age at outcome assessment (child)	Outcomes	Summary of results & conclusions as presented in the paper	Limitations
[25] Alati (2013)	UK	7,062	Maternal-paternal comparison	na	na	11 years	Academic achievement: Key Stage 2 scores (standardised)	Maternal alcohol consumption abstainers: mean 102·0 (SD 9·1); <1 glass/week: mean 102·8 (SD 8·7) Paternal alcohol consumption abstainers: mean 98·9 (SD 11); <1 glass/week: mean 101·1 (SD 9·1)	Different confounding structures for the association of maternal vs. paternal alcohol with the outcome
[23] Alati (2008)	UK	4,332	Maternal-paternal comparison	na	na	8 years	IQ: Wechsler Intelligence Scale for Children (WISC)	Maternal alcohol consumption abstainers: mean 105·7 (SD 16·2); <1 glass/week: mean 106·4 (SD 16·3) Paternal alcohol consumption abstainers: mean 102·2 (SD 16·8); <1 glass/week: mean 104·0 (SD 16·7)	Different confounding structures for the association of maternal vs. paternal alcohol with the outcome

Abbreviations: OR: Odds ratio CI: Confidence intervals MD: Mean difference SD: standard deviation IQ: Intelligence quotient.

Discussion

Main findings: In this comprehensive systematic review of the literature on the effects of low levels of alcohol drinking in pregnancy, the two main findings are: i) a surprisingly limited number of prospective studies specifically addressing the question of whether light maternal alcohol consumption (i.e. up to 32g/week (or 4 UK units) has any causal effect (adverse or beneficial) on infant and later offspring outcomes and pregnancy outcomes, and, as a result, ii) a paucity of evidence demonstrating a clear detrimental effect, or safe limit, of light alcohol consumption on outcomes. The upper limit that we chose to examine here is that of the current version of the UK National Institute for Health and Care Excellence (NICE) guidelines.[47] The question we have attempted to address is very important given the mixed advice that women are given with regards to whether they should abstain completely or be allowed light alcohol consumption in pregnancy. The lack of research evidence to address this question is notable.

Strengths and limitations: Strengths of this review include the completeness of searches with a focused research question aimed at informing alcohol in pregnancy guidelines. In addition to observational studies' biases minimised by only including those with prospective assessment of exposure and prioritising results adjusted for main confounders. Another strength of this review is the unique effort to include alternative study designs to further improve causal inference alongside standard analytical approaches. The main limitation of results on the effects of light drinking in pregnancy from standard analytical approaches is bias due to residual confounding. SE position is a complex, multi-faceted entity. Several studies have attempted to adjust for SE position by collecting information on, for example, maternal education, family-level SE position around the time of the pregnancy, home address-based deprivation index etc. Few studies included more than one of these measured [22 29-31]. Whereas we consider attempting to adjust for at least one of these characteristics to be a minimum requirement to account for some of the confounding introduced by SE position, there remains scope for residual confounding.[48] Given the

strong relationship between SE position and both the exposure (alcohol use in pregnancy) and outcomes in this review, any degree of residual confounding is of course an issue when interpreting the effect estimates from the observational studies included in this review. Women who drink low amounts of alcohol may be more likely to be of higher socio-economic position, compared to abstainers, at least in developed settings in recent years,[49] and both of these characteristics are associated with better pregnancy and cognitive outcomes.[50] Maternal smoking and ethnicity are also known correlates of maternal alcohol use, and risk factors for e.g. low birth weight.[51] Most studies included in this review adjusted for at least some of these factors. However, due to the small number of studies included for any given outcome, it was impossible to formally investigate the effect of incomplete adjustment for some (or all) of these confounders. Additionally, for most outcomes, we could not pool eligible studies for various reasons (e.g. too few studies, lack of standard errors) and that we limited our review to a number of pre-specified outcomes including the most common pregnancy-related outcomes and childhood outcomes related to FASD. This also was the case for identifying effects based on time of exposure, which is also a limitation.

The inclusion of only English language studies may have led to missing some studies, however there is little evidence that exclusion of non-English language studies leads to systematic bias in systematic reviews of conventional medicine.[52-55]

Interpretation: This review demonstrates the paucity and poor quality of evidence addressing this important public health question, and the difficulty of designing studies that can effectively evaluate the causal impact of low alcohol consumption whilst minimising bias and confounding. It also shows the value of reporting measures of effect for meaningful categories of the exposure. Whilst many studies reported that associations did not differ from linearity prior to providing a single coefficient for the dose-response association, it is possible that statistical power limited the ability to detect non-linear associations in single studies.

Such detail is especially important when there are controversies about the shape of the association of interest (linear, U or J-shaped) and/or the existence of safe thresholds. Outstanding questions also remain about the effects of maternal alcohol consumption at different stages of conception and pregnancy. Alternative analytical approaches such as sibling comparisons[56] and the use of instrumental variable approaches[57] as well as triangulating the totality of evidence from multiple study types[58] (formally or informally) are needed in order to strengthen confidence in the direction and size of any potential causal relationships.

The recently proposed change in the guidelines for alcohol use in pregnancy in the UK to complete abstinence, would be an application of the precautionary principle. This review confirmed some increased risk of babies being born SGA but little direct evidence of any other detrimental effect for maternal drinking up to 32g/week. However, there have been few well-conducted studies examining this specific category of exposure. This issue remains of great public health importance, with alcohol consumption during pregnancy prevalent in the UK, Ireland, New Zealand and Australia with up to 80% of women consuming some alcohol during pregnancy.[59] For some, the evidence of the potential for harm – mostly coming from animal experiments and human studies of effects due to higher levels of exposure will be sufficient to advocate that guidelines should advise women to avoid all alcohol in pregnancy, while others will wish to retain the existing wording of guidelines.[60] Here we found that maternal alcohol consumption of up to 32g/week was associated with an 10% increased risk of preterm birth (95%CI: 0·95 to1·28). In comparison, light to moderate smoking (<20 cigarettes per day) is associated with a 22% increased risk of preterm birth (95% CI: 1·13 to 1·32).[61]

In conclusion, we found limited evidence for a causal role of light drinking in pregnancy, compared to abstaining, on most of the outcomes examined. Despite the distinction between light drinking and abstinence being the point of most tension and confusion for health professionals and pregnant women and contributing to inconsistent guidance and advice

now and in the past, our extensive review shows that this specific question is not being researched thoroughly enough, if at all. In addition, there has been no evidence regarding possible benefits of light alcohol consumption versus absence. Further studies, including those using designs that improve causal inference, are required to provide further evidence and a better estimation of the likely effects. Formulating guidance on the basis of the current evidence is challenging. However, describing the paucity of current research and explaining that “absence of evidence is not evidence of absence”, appears warranted.

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Transparency declaration

I, Loubaba Mamluk, the corresponding author of this manuscript, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflict of interest:

The authors have nothing to disclose.

This work has not been submitted for publication elsewhere.

Disclosure

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Transparency declaration

The lead author (Loubaba Mamluk) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing Statement

NA

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Figure 1. Flowchart of search strategy including primary reasons for article exclusion.

Figure 2. Pooled mean difference for birthweight comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (7 studies). **'**Adjusted' refers to adjusted for both smoking and a measure of socio-economic status. CI: Confidence intervals.

Figure 3a) Odd Ratios for preterm birth comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (9 studies); **3b)** Odd Ratios for small for gestational age comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (7 studies) **3c)** Odd Ratios for low birthweight comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (6 studies). OR: Odds ratio, CI: Confidence intervals. Pooled OR includes both adjusted and unadjusted estimates from studies, **'**Adjusted' refers to adjusted for both smoking and a measure of socio-economic status.

Supplementary figure 1a) Odds ratios for externalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (3 studies); **1b)** Odds ratios for internalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (2 studies); OR: Odds ratio, CI: Confidence intervals.

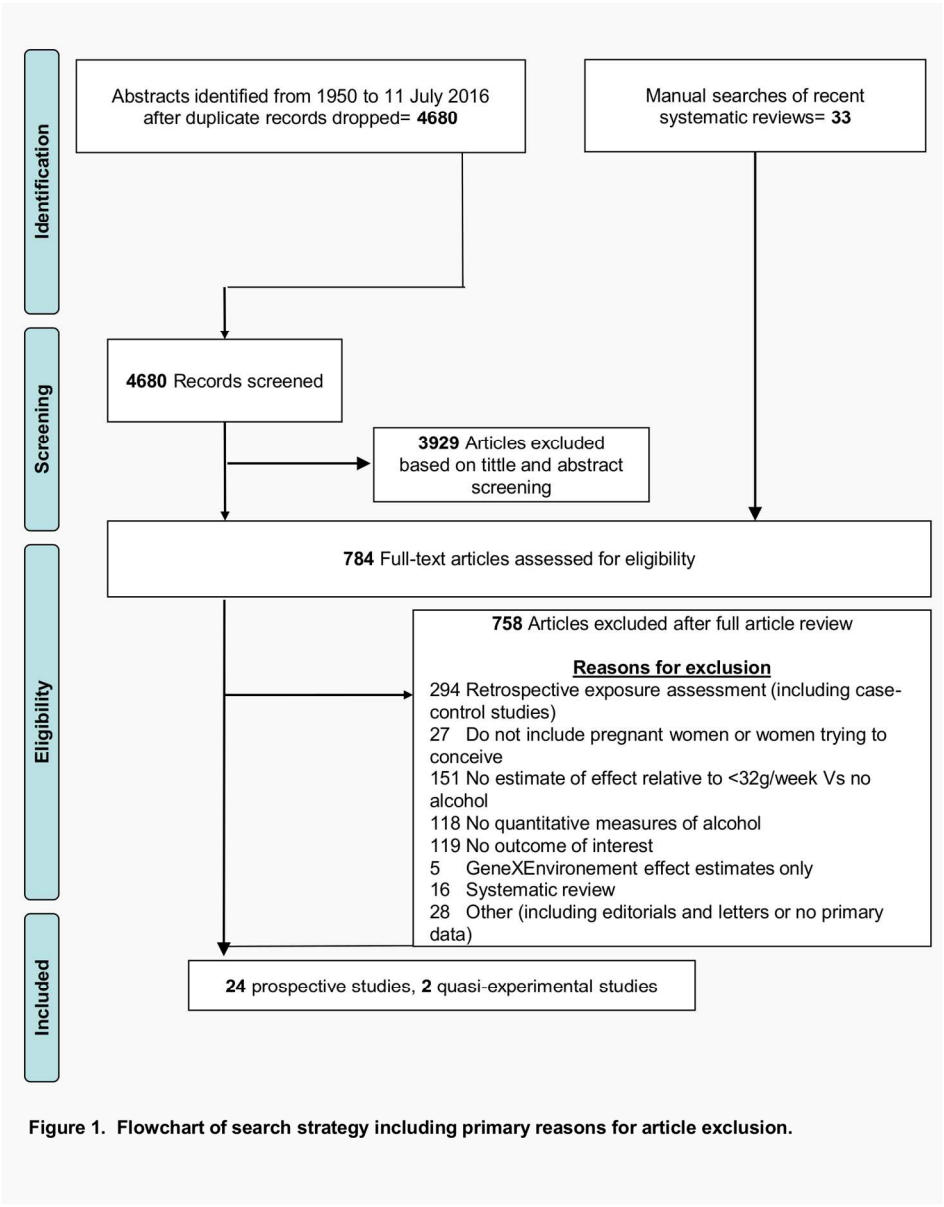

Figure 1. Flowchart of search strategy including primary reasons for article exclusion.

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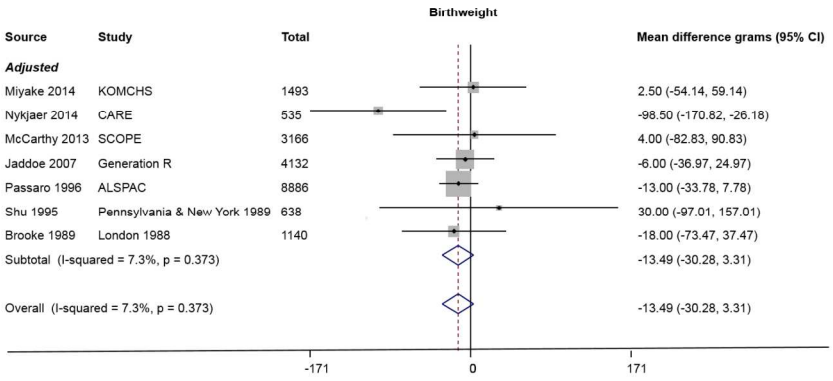

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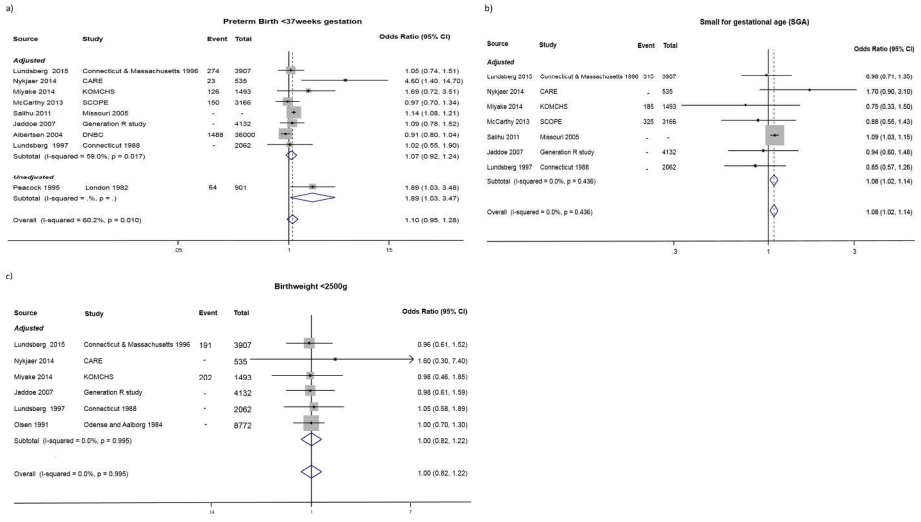

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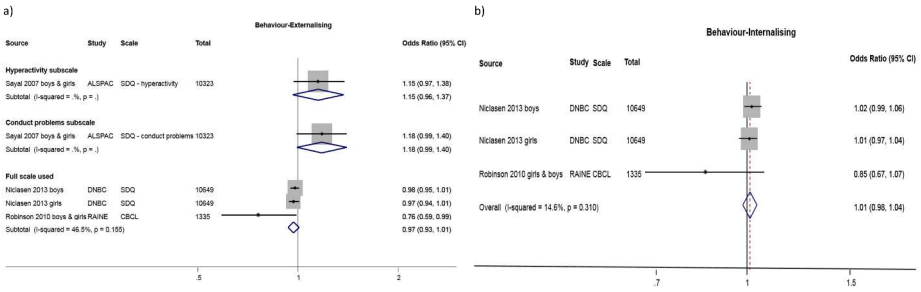
297x209mm (300 x 300 DPI)



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UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Systematic review of the effects of low-moderate prenatal alcohol exposure on pregnancy and childhood outcomes

Loubaba Mamluk, Luisa Zuccolo, Theresa Moore, Alison Richards

Citation

Loubaba Mamluk, Luisa Zuccolo, Theresa Moore, Alison Richards. Systematic review of the effects of low-moderate prenatal alcohol exposure on pregnancy and childhood outcomes. PROSPERO 2015:CRD42015015941 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42015015941

Review question(s)

To determine what is known about the effects of prenatal alcohol exposure, corresponding to low-to-moderate levels of maternal consumption, on pregnancy outcomes. These include pregnancy complications, delivery outcomes and Fetal Alcohol Syndrome (FAS) features. This will include the assessment of systematic reviews and meta-analyses. A particular focus will be placed on identifying practical and meaningful outcomes of alcohol toxicity during pregnancy.

Searches

Publications will be identified by searching the following major relevant databases: Medline, Embase, web of science and Psychinfo. All databases will be searched from inception. Internet searches will be carried out using Google Scholar. Attempts to identify further studies will be made by examining the reference lists of included studies and of previous reviews. All studies to be restricted to those published in the English language only.

Types of study to be included

1) Prospective studies and systematic reviews/meta-analyses of prospective studies (cohort or case-control studies nested in a cohort). 2) Natural experiments / studies using instrumental variables to improve casual inference, including Mendelian Randomization (MR) studies 3) Sibling comparison studies 4) Parental comparisons

Condition or domain being studied

Pregnancy and delivery outcomes as well as offspring outcomes (from the domains affected by Fetal Alcohol Syndrome (FAS))

Participants/ population

Pregnant women or women who are trying to become pregnant sampled from the general population. Cohorts of pregnant women with alcohol abuse/dependency will be excluded.

Intervention(s), exposure(s)

Inclusion: low–to-moderate levels of prenatal alcohol consumption (up to 10.4 UK units or 83 g/week).

Exclusion: studies will be excluded if there was no quantitative measure of alcohol consumption that could be converted to UK standard units or grams of alcohol and if there was insufficient data for an (adjusted and/or crude) effect measure of low–moderate consumption to be extracted. Cohorts of pregnant women with alcohol abuse/dependency will be excluded.

Comparator(s)/ control

women with no or very sporadic alcohol consumption in pregnancy.

Outcome(s)

Primary outcomes

Outcomes: (in both children and adults)

1) Pregnancy complications

- Intra uterine growth restrictions (IUGR)

- Miscarriage

- Premature labour and birth- Gestational age

- Preeclampsia and gestational hypertension

- Low amniotic fluid (oligohydramnios)

- Gestational diabetes

- Placenta previa

2) Delivery outcomes

- Birth weight/ low birth weight/ small for gestational age (SGA)

- Still birth

- Delivery intervention (including vacuum extraction, forceps delivery, Caesarean section)

- Apgar score

3) FAS features

- Facial malformation

- Growth restrictions (height- measurements of growth restriction)

- Cranium size/ head circumference

- Developmental delays

- Behaviour complications

- Cognitive impairment / IQ

- Attention scores / Attention deficit and hyperactivity disorder (ADHD)

Secondary outcomes
none

Data extraction, (selection and coding)
Selection of studies:

Titles and abstracts will be screened independently by one reviewer (a random selection of 20% will also be screened by a second reviewer independently) with inclusion/exclusion being decided according to prespecified criteria. Discrepancies will be discussed and disagreements resolved through consensus. The full-text of each of the articles identified through screening of titles and abstracts will be obtained in order to determine their inclusion in the review.

Data extraction:

Data extraction will be carried out using Microsoft Access. This will be piloted on a small selection of studies and adjusted as necessary. Relevant data will be documented from each identified study including information on study design and location, population characteristics, exposures studied (including timing of exposure), methods used to ascertain exposures, outcomes studied, method of outcome ascertainment (including person reporting the outcome, whether parent, teacher, health professional, researcher, child…), study results (from both unadjusted and fully adjusted regressions), statistical adjustments etc. Data extraction will be carried out independently by one reviewer and a random selection of 20% will checked by a second reviewer. Discrepancies will be resolved through discussion or referral to a third reviewer. Where necessary, authors will be contacted for additional information.

Risk of bias (quality) assessment

Studies that did not adjust for smoking and maternal education/social class as potential confounders in their final model will be considered to be of low evidence quality.

Strategy for data synthesis

The impact of low-to-moderate alcohol use on pregnancy and related outcomes will be investigated using high-low methods of meta-analysis techniques; however, due to anticipated low number of studies for some outcomes, a formal meta-analysis may not be appropriate for some of the outcomes. Where meta-analysis is not possible, a narrative summary of findings will be carried out. Random-effect meta-analysis will be performed alongside fixed-effect in the presence of high levels of between-studies heterogeneity (measured through I2). Item response theory (IRT) will be used to combining results from different scales if required. The likelihood of small study bias deriving from publication bias will further be assessed through drawing funnel plots.

Analysis of subgroups or subsets

Where the included number of studies in the meta-analysis is large enough, sub-group analyses will be performed for 1) studies adjusting for smoking and maternal education/social class; 2) studies reporting separately on the effects of alcohol use in different gestational periods; 3) studies using different exposure/outcome assessments.

Dissemination plans

We anticipate dissemination to regional and national public health directors

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Anticipated or actual start date
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Anticipated completion date
01 September 2015

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Conflicts of interest
None known

Language
English

Country
England

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Alcohol Drinking; Humans; Pregnancy Outcome; Prenatal Exposure Delayed Effects

Stage of review
Ongoing

Date of registration in PROSPERO
19 January 2015

Date of publication of this revision
25 February 2015

DOI
10.15124/CRD42015015941

Stage of review at time of this submission	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	1
2	Hypothesis statement	4
3	Description of study outcome(s)	6&7
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	supplementary table 1
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	7
11	Search software used, name and version, including special features used (eg, explosion)	supplementary table 1
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	13
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6

18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7&8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	supplementary table 2 & 8
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8
22	Assessment of heterogeneity	Figures 2&3
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	9&10
24	Provision of appropriate tables and graphics	27-36
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2&3
26	Table giving descriptive information for each study included	Table 1-3
27	Results of sensitivity testing (eg, subgroup analysis)	Figures 2&3
28	Indication of statistical uncertainty of findings	19

Supplementary Table 1. Search Strategy 1950 to 11·07·2016. MEDLINE, PsycINFO, EMBASE on Ovid; the Cochrane Library including CENTRAL (the Cochrane Central Database of Controlled Trials) on Wiley Interscience; and Science Citation Index, Social Science Citation Index, on Web of Science.

1 exp pregnancy/ (719661)

2 Pregnant Women/ (5199)

3 preconception care/ or prenatal care/ (21644)

4 exp "embryonic and fetal development"/ (212127)

5 Fetus/ (68424)

6 exp Pregnancy Complications/ (343999)

7 (prepregnan$ or conception or preconception or pregnan$ or prenatal$ or pre-natal$ or f?etal or f?etus or in utero).ti,ab. (588557)

8 Maternal exposure/ (5534)

9 or/1-8 (1079283)

10 Ethanol/ (73449)

11 Alcohol dehydrogenase/ (5809)

12 Aldehyde Oxidoreductases/ (3672)

13 exp Drinking Behavior/ (57821)

14 Temperance/ (2430)

15 alcohol$.ti. (106954)

16 (alcohol dehydrogenase or acetaldehyde dehydogenase).ti,ab. (8557)

17 ((alcohol or alcoholic) adj3 (drink$ or exposure or consumption or consume$ or consuming or low or light or moderat$ or abstin$ or abstain$)).ti,ab. (49470)

18 ((low or light or moderate or abstin$ or abstain$ or pattern$ or behavio?r$) adj3 drink$).ti,ab. (10558)

19 (ADH1B$ or teetotal$ or temperance or nondrink$ or non-drink$).ti,ab. (3093)

20 Genome-Wide Association Study/ or Linkage Disequilibrium/ or genotype/ or phenotype/ or polymorphism, genetic/ or (polymorphism$ or ((gene or genes or genetic or genotyp$) adj3 (instrument$ or variant$ or variable$ or variability or variabilities or variance$))).ti,ab. (494904)

21 *Alcohols/ or exp *Alcohol-Related Disorders/ or (alcohol adj3 (misuse or "use" or abuse or addict$ or dependence or response$ or susceptibility)).ti,ab. (110843)

22 20 and 21 (3108)

23 or/10-19,22 (213050)

24 9 and 23 (11403)
25 letter/ (861500)
26 editorial/ (368458)
27 news/ (166329)
28 exp historical article/ (325965)
29 Anecdotes as topic/ (4586)
30 comment/ (610211)
31 case report/ (1708277)
32 (letter or comment$).ti. (100442)
33 or/25-32 (3417468)
34 randomized controlled trial/ or Randomized Controlled Trials as Topic/ or random$.ti,ab. (888907)
35 33 not 34 (3386180)
36 animals/ not humans/ (3889478)
37 exp Animals, Laboratory/ (730783)
38 exp Animal Experimentation/ (6477)
39 exp Models, Animal/ not humans/ (310115)
40 exp rodentia/ (2688128)
41 (rat or rats or mouse or mice).ti. (1123907)
42 or/35-41 (7849766)
43 24 not 42 (6498)
44 meta-analysis/ (52850)
45 meta-analysis as topic/ (13933)
46 (meta analy$ or metaanaly$ or metanaly$ or meta regression).ti,ab. (72390)
47 ((systematic$ or evidence$ or realist or narrative or literature) adj2 (review$ or overview$)).ti,ab. (171877)
48 "review of reviews".ti,ab. (211)
49 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab. (27094)
50 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (28877)
51 (search$ adj4 literature).ab. (30686)

52 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or cinahl or science Citation index or bids or cancerlit).ab. (95294)

53 cochrane.jw. (11053)

54 ((multiple treatment$ or indirect or mixed) adj2 comparison).ti,ab. (991)

55 or/44-54 (293491)

56 43 and 55 (201)

57 epidemiologic studies/ (6077)

58 ep.fs. (1223653)

59 exp case control studies/ (691899)

60 exp cohort studies/ (1394149)

61 cross-sectional studies/ (185407)

62 Mendelian Randomization Analysis/ (229)

63 (case control or negative control).ti,ab. (93097)

64 (cohort adj (study or studies or analys$)).ti,ab. (98537)

65 ((follow up or observational) adj (study or studies)).ti,ab. (87771)

66 ((longitudinal$ or retrospectiv$ or prospectiv$) and (study or studies or studied or review$ or analys$ or cohort$)).ti,ab. (870699)

67 cross sectional.ti,ab. (183479)

68 (mendel$ or natural experiment$).ti,ab. (11082)

69 ((family or sibling or population) adj3 (study or studies)).ti,ab. (115245)

70 or/57-69 (2937160)

71 exp guideline/ (25834)

72 guidelines as topic/ or practice guidelines as topic/ (114690)

73 guideline$.mp. (291621)

74 or/71-73 (291621)

75 55 or 70 or 74 (3362878)

76 43 and 75 (3349)

77 limit 76 to english language (3096)

78 ((smok$ or drug$ or tobacco or nicotine or cigarette$ or substance$ or methamphetamine$ or amphetamine$ or cocaine$ or heroin or cannabis or marijuana) not (alcohol or alcoholic or drink$)).ti. (489662)

79 77 not 78 (2822)

Supplementary Table 2. Lists of confounders adjusted for by each study

Study (year)	Confounders
[26] Lundsberg (2015)	Parity, maternal age, education, BMI, marital status, ethnicity, caffeine, smoking, exercise, work, prenatal and multivitamin use, passive smoke exposure, marijuana use, cocaine use, study cohort, preterm labour, respiratory problem, infant gender, bleeding, nausea/vomiting, hypertension, incompetent cervix, placental problems, sexually transmitted disease, induction/augmentation, maternal asthma, gestational diabetes.
[27] Nykjaer (2014)	Maternal pre-pregnancy weight, height, age, parity, ethnicity, salivary cotinine levels, caffeine intake, education, energy intake, gestation and baby's sex
[28] Niclasen (2014)	Parental smoking, parental education, parental pre-pregnancy psychiatric diagnoses, and maternal psychological well-being in pregnancy.
[29] Miyake (2014)	Low birth weight, preterm birth: maternal age, region of residence, number of children, family structure, maternal education, maternal employment, body mass index, maternal smoking during pregnancy, and baby's gender. Small for gestational age: maternal age, region of residence, number of children, family structure, maternal education, maternal employment, body mass index, maternal smoking during pregnancy, gestational age, and baby's gender.
[45] Faebo Larsen (2013)	Sex, gestational age, intrauterine growth restriction, maternal age, mother's occupational status, maternal smoking (ever) in first trimester, amount of maternal smoking and alcohol consumption in first trimester.
[22] Sayal (2013)	Maternal age, parity, highest level of maternal education, daily frequency of smoking, use of cannabis and/or other illicit drugs during the first trimester, homeownership, whether currently married, high scores (>12) on the Edinburgh Postnatal Depression Scale, and child gestational age, birth weight and gender.
[30] McCarthy (2013)	Maternal age, smoking, years of schooling, ethnicity, body mass index, infant sex, maternal status, family income, and drug use during pregnancy. Adjusted for clustering. Birthweight adjusted for gestational age at delivery.
[40] Andersen (2012)	Number of previous abortions, coffee consumption, changes in alcohol consumption since prior to pregnancy and smoking. Effect of coffee consumption and smoking was stratified according to period. The model is stratified according to maternal age and parity.
[21] Salihu (2011)	Maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, maternal height, gender of the infant, and year of birth
[31] Robinson (2010)	Maternal age, maternal education, presence of the biological father in the family home, family income, stress in pregnancy, child's age at follow up (and child's age at follow-up squared), and maternal cigarette smoking.
[32] Jaddoe (2007)	Controlled for maternal body mass index, smoking, educational level, height, ethnicity, parity and age and infant gender; birth weight and low birth weight models also controlled for gestational age.
[43] Bille (2007)	Parental age and social class.
[33] Sayal (2007)	Gender, smoking, cannabis use and use of illicit drugs in the first trimester, highest level of maternal education, home ownership, marital status, parity, maternal age group, high EPDS score, child ethnicity, gestational age group, and birth weight.
[34] Albertsen (2004)	Type 1 diabetes, age, previous preterm delivery, smoking during pregnancy, coffee consumption during pregnancy, occupational status in the household, parity, and total alcohol consumption during pregnancy.
[35] Lundsberg (1997)	Small for gestational age: smoking in month 7, ethnicity, weight, height, infant sex, parity, bleeding during pregnancy, high blood pressure, and preeclampsia/eclampsia. Low birthweight: smoking in month 7, height, weight, ethnicity, infant sex, parity, coffee use in month 7, exercise in third trimester, employment, bleeding during pregnancy, high blood pressure, pre-eclampsia/eclampsia, anomalies, and placental problems. Preterm delivery: smoking in month 7, height, parity, age, caffeine use in month 7, exercise first 16 weeks, bleeding during pregnancy, high blood pressure, pre-eclampsia/eclampsia, anomalies, and placental problems.
[41] Windham (1997)	Maternal age, prior spontaneous abortion, gestational age at interview, and cigarette and caffeine consumption in week before interview.
[36] Passaro (1996)	Gestational age, infant sex, parity, maternal smoking, and maternal body mass index.
[37] Shu (1995)	Gestational age, parity, smoking and income.
[20] Peacock (1995)	Unadjusted
[38] Olsen (1991)	Age, school education, parity, alcohol and smoking entered the model as "dummy variables".
[42] Ogston (1992)	Gestational age at birth, sex, mother's age, parity and smoking.
[46] Parry (1992)	Gestational age at birth, sex, mother's age, parity and smoking.
[39] Brooke (1989)	Gestational age, sex, maternal height, and parity
[44] Ernhart (1989)	Parity, smoking, race and year of study.

Supplementary Table 3. Assessment of studies using the The Newcastle-Ottawa Scale (NOS)

Risk of bias questions / Study ID	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design/analysis	Assessment of outcome blind/ record linkage	Follow-up long enough for outcome to occur	Adequacy of follow up of cohorts
Albertson 2003	✓	✓	✓	✓	✓	✓	✓	✓
Anderson 2012	✓	✓	✓	✓	✓	✓	✓	✓
Bille 2007	✓	✓	✓	✓	✓	✓	✓	?
Brooke 1989	✓	✓	✓	✓	✓	✓	✓	✓
Erhart	x	✓	✓	✓	?	✓	✓	x
Jaddoe 2007	✓	✓	x	✓	✓	✓	✓	✓
Larsen 2013	✓	✓	✓	✓	✓	x	✓	x
Lundsberg (Lisbet) 2015	?	✓	✓	✓	✓	✓	✓	✓
Lundsberg (Lisbet) 1997	?	✓	✓	✓	✓	✓	✓	✓
McCarthy 2013	✓	✓	✓	✓	✓	✓	✓	✓
Miyake 2014	?	✓	x	✓	✓	✓	✓	✓

Niclasen 2013	?	✓	?	✓	x	x	✓	?
Nykjaer 2014	x	✓	x	✓	✓	✓	✓	✓
Ogston 1992	?	✓	✓	✓	x	✓	✓	✓
Olsen 1991	?	✓	x	✓	✓	✓	✓	✓
Parry 1992	?	✓	✓	✓	✓	x	✓	x
Passaro 1996	?	✓	x	✓	✓	✓	✓	✓
Peacock 1995	?	✓	✓	✓	x	?	✓	✓
Robinson 2010	?	✓	x	✓	✓	x	✓	✓
Salihu 2011	?	✓	x	✓	✓	?	✓	✓
Sayal 2012	✓	✓	x	✓	✓	?	✓	✓
Sayal 2006	✓	✓	x	✓	✓	x	✓	✓
Shu 1995	✓	✓	✓	✓	x	✓	✓	✓
Windham 1997	x	✓	✓	✓	✓	✓	✓	✓

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5&6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 & 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	supTable 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7 & 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6 & 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Figure 2&3 supfigure1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Figure 2&3 supfigure1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2&3 supfigure1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2&3 supfigure1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 2&3

			supfigure1
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13&14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13 & 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

BMJ Open

Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses.

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Reproductive medicine
Keywords:	PAEDIATRICS, EPIDEMIOLOGY, Maternal medicine < OBSTETRICS

Systematic Review & Meta-analysis

Title: Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses.

Running tittle: Low alcohol consumption and pregnancy and childhood outcomes.

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Supplementary Tables: 3
Supplementary Figures:1
Supplementary Document:1
Number of references: 61

Abstract:

Objectives: To determine the effects of low-to-moderate levels of maternal alcohol consumption in pregnancy on pregnancy and longer-term offspring outcomes.

Search Strategy: Medline, Embase, Web of Science, and Psychinfo from inception to 11-07-2016.

Selection Criteria: Prospective observational studies, negative control and quasi-experimental studies of pregnant women estimating effects of light drinking in pregnancy (≤32g/week) versus abstaining. Pregnancy outcomes such as birth weight, and features of fetal alcohol syndrome were examined.

Data Collection and Analysis: One reviewer extracted data and another checked extracted data. Random effects meta-analyses were performed where applicable, and a narrative summary of findings was carried out otherwise.

Main Results: 24 cohort and two quasi-experimental studies were included. With the exception of birth size and gestational age, there was insufficient data to meta-analyse or make robust conclusions. Odds of small-for-gestational-age (SGA) and preterm birth were higher for babies whose mothers consumed up to 32g/week versus none, but estimates for preterm birth were also compatible with no association: summary odd ratios (OR) 1·08, 95% confidence intervals (CI) (1·02 to 1·14), I^2 0%, (7 studies, all estimates were adjusted) OR 1·10, 95%CI (0·95 to1·28), I^2 60%, (9 studies, includes one unadjusted estimates) respectively. The earliest time points of exposure were used in the analysis.

Conclusion: Evidence of the effects of drinking <=32g/w in pregnancy is sparse. As there was some evidence that even light prenatal alcohol consumption is associated with being SGA and preterm delivery, guidance could advise abstention as a precautionary principle, but should explain the paucity of evidence.

Keywords: Alcohol, pregnancy, systematic review.

Strengths and Limitations of this study:

Strengths

- Completeness of searches with a focused research question aimed at informing alcohol in pregnancy guidelines.
- Biases minimised by only including those with prospective assessment of exposure and prioritising results adjusted for main confounders.
- Unique effort to include alternative study designs to further improve causal inference alongside standard analytical approaches.

Limitations

- Limitation of results on the effects of light drinking in pregnancy from standard analytical approaches is bias due to residual confounding.
- The inclusion of only English language studies may have led to missing some studies, however there is little evidence that exclusion of non-English language studies leads to systematic bias in systematic reviews of conventional medicine.
- We could not pool eligible studies for various reasons (e.g. too few studies, lack of standard errors)

Keywords: Alcohol, pregnancy, systematic review.

Introduction

Alcohol is a known teratogen[1] and the evidence about the risks of heavy alcohol consumption during pregnancy on intellectual ability, birth defects, behaviour, fine motor skills, and mental health (comprising fetal alcohol spectrum disorder – FASD)[2] is clear and compelling.[3] Internationally, clinical guidelines recommend that pregnant women should abstain from heavy or "binge" drinking.[4] However, until recently UK guidelines advised women to avoid drinking alcohol while trying to conceive, and in the first trimester, but at the same time indicated that consumption should be restricted to within "1 to 2 UK units, once or twice a week".[5] The UK Chief Medical Officer (CMO) commissioned a review of guidelines on alcohol consumption during pregnancy. Based on a review of reviews, the Guidelines Development Expert Group has recently proposed a change to guidelines such that women should be advised to abstain from alcohol when pregnant and/or trying to conceive,[6] based on the precautionary principle (i.e. "better safe than sorry"), in the absence of robust evidence.

Our aim 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 in pregnancy on pregnancy and longer term offspring outcomes. Here we report on alcohol consumption of up to two UK units of alcohol up to twice a week (the equivalent of ~ 32g/week), compared to no alcohol. In the absence of evidence from randomised controlled trials, we examine observational studies of pregnant women from the general population with prospective assessment of alcohol exposure, to reduce recall bias. In particular, we specifically seek out quasi-experimental studies, negative control comparisons, and Mendelian randomisation analyses in order to reduce the impact of confounding and measurement error on the effect estimates.

Methods

Selection strategy and selection criteria

A full protocol of this systematic review carried out using PRISMA guidelines (supplementary document)[7] is available from the PROSPERO systematic review register (registration number CRD4201501594); http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015015941).

In brief, eligible studies were defined as epidemiological studies of pregnant women or women trying to conceive with prospective assessment of prenatal alcohol exposure (i.e. before birth), sampled from general population. The protocol specifically included studies using standard analytical approaches (e.g. multivariable regression analysis), as well as studies that used innovative analytical methods to improve causal inference, 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 to the association of the same outcomes with consumption among fathers, under the assumption that confounding is likely to be similar but that if there was a direct causal effect of maternal consumption on outcomes, maternal associations would be stronger); and Mendelian randomisation studies (using genetic variants associated with alcohol consumption and metabolism). We considered these analytical approaches to be the most appropriate in terms of their ability to minimise bias from confounding and other sources. Our original protocol included studies exploring the effects of prenatal alcohol consumption up to 83g/week (the commonly used threshold for moderate consumption [8-10]) versus abstinence. Here we have focused specifically on low alcohol consumption, i.e. up to 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.[5] This specific cut off value has not been reviewed and is the main point of discussion as the guideline change from low consumption

(equating to 1 to 2 UK units, once or twice a week or 32g/week) to abstinence (reference group).

Outcomes included: 1) pregnancy outcomes: still birth (pregnancy loss after week 24; miscarriage; gestational length and preterm delivery (<37 weeks gestation); hypertensive disorders of pregnancy; gestational diabetes; small for gestational age (SGA), < 10th percentile in weight or <−2 standard deviation scores) and birth size (weight (including low birth weight defined as <2500g), length, and head circumference); low amniotic fluid (oligohydramnios); placenta previa; placental abruption; assisted delivery (including vacuum extraction, forceps delivery, Caesarean section); Apgar score at birth; admission to neonatal unit; congenital malformations. 2) Features of foetal alcohol spectrum disorder (FASD): childhood growth restriction; cranium size and head circumference; developmental delays; behaviour problems; cognitive impairment and intelligent quotient (IQ); facial malformations. We adopted study specific definitions for all outcomes.

Studies were excluded if: there was no quantitative measure of alcohol consumption that could be converted to grams of alcohol/week; there was insufficient data to estimate the effect size of the association of our pre-defined low consumption categories versus abstinence with any outcome, including studies that analysed alcohol as a continuous variable (i.e. assuming the same linear or log linear effect across the entire alcohol distribution); the lowest exposure category (compared to non-drinkers) had an upper bound exceeding 32g/week, or was unspecified; they were cohort studies of pregnant women with alcohol abuse/dependency; they were case-control studies or cohort studies with retrospective alcohol consumption assessment (e.g. after birth).

The following databases were searched: MEDLINE, PsycINFO, EMBASE on Ovid; the Cochrane Library including CENTRAL (the Cochrane Central Database of Controlled Trials) on Wiley Interscience; and Science Citation Index, Social Science Citation Index, on Web of Science from inception to 11 July 2016 (supplementary Table 1). We limited the search to

English language papers and excluded animal studies, letters, editorials, and conference proceedings for which there were no full-text papers. Searches were tailored to each database by investigators. The search focused on published medical literature and did not include grey literature. We additionally performed manual searches of the reference lists of: (i) all papers included in recent systematic reviews of the effects of prenatal alcohol exposure on the outcomes of interest; and (ii) all recent papers citing those reviews. Titles and abstracts, and full texts if necessary, were screened independently by two reviewers. Discrepancies were discussed and disagreements resolved through consensus. We assessed potential for bias in included studies by assessing how well the study adjusted for several main confounders known to impact on the exposure-outcome associations (socioeconomic positioning as measured by the individual study, smoking during pregnancy, maternal age, and ethnicity). We considered the potential for confounding and bias across studies included in the analyses and described it narratively alongside summary results.

Data extraction

Data were extracted into a custom-built Microsoft Access database. We extracted the following information from each study: title, authors, publication year, country/region, study design, population characteristics (sample size, methods of sampling, age distribution, and ethnicity), measures of exposure (assessment method; including timing and quantification of alcohol consumption, reference group (abstinence), exposure (e.g 1-2 units or 2-4 units), and information on unit equivalence if stated), outcome assessment methods (including whether this was abstracted from medical records, obtained via a research interview and the person reporting the outcome e.g. parent, teacher, health professional, researcher or child), model adjustments, and study results. If a study reported more than one result for each outcome, we extracted all of them (e.g. relative to different timing of exposure, model adjustments, etc.). Information from each included paper was extracted by one reviewer (LM) and subsequently checked for accuracy and completeness by another reviewer

(HE).[11] Extraction errors were minimal and were resolved through discussion between extractor and checker.

Alcohol unit conversion

Alcohol consumption in drinks/week was converted into grams/week based on the pure ethanol equivalent of one drink, as stated in each individual article, or otherwise inferred based on the definition of standard drinks in the country where the study took place.

Data analysis

The association of low alcohol use with pregnancy and related outcomes was investigated comparing the highest category within the range of 0-32g/week to abstention (during pregnancy). In studies providing data across several categories of intake within the 0-32g/week range, we used the effect estimate for the highest category of intake. If studies reported on exposure to alcohol during different trimesters, we included estimates relative to the earliest exposure. This is because for some outcomes, the first trimester tends to be the most critical timing/window of exposure [12] [13] and because most studies that only reported on one time point reported on exposure in early gestation. Similarly, if results were available from both unadjusted and adjusted regressions, we prioritised fully adjusted results, as a way of minimising the impact of confounding by important factors such as maternal smoking, age, socio-economic position and ethnicity. In case of multiple results from the same cohort (relative to the same outcome), we analysed those pertaining to the largest population size (i.e. conducted on the least 'selected' population as result of exclusions, to minimise selection bias). Results from all studies that fulfilled our inclusion criteria were summarised, together with information about the study. Where appropriate, we additionally pooled results for each outcome. Authors were not contacted for extra data. Results from Different study designs have been reviewed separately. Individual study estimates were pooled using random effects meta-analysis. Where only two studies were available to meta-analyse, results were pooled unless they were very different from each

other ($I^2 \geq 50\%$).[14] In this case, a narrative summary of findings was carried out and results were reported in Table 2. Where a study only reported unadjusted results, we kept these separate in the forest plots (sub-group analysis) but then also showed overall pooled estimates combining all results.

Planned sub-group analyses by trimester could not be performed due to insufficient number of included studies with this information.

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS)[15] was used to assess risk of bias for included reports. This is an eight-item questionnaire assessing the following: representativeness of the exposed cohort; selection of the non-exposed cohort; exposure assessment methods; absence of outcome (of interest) at the start of the study; comparability of exposed and non-exposed groups (with regard to confounding variables); blind assessment of exposure and outcome; and length and adequacy of follow up. NOS allocates 'stars' for adequate methods, but does not specifically advise calculating the sum of allocated stars to give an overall score. Scores for quality are not helpful in assessing the effect of risk of bias on a meta-analysis so we report each item separately in line with recommended methods [16 17]. To be assessed as adequate for comparability of cohorts (risk of confounding) a study had to control for the following four pre-specified potential confounding factors related to foetal development: maternal age, socio-economic status (SES), ethnicity, and smoking.

The likelihood of small study bias, such as publication bias, could not be assessed through visual inspection of funnel plots for pooled analyses as no outcome was assessed by 10+ studies [18]. Statistical analyses were carried out using Stata version 13.1 (StataCorp, College Station, TX, USA).[19]

Results

A flowchart of the article review process is shown in Figure 1. A total of 4680 citation records were identified from searching the four relevant databases. A manual search of recent

systematic reviews identified 33 additional articles. After exclusions, 24 prospective studies analysed using standard approaches and two quasi-experimental studies were included, reporting on 30 outcomes in total.

Risk of bias

Six studies (Albertson 2003; Anderson 2012; Bille 2007; Brooke 1989; Lundsberg 2015; McCarthy 2013) had low risk of bias for all eight NOS items and were therefore considered at low risk of bias overall. All studies were judged to be at a low risk of bias for the following three NOS items (supplementary Table 3): selection of the non-exposed cohort (always from the same source population as the exposed cohort); the absence of outcome at the start of the study; and adequate length of follow up for outcome to have occurred. Fourteen studies had adequate ascertainment of exposure as these were all based on structured interviews or validated records. Objective outcome assessments (assessor unaware of the exposure status) were reported in 16 of the studies. For five others either parent self-report was used (high risk), and for the remaining three the method of outcome assessment was not reported (unclear risk). Eleven studies did not report enough detail to decide if cohorts were representative of the population, therefore only 10 could be judged as low risk. Only four studies did not control for the pre-specified potential confounding factors, and one did not report enough detail to permit judgement. Thus, in the majority of studies (19) the compared groups were similar. Nineteen studies had adequate follow up of the cohort (small loss to follow up). Only three were judged high risk for this item and two studies presented insufficient information to make a clear judgment.

Studies included in the meta-analysis are presented in Table 1. Standard analytical approaches pooled estimates for continuous and binary outcomes are presented in Figure 2 and 3 respectively. Figure 2 presents results for birthweight (7 studies). Figure 3A presents results for preterm delivery (9 studies) Figure 3B, presents results for SGA (7 studies), and results for low birthweight (6 studies) are given in Figure 3C.

The meta-analysis yielded a summary OR of 1·10 (95% CI 0·95; 1·28) for preterm delivery, but there was substantial statistical heterogeneity between studies (I^2=60%), due to a large Danish study reporting a protective effect (Figure 3A). Additionally, most studies assessing preterm birth had corrected for main confounders know to be associated with preterm birth, with the exception of [20] that did not correct for any. There was also modest evidence for an increased risk of being SGA (OR 1·08, 95% CI 1·02; 1·14) for a total of 288512 participants, although this was almost entirely driven by a single US study contributing 95% of the participants to this meta-analysis (Figure 3B). The birthweight meta-analysis yielded a summary effect of -13·49g (95% CI -30·28g; +3·31g) for offspring of light drinkers versus non-drinkers (Figure 2). Summary effect for birthweight <2500g was, OR 1·00, 95% CI 0·82; 1·22 (Figure 3C).

Other outcomes were typically reported by a limited number of studies and mostly could not be meta-analysed due to clinical heterogeneity in outcome assessment or incompleteness of published data (supplementary Figure 1, and Table 2). Based on two studies with data on behavioural outcomes, there was little evidence of any effect for internalising symptoms but a suggestion that light drinking in pregnancy protected against high externalising behaviour scores (OR 0·97, (95%CI 0·93; 1·01, supplementary Figure 1)). However, an additional study assessing conduct problems and hyperactivity (in the same externalising domain) reported results in the opposite direction, which could not be meta-analysed due to different outcome definitions.

Table 2 presents results of included studies that did not contribute to the meta-analyses for various reasons. There was no strong evidence of association between consuming up to 32 g/week of alcohol and any of the remaining outcomes excluded from meta-analyses, with three exceptions: a very large US study showing increased risk of placental abruption and decreased risk of pre-eclampsia (OR 1·24, 95%CI 1·05; 1·46 and OR 0·82, 95% CI 0·74; 0·90, respectively)[21], and a single British study reporting better cognitive outcomes in children exposed to light maternal drinking in pregnancy.[22]

We did not include funnel plots as no outcome was assessed by 10+ studies.

Of all included results, only two were unadjusted[20 23], and most of the others were adjusted for maternal smoking, age and socio-economic position (supplementary Table 2). Studies that did not adjust for ethnicity were generally conducted in homogenous populations. Due to the small number of studies for each outcome, we could not further investigate the effect of adjusting for all or some of these confounders. Similarly, there was insufficient data to examine the effect of timing of exposure on outcomes.

Alternative analytical approaches

Two negative control publications[24] based on the same UK cohort met our inclusion criteria (Table 3).[23 25] They investigated the effects of maternal alcohol consumption on childhood educational achievement[25] and IQ.[23] Offspring exposed to maternal consumption of <12g/week of alcohol in the first trimester did not have worse outcomes compared to those of mothers who abstaining from alcohol, and a similar pattern was found for paternal alcohol consumption.

One further quasi-experimental study, one natural experiment and five Mendelian randomisation studies were excluded from the present review because they did not specifically test the effect of consuming up to 32g/week in pregnancy versus abstaining. These will be included in a forthcoming review focused on estimating the causal effects of prenatal alcohol exposure based on alternative study designs and analytical approaches to strengthen causal evidence.

Table 1. Prospective studies examining the effects of prenatal alcohol exposure on pregnancy outcomes (studies included in the meta-analysis)

Study (year)	Country	Event	Total number	Outcomes	Timing of exposure	Age at outcome assessment (child)	Adjusted (yes/no)
[26] Lundsberg (2015)	USA	191 315 274	3,907	Birth weight (<2500g) SGA (< 10th percentile) Preterm birth (<37 weeks)	1st trimester	Birth	Yes
[27] Nykjaer (2014)	UK	- - - - 23	535	Birth weight (g) Customised birth centile SGA (< 10th centile) Low birth weight (<2500g) Preterm birth (<37 weeks)	1st trimester	Birth	Yes
[28] Niclasen (2014)	Denmark	-	10,649	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ), Parent report Boys Internalising behaviour Girls Internalising behaviour Boys Externalising behaviour Girls Externalising behaviour	Entire pregnancy	7 years	Yes
[29]Miyake (2014)	Japan	126 185 - 202	1,493	Preterm birth (<37 weeks) SGA (< 10th percentile) Adjusted mean birth weight Low birth weight (<2500g)	Between 5th and 39th weeks of pregnancy	0-11 months	Yes
[30] McCarthy (2013)	New Zealand, Australia, UK, and Ireland	- 325 150	3166	Birthweight SGA (< 10th percentile) Preterm birth (<37 weeks)	1st trimester	Birth	yes
[21] Salihu (2011)	USA	-	-	Preterm birth (<37 weeks) SGA (< 10th percentile)	Within the gestational age range 20-44 weeks	Birth	Yes
[31] Robinson (2010)	Australia	202	1335	Clinically significant problems (T score ≥60),Child Behaviour Checklist (CBCL) Parent report Internalising behaviour Externalising behaviour	2nd trimester	2-14 years inclusive	Yes
[32] Jaddoe (2007)	Holland; UK	- - -	4,132	Low birth weight SGA (weight < −2 standard deviation scores) Preterm birth (<37 weeks) Birth weight	Late pregnancy	Birth	Yes
[33] Sayal (2007)	UK	-	10,323	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Hyperactivity* - Externalising	1st trimester	7.75 years	Yes
[33] Sayal (2007)	UK	-	10,323	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report C*onduct problems*- Externalising	1st trimester	7.75 years	Yes
[34] Albertsen (2004)	Denmark	1488	29,463	Preterm birth (<37 weeks) Moderate preterm birth (32-37 weeks) Very preterm birth (<32 weeks)	During pregnancy	Birth	Yes
[35] Lundsberg (1997)	USA		2,062	SGA (lowest 10th percentile) Low birth weight Preterm delivery (<37 weeks)	1st trimester	Birth	Yes
[36] Passaro (1996)	UK		8,886	Birth weight (g)	At booking for antenatal care (before 24 weeks gestation)	Birth	Yes
[37] Shu (1995)	USA		638	Birth weight (g)	Throughout pregnancy (12.9, 28 & 36 weeks gestation)	Birth	Yes
[20] Peacock (1995)	UK	64	901	Preterm birth (<37 weeks)	At booking for antenatal care (before 24 weeks gestation)	Birth	No

[38] Olsen (1991)	Denmark	8772	Birth weight (<2500g)	During the first 36 weeks gestation	Birth	yes
[39] Brooke (1989)	UK	1,140	Birthweight (g)	Early pregnancy	Birth	yes

SGA: small for gestation age

Table 2. Prospective studies examining the effects of prenatal alcohol exposure on pregnancy outcomes (results not included in the meta-analysis)

Outcome	Study (year)	Country (Total number)	Outcome details	Reason not included in meta-analysis	Age at outcome assessment (child)	Results [1]	Adjusted (yes/no)
Pregnancy outcomes							
Stillbirth	[40] Andersen (2012)	Denmark (89,322)	Stillbirth	Estimates are in different directions	(Outcome confirmed via National / Hospital Registries, or from maternal report)	OR 0·90 (95% CI 0·73 – 1·12)	Yes
	[21] Salihu (2011)	USA (1,226,685)	Stillbirth	Estimates are in different directions	Birth	OR 1·10 (95% CI 0·88 – 1·39)	Yes
Miscarriage	[40] Andersen (2012)	Denmark (89,322)	Miscarriage in first trimester	Only study with this outcome	(Outcome confirmed via National / Hospital Registries, or from maternal report)	OR 1·05 (95% CI 0·94 – 1·18)	Yes
	[41] Windham (1997)	USA (5,324)	Spontaneous abortion occurring ≤20 weeks gestation	Only study with this outcome	(Outcome confirmed via medical records)	OR 1·0 (95% CI 0·7 – 1·5)	Yes
Gestational age and preterm birth	[36] Passaro (1996)	UK (10,539)	Gestational age	Only study with this outcome	Birth	Mean gestational age 40·1 (SD 1·9) for those exposed, compared to 40·1 (SD 2·0) for those unexposed.	Yes
	[42] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Per cent of infants with gestational age <37 weeks			3·7% in those exposed compared to 3·9% in those unexposed.	Yes
Birthweight	[42] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mean birthweight (g) in non-smokers	SE/SD not reported	Birth	3414g in those exposed, compared to 3363g in those unexposed.	Yes
	[42] Ogston (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mean birthweight (g) in smokers	SE/SD not reported	Birth	3225g in those exposed, compared to 3225g in those unexposed.	Yes
Placenta-related	[21] Salihu (2011)	USA (1,226,685)	Placental abruption	Only study with this outcome	Birth	OR 1·24 (95% CI 1·05 – 1·46)	Yes
	[21] Salihu (2011)	USA (1,226,685)	Placenta previa	Only study with this outcome	Birth	OR 1·11 (95% CI 0·87 – 1·43)	Yes
Pre-eclampsia	[21] Salihu (2011)	USA (1,226,685)	Pre-eclampsia	Only two studies with this outcome	Birth	OR 0·82 (95% CI 0·74 – 0·90)	Yes
	[30] McCarthy (2013)	New Zealand, Australia, Ireland, UK	Pre-eclampsia	Only two studies with this outcome	Birth	OR 0·59 (95% CI 0·35 – 0·99)	Yes
Height	[26] Lundsberg (2015)	USA (4,496)	Lowest 10th percentile of birth length	Only study with this outcome	Birth	OR 1·10 (95% CI 0·78 – 1·54)	Yes
Head circumference	[26] Lundsberg (2015)	USA (4,496)	Lowest 10th percentile of head circumference	Only study with this outcome	Birth	OR 1·08 (95% CI 0·83 – 1·42)	Yes
Apgar score	[26] Lundsberg (2015)	USA (4,496)	Apgar <7 at 5 minutes	Only study with this outcome	Birth	OR 1·61 (95% CI 0·67 – 3·84)	Yes
Admission to Neonatal Intensive Care Unit (NICU)	[26] Lundsberg (2015)	USA (4,496)	Admission to NICU	Only study with this outcome	Birth	OR 1·12 (95% CI 0·86 – 1·46)	Yes
Features of foetal alcohol spectrum disorder (FASD)							
Malformations	[26] Lundsberg (2015)	USA (4,496)	Major malformations	Only study with this outcome	Birth	OR 0·78 (95% CI 0·40 – 1·50)	Yes

	[43] Bille (2007)	Denmark (1020)	Oral clefts	Only study with this outcome	Birth	OR 1·06 (95% CI 0·74 – 1·50)	Yes
	[44] Ernhart (1989)	USA (873)	Craniofacial anomalies	SE/SD not reported	Birth	Mean craniofacial anomalies was 1·92 for those exposed, compared to 1·85 for those unexposed (p=0·26)	Yes
	[44] Ernhart (1989)	USA (873)	Total anomalies	SE/SD not reported	Birth	Mean total anomalies was 2·60 for those exposed, compared to 2·53 for those unexposed (p=0·28)	Yes
Motor development	[45] Faebo Larsen (2013)	Denmark (32,097)	Developmental Coordination Disorder (DCD)	Only study with this outcome	7 years	OR 0·85 (95% CI 0·70 – 1·03)	Yes
Behaviour /development	[33] Sayal (2007)	UK (967)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Conduct problems*	Later age used in analysis	3.9 years	OR 1·14 (95% CI 0·98 – 1·32)	Yes
	[33] Sayal (2007)	UK (1077)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) parent report *Hyperactivity*	Later age used in analysis	3.9 years	OR 0·99 (95% CI 0·86 – 1·16)	Yes
	[33] Sayal (2007)	UK (257)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) teacher report *Conduct problems*	Parent report used in analysis instead	7.75- 9 years	OR 1·41 (95% CI 1·02– 1·94)	Yes
	[33] Sayal (2007)	UK (525)	10% with highest problem scores, Strengths & Difficulties Questionnaire (SDQ) teacher report *Hyperactivity*	Parent report used in analysis instead	7.75- 9 years	OR 1·20 (95% CI 0·96– 1·51)	Yes
	[46] Parry (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Mental Development Index, Bayley Scales of Infant Development	No SE/SD reported for reference group	18 months	Mean increase of 1·80 points (SE 1·1) for those exposed compared to unexposed.	Yes
	[46] Parry (1992)	Netherlands, Scotland, France, Spain, Denmark, Germany, Portugal (8,453)	Psychomotor Development Index, Bayley Scales of Infant Development	No SE/SD reported for reference group	18 months	Mean increase of 0·81 points (se 0·8) for those exposed compared to unexposed.	Yes
Cognition	[22] Sayal (2013)	UK (10,558)	Key Stage 2 scores	Only study with this outcome	11 years	Mean increase of 0·38 (95% CI -0·02 – 0·78) on KS2 score for those exposed compared to unexposed.	Yes
	[23] Alati (2008)	UK (4,332)	IQ, Weschler Intelligence Scale for Children (WISC-III)	Only study with this outcome	8 years	Mean IQ score 106·4 (SD 16·3) in those exposed, compared to 105·7 (SD 16·2) in those unexposed, p=0·10.	No

[1] Odds Ratio results compare the odds of outcome in those exposed to ≤32g AA per week. SE: Standard error SD: standard deviation SGA: small for gestation age IQ: intelligence quotient.

Table 3. Quasi-experimental studies examining the effects of prenatal alcohol exposure on pregnancy outcomes.

Study (year)	Country	Total Number	Study type	Gene	SNP-rs number	Age at outcome assessment (child)	Outcomes	Summary of results & conclusions as presented in the paper	Limitations
[25] Alati (2013)	UK	7,062	Maternal-paternal comparison	na	na	11 years	Academic achievement: Key Stage 2 scores (standardised)	Maternal alcohol consumption abstainers: mean 102·0 (SD 9·1); <1 glass/week: mean 102·8 (SD 8·7) Paternal alcohol consumption abstainers: mean 98·9 (SD 11); <1 glass/week: mean 101·1 (SD 9·1)	Different confounding structures for the association of maternal vs. paternal alcohol with the outcome
[23] Alati (2008)	UK	4,332	Maternal-paternal comparison	na	na	8 years	IQ: Wechsler Intelligence Scale for Children (WISC)	Maternal alcohol consumption abstainers: mean 105·7 (SD 16·2); <1 glass/week: mean 106·4 (SD 16·3) Paternal alcohol consumption abstainers: mean 102·2 (SD 16·8); <1 glass/week: mean 104·0 (SD 16·7)	Different confounding structures for the association of maternal vs. paternal alcohol with the outcome

Abbreviations: OR: Odds ratio CI: Confidence intervals MD: Mean difference SD: standard deviation IQ: Intelligence quotient.

Discussion

Main findings: In this comprehensive systematic review of the literature on the effects of low levels of alcohol drinking in pregnancy, the two main findings are: i) a surprisingly limited number of prospective studies specifically addressing the question of whether light maternal alcohol consumption (i.e. up to 32g/week (or 4 UK units) has any causal effect (adverse or beneficial) on infant and later offspring outcomes and pregnancy outcomes, and, as a result, ii) a paucity of evidence demonstrating a clear detrimental effect, or safe limit, of light alcohol consumption on outcomes. The upper limit that we chose to examine here is that of the current version of the UK National Institute for Health and Care Excellence (NICE) guidelines.[47] The question we have attempted to address is very important given the mixed advice that women are given with regards to whether they should abstain completely or be allowed light alcohol consumption in pregnancy. The lack of research evidence to address this question is notable.

Strengths and limitations: Strengths of this review include the completeness of searches with a focused research question aimed at informing alcohol in pregnancy guidelines. In addition to observational studies' biases minimised by only including those with prospective assessment of exposure and prioritising results adjusted for main confounders. Another strength of this review is the unique effort to include alternative study designs to further improve causal inference alongside standard analytical approaches. The main limitation of results on the effects of light drinking in pregnancy from standard analytical approaches is bias due to residual confounding. SE position is a complex, multi-faceted entity. Several studies have attempted to adjust for SE position by collecting information on, for example, maternal education, family-level SE position around the time of the pregnancy, home address-based deprivation index etc. Few studies included more than one of these measured [22 29-31]. Whereas we consider attempting to adjust for at least one of these characteristics to be a minimum requirement to account for some of the confounding introduced by SE position, there remains scope for residual confounding.[48] Given the

strong relationship between SE position and both the exposure (alcohol use in pregnancy) and outcomes in this review, any degree of residual confounding is of course an issue when interpreting the effect estimates from the observational studies included in this review. Women who drink low amounts of alcohol may be more likely to be of higher socio-economic position, compared to abstainers, at least in developed settings in recent years,[49] and both of these characteristics are associated with better pregnancy and cognitive outcomes.[50] Maternal smoking and ethnicity are also known correlates of maternal alcohol use, and risk factors for e.g. low birth weight.[51] Most studies included in this review adjusted for at least some of these factors. However, due to the small number of studies included for any given outcome, it was impossible to formally investigate the effect of incomplete adjustment for some (or all) of these confounders. Additionally, for most outcomes, we could not pool eligible studies for various reasons (e.g. too few studies, lack of standard errors) and that we limited our review to a number of pre-specified outcomes including the most common pregnancy-related outcomes and childhood outcomes related to FASD. This also was the case for identifying effects based on time of exposure, which is also a limitation.

The inclusion of only English language studies may have led to missing some studies, however there is little evidence that exclusion of non-English language studies leads to systematic bias in systematic reviews of conventional medicine.[52-55]

Interpretation: This review demonstrates the paucity and poor quality of evidence addressing this important public health question, and the difficulty of designing studies that can effectively evaluate the causal impact of low alcohol consumption whilst minimising bias and confounding. It also shows the value of reporting measures of effect for meaningful categories of the exposure. Whilst many studies reported that associations did not differ from linearity prior to providing a single coefficient for the dose-response association, it is possible that statistical power limited the ability to detect non-linear associations in single studies.

Such detail is especially important when there are controversies about the shape of the association of interest (linear, U or J-shaped) and/or the existence of safe thresholds. Outstanding questions also remain about the effects of maternal alcohol consumption at different stages of conception and pregnancy. Alternative analytical approaches such as sibling comparisons[56] and the use of instrumental variable approaches[57] as well as triangulating the totality of evidence from multiple study types[58] (formally or informally) are needed in order to strengthen confidence in the direction and size of any potential causal relationships.

The recently proposed change in the guidelines for alcohol use in pregnancy in the UK to complete abstinence, would be an application of the precautionary principle. This review confirmed some increased risk of babies being born SGA but little direct evidence of any other detrimental effect for maternal drinking up to 32g/week. However, there have been few well-conducted studies examining this specific category of exposure. This issue remains of great public health importance, with alcohol consumption during pregnancy prevalent in the UK, Ireland, New Zealand and Australia with up to 80% of women consuming some alcohol during pregnancy.[59] For some, the evidence of the potential for harm – mostly coming from animal experiments and human studies of effects due to higher levels of exposure will be sufficient to advocate that guidelines should advise women to avoid all alcohol in pregnancy, while others will wish to retain the existing wording of guidelines.[60] Here we found that maternal alcohol consumption of up to 32g/week was associated with an 10% increased risk of preterm birth (95%CI: 0·95 to1·28). In comparison, light to moderate smoking (<20 cigarettes per day) is associated with a 22% increased risk of preterm birth (95% CI: 1·13 to 1·32).[61]

In conclusion, we found limited evidence for a causal role of light drinking in pregnancy, compared to abstaining, on most of the outcomes examined. Despite the distinction between light drinking and abstinence being the point of most tension and confusion for health professionals and pregnant women and contributing to inconsistent guidance and advice

now and in the past, our extensive review shows that this specific question is not being researched thoroughly enough, if at all. In addition, there has been no evidence regarding possible benefits of light alcohol consumption versus absence. Further studies, including those using designs that improve causal inference, are required to provide further evidence and a better estimation of the likely effects. Formulating guidance on the basis of the current evidence is challenging. However, describing the paucity of current research and explaining that “absence of evidence is not evidence of absence”, appears warranted.

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Loubaba Mamluk: Drafting the protocol, preparing the data extraction database, data screening and collection (lead reviewer), data analysis, figures, tables, data interpretation, and drafting the manuscript. Hannah B Edwards: screening, data collection, data quality checking, data interpretation, and preparation of final manuscript. Theresa HM Moore: Advising on the protocol, preparing the protocol, screening title and abstract. Timothy Jones: Data extraction and full text screening. Sharea Ijaz: Abstract and full text screening. Jelena Savović: protocol development/study design (including the development of searching, article screening and data collection strategies), oversaw and managed the review process and the review team, provided methodological advice for the review and meta-analysis conduct, and critically revised the manuscript. George Davey Smith: Obtained funding, formulation of project plan, review of progress and of the manuscript. Jenny L. Donovan: Obtained funding and contributed to drafting the manuscript, and approved the final version. Verity Leach: Data extraction. Deborah Lawlor: contributed to the study design, data interpretation and review of earlier manuscript drafts; she approved the final version that has been submitted. Sarah J. Lewis: contributed to the study design, data interpretation and review of earlier manuscript drafts; she approved the final version that has been submitted. Abigail Fraser: Contributed to the study design, data analysis and interpretation and drafting of manuscript. Luisa Zuccolo: Contributed to the study design, data analysis and interpretation and drafting of manuscript. I, Loubaba Mamluk, the corresponding author of this manuscript, certify that I have full access to all the data in the study and had final responsibility for the decision to submit for publication.

Transparency declaration

I, Loubaba Mamluk, the corresponding author of this manuscript, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflict of interest:

The authors have nothing to disclose.

This work has not been submitted for publication elsewhere.

Disclosure

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Transparency declaration

The lead author (Loubaba Mamluk) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing Statement

NA

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Figure 1. Flowchart of search strategy including primary reasons for article exclusion.

Figure 2. Pooled mean difference for birthweight comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (7 studies). **'**Adjusted' refers to adjusted for both smoking and a measure of socio-economic status. CI: Confidence intervals.

Figure 3a) Odd Ratios for preterm birth comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (9 studies); **3b)** Odd Ratios for small for gestational age comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (7 studies) **3c)** Odd Ratios for low birthweight comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (6 studies). OR: Odds ratio, CI: Confidence intervals. Pooled OR includes both adjusted and unadjusted estimates from studies, **'**Adjusted' refers to adjusted for both smoking and a measure of socio-economic status.

Supplementary figure 1a) Odds ratios for externalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (3 studies); **1b)** Odds ratios for internalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (2 studies); OR: Odds ratio, CI: Confidence intervals.

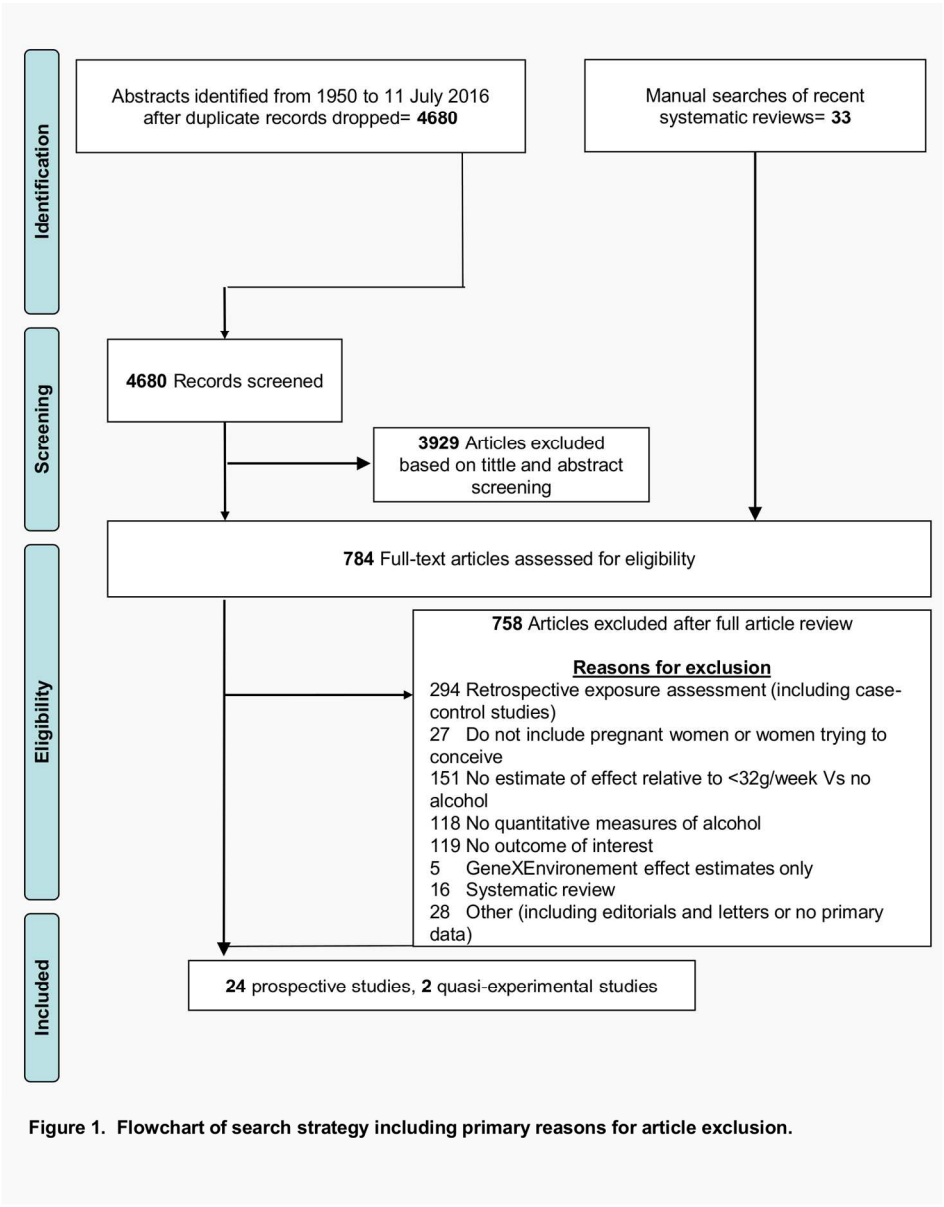

Figure 1. Flowchart of search strategy including primary reasons for article exclusion.

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143x183mm (300 x 300 DPI)

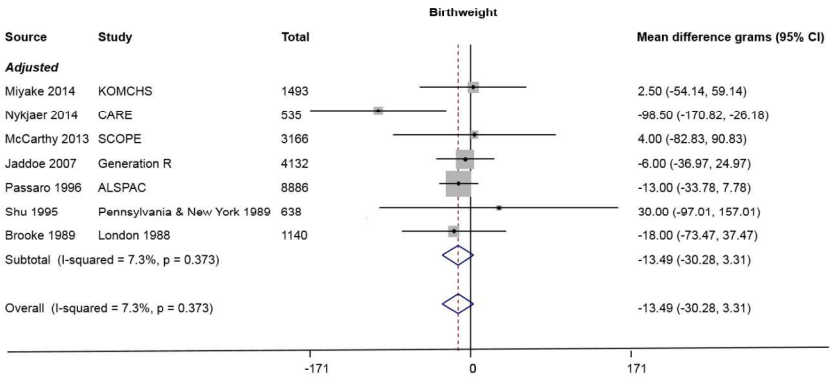
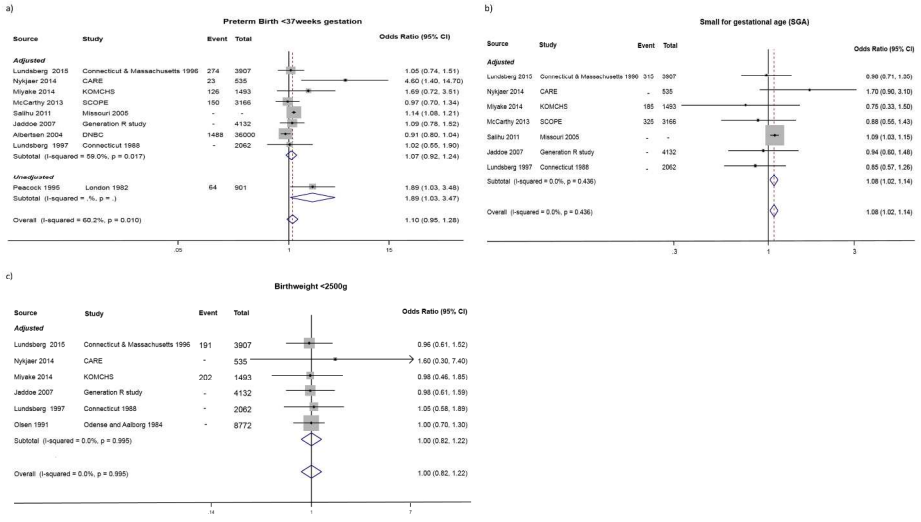


Figure 2. Pooled mean difference for birthweight comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (7 studies). 'Adjusted' refers to adjusted for both smoking and a measure of socio-economic status. CI: Confidence intervals.

Figure 2. Pooled mean difference for birthweight comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (7 studies). 'Adjusted' refers to adjusted for both smoking and a measure of socio-economic status. CI: Confidence intervals.

297x209mm (300 x 300 DPI)



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UNIVERSITY of York
Centre for Reviews and Dissemination

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PROSPERO International prospective register of systematic reviews

Systematic review of the effects of low-moderate prenatal alcohol exposure on pregnancy and childhood outcomes

Loubaba Mamluk, Luisa Zuccolo, Theresa Moore, Alison Richards

Citation

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Review question(s)

To determine what is known about the effects of prenatal alcohol exposure, corresponding to low-to-moderate levels of maternal consumption, on pregnancy outcomes. These include pregnancy complications, delivery outcomes and Fetal Alcohol Syndrome (FAS) features. This will include the assessment of systematic reviews and meta-analyses. A particular focus will be placed on identifying practical and meaningful outcomes of alcohol toxicity during pregnancy.

Searches

Publications will be identified by searching the following major relevant databases: Medline, Embase, web of science and Psychinfo. All databases will be searched from inception. Internet searches will be carried out using Google Scholar. Attempts to identify further studies will be made by examining the reference lists of included studies and of previous reviews. All studies to be restricted to those published in the English language only.

Types of study to be included

1) Prospective studies and systematic reviews/meta-analyses of prospective studies (cohort or case-control studies nested in a cohort). 2) Natural experiments / studies using instrumental variables to improve casual inference, including Mendelian Randomization (MR) studies 3) Sibling comparison studies 4) Parental comparisons

Condition or domain being studied

Pregnancy and delivery outcomes as well as offspring outcomes (from the domains affected by Fetal Alcohol Syndrome (FAS))

Participants/ population

Pregnant women or women who are trying to become pregnant sampled from the general population. Cohorts of pregnant women with alcohol abuse/dependency will be excluded.

Intervention(s), exposure(s)

Inclusion: low–to-moderate levels of prenatal alcohol consumption (up to 10.4 UK units or 83 g/week).

Exclusion: studies will be excluded if there was no quantitative measure of alcohol consumption that could be converted to UK standard units or grams of alcohol and if there was insufficient data for an (adjusted and/or crude) effect measure of low–moderate consumption to be extracted. Cohorts of pregnant women with alcohol abuse/dependency will be excluded.

Comparator(s)/ control

women with no or very sporadic alcohol consumption in pregnancy.

Outcome(s)

Primary outcomes

Outcomes: (in both children and adults)

1) Pregnancy complications

- Intra uterine growth restrictions (IUGR)

- Miscarriage

- Premature labour and birth- Gestational age

- Preeclampsia and gestational hypertension

- Low amniotic fluid (oligohydramnios)

- Gestational diabetes

- Placenta previa

2) Delivery outcomes

- Birth weight/ low birth weight/ small for gestational age (SGA)

- Still birth

- Delivery intervention (including vacuum extraction, forceps delivery, Caesarean section)

- Apgar score

3) FAS features

- Facial malformation

- Growth restrictions (height- measurements of growth restriction)

- Cranium size/ head circumference

- Developmental delays

- Behaviour complications

- Cognitive impairment / IQ

- Attention scores / Attention deficit and hyperactivity disorder (ADHD)

Secondary outcomes
none

Data extraction, (selection and coding)
Selection of studies:

Titles and abstracts will be screened independently by one reviewer (a random selection of 20% will also be screened by a second reviewer independently) with inclusion/exclusion being decided according to prespecified criteria. Discrepancies will be discussed and disagreements resolved through consensus. The full-text of each of the articles identified through screening of titles and abstracts will be obtained in order to determine their inclusion in the review.

Data extraction:

Data extraction will be carried out using Microsoft Access. This will be piloted on a small selection of studies and adjusted as necessary. Relevant data will be documented from each identified study including information on study design and location, population characteristics, exposures studied (including timing of exposure), methods used to ascertain exposures, outcomes studied, method of outcome ascertainment (including person reporting the outcome, whether parent, teacher, health professional, researcher, child…), study results (from both unadjusted and fully adjusted regressions), statistical adjustments etc. Data extraction will be carried out independently by one reviewer and a random selection of 20% will checked by a second reviewer. Discrepancies will be resolved through discussion or referral to a third reviewer. Where necessary, authors will be contacted for additional information.

Risk of bias (quality) assessment

Studies that did not adjust for smoking and maternal education/social class as potential confounders in their final model will be considered to be of low evidence quality.

Strategy for data synthesis

The impact of low-to-moderate alcohol use on pregnancy and related outcomes will be investigated using high-low methods of meta-analysis techniques; however, due to anticipated low number of studies for some outcomes, a formal meta-analysis may not be appropriate for some of the outcomes. Where meta-analysis is not possible, a narrative summary of findings will be carried out. Random-effect meta-analysis will be performed alongside fixed-effect in the presence of high levels of between-studies heterogeneity (measured through I2). Item response theory (IRT) will be used to combining results from different scales if required. The likelihood of small study bias deriving from publication bias will further be assessed through drawing funnel plots.

Analysis of subgroups or subsets

Where the included number of studies in the meta-analysis is large enough, sub-group analyses will be performed for 1) studies adjusting for smoking and maternal education/social class; 2) studies reporting separately on the effects of alcohol use in different gestational periods; 3) studies using different exposure/outcome assessments.

Dissemination plans

We anticipate dissemination to regional and national public health directors

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None known

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Subject index terms
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Stage of review
Ongoing

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Date of publication of this revision
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10.15124/CRD42015015941

Stage of review at time of this submission	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

PROSPERO

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Supplementary Table 1. Search Strategy 1950 to 11·07·2016. MEDLINE, PsycINFO, EMBASE on Ovid; the Cochrane Library including CENTRAL (the Cochrane Central Database of Controlled Trials) on Wiley Interscience; and Science Citation Index, Social Science Citation Index, on Web of Science.

1	exp pregnancy/ (719661)
2	Pregnant Women/ (5199)
3	preconception care/ or prenatal care/ (21644)
4	exp "embryonic and fetal development"/ (212127)
5	Fetus/ (68424)
6	exp Pregnancy Complications/ (343999)
7	(prepregnan$ or conception or preconception or pregnan$ or prenatal$ or pre-natal$ or f?etal or f?etus or in utero).ti,ab. (588557)
8	Maternal exposure/ (5534)
9	or/1-8 (1079283)
10	Ethanol/ (73449)
11	Alcohol dehydrogenase/ (5809)
12	Aldehyde Oxidoreductases/ (3672)
13	exp Drinking Behavior/ (57821)
14	Temperance/ (2430)
15	alcohol$.ti. (106954)
16	(alcohol dehydrogenase or acetaldehyde dehydogenase).ti,ab. (8557)
17	((alcohol or alcoholic) adj3 (drink$ or exposure or consumption or consume$ or consuming or low or light or moderat$ or abstin$ or abstain$)).ti,ab. (49470)
18	((low or light or moderate or abstin$ or abstain$ or pattern$ or behavio?r$) adj3 drink$).ti,ab. (10558)
19	(ADH1B$ or teetotal$ or temperance or nondrink$ or non-drink$).ti,ab. (3093)
20	Genome-Wide Association Study/ or Linkage Disequilibrium/ or genotype/ or phenotype/ or polymorphism, genetic/ or (polymorphism$ or ((gene or genes or genetic or genotyp$) adj3 (instrument$ or variant$ or variable$ or variability or variabilities or variance$))).ti,ab. (494904)
21	*Alcohols/ or exp *Alcohol-Related Disorders/ or (alcohol adj3 (misuse or "use" or abuse or addict$ or dependence or response$ or susceptibility)).ti,ab. (110843)
22	20 and 21 (3108)
23	or/10-19,22 (213050)

24 9 and 23 (11403)
25 letter/ (861500)
26 editorial/ (368458)
27 news/ (166329)
28 exp historical article/ (325965)
29 Anecdotes as topic/ (4586)
30 comment/ (610211)
31 case report/ (1708277)
32 (letter or comment$).ti. (100442)
33 or/25-32 (3417468)
34 randomized controlled trial/ or Randomized Controlled Trials as Topic/ or random$.ti,ab. (888907)
35 33 not 34 (3386180)
36 animals/ not humans/ (3889478)
37 exp Animals, Laboratory/ (730783)
38 exp Animal Experimentation/ (6477)
39 exp Models, Animal/ not humans/ (310115)
40 exp rodentia/ (2688128)
41 (rat or rats or mouse or mice).ti. (1123907)
42 or/35-41 (7849766)
43 24 not 42 (6498)
44 meta-analysis/ (52850)
45 meta-analysis as topic/ (13933)
46 (meta analy$ or metaanaly$ or metanaly$ or meta regression).ti,ab. (72390)
47 ((systematic$ or evidence$ or realist or narrative or literature) adj2 (review$ or overview$)).ti,ab. (171877)
48 "review of reviews".ti,ab. (211)
49 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab. (27094)
50 (search strategy or search criteria or systematic search or study selection or data extraction).ab. (28877)
51 (search$ adj4 literature).ab. (30686)

52 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or cinahl or science Citation index or bids or cancerlit).ab. (95294)

53 cochrane.jw. (11053)

54 ((multiple treatment$ or indirect or mixed) adj2 comparison).ti,ab. (991)

55 or/44-54 (293491)

56 43 and 55 (201)

57 epidemiologic studies/ (6077)

58 ep.fs. (1223653)

59 exp case control studies/ (691899)

60 exp cohort studies/ (1394149)

61 cross-sectional studies/ (185407)

62 Mendelian Randomization Analysis/ (229)

63 (case control or negative control).ti,ab. (93097)

64 (cohort adj (study or studies or analys$)).ti,ab. (98537)

65 ((follow up or observational) adj (study or studies)).ti,ab. (87771)

66 ((longitudinal$ or retrospectiv$ or prospectiv$) and (study or studies or studied or review$ or analys$ or cohort$)).ti,ab. (870699)

67 cross sectional.ti,ab. (183479)

68 (mendel$ or natural experiment$).ti,ab. (11082)

69 ((family or sibling or population) adj3 (study or studies)).ti,ab. (115245)

70 or/57-69 (2937160)

71 exp guideline/ (25834)

72 guidelines as topic/ or practice guidelines as topic/ (114690)

73 guideline$.mp. (291621)

74 or/71-73 (291621)

75 55 or 70 or 74 (3362878)

76 43 and 75 (3349)

77 limit 76 to english language (3096)

78 ((smok$ or drug$ or tobacco or nicotine or cigarette$ or substance$ or methamphetamine$ or amphetamine$ or cocaine$ or heroin or cannabis or marijuana) not (alcohol or alcoholic or drink$)).ti. (489662)

79 77 not 78 (2822)

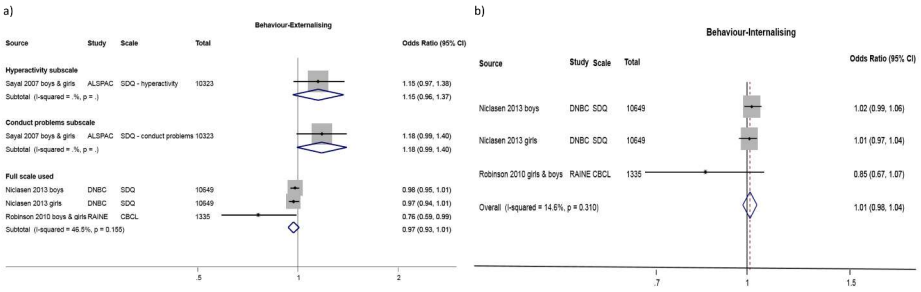
Supplementary Table 2. Lists of confounders adjusted for by each study

Study (year)	Confounders
[26] Lundsberg (2015)	Parity, maternal age, education, BMI, marital status, ethnicity, caffeine, smoking, exercise, work, prenatal and multivitamin use, passive smoke exposure, marijuana use, cocaine use, study cohort, preterm labour, respiratory problem, infant gender, bleeding, nausea/vomiting, hypertension, incompetent cervix, placental problems, sexually transmitted disease, induction/augmentation, maternal asthma, gestational diabetes.
[27] Nykjaer (2014)	Maternal pre-pregnancy weight, height, age, parity, ethnicity, salivary cotinine levels, caffeine intake, education, energy intake, gestation and baby's sex
[28] Niclasen (2014)	Parental smoking, parental education, parental pre-pregnancy psychiatric diagnoses, and maternal psychological well-being in pregnancy.
[29] Miyake (2014)	Low birth weight, preterm birth: maternal age, region of residence, number of children, family structure, maternal education, maternal employment, body mass index, maternal smoking during pregnancy, and baby's gender. Small for gestational age: maternal age, region of residence, number of children, family structure, maternal education, maternal employment, body mass index, maternal smoking during pregnancy, gestational age, and baby's gender.
[45] Faebo Larsen (2013)	Sex, gestational age, intrauterine growth restriction, maternal age, mother's occupational status, maternal smoking (ever) in first trimester, amount of maternal smoking and alcohol consumption in first trimester.
[22] Sayal (2013)	Maternal age, parity, highest level of maternal education, daily frequency of smoking, use of cannabis and/or other illicit drugs during the first trimester, homeownership, whether currently married, high scores (>12) on the Edinburgh Postnatal Depression Scale, and child gestational age, birth weight and gender.
[30] McCarthy (2013)	Maternal age, smoking, years of schooling, ethnicity, body mass index, infant sex, maternal status, family income, and drug use during pregnancy. Adjusted for clustering. Birthweight adjusted for gestational age at delivery.
[40] Andersen (2012)	Number of previous abortions, coffee consumption, changes in alcohol consumption since prior to pregnancy and smoking. Effect of coffee consumption and smoking was stratified according to period. The model is stratified according to maternal age and parity.
[21] Salihu (2011)	Maternal age, parity, race, smoking, education, marital status, adequacy of prenatal care, maternal height, gender of the infant, and year of birth
[31] Robinson (2010)	Maternal age, maternal education, presence of the biological father in the family home, family income, stress in pregnancy, child's age at follow up (and child's age at follow-up squared), and maternal cigarette smoking.
[32] Jaddoe (2007)	Controlled for maternal body mass index, smoking, educational level, height, ethnicity, parity and age and infant gender; birth weight and low birth weight models also controlled for gestational age.
[43] Bille (2007)	Parental age and social class.
[33] Sayal (2007)	Gender, smoking, cannabis use and use of illicit drugs in the first trimester, highest level of maternal education, home ownership, marital status, parity, maternal age group, high EPDS score, child ethnicity, gestational age group, and birth weight.
[34] Albertsen (2004)	Type 1 diabetes, age, previous preterm delivery, smoking during pregnancy, coffee consumption during pregnancy, occupational status in the household, parity, and total alcohol consumption during pregnancy.
[35] Lundsberg (1997)	Small for gestational age: smoking in month 7, ethnicity, weight, height, infant sex, parity, bleeding during pregnancy, high blood pressure, and preeclampsia/eclampsia. Low birthweight: smoking in month 7, height, weight, ethnicity, infant sex, parity, coffee use in month 7, exercise in third trimester, employment, bleeding during pregnancy, high blood pressure, pre-eclampsia/eclampsia, anomalies, and placental problems. Preterm delivery: smoking in month 7, height, parity, age, caffeine use in month 7, exercise first 16 weeks, bleeding during pregnancy, high blood pressure, pre-eclampsia/eclampsia, anomalies, and placental problems.
[41] Windham (1997)	Maternal age, prior spontaneous abortion, gestational age at interview, and cigarette and caffeine consumption in week before interview.
[36] Passaro (1996)	Gestational age, infant sex, parity, maternal smoking, and maternal body mass index.
[37] Shu (1995)	Gestational age, parity, smoking and income.
[20] Peacock (1995)	Unadjusted
[38] Olsen (1991)	Age, school education, parity, alcohol and smoking entered the model as "dummy variables".
[42] Ogston (1992)	Gestational age at birth, sex, mother's age, parity and smoking.
[46] Parry (1992)	Gestational age at birth, sex, mother's age, parity and smoking.
[39] Brooke (1989)	Gestational age, sex, maternal height, and parity
[44] Ernhart (1989)	Parity, smoking, race and year of study.

Supplementary Table 3. Assessment of studies using the The Newcastle-Ottawa Scale (NOS)

Risk of bias questions / Study ID	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design/analysis	Assessment of outcome blind/ record linkage	Follow-up long enough for outcome to occur	Adequacy of follow up of cohorts
Albertson 2003	✓	✓	✓	✓	✓	✓	✓	✓
Anderson 2012	✓	✓	✓	✓	✓	✓	✓	✓
Bille 2007	✓	✓	✓	✓	✓	✓	✓	?
Brooke 1989	✓	✓	✓	✓	✓	✓	✓	✓
Erhart	x	✓	✓	✓	?	✓	✓	x
Jaddoe 2007	✓	✓	x	✓	✓	✓	✓	✓
Larsen 2013	✓	✓	✓	✓	✓	x	✓	x
Lundsberg (Lisbet) 2015	?	✓	✓	✓	✓	✓	✓	✓
Lundsberg (Lisbet) 1997	?	✓	✓	✓	✓	✓	✓	✓
McCarthy 2013	✓	✓	✓	✓	✓	✓	✓	✓
Miyake 2014	?	✓	x	✓	✓	✓	✓	✓

Niclasen 2013	?	✓	?	✓	x	x	✓	?
Nykjaer 2014	x	✓	x	✓	✓	✓	✓	✓
Ogston 1992	?	✓	✓	✓	x	✓	✓	✓
Olsen 1991	?	✓	x	✓	✓	✓	✓	✓
Parry 1992	?	✓	✓	✓	✓	x	✓	x
Passaro 1996	?	✓	x	✓	✓	✓	✓	✓
Peacock 1995	?	✓	✓	✓	x	?	✓	✓
Robinson 2010	?	✓	x	✓	✓	x	✓	✓
Salihu 2011	?	✓	x	✓	✓	?	✓	✓
Sayal 2012	✓	✓	x	✓	✓	?	✓	✓
Sayal 2006	✓	✓	x	✓	✓	x	✓	✓
Shu 1995	✓	✓	✓	✓	x	✓	✓	✓
Windham 1997	x	✓	✓	✓	✓	✓	✓	✓



Supplementary figure 1a) Odds ratios for externalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (3 studies); **1b)** Odds ratios for internalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (2 studies); OR: Odds ratio, CI: Confidence intervals.

Supplementary figure 1a) Odds ratios for externalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (3 studies); 1b) Odds ratios for internalising behaviour comparing low alcohol consumption (up to 32g/week) with no alcohol consumption (2 studies); OR: Odds ratio, CI: Confidence intervals.

297x209mm (300 x 300 DPI)

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	1
2	Hypothesis statement	4
3	Description of study outcome(s)	6&7
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	7
8	Search strategy, including time period included in the synthesis and key words	supplementary table 1
9	Effort to include all available studies, including contact with authors	7
10	Databases and registries searched	7
11	Search software used, name and version, including special features used (eg, explosion)	supplementary table 1
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	13
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6

18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7&8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	supplementary table 2 & 8
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8
22	Assessment of heterogeneity	Figures 2&3
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	9&10
24	Provision of appropriate tables and graphics	27-36
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2&3
26	Table giving descriptive information for each study included	Table 1-3
27	Results of sensitivity testing (eg, subgroup analysis)	Figures 2&3
28	Indication of statistical uncertainty of findings	19

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5&6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 & 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	supTable 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7 & 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6 & 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Figure 2&3 supfigure1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Figure 2&3 supfigure1
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2&3 supfigure1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2&3 supfigure1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 2&3

			supfigure1
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13&14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13 & 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17