

Systematic review of effects of low–moderate prenatal alcohol exposure on pregnancy outcome

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Objective The aim of this study was to review systematically the available evidence on studies in humans on the effects of low–moderate levels of prenatal alcohol consumption (up to 10.4 UK units or 83 g/week) compared with consumption of no alcohol on pregnancy outcome.

Design Systematic review.

Population Pregnant women or women who are trying to become pregnant.

Methods The search strategy included Medline, Embase, Cinahl and PsychInfo for the years 1970–2005. Titles and abstracts were read by two researchers and inclusion/exclusion being decided according to prespecified criteria. All the included articles were then obtained and read in full by the two researchers to decide on inclusion. The articles were assessed for quality using the Newcastle–Ottawa Quality Assessment Scales.

Main outcome measures Outcomes considered were miscarriage, stillbirth, intrauterine growth restriction, prematurity, birthweight, small for gestational age at birth and birth defects including fetal alcohol syndrome.

Results The search resulted in 3630 titles and abstracts, which were narrowed down to 46 relevant articles. At low–moderate levels of consumption, there were no consistently significant effects of alcohol on any of the outcomes considered. Many of the reported studies had methodological weaknesses.

Conclusions This systematic review found no convincing evidence of adverse effects of prenatal alcohol exposure at low–moderate levels of exposure. However, weaknesses in the evidence preclude the conclusion that drinking at these levels during pregnancy is safe.

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Introduction

There is now a large volume of literature on the effects of maternal alcohol consumption during pregnancy on the developing embryo, fetus and child. It is generally accepted that both abusive and heavy drinking are associated with fetal alcohol syndrome (FAS) and fetal alcohol effects such as growth restriction, birth defects and neurodevelopmental problems.¹

The current UK Department of Health guidelines recommend that women who are trying to become pregnant or are at any stage of pregnancy should not drink more than 1 or 2 units of alcohol once or twice a week and should avoid episodes of intoxication.² Since most pregnant women either abstain from alcohol or drink at low–moderate levels,³ any evidence on the effects of drinking at this level during pregnancy will be of interest to pregnant women, clinicians and public health practitioners.

We therefore searched for studies that compared women with an intake of less than 84 g of alcohol per week, i.e. less than 12 g/day (1 UK unit contains 8 g of alcohol), with those who abstained during their pregnancy. Half a pint of ordinary strength beer, lager or cider contains 8 g of alcohol; a small glass of ordinary strength wine contains 12 g and a small pub measure of spirits contains 8 g. The objective of this systematic review was to assess whether drinking up to this amount was associated with a greater risk of adverse pregnancy outcome compared with total abstinence.

Methods

Studies were included if they were case–control, cohort or cross-sectional studies published between January 1970 and July 2005 in the English language in a peer-reviewed journal; if they included data on the relevant outcomes: miscarriage,

stillbirth, intrauterine growth restriction (IUGR), preterm birth, (low) birthweight, small for gestational age (SGA) at birth or birth defects including FAS and if average weekly alcohol consumption was grouped into two or more categories. The ranges of at least two of these categories had to be contained within the range of less than 84 g/week and could include an abstainer or an infrequent drinker (<6 g/week) group. Studies were excluded if there was no quantitative measure of alcohol consumption that could be converted to UK standard units or grams of alcohol, if average alcohol consumption was treated only as a continuous (and not as a grouped) variable and not limited to the low–moderate range, if there was insufficient data for an (adjusted and/or crude) effect measure of low–moderate consumption to be extracted, if it was a duplicate publication or if the study was only available in abstract form.

A computerised literature search was undertaken using the WebSpirs 5 software of Medline (1970–2005), Embase (1980–2005), Cinahl (1982–2005) and PsychInfo (1972–2005). Mesh headings and free-text terms were used for the exposure and outcomes. The search was limited to studies where 'low', 'light', 'social', 'moderate' or 'dose' appeared in the text in relation to the exposure. The results were then 'filtered' using the 'high-sensitivity' filter for aetiological studies.⁴ A copy of the search strategy is available from the authors.

Titles and abstracts (if present) of all studies identified were reviewed independently by two members of the research team to identify potentially relevant articles; differences were resolved by discussion. Articles deemed relevant or of uncertain relevance were obtained and read in full. These articles were reviewed against the inclusion/exclusion criteria independently by two members of the research team to determine which article to include. Reasons for exclusion were identified and are available from the authors.

The quality of all the included studies was assessed using the Newcastle–Ottawa Scale as recommended by the Cochrane Non-Randomized Studies Methods Working Group.⁵ It uses a system in which a study is judged on three areas: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or the outcome of interest for case–control or cohort studies, respectively.

A data extraction form (available from the authors) was designed, piloted and revised. Each included article was read and data were extracted by a member of the study team; a second member checked table entries for accuracy against the original article. For each of the outcomes, data were synthesised into tables, giving descriptive information for each study included. Where authors did not provide effect measures with 95% confidence intervals or perform statistical testing, we attempted to do this, where possible, from summary statistics. These are shown as italics face text.

It was not anticipated that a meta-analysis would be appropriate, given the likely heterogeneity in methods of

the different studies. The studies have been grouped by outcome, summarised in tables and are discussed below.

Results

Searches of the databases resulted in 3275 articles (Figure 1). Of these articles, 308 were marked as either relevant (121) or of uncertain relevance (187) on the basis of their title and abstract (where available). Full text of these articles was obtained. In addition, 87 articles from the bibliographies of a key text and review articles were also obtained (395 in total). Of these articles, 46 were included in the review. A brief summary of these studies is shown in Table 1.

Miscarriage

There were eight studies describing the effects of low–moderate alcohol consumption on miscarriage (Table S1). Information about miscarriage was derived from maternal self-report,⁶ hospital records,^{7–10} record linkage¹¹ and in one case daily urine specimens.¹² Miscarriage was limited to the first trimester in one study,⁸ up to 20 weeks of gestation in two^{9,10} and up to 27/28 weeks of gestation in the rest. All but one of the eight studies used hospital or antenatal populations and thus would not have been able to include very early pregnancy loss.

The case–control study by Long *et al.*⁸ limited to first trimester miscarriages reported that women drinking 1–10 units of alcohol per week (up to 80 g) had a relative risk (RR) of 3.79 (95% CI 1.18–12.17) compared with abstainers. This was adjusted for confounders, but exactly which confounders was not stated. Moreover, alcohol exposure was 'pre-pregnancy',

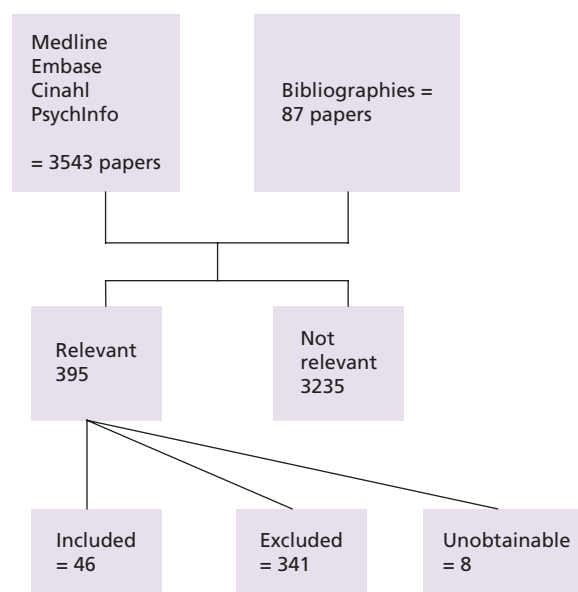


Figure 1. Results of the search.

Table 1. Summary of the studies included in the review*

Outcome	No. of studies	Total no. of women	Alcohol data collected AN/PN	Results	Comments
Miscarriage ⁶⁻¹³	8	115 958	6 AN, 2 PN	Five studies found significant increase, RR ranged from 2.0 to 3.79, OR 1.1	Some of these studies unadjusted for confounding or only in smokers
Stillbirth ¹³⁻¹⁷	5	56 110	2 AN, 3 PN	One study found significant increase in 25-60 g/week, OR 7.6	The high odds ratio was based on small numbers
Impaired growth ¹⁸⁻²⁴	7	129 439	2 AN, 5 PN	One study found significant increase in impaired growth	This analysis was unadjusted for confounders
Birthweight ^{14,20-22,25-38,41,56}	19	175 882	12 AN, 7 PN	One study found a significant increase in low birthweight	This analysis was unadjusted for confounders
Preterm birth ^{14,20-21,24,27,32-46}	16	178 639	10 AN, 6 PN	One study found a significant increase in preterm birth	Did not control for socio-economic status
Malformations ^{13-14,26,47-49}	6	57 798	4 AN, 1 PN, 1 both AN and PN	One study found a significant increase in major malformations	Included white women only and unadjusted for confounders

AN, antenatal; PN, postnatal.

*Some studies reported more than one outcome.

but it was not clear how long prior to pregnancy. The other case-control study⁹ reported an adjusted odds ratio of 1.2 (95% CI 0.81-1.90) for up to 72 g/week compared with less than 6 g/week.

The cohort studies reported rates of miscarriage in non-drinkers (or <6 g/week) ranging from 1.4¹¹ to 20.5%.⁶ In those who consumed up to 48 g/week, rates of miscarriage ranged from 1.7¹³ to 32%.¹² Three studies used survival analysis to calculate hazard ratios.¹⁰⁻¹² Adjusted for the major confounders, these ranged from 0.8 (first trimester, 36-48 g/week)¹¹ to 2.1 (1-48 g/week).¹² This latter result was of borderline statistical significance.

Of the eight studies, five found that women who consumed less than 84 g/week (i.e. less than one drink per day) were at significantly increased risk of miscarriage. However, two of these studies had significant limitations; in the third article, the only significant result was among the heavy smokers, and the results in the remaining two were of only borderline statistical significance.

Stillbirth

The association between low-moderate levels of alcohol consumption during pregnancy and stillbirth has been examined in five studies, three cohort and two case-control (Table 2).¹³⁻¹⁷ All the five studies used large hospital or maternity data sets. In the three cohort studies, rates of stillbirth were between 3 and 6 per thousand births.^{13,17} Three of the studies reported higher rates of stillbirth in women who did not drink at all.^{13,14,17} All these studies had limitations as shown in Table 2.

The only article reporting results not subject to recall bias and adjusting for confounders also used a validated questionnaire to ask about alcohol consumption.¹⁶ They found that although low-moderate levels of alcohol consumption during pregnancy was associated with slightly higher rates of stillbirth, this was not statistically significant. They also reported no interaction or effect modification with smoking.

Impaired growth

There were seven studies in which IUGR or SGA was the reported outcome (Table S2). IUGR is an intrauterine diagnosis based on failing growth on serial ultrasound; SGA is diagnosed at birth. Definitions of IUGR and SGA varied. Some studies used the 5th or the 10th percentile of birthweight for gestational age and^{18,20} some corrected for race and sex²¹ and parity.²² One used a ratio of observed to expected birthweight for gestational age, sex and parity.²³

Only one of the studies found a significant positive association between low-moderate levels of alcohol consumption and IUGR.²⁴ However, the relevant analysis in this article was not adjusted for potential confounders and may therefore be misleading. This was also true of the study by Whitehead and Lipscomb.²²

Table 2. Stillbirth

First author, year of publication, country, study type	Period and numbers recruited	Measures of alcohol exposure and outcome	Results			Comments		
Davis, 1982, ¹³ UK, cohort study	1980, 973 babies, 7 stillbirths	Questionnaire at booking visit, outcomes from hospital notes	g/24 hours	% stillbirth		White women only. Study unadjusted for potential confounders		
			0	0.4				
			1–8	0.3				
			RR 1.0 (0.2–4.4)					
Faden, 1997, ¹⁶ USA, nested case–control study	1988, 3309 stillbirths, 9953 live births	Written self-report postpartum, outcome from National Maternal and Infant Health Survey	g alcohol	Weighted %		Reported as a representative sample, but authors do not state how sample was taken. Response rates were 74% for live births and 69% for stillbirths. Weighted % reported to correct for oversampling of low birthweight and black infants. However, not adjusted for confounders in this analysis		
			None	Live births	Stillbirths			
			<12/month	79.3	84.5			
			12/month	10.8	7.8			
			13–36/month	3.5	1.7			
			12/week	2.5	2.1			
			13–24/week	1.3	1.35			
25–60/week	1.3	0.8						
			0.8	1.0				
Kesmodel, 2002, ¹⁷ Denmark, cohort study	1989–96, 24 768 including 116 stillbirths	Questionnaire in early pregnancy, outcome data from birth registration forms and Danish Medical Birth Register through record linkage	g/week	% stillbirth		Questions about alcohol consumption validated against other methods. Odds ratio adjusted for maternal smoking, caffeine, age, pre-pregnancy body mass index, marital and occupational status, education, parity and sex of child. No interaction or effect modification with smoking		
			<12	0.4				
			12–24	0.5				
			25–48	0.6				
			g/week	Adjusted OR (95% CI)				
<12	1.0							
12–24	1.3 (0.8–2.0)							
25–48	1.3 (0.6–2.5)							
Little, 1993, ¹⁵ USA, case–control study	1980, 1835 cases, 2832 live birth controls	Postpartum questionnaire, outcome data from birth/death certificates and hospital records	% live births	% AP deaths	% IP death	OR (AP/IP) (95% CI)	'Before' and 'during' pregnancy not defined. Response rate 78%, further 22% excluded because of incomplete telephone interviews. Differential response rate not mentioned. Only 39% of cases included in analysis because of exclusion of multiple births and women with serious medical conditions. No adjustment for confounders in this analysis. Potential for recall bias	
			Alcohol use prior to pregnancy (g/day)					
			0	40.9	45.5	48.7		1.0
			0.2–2.4	37.6	33.6	36.0		0.8 (0.7–0.9)
			2.5–6.0	11.4	11.4	11.6		0.9 (0.7–1.1)
			6.1–12.0	5.8	5.2	1.6		0.7 (0.5–1.0)
			Alcohol use during pregnancy (g/day)					
			0	51.8	57.4	63.2		1.0
			0.2–2.4	42.8	39.2	35.3		0.8 (0.7–0.9)
			2.5–6.0	3.7	2.2	1.0		0.5 (0.3–0.8)
6.1–12.0	0.7	0.7	0.0	0.7 (0.2–1.8)				
Marbury, 1983, ¹⁴ USA, cohort study	About 1982, 12 440 births including 73 stillbirths	Retrospectively by PN interview, outcome from medical records	g/week	% stillborn		RR (95% CI)		
			0	0.6		1.0		
			1–24	0.6		1.0 (0.5–1.9)		
			25–72	0.4		0.7 (0.2–2.1)		

AP, antepartum; IP, intrapartum; PN, postnatal.

Three studies found that low-moderate levels of alcohol consumption appeared to be mildly protective against IUGR.^{18,20,22} However, one study adjusted for previous low birthweight,¹⁸ which may represent overadjustment if the previous baby was also exposed to alcohol *in utero*.

Birthweight

There were 19 studies that examined the association between alcohol consumption and birthweight (mainly low birthweight) (Table S3). All were cohort studies, ranging in size from 412²⁵ to 40 445.¹⁸ Birthweight and alcohol consumption are both strongly associated with cigarette smoking, making this a potential confounding factor. Six studies did not adjust for this factor in their analyses investigating the association with low-moderate alcohol consumption,^{17,26-30} although some did in other analyses. Another important variable in this context is ethnicity as both birthweight and alcohol consumption are associated with this. Of the 12 studies that carried out some adjustment, only 3 either adjusted for ethnicity^{18,20,21} or included only white women or only black women.^{25,31}

There were few statistically significant results. One study reported a significant increase in the risk of low birthweight with the consumption of <2.4 g of alcohol per day (adjusted RR 3.20, 95% CI 1.87-5.46).²⁰ However, at 2.4-6.0 g/day, compared with abstinence, the RR was lower at 1.36 (95% CI 0.48-3.88). Other studies reported a possible protective effect of light drinking; mean birthweight was slightly higher, for example, an odds ratio for low birthweight of 0.79 (95% CI 0.70-0.90) associated with consuming 12-24 g/week;¹⁸ other studies reported similar findings.^{21,32-36}

Preterm birth

There were 16 studies meeting the inclusion criteria that considered preterm birth as an outcome (Table S4). Of these, two were case-control studies,^{37,38} which suffered from possible lack of blinding to case/control status, potential for recall bias and one³⁷ that failed to control for potential confounders.

Of the 14 cohort studies, half were based on very large data sets, ranging in size from 8469³⁹ to 40 892 and⁴⁰ the other half on a smaller scale, ranging from 952²⁷ to 4111.⁴¹ Half of the articles estimated gestational age from the date of last menstrual period and/or by ultrasound. However, two articles used the Dubowitz examination, which is based on specific physiological and neurological characteristics of the neonate;^{27,37} in three studies, it is implied that gestational age was from the birth registration form or from the hospital records,^{17,18,42} and two studies did not state how gestational age was estimated.^{34,43}

Adjustment for confounding was carried out in nine studies,^{18,20,23,34,39,40,43-45} although in some of these studies, the adjustment was performed in other analyses in which alcohol consumption was more broadly grouped or when examining other associations. A further two studies did not

control for socio-economic status (through social class, education or occupation).^{20,44} However, some studies may have overadjusted, controlling for previous low birthweight or preterm birth or miscarriage, which may themselves have been associated with alcohol consumption during a previous pregnancy.

Despite the different methods and limitations of these studies, all except one study found either no effect or a reduction in risk of prematurity with the consumption of up to 72 g of alcohol per week. The exception was a US study based on two health maintenance organisations and 11 private practices.²⁰ They found RR of 2.11 and 2.15 in women consuming <2.4 and 2.4-6.0 g/day, respectively, at 7 months of gestation. However, they did not control for socio-economic status.

Three studies found a significant protective effect of low alcohol consumption.^{18,42,45} This occurred at up to 24 g/week.

Malformations

There were six studies that examined the association between low-moderate levels of alcohol consumption and incidence of malformations, including fetal alcohol effects, in the baby (Table 3)^{13-14,26,47-49}. Four studies analysed total malformations,^{17,26,46,48} two included major malformations^{13,48} and two examined anomalies related to fetal alcohol effects.^{45,49} Major malformation was undefined in one study¹³ and defined in the another study⁴⁸ as causing functional impairment or requiring surgical correction. Only two studies adjusted for potential confounders in the relevant analyses,^{46,48} the latter may have overadjusted by including previous malformed infant or miscarriages that may have been associated with alcohol exposure. Exposure to alcohol was assessed by interview or questionnaire antenatally in all but one study.¹⁷ In four studies, the neonatal assessment was blinded to alcohol consumption.⁴⁶⁻⁴⁹ In the other studies, it was either not stated or data were from routine statistics.²⁶

Only one of the studies¹³ reported a significant association between low-moderate levels of alcohol consumption and malformations. However, that study included white women only and was unadjusted for potential confounders.

Discussion

In summary, from the existing evidence, it is difficult to determine whether there was any adverse effect on pregnancy outcome associated with low-moderate levels of prenatal alcohol consumption. Although there was no consistent evidence of adverse effect, this does not mean that it is safe for women to drink at these levels during pregnancy; the existing evidence is inconclusive.

Small amounts of alcohol appeared to have a mildly protective effect for several of the outcomes, including stillbirth, IUGR and birthweight, i.e. babies of women who abstained had poorer outcomes than babies of women who drank small

Table 3. Malformations

First author, year of publication, country, study type	Period and numbers recruited	Measures of alcohol exposure and outcome	Results				Comments
Davis, 1982, ¹³ UK, cohort study	1980, 973 women, 6 malformations	Questionnaire at booking visit, outcomes from hospital notes	g/24 hours 0 1–8		% major malformations 0 0.6	White women only. Study unadjusted for potential confounders. Major malformations undefined	
Ernhart, 1989, ⁴⁷ USA, cohort study	3-year period (not stated when), 239–873 women depending on measure	Alcohol exposure estimated three ways: <i>in pregnancy</i> by interview relating to 2 weeks preceding each AN visit, <i>retrospective</i> by interview 5 years later about the index pregnancy and <i>embryonic</i> equation derived from separate sample to estimate exposure before woman knew she was pregnant. Outcomes from neonatal examination	g/day	In pregnancy	Mean anomalies tally	Embryonic	Disadvantaged population, oversampled women screening positive for alcoholism. Neonatal examination blind to exposure to alcohol in pregnancy. <i>Retrospective</i> data at 5 years unlikely to be accurate, potential for recall bias. Matched or adjusted for parity, smoking, race, date of recruitment, drug abuse, pre-pregnancy weight and weeks of gestation at registration. Multiple outcomes investigated and multiple testing performed
			0	2.5	Retrospective	2.2	
			1–2.4	2.6	2.8	2.4	
			2.5–6	2.6	2.8	2.5	
			g/day	In pregnancy	Mean anomalies tally	In pregnancy	
			0	1.9	In pregnancy	1.6	
1–2.4	1.9	2.1	1.8				
2.5–6	2.0	1.9	1.9				
Multiple one-tailed <i>t</i> tests: all nonsignificant							
Lumley, 1985, ²⁶ Australia, cohort study	1981–82, 10 319 women	Alcohol consumption estimated in early pregnancy (method not stated), outcome data from the Tasmanian perinatal statistics	g/week 0 1–24 25–72		% malformed (95% CI) 2.3 (1.8–2.7) 2.5 (2.1–2.9) 2.7 (1.3–4.1)	Study based on all Tasmanian births from 1981–82. However, only 69% data on alcohol consumption. Nonrespondents similar in terms of parity and SES but significantly lower birthweight. No adjustment for confounders in this analysis. Difference between abstainers and light drinkers not seen consistently within parity or SES	
Marbury, 1983, ¹⁴ USA, cohort study	About 1982, 12 440 women	Postpartum interview, outcomes from medical records	g/week 0 1–24 25–72	Major malformations, %, RR (95% CI) 2.6, 1.0 3.0, 1.1 (0.8–1.5) 3.3, 1.3 (0.8–1.9)	Minor malformations, %, RR (95% CI) 6.1, 1.0 6.3, 1.0 (0.8–1.3) 4.9, 0.8 (0.6–1.1)	% malformed unadjusted in this analysis. Adjustment only carried out on regrouped drinking variable. Potential for recall bias	

(continued)

Table 3. (Continued)

First author, year of publication, country, study type	Period and numbers recruited	Measures of alcohol exposure and outcome	Results					Comments
			g/week	Rate (%)	All malformations, adjusted OR (95% CI)	Rate	Major malformations, adjusted OR (95% CI)	
Mills, 1987, ⁴⁸ USA, cohort study	1974–77, 32 870 women	Questionnaire relating to first trimesters; outcomes from discharge diagnoses, notes and autopsy reports, blind to alcohol exposure	0	7.8	1.0 1.0 (0.9–1.0)	1.6 1.8	1.0 1.2 (1.0–1.4)	Adjusted for maternal age, race, education, parity, previous malformed infant or miscarriage, smoking, diabetes mellitus and exposure to radiation. May be overadjusted
			<12	7.7				
Olsen, 1995, ⁴⁹ Denmark, cohort study	1988–89, 323 women	Questionnaire at First antenatal visit and interview subsequently, outcomes measured from photos at birth and 18 months after birth	0	20.8	Nose, upper lip (standardised units) Before pregnancy	0.38 0.41	Oversampled women who consumed 5+ drinks per week. Measurement from photos blind to alcohol exposure during pregnancy, but correlation between observers inconsistent. The data in previous column relate to newborns. A similar pattern was observed at 18 months. However, features associated with FAS may not become apparent until 2 years. Unadjusted for confounders in this analysis	
			1–48	22.3				
			0	22.4	First trimester	0.39 0.42		
			1–48	22.3				
			0	21.6	First and second trimester	0.41 0.41		
			1–48	22.5				

AN, antenatal; SES, socio-economic status.

amounts of alcohol during pregnancy. One possible explanation for this may be the 'healthy drinker effect' in which women with a poor obstetric history were more likely to abstain from drinking alcohol.⁵⁰ It may also be that low–moderate drinking during pregnancy is genuinely beneficial, but further research is required to test this hypothesis rigorously.

For pragmatic reasons, searches were limited to English language studies in the four bibliographic databases Medline, Embase, PsychInfo and Cinahl. We did not attempt to access the 'grey' literature nor did we request further data from the authors. We scanned 3630 titles that were systematically narrowed down to 46 publications. Very few of the retrieved articles specifically addressed low–moderate levels of alcohol consumption. Most of the articles made comparisons across a number of different levels of consumption. Therefore, in many cases, we had to calculate effect estimates from summary statistics provided.

The systematic review may have been affected by publication bias in which studies with positive results are both more likely to be submitted and more likely to be accepted for publication. However, given that many clinicians have been sceptical about the effects of alcohol on the fetus, it is also plausible that studies finding a negative effect could have been more likely to be published.

The quality of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scales. This scale has been used in other Cochrane reviews of nonrandomised studies such as the use of antiepileptic drugs during pregnancy.⁵¹ Generally, the studies included in this review scored quite highly. However, this was not a true reflection of the quality of many of the studies that had problems specific to carrying out research in the area of prenatal alcohol exposure and that were not covered in the general quality assessment scale, for example, a common problem related to the timing of the questions about alcohol consumption. Women were frequently asked after delivery how much they drank during pregnancy, when the outcome was already apparent. The potential for recall bias is clear. The higher quality studies used validated questionnaires or interviews administered antenatally to ask about specific time periods both prior to pregnancy recognition and during pregnancy.

The majority of the included studies were from the USA. The generalisability of these results to other countries may be questionable. Differences in drinking patterns, the extent to which women underreport drinking during pregnancy and ascertainment of outcomes may all differ between the USA and other countries.

In attempting to be as broad as possible in our inclusion criteria, studies were included if they had at least two categories of consumption within the 12 g/day limit. The majority of these articles also reported outcomes for higher consumption. When studies did report outcomes within these low–moderate categories of consumption, it was often as a first step in the

analysis. At this point, they were often unadjusted for potential confounders. Therefore, although appropriate adjustment for potential confounders was made, in many cases, this could not be related to the low–moderate comparisons.

Residual confounding may have been a problem in many studies because of inaccuracy in measuring confounders such as cigarette smoking and the effect of socio-economic status or by not adjusting for other important confounders.

Although we are not aware of any other systematic reviews or meta-analyses of the effects of low–moderate levels of alcohol consumption on pregnancy outcome, we identified two meta-analyses that studied a range of moderate consumption, the upper range of which was much higher than we considered, which we consider may be relevant.

Polygenis *et al.*⁵² conducted a meta-analysis of moderate alcohol consumption during pregnancy and the incidence of fetal malformations. Moderate consumption was defined as the range of 24–168 g/week. The meta-analysis included 130 810 pregnancy outcomes and reported a RR for fetal malformation of 1.01 (95% CI 0.94–1.08). Another meta-analysis examined the association between moderate alcohol consumption and miscarriage, stillbirth and premature birth.⁵³ Definition of 'moderate consumption' was the same as by Polygenis *et al.*⁵² Odds ratios for miscarriage were 1.35 (95% CI 1.09–1.67), for stillbirth, 0.65 (95% CI 0.46–0.91) and for premature birth, 0.95 (95% CI 0.79–1.15). However, the result for stillbirth was considered unstable and inconclusive because of the small number of studies, and significant heterogeneity existed among the individual odds ratios for miscarriage. These results are broadly in line with those from this systematic review, allowing for the higher consumption. In contrast with these two studies, we did not attempt to conduct meta-analyses in this review because of the considerable heterogeneity in the methods of the various studies.⁵⁴

Future research needs to consider the accuracy and validity of estimates of alcohol consumption. Women tend to underreport alcohol consumption during pregnancy unless the information is collected in a careful and sensitive manner.⁵⁵ More studies concentrating specifically on low–moderate levels of alcohol consumption would be of benefit and would allow for more detailed analysis of this area.

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Supplementary material

The following supplementary material is available for this article:

Table S1. Miscarriage.

Table S2. Impaired growth.

Table S3. Birthweight.

Table S4. Preterm birth.

This material is available as part of the online article from: <http://www.blackwell-synergy.com/doi/abs/10.1111/j.1471-0528.2006.01163.x>.

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