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REVIEW

Low–moderate prenatal alcohol exposure and offspring attention-deficit hyperactivity disorder (ADHD): systematic review and meta-analysis

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Abstract

Purpose To evaluate the available evidence on the association between low-to-moderate prenatal alcohol exposure (PAE) and the development of attention-deficit hyperactivity disorder (ADHD) symptoms in the offspring.

Methods We systematically reviewed and meta-analysed studies reporting an association between low and/or moderate PAE and offspring ADHD symptoms (attention and/or hyperactivity). Systematic searches were performed in EMBASE, Pubmed, Medline, and PsycINFO and reviewed from selected references. Random effects modelling was conducted to pool adjusted odds ratios (OR) in different alcohol consumption levels (≤ 20 g/week, ≤ 50 g/week, and ≤ 70 g/week). Stratified analysis by sex per alcohol level was conducted to investigate the difference on OR and the magnitude between-study heterogeneity.

Results Ten studies were included in the systematic review and six in the meta-analysis. Eight studies found no association and two studies suggested an apparent protective effect of low PAE in hyperactivity/inattention symptoms in boys. These results were confirmed by the meta-analysis showing no association between ≤ 20 g/week [OR 1.01 (0.68–1.49)], ≤ 50 g/week [OR 0.94 (0.85–1.03)] and ≤ 70 g/week [OR 0.94 (0.86–1.02)] and ADHD symptoms, with no evidence of publication bias. Stratified analysis by sex for a PAE ≤ 50 g/week exposed less risk of ADHD symptoms in boys compared to girls [OR 0.89 (0.83–0.96)].

Conclusions We found no increased risk of ADHD symptoms in offspring born to mothers who drank alcohol up to 70 g/week.

Keywords Alcohol · Consumption · Pregnancy · ADHD · Prenatal · Systematic review · Hyperactivity · Behaviour · Attention

Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common behavioural disorder in childhood worldwide and the most prevalent mental health disorder in Australian children and adolescents [1, 2]. ADHD is characterised by an early onset of inattention, and/or hyperactivity symptoms more frequent and severe than other individuals at the same age [2, 3]. Symptom expression and comorbidities which exhibit considerable variation are likely to persist during childhood to adolescence and are associated with significant functional impairments in adults [4, 5]. ADHD is also a risk factor for other psychiatric and substance use disorders, which makes it a significant and growing public health concern [6]. It is estimated that the heritability of this disorder is greater than 70%, but it is also accepted that between 10 and 40% is accounted for by environmental and developmental factors, including the prenatal environment [7, 8].

Several reports have linked in utero alcohol exposure with predisposition to behavioural disorders with ADHD-like symptoms [3, 8, 9]. Alcohol consumed by expectant mothers may interfere with the normal development of the fetus and lead to physical and neurological damage with lifelong health consequences [10]. Since the teratogenic effects of heavy alcohol use during pregnancy were identified,

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numerous studies have associated prenatal alcohol exposure (PAE) to a range of cognitive and behavioural problems in offspring [11, 12]. Specifically, impairments consistent with ADHD have been linked to children born to mothers who consumed alcohol during pregnancy [9, 10, 13]. However, the quantity and the frequency of alcohol needed to be consumed for such effects to become apparent remain a highly contentious issue in public health research. There is strong evidence that heavy PAE and binge drinking during pregnancy (four drinks for women, around 56 g of pure alcohol, in a single occasion) [14] are associated with ADHD symptoms in offspring [9, 10]. What is less clear is the potential damage that low-to-moderate levels of alcohol during pregnancy may have on the fetus [9, 15] and the available evidence regarding the effects of low-to-moderate PAE on neurodevelopment is inconsistent [9, 12]. Consequently, it is difficult to have evidence based agreement on how much alcohol is safe to drink while pregnant.

In Australia, the National Health and Medical Research Council (NHMRC) recommends that the safest option is to abstain from drinking while pregnant or planning a pregnancy due to uncertainty of safe alcohol levels [15]. The current guidelines are more conservative than previous Australian Guidelines which in 2001 recommended that pregnant women who decide to consume alcohol should drink less than 7 standard drinks a week, and, no more than 2 standard drinks (spread over at least 2 h) a day [16]. Despite recommendations of total abstinence in recent guidelines from USA, UK and Australia, there is evidence that many women still consume alcohol while pregnant [17]. For example, according to the National Drug Strategy Household Survey in 2013 nearly half (47%) of Australian pregnant women reported drinking some alcohol at some stage in their pregnancy [18]. More than half (56%) consumed alcohol before pregnancy recognition, and 26% percent continued drinking throughout the pregnancy, though nearly all reduced their alcohol use to 1–2 standard drinks per drinking occasion [18].

The uncertainty concerning the effects of low-to-moderate alcohol use on the fetus may at least partly explain why nearly 30% of these women decide not to abstain from drinking despite policy recommendations. For women who are pregnant, misinformation and inappropriate counselling regarding alcohol consumption during pregnancy may also increase anxiety and stress; it may lead to unwarranted termination of pregnancy, or may minimise the perception of risk of alcohol consumption [19]. This emphasises the need to further investigate the level of harm associated with in utero exposure to light-to-moderate patterns of alcohol consumption. To our knowledge, there is no meta-analysis of the relationship of low and moderate PAE and ADHD symptoms. The aim of this meta-analysis is to evaluate the available evidence and develop a better understanding of the association between low-moderate PAE and the development of ADHD-like symptoms.

Methods

Search strategy

We used preferred reporting items for systematic reviews and meta-analysis (PRISMA) guideline [20]. Searches in EMBASE, Pubmed, Medline, and PsycINFO were performed to identify relevant studies which analysed the association between prenatal alcohol exposure and ADHD-related symptoms/behaviours. Articles were also identified by reviewing references cited in relevant articles and reviews. The search was restricted to human studies published from 2003 since a highly related search in review published on the same year [3]. The key terms used in the systematic search were: alcohol, drinking, consumption, antenatal, pregnancy, ADHD, hyperactivity, behaviour, neurodevelopment, and attention.

Eligibility criteria

Inclusion criteria was discussed and predetermined. We included all the studies that extracted their data from a prospective cohort study and presented information on the relation of low and/or moderate prenatal alcohol exposure and ADHD or any ADHD-like symptoms/behaviours. Studies must have measured the outcome in individuals aged 2–17 years, had quantitative analysis of alcohol consumption during pregnancy, and controlled for relevant confounders (i.e., maternal smoking during pregnancy, SES, age, maternal education). Studies in which information on alcohol consumption during pregnancy was obtained after the offspring were 1 year old which were excluded to minimise the influence of recall bias. Since our study only focuses on low and moderate PAE, studies analysing alcohol consumption as a continuous variable were also excluded due to the difficulty of categorising alcohol consumption into low and moderate gradients. By applying this criterion, we automatically excluded studies that investigated heavy and binge drinking as the exposure. We also excluded case reports, conference abstract and review papers.

Data extraction

We extracted study description, methodology and results, which include study design and setting, sample characteristics, instruments used, alcohol quantification, ADHD symptoms assessed, age of measurement, analyses, adjusted estimates for the presence of ADHD-related symptoms, and 95% confidence intervals. Eligible studies differed vastly in

the definition or classifications for low and moderate alcohol consumption, in their definition of unit of alcohol as well as their definition of a standard drink. Standard drink definitions varied from 8 to 20 g of pure alcohol according to the country from which the data was taken [21]. Due to the heterogeneity of these definitions and to make the studies comparable, we transformed the consumption levels in grams of alcohol per week (g/week). To achieve these, we multiplied the units/drinks of alcohol by the grams of pure alcohol contained in each unit/drink. The resulting variable contained three alcohol exposure levels ≤ 20 g/week (any consumption up to 20 g/week), ≤ 50 g/week (any consumption up to 50 g/week), and ≤ 70 g/week (any consumption up to 70 g/week), with non-exposure (0 g/week) as the reference group.

Quality assessment

The quality of each study was assessed using the Newcastle–Ottawa scale [22] for cohort studies. Given the strong association between socioeconomic status (SES) and both alcohol consumption and neuropsychological problems in offspring [19, 23], the quality assessment specifically measured whether articles controlled for one or more confounders related to SES. Points from each scale components were added to come up with a score; the highest score achievable in the scale was nine points.

Analysis and risk bias across studies

All studies were included in the narrative analysis for the systematic review. In the event of multiple studies using the same cohort, we chose only the study which reported estimates for the offspring at their oldest age for the meta-analysis. In the event of multiple measurement of the outcome, only the parent-rated measurement was considered for the meta-analysis. Random effects meta-analysis was conducted to pool (OR) using adjusted estimates from the studies. It assumes that heterogeneity exist among the studies. Apart from the overall OR, stratified analyses were also conducted for males and females. Heterogeneity among studies meta-analysed was evaluated using I^2 statistic and Cochran's Q and publication bias was measured using Begg's test.

We conducted random effects meta-regression to identify possible sources of heterogeneity between studies. Five moderators (quality score, age of outcome measurement, outcome definition, timing of alcohol assessment, and type of confounders) were analysed using univariate and multivariate models in the metan package in Stata14. Age of outcome measurement was dichotomised into childhood (9 years old and below) or adolescence (11–19 years old). Outcomes were defined as 'attention deficit only', 'hyperactivity only' or 'attention deficit and hyperactivity'. We dichotomised timing of alcohol assessment as during and after pregnancy, and adjustment for socioeconomic confounders as "yes" or "no".

Results

Study selection

Databases searches resulted in 1981 articles after removing duplicates. Of these, 131 were selected as relevant based on their title and abstract. After reviewing study methods, 25 articles were selected for a full-text review. Of these, ten met our eligibility criteria and were included in our Systematic review, and six were included in the meta-analysis (Fig. 1).

Study characteristics and quality assessment

Table 1 shows an overview of the characteristics of the ten selected studies. Four studies were from Denmark, four from the UK and two from Australia. All the studies were prospective birth cohort studies (Table 1). Seven studies collected information on maternal alcohol consumption prenatally, one study at 3 months postpartum and two studies at 9 months postpartum. Six studies measured attention and/or hyperactivity symptoms using the Strengths and Difficulties Questionnaire (SDQ), two using the Child Behaviour Checklist (CBCL), and two using the Test of Everyday Attention for Children (TEACh). The sample sizes of the included studies vary between 1327 and 37,152 individuals; length of follow-up varies between 5 and 15 years and the percentages of boys and girls in studies that did separate gender analysis were 51% boys and 49% girls. All the studies selected scored between seven and eight points on the Newcastle–Ottawa scale.

Study results and publication bias

Regarding the association of ADHD-related symptoms and alcohol consumption during pregnancy, three studies suggested an apparent protective effect of low PAE on hyperactivity/inattention symptoms. Kelly et al. (2009) found that boys born to mothers who drank between 8 and 16 g of alcohol a week were less likely to have high hyperactivity scores at 3 years compared to children born to mothers that abstain from consuming alcohol during pregnancy [24]. Another study by Kelly et al. (2012) found that lower hyperactivity scores in children of mothers who drank between 8 and 16 g of alcohol a week at age 5 years compared to abstainers were no longer seen after adjustment [25]. Similarly, Niclasen et al. (2014) found that boys with mothers who drank 25–48 g a week (> 2–4 drinks) had lower

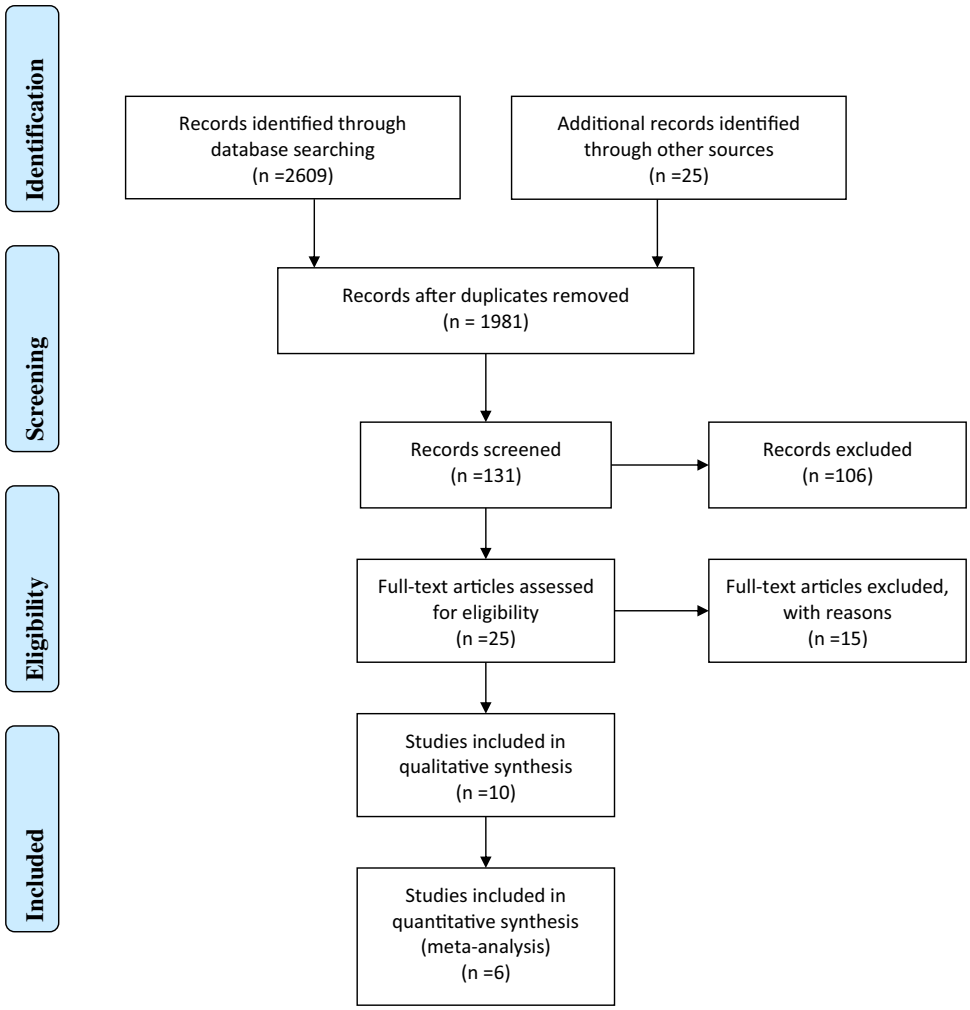

Fig. 1 Information of phases of the Systematic review using PRISMA flow-diagram [20]

hyperactivity/inattention scores than boys whose mothers abstained during pregnancy [26].

The remaining studies found no associations. Sayal et al. (2007) suggested an association between light PAE (less than 8 g/per week) in early pregnancy and increased conduct problems at 8 years old, but not with hyperactivity symptoms [27]. Three years later when the same cohort was 11 years old, another study reported no relationship between PAE with less than 8 g of alcohol per week and risk of hyperactivity/inattention [28]. Similar findings were reported by Kesmodel et al. and Underbjerg et al. who looked at low-to-moderate alcohol consumption during pregnancy (12–48 g/week) and attention in children aged 5 years [29, 30]. Underbjerg et al. found that mean scores for children of mothers who drank 12–48 g/week and 60–96 g/week (1–4 and 5–8 drinks per week) were almost identical to the scores of children born to abstainers [29]. Two Australian studies did not find any increased risk of attention problems in offspring of mothers who reported low-to-moderate alcohol use (< 70 g/week and < 98 g/week) [31, 32]. Rodriguez et al. analysed data from three cohorts and found no consistent associations between PAE and inattention/hyperactivity symptoms when pooling and adjusting the estimates from all three [33].

From the six studies eligible for meta-analysis, we found no effect for low–moderate alcohol consumption (see Table 2). The absence of publication bias and minimal level of heterogeneity was also observed among the studies. All the five moderators did not explain between-study heterogeneity after meta-regression. We also conducted subgroup analysis by sex and limited alcohol use to ≤ 20 g/week and ≤ 50 g/week; data were not available to extract stratified estimates for alcohol levels between 51 and 70 g/week. Stratification by sex (Fig. 2) for PAE of ≤ 20 g/week showed no difference between males and females confirming meta-regression results (OR 0.96; 95% CI 0.67–1.38 and OR 1.06; 95% CI 0.72–1.56, respectively). Analysis of the ≤ 50 g/week alcohol level showed reduced risk of ADHD symptoms among male (OR 0.89; 95% CI 0.83–0.96) compared to female offspring (OR 0.96; 95% CI 0.86–1.07). Unlike the female subgroup, four out of five studies in the male subgroup have an OR < 1.00 indicating a minimal level of between-study heterogeneity ($Q = 3.64$; $p = 0.46$; $I^2 = 0.00\%$)

Table 1 Characteristics of the studies

First author and year	Country	Cohort	Sample size at follow-up	Exposure measurement		Outcome measurement				
				Pre- or post-natal	Time of assessment	Symptom assessed	Tool	Age at follow-up	Estimate	Nos score
Kesmodel (2012)	Denmark	DNBC	1628	Prenatal	7–39 weeks	Attention	TEACH	5 years	MD	7
Kelly (2012)	UK	UK MCS	11,485	Post-natal	9 months	Hyperactivity	SDQ	5 years	OR	8
Kelly (2009)	UK	UK MCS	9413	Post-natal	9 months	Hyperactivity	SDQ	3 years	OR	8
Niclasen (2012)	Denmark	DNBC	37,152	Prenatal	16 weeks	Hyperactivity/inattention	SDQ	7 years	OR	7
O'Leary (2010)	Australia	Western Australia	1327	Post-natal	3 months	Attention	CBCL	8 years	OR	7
O'Callaghan (2007)	Australia	MUSP	5139	Prenatal	19 ± 6 weeks	Attention	CBCL	14 years	OR	8
Rodriguez (2009)	Denmark	ABC	4968	Prenatal	36 weeks	Hyperactivity/inattention	SDQ	10–12 years	OR	7
		HHT	7844	Prenatal	Up to 36 weeks	Hyperactivity/inattention	SDQ	15 years	OR	7
		NBC	8525	Prenatal	Up to 24 weeks	Hyperactivity/inattention	SDQ	7–8 years	OR	7
Sayal (2013)	UK	ALSPAC	6587	Prenatal	18 weeks	Hyperactivity/inattention	SDQ	11 years	MD	8
Sayal (2007)	UK	ALSPAC	8046	Prenatal	18 weeks	Hyperactivity/inattention	SDQ	4–8 years	OR	8
Underbjerg (2012)	Denmark	DNBC	1628	Prenatal	7–39 weeks	Attention	TEACH	5 years	MD	7

[a]All were cohort prospective studies

as shown in Fig. 2b. We also performed a sensitivity analysis (Trim and Fill method) by incorporating all studies regardless of the cohort used and we found consistent results.

Discussion

The results of this meta-analysis suggest that there is no increased risk of ADHD-like symptoms in offspring born to mothers who drank up to 70 g/week. Analysis by sex showed that alcohol consumption of up to 50 g during pregnancy decreased the odds of ADHD-like symptoms in male offspring, which is in the opposite direction to what was expected. This result should be interpreted with caution as we cannot disregard the possibility that the results may have been affected by residual confounding or other post-natal exposure that studies did not account for. As discussed in some of the studies, important differences on background characteristics were observed between the women who reported low and moderate alcohol intake and those who reported abstaining. Women who drank low and moderate alcohol consumption tended to be more educated [26], and from higher SES compared to abstainers [24, 25]. Therefore, if women from higher SES consume alcohol moderately, an observed protective association may mask protective effects from SES rather than a beneficial effect from moderate alcohol use in pregnancy [26]. In turn, PAE may show to lead to adverse behaviours in offspring of mothers from low SES, as higher SES might have a buffer effect on the adverse outcomes of high PAE on the child [19]. This interpretation may be supported by another study which found that offspring with Fetal Alcohol Syndrome and other alcohol related effects had greater prevalence of ADHD when born to women from a lower SES compared to children of women from higher SES. Both groups of women had histories of chronic alcoholism and their reported alcohol consumption was equivalent [34].

More sophisticated epidemiological techniques have been developed to account for endogeneity of the risk factor which may result in spurious causal interpretation [35]. Parental offspring comparisons have been used to disentangle environmental factors from prenatal exposures [35, 36]. This method, known as negative control [37] has been used in previous studies of prenatal alcohol and smoking exposures and offspring outcomes. After using this approach Gustavson et al. (2017) found that the association between maternal smoking during pregnancy and child ADHD diagnosis was not stronger than the association between paternal smoking, grandmother's smoking when pregnant with mother, or maternal smoking in previous pregnancies and child ADHD diagnosis [38]. A study by Alati et al. found a similar association between maternal smoking and PAE with offspring IQ when compared with the association of paternal

Table 2 Effect of low-to-moderate alcohol during pregnancy on ADHD symptoms among offspring

Alcohol level/study	*n*	Pooled estimate		Heterogeneity			Publication bias	
		OR	95% CI	*Q*	*p* value	I^2	*b*	*p* value
≤ 20 g/week	2	1.01	0.68–1.49	7.60	0.01	87%	1.00	0.317
Kelly et al. [25]		0.83	0.69–1.00					
Sayal et al. [28]		1.24	1.00–1.54					
≤ 50 g/week	4	0.94	0.85–1.03	9.98	0.04	60%	0.49	0.624
Niclasen et al. [26]		0.92	0.86–0.98					
Kelly et al. [25]		0.84	0.71–0.98					
Rodriguez et al. [33][a]		0.85	0.7–1.03					
Rodriguez et al. [33][b]		0.95	0.82–1.10					
Sayal et al. [28]		1.23	1.00–51					
≤ 70 g/week	6	0.94	0.86–1.02	10.59	0.10	43%	1.05	0.293
Niclasen et al. [26]		0.92	0.86–0.98					
Kelly et al. [25]		0.84	0.71–0.98					
Rodriguez et al. [33][a]		0.85	0.70–1.03					
Rodriguez et al. [33][b]		0.95	0.82–1.10					
Sayal et al. [28]		1.23	1.00–1.51					
O'Leary et al. [31]		1.17	0.64–2.14					
O'Callaghan et al. [32]		0.90	0.70–1.3					

n number of studies, *Q* Cochran's Q, *b* bias coefficient

[a]Using the ABC cohort

[b]Using HHT cohort

alcohol and tobacco consumption [36]. Another method, Mendelian Randomization (MR), analyses the association between an outcome and a genetic variant that has effects on the exposure or mimics the biological link between the exposure and the outcome [35]. A study which used both traditional epidemiological adjustment and MR analysis found a detrimental effect on school performance in the children of mothers who drank during pregnancy only when using the MR method [39]. None of the studies in this review applied these sophisticated epidemiological methods to their analysis, therefore, we cannot disregard that the relationship, or lack thereof, between ADHD-related behaviours and PAE may be generated by socially patterned environmental or genetic factors.

Strengths and limitations

The strengths of this meta-analysis are the prospective cohort design of all the studies and the group structure for the meta-analysis. We grouped the alcohol categories by grams of alcohol consumption per week. This allowed us to compare groups by the actual amount of alcohol consumed and not by the definition of each publication, which differed vastly between the studies. In addition, none of the categories included for this analysis included binge drinking according to the definition of binge drinking used in the article's respective country.

Our study also has some limitations. It was not possible to remove the occasional or light drinkers from the moderate groups. All categories of alcohol consumption analysed in this study included any amount of alcohol up to 20; 50 or 70 g/week. The inclusion of occasional or light drinkers is likely to attenuate the effect estimates. Further, our analysis only considered weekly intake and could not assess associations with greater amounts alcohol consumed per drinking occasion. In addition, alcohol consumption during pregnancy was based on mothers' self-reports in all the selected studies, so there is potential of under-reporting alcohol consumption during pregnancy due to social desirability [19]. However, some of the studies collected data on alcohol consumption more than 15 years ago, at a time when there was less stigma attached to alcohol use in pregnancy and guidelines were less conservative than in the present day. Under-reporting due to retrospective recall bias may have affected accuracy as three studies collected data for alcohol consumption retrospectively at 3 months [31] and 9 months postpartum [24, 25]. In most of the selected studies, women were approached once during or after the pregnancy regarding their alcohol consumption. A single measure will not give accurate and detailed information of the pattern, frequency and quantity of consumption throughout the pregnancy, however, this information is difficult to obtain from cohort studies [29]. Prospective longitudinal studies (all the studies included in this meta-analysis) are also prone to attrition bias [19]. Most of the selected studies reported

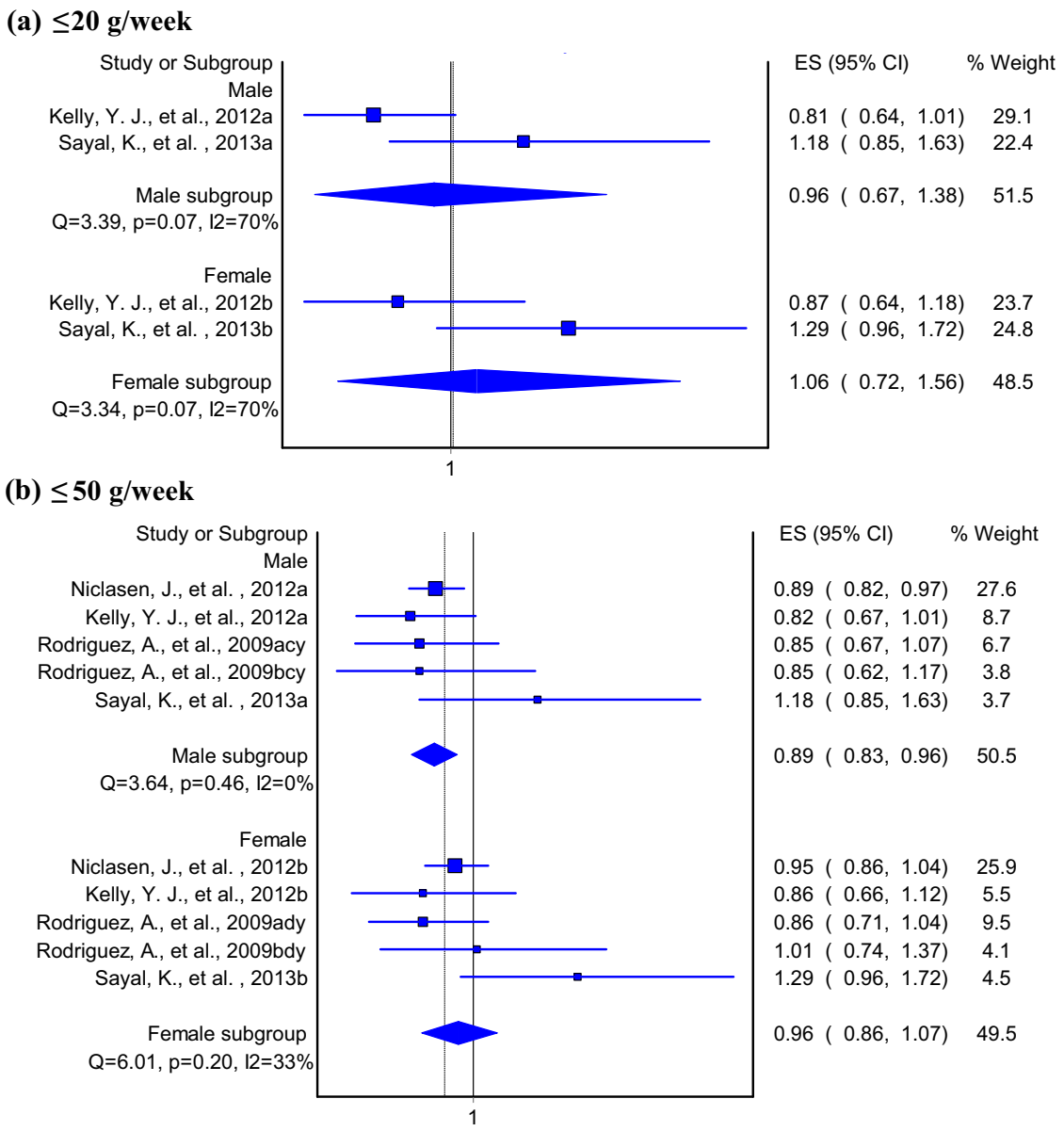

Fig. 2 Meta-analysis of low-to-moderate alcohol exposure on ADHD symptoms stratified by sex

that mothers who were lost to follow-up were younger, less educated, less likely to be married and had more disadvantaged SES compared with the participants [24, 25, 27, 28, 31–33]. This difference in the characteristic of participants and non-participants may have influenced the findings of the selected studies.

Interpretation

This analysis focused on exploring associations between light and moderate drinking and ADHD-related behaviour. Our study only analysed weekly alcohol intake, we did not investigate any outcomes from binge drinking or amount of alcohol used per occasion. In addition, we did not investigate other offspring's health outcome which may be affected by exposure to light or moderate drinking during pregnancy. Therefore, our results should not be seen as suggesting that there is a clear safe threshold limit of alcohol consumption during pregnancy. Rather, they should be seen as an objective appraisal of the current, perhaps limited, literature in this area. Pregnant women should still adhere to current national alcohol guidelines recommending no alcohol consumption during pregnancy.

Conclusion

This study found no effect of moderate and light PAE in children. The small beneficial effect found among male offspring may be explained by the positive relationship of SES and PAE. Future research on the relationship of low alcohol consumption during pregnancy and ADHD-like symptoms using more sophisticated epidemiological techniques is warranted to increase our understanding of the mechanisms behind these associations.

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Compliance with ethical standards

Conflict of interests No conflict of interest declared.

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