The Journal of Obstetrics and Gynaecology

Journal of Obstetrics and Gynaecology

ISSN: 0144-3615 (Print) 1364-6893 (Online) Journal homepage: https://www.tandfonline.com/loi/ijog20

Gestational weight gain and risk of autism spectrum disorders in offspring: a systematic review and meta-analysis

Zhao-Xu Tian, Man Wan, Ya-Ling Gao, Bi-Fang Wu, Yun Xie, Jie Liu, Rui-Zhang Su, Li-Li Tian & Yi-Qun Hu

To cite this article: Zhao-Xu Tian, Man Wan, Ya-Ling Gao, Bi-Fang Wu, Yun Xie, Jie Liu, Rui-Zhang Su, Li-Li Tian & Yi-Qun Hu (2019): Gestational weight gain and risk of autism spectrum disorders in offspring: a systematic review and meta-analysis , Journal of Obstetrics and Gynaecology, DOI: 10.1080/01443615.2019.1676211

To link to this article: https://doi.org/10.1080/01443615.2019.1676211

JOURNAL OF OBSTETRICS AND GYNAECOLOGY
https://doi.org/10.1080/01443615.2019.1676211

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Gestational weight gain and risk of autism spectrum disorders in offspring: a systematic review and meta-analysis

Zhao-Xu Tian[a,b,c*], Man Wan[a,b*], Ya-Ling Gao[a,d*], Bi-Fang Wu[a,b], Yun Xie[a,b], Jie Liu[a,b], Rui-Zhang Su[a,b], Li-Li Tian[a,e] and Yi-Qun Hu[a,b]

[a]Department of Digestive Medicine, Xiamen University Affiliated Zhong Shan Hospital, Xiamen University Medical School, Xiamen, China; [b]Department of Gastroenterology, Zhongshan Hospital Affiliated to Xiamen University, Xiamen, China; [c]Ninth People's Hospital of Chongqing, Shanghai, China; [d]XiaHe Division, Zhongshan Hospital Affiliated to Xiamen University, Xiamen, China; [e]Department of Gynaecology and Obstetrics, Zhongshan Hospital Affiliated to Xiamen University, Xiamen, China

ABSTRACT

It has been revealed that gestational weight gain (GWG) influences the risk of autism spectrum disorder (ASD) in the offspring, but the findings are inconsistent. The current study aimed to evaluate the relationship between GWG and risk of ASD in offspring. Four electronic databases were searched up to August 28 2018 to identify observational studies reporting the association between GWG and risk of ASD in the offspring. Nine studies which met the inclusion criteria were included in the systematic review. Finally, five studies with a total of 3793 children with ASD were included in the meta-analysis. The-results indicated that excessive GWG might increase the risk of ASD in offspring ($p = .0008$, OR = 1.23, 95% confidence interval (CI) 1.09–1.38). More high quality cohort studies are needed to confirm this result. This research has the potential to inspire new research on ASD and promote efforts to design appropriate interventions against excessive GWG.

IMPACT STATEMENT

- **What is already known on this subject?** It has been revealed that gestational weight gain (GWG) influences the risk of autism spectrum disorder (ASD) in the offspring, but the findings are inconsistent.
- **What the results of this study add?** This is the first systematic review and meta-analysis on the association between GWG and ASDs in offspring. This study suggested that excessive GWG was associated with higher risk of ASD in offspring.
- **What the implications are of these findings for clinical practice and/or further research?** More high quality cohort studies are needed to confirm this result. This research has the potential to inspire new research on ASD and promote efforts to design appropriate interventions against excessive GWG.

KEYWORDS

Gestational weight gain; meta-analysis; ASD; systematic review; GWG; autism spectrum disorders; autism

Background

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterised by impairment in communication and social interaction, as well as restricted, repetitive patterns of behaviour, and interests or activities (Zwaigenbaum and Penner 2018). The last 20 years of epidemiological survey data indicate that the prevalence of ASD has increased on a global scale, and its prevalence rate is estimated to be around 1% (Lord et al. 2018). Most children with ASD have a poor prognosis. After adulthood, they do not have the ability to live, study and work independently and become a heavy burden to their families as well as society (Lavelle et al. 2014). Autism is a complex disorder which originates from a combination of genetic and environmental factors. The potential risk factors for ASD include maternal gestational diabetes, maternal bleeding during pregnancy, prenatal exposure to valproate and antidepressant, and parental socioeconomic status (Williams et al. 2010; Matelski and Van de Water 2016). The most recent meta-analysis revealed that pre-pregnancy obesity is associated with increased risk of ASD in offspring (Sanchez et al. 2018). Several previous studies indicate that pre-pregnancy obesity may affect the development of the offspring's nervous system through the intestinal flora, oxidative stress and inflammation-induced mal-programming and leptin resistance mechanism in offspring, leading to an increased risk of offspring ASD (Dodds et al. 2011; Buffington et al. 2016; van der Burg et al. 2016). Further, gestational weight gain (GWG) is also associated with changes in intestinal flora, increased levels of inflammatory and activated leptin resistance mechanism (Diez et al. 2014; Cordner and Tamashiro 2015; Buffington et al. 2016). In this context, epidemiological studies have investigated the

CONTACT Li-Li Tian 1514218545@qq.com; Yi-Qun Hu hyq0826@xmu.edu.cn Department of Digestive Medicine, Xiamen University Affiliated Zhong Shan Hospital, Xiamen University Medical School, Xiamen 361004, China
*These authors contributed equally to this work.

association between GWG and ASD. However, their findings are inconsistent. For example, the study by Bilder et al. (2013) and Xiang et al. (2015) revealed a positive association between GWG and risk of ASD, while the study by Jo et al. (2015) and Hendrix et al. (2012) did not show any statistically significant results.

There is currently no systematic review or meta-analysis to examine the relationship between GWG and offspring ASD. Thus, this systematic review and meta-analysis was carried out to elucidate the possibility of such an association.

Methods

Data sources and search strategy

A systematic review of published studies and a meta-analysis of case-control and cohort studies was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (Stroup et al. 2008). A search for journal studies published in English or Chinese was conducted including all previous researches until August 28 2018, in the medical databases PubMed, EBSCO, Web of Science and Chinese National Knowledge Infrastructure. The search terms applied in the search for eligible studies included: 'Disorder, Autistic', 'Disorders, Autistic', 'Kanner's Syndrome', 'Kanner Syndrome', 'Kanners Syndrome', 'Autism, Infantile', 'Infantile Autism', 'Autism', 'Autism, Early Infantile', 'Early Infantile Autism', 'infantile Autism, Early', 'ASDs', 'ASD'; 'Gain, Weight', 'Gains, Weight', 'Weight Gains', 'weight gain', 'weight change', 'weight increase' and 'Autism spectrum disorder'. For complete review of all available studies, the reference lists of eligible articles as well as the relevant systematic review articles returned in the search were scanned while the abstracts of all relevant scientific meetings were examined.

Inclusion criteria

This work included case control studies and cohort studies meeting the following inclusion criteria: (1) written in Chinese or English; (2) singleton pregnancies; (3) reported an association between GWG and the risk of autism; (4) pre-pregnancy weight was categorised as underweight, normal weight, overweight or obese; (5) GWG was classified as insufficient, normal and excessive GWG based on the Institute of Medicine (IOM) recommendations or appropriate cut-off points. The recommended weight gains for underweight (BMI $< 18.5\,kg/m^2$), normal weight (BMI $= 18.5$–$24.9\,kg/m^2$), overweight (BMI $= 25.0$–$29.9\,kg/m^2$) and obese women (BMI $> 30.0\,kg/m^2$) were 12.5–18, 11.5–16, 7.0–11.5 and 5.0–9.0 kg, respectively.

Data extraction

All the studies retrieved from the databases and bibliographies were independently evaluated to ensure that they met the above described inclusion criteria. The potential relevance of the titles and abstracts was independently evaluated by two reviewers (Man Wan and Yun Zhou). Any disagreements were resolved through consensus with a third reviewer when necessary. The following information was extracted from each study: first author's name, year of publication, country of study, study design, sample size, maternal obesity criteria, GWG criteria, data source, diagnostic criteria for ASD, adjusted covariates, and unadjusted or adjusted RR, OR, as well as HR with corresponding 95% confidence interval (CI).

Quality assessment

The quality assessment of the included studies was carried out using an improved Newcastle-Ottawa Scale (Stang 2010). Three main aspects of each study were evaluated including: selection, comparability and exposure. Each satisfactory answer was assigned one 'star' and studies with six or more stars were considered to be of high quality. Two authors (Jie Liu and Bi-Fang Wu) conducted the quality assessment independently, and the final score of each included study was adjudicated by the primary author (Zhao-Xu Tian) after reviewing the original paper.

Statistical methods

For meta-analyses, the degree of GWG was defined based on the appropriate cut-offs in the original paper or recommendations in the guideline, and was classified as insufficient, normal or excessive. A random-effects model was used to calculate summary ORs and 95%CI for inadequate, and excessive GWG versus the normal GWG. RR in the cohort studies was considered as the approximations of OR, considering the low absolute risk of ASD. Heterogeneity between the studies was estimated using I^2 statistics. I^2 values of 25%, 50% and 75%, were respectively considered to be low, moderate and high degrees of heterogeneity. If the literature included more than 10, a funnel plot was used to detect potential publication bias (Sterne et al. 2011). A sensitivity analysis was performed on the meta-analysis results by sequentially excluding each study at a time. All analyses were performed using RevMan 5.3.3 provided by the Cochrane Collaboration.

Results

Results of literature search

Figure 1 shows the process for the study selection. The initial search in four different electronic databases yielded 880 records, of which 201 were duplicates and were excluded, leaving 658 records for title and abstract screening. Twenty-one publications qualified for full text screening based on the inclusion criteria. Nine studies (Dodds et al. 2011; Hendrix et al. 2012; Bilder et al. 2013; Gardner et al. 2015; Jo et al. 2015; Xiang et al. 2015; Ziyu et al. 2015; Qiu et al. 2018; Shen et al. 2018) focussing on associations between GWG and risk of ASDs in offspring met all the eligibility criteria and were included in the qualitative development of this review. Of the nine identified studies, five studies (Dodds et al. 2011; Gardner et al. 2015; Ziyu et al. 2015; Qiu et al. 2018; Shen

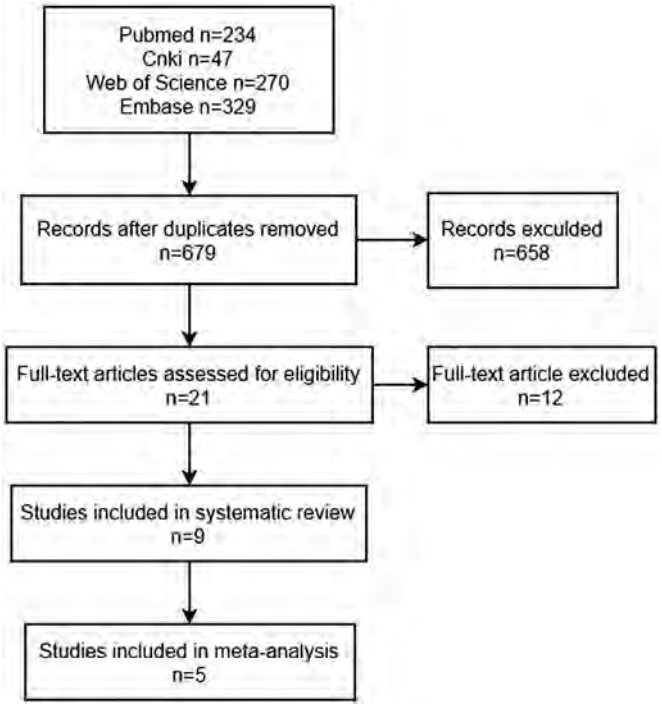

Figure 1. Flowchart of the study selection process.

et al. 2018) reported sufficient data in the required format and were included in the current meta-analyses.

Description of studies

Table 1 lists the descriptive characteristics of the studies. Four studies (Hendrix et al. 2012; Ziyu et al. 2015; Qiu et al. 2018; Shen et al. 2018) were retrospective case-control trials, and five (Dodds et al. 2011; Cordner and Tamashiro 2015; Gardner et al. 2015; Jo et al. 2015; Xiang et al. 2015) were retrospective cohort studies. Four studies (Hendrix et al. 2012; Bilder et al. 2013; Jo et al. 2015; Xiang et al. 2015) were from the US, three (Ziyu et al. 2015; Qiu et al. 2018; Shen et al. 2018) were from China, one (Gardner et al. 2015) was from Sweden and one (Dodds et al. 2011) was from Canada. The nine studies involved 4980 children with ASDs. GWG collection was self-reported in six studies (Hendrix et al. 2012; Jo et al. 2015; Xiang et al. 2015; Ziyu et al. 2015; Qiu et al. 2018; Shen et al. 2018); three studies (Dodds et al. 2011; Bilder et al. 2013; Gardner et al. 2015) were diagnosed by medical staff. Five studies (Dodds et al. 2011; Gardner et al. 2015; Ziyu et al. 2015; Qiu et al. 2018; Shen et al. 2018) reported the odds ratios (ORs) and 95%CIs according to excessive or inadequate number of events compared to children born to mothers with normal weight, two studies (Bilder et al. 2013; Xiang et al. 2015) reported the continuous data, one study (Hendrix et al. 2012) did not present data. Of the four studies (Gardner et al. 2015; Ziyu et al. 2015; Qiu et al. 2018; Shen et al. 2018), GWG was classified as insufficient, normal and excessive based on recommendations by the IOM; one study (Dodds et al. 2011) defined 'excessive' as GWG of more than 18 kg and 'inadequate' as GWG of less than 7 kg. Two studies (Gardner et al. 2015; Shen et al. 2018) reported complete data for GWG with normal pre-gestational BMI while Xiang et al. (2015) used the IOM recommendations. The methodological quality of the nine studies was evaluated according to the NOS. Scores ranged from 5 to 8 on the Newcastle-Ottawa scale (Table 2).

GWG and risk of ASD in offspring

Of the nine studies, four were excluded from the final meta-analysis because they did not provide data. Both studies by Xiang et al. (2015) and Bilder et al. (2013) suggested that GWG was associated with risk of ASD in offspring. The study by Bilder et al. (2013) included two cohort studies. In the research-based on ASD cohort of Utah children ($n = 288$) and their unaffected siblings ($n = 493$), GWG was found to be significantly associated with ASD (OR = 1.17, 95%CI: 1.01–1.35 for each five pounds of weight gained). Jo et al. (2015) and Hendrix et al. (2012) suggested that GWG was not associated with the risk of ASD in offspring. The detailed description of the specific research is provided in Table 1.

Five studies reported the ORs and 95%CIs for the association between excessive GWG and ASD in offspring. Through a random-effects model (Figure 2(A)), the meta-analysis revealed that excessive GWG was associated with increased risk of ASD in offspring ($p = .0008$, OR = 1.23, 95%CI 1.09–1.38). No significant statistical heterogeneity was observed ($I^2 = 36\%$; $p = .18$). In a sensitivity analysis, the influence of each study on the overall effect was investigated, and the pooled OR ranged from 1.16 to 1.3 (Table 3). These results revealed that the conclusion was robust.

Four studies (Dodds et al. 2011; Gardner et al. 2015; Qiu et al. 2018; Shen et al. 2018) which reported the relationship between inadequate GWG and offspring ASD were included in the meta-analysis. The meta-analysis revealed that there was no association between inadequate GWG and risk of ASDs ($p = .73$, OR = 1.03, 95%CI 0.86, 1.24) (Figure 2(B)). Statistical heterogeneity revealed a medium–high heterogeneity ($I^2 = 57\%$). When Shen et al.'s study (Shen et al. 2018) was removed, the I^2 values decreased from 57% to 0%, and the change caused a significant difference ($p = .009$, OR = 1.15, 95%CI 1.03, 1.28), which suggests that the previous conclusion had poor stability (Table 3). Considering that the proportion of obese mothers was small and unreliable for studying gestational diseases, the study by Shen et al. did not explore the association between BMI and GWG and the risk of ASD separately among obese mothers as compared with other studies, and they did not adjust for the confounding variables related to the risk of autism such as GDM or gestational hypertension. Previous research showed that GDM or gestational hypertension was the risk factor for ASD (Xiang et al. 2015; Maher et al. 2018). Therefore, as mentioned above, the current study could not determine whether inadequate GWG is associated with offspring ASD.

The meta-analysis revealed that excessive GWG alongside normal maternal baseline BMI was significantly associated with the risk of ASDs in offspring ($I^2 = 0\%$; $p = .0005$, OR = 1.24, 95%CI 1.10, 1.40) (Figure 3(A)), while inadequate GWG was not ($I^2 = 89\%$; $p = .97$, OR = 0.99, 95%CI 0.64,

Table 1. Characteristics of included studies in the systematic review and meta-analysis.

Author	Country	Study and design	Participants (ASD/NCG)	BMI standard	Weight gain standard	Source of weight gain	Autism criteria	Adjusted covariates	Result
Shen et al. (2018)	China	The case-control study	705/2236	The guidelines of Chinese adults overweight and obesity prevention 2006	IOM Pregnancy Weight Guidelines 2009	Self-reported	DSM-IV	Child's gender, child age (continuous variable), parental age (continuous variable), maternal history of alcoholism/drug use during pregnancy (coded as yes or no) and family annual income	Excessive: OR, 1.33 [1.02, 1.72]. Inadequate: OR, 0.85 [0.69, 1.06]
Qiu et al. (2018)	China	The case-control study	36/72	The guidelines of Chinese adults overweight and obesity prevention 2006	IOM Pregnancy Weight Guidelines 2009	Self-reported	DSM-IV	Paternal BMI, maternal BMI, maternal age, birth weight, gestational age, folic acid supplementation during pregnancy	Excessive: OR, 1.11 [0.36, 3.41]. Inadequate: OR, 0.73 [0.29, 1.84]
Ziyu (2015)	China	The case-control study	181/181	WHO 1995	IOM Pregnancy Weight Guidelines 2009	Self-reported	DSM-IV	Maternal education, maternal age, foetal times, threatened abortion, pregnancy nutrition, maternal history of disease, maternal history of drug	Excessive: OR, 1.64 [1.21, 2.22]
Gardner et al. (2015)	Swedish	The Stockholm Youth Cohort	1947/112,165	WHO 1995	IOM Pregnancy Weight Guidelines 2009	Medical staff	ICD-9, ICD-10 and DSM-IV codes	Maternal BMI, gestational age at birth, sex, birth year of the child, parity, maternal age, paternal age, maternal country of birth, SES factors and parental history of psychiatric treatment	Excessive: OR, 1.12 [1.01, 1.24]. Inadequate: OR, 1.17 [1.04, 1.32]
Dodds et al. (2011)	Canada	Nova Scotia cohort	924/128,809	WHO 1995	Excessive: $\geq$18 kg. Inadequate: $\leq$7 kg	Medical staff	ICD-9 or ICD-10	Bling with ASD, maternal psychiatric disorders, maternal neurological illness, maternal age at delivery, marital status income support during birth year or first 2 years, previous pregnancy with a foetal death. Previous pregnancy with a neonatal death, Previous pregnancy with a low birth weight infant, previous pregnancy with a preterm delivery, etc. (15)	Excessive: RR, 1.19 [1.02, 1.39]. Inadequate: RR, 1.10 [0.87, 1.39]
Xiang et al. (2015)	US	KPSC hospitals cohort	708/68,517	WHO 1995	Continuous data	Self-reported	ICD-9	Un-adjusted	Per 4 kg increase (HR, 1.67; 95%CI, 1.10–2.53)
Bilder et al. (2013)	US	Utah Genetics Study cohort (an ASD genetics study)	211/361	WHO 1995	Continuous data	Medical staff		Maternal age, paternal age, maternal education, paternal education, parity, prepregnancy BMI	Per 5-lb increase (OR: 1.20; 95%CI, 1.01–1.42)
	US	ADDM Network cohort	83/9753						Per 5-lb increase. (OR: 1.12; 95%CI, 1.05–1.21)

(*continued*)

Table 1. Continued.

Author	Country	Study and design	Participants (ASD/NCG)	BMI standard	Weight gain standard	Source of weight gain	Autism criteria	Adjusted covariates	Result
Jo et al. (2015)	US	The Infant Feeding Practices Study II cohort	25/NR	WHO 1995	IOM Pregnancy Weight Guidelines 2009	Self-reported	Unknown	Maternal age, maternal race or ethnicity, marital status, mother's education, poverty-to-income ratio, smoking during third trimester, parity, child's gender, child's current BMI and child's enrichment. Birth weight, pregnancy weight gain, gestational diabetes, breastfeeding and postpartum depression	No association. (no data were provided)
Hendrix et al. (2012)	US	The case-control study	70/70	WHO 1995	IOM Pregnancy Weight Guidelines 2009	Self-reported	Unknown	BMI category, season of birth, gender known prior to birth, high blood pressure diagnosed, offspring gender	Bivariate tests: GWG appropriate for BMI category (OR: 0.67; 95%CI, 0.31–1.47)

NCG: normal control group; IOM: The Institute of Medicine; WHO: World Health Organization; BMI: body mass index; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; OR: odds ratio; HR: hazard ratio; GWG: gestational weight gain; NR: not reported

Table 2. Quality assessment of the included studies by the Newcastle-Ottawa Scale.

Study	Design	Selection	Comparability	Exposure	Total scores
Dodds et al. (2011)	Cohort	2	2	2	6
Gardner et al. (2015)	Cohort	2	1	2	6
Ziyu (2015)	Case-control	3	1	1	5
Qiu et al. (2018)	Case-control	3	1	1	5
Shen et al. (2018)	Case-control	4	1	1	6
Xiang et al. (2015)	Cohort	4	2	2	8
Bilder et al. (2013)	Cohort	4	1	2	7
Jo et al. (2015)	Cohort	3	1	1	5
Hendrix et al. (2012)	Cohort	4	2	1	7

1.53) (Figure 2(B)). A sensitivity analysis was not carried out due to lack of included studies.

Subgroup meta-analysis

Table 4 shows the findings of subgroup meta-analysis based on the study design, GWG criteria and adjusted or unadjusted confounders. For children born to excessive GWG mothers, the summary risk estimates for ASD were generally comparable and similar to those of overall result when stratified by different factors. Stronger associations between excessive and ASD risk were observed in case-control studies (OR = 1.44, 95%CI 1.18, 1.75), studies (OR = 1.24, 95%CI 1.08, 1.41) with certain adjusted confounders and GWG studies (OR = 1.28, 95%CI 1.05, 1.56) based on recommendations by the IOM. For children born to inadequate GWG mother, no difference was observed in the association after stratification by GWG criteria and adjustment for confounder. Whereas, the summary of risk estimates for ASD (p = .007; OR = 1.16, 95%CI 1.04, 1.28) in cohort studies were opposite to those of overall result when stratified by study design, which indicated that the current results were not robust. It was speculated that the inconsistency of the results was due to the interference caused by design of Shen et al.'s research.

Discussion

This is the first systematic review and meta-analysis on the association between GWG and ASDs in offspring. This study suggested that excessive GWG was associated with higher risk of ASD in offspring. For inadequate GWG, higher risk of offspring ASD was observed compared with normal GWG, while statistical heterogeneity showed a significant heterogeneity (I^2 = 57%). When Shen et al.'s study we removed or subgroup meta-analysis of cohort studies was conducted, the individual summary risk estimates for ASD were contrary to those of the overall results. Shen et al.'s research (Shen et al. 2018) was a case-controlled study, which did not explore the association between BMI and GWG with risk of autism among obese mothers separately and did not adjust for the confounding variables related to the risk of autism such as GDM or gestational hypertension. Several previous studies have confirmed that gestational diabetes and pre-pregnancy obesity were associated with offspring autism. Therefore, the effect of inadequate GWG on the incidence of offspring ASD is still unclear. For lack of data, this work conducted a meta-

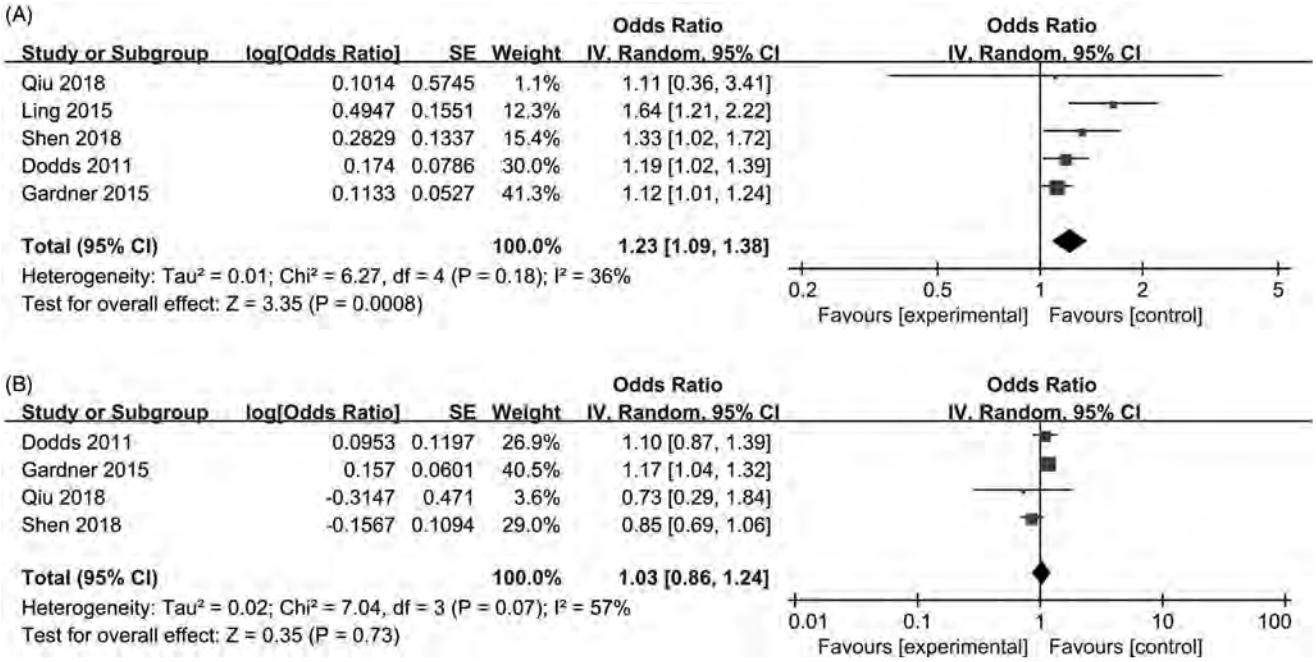

Figure 2. (A) Excessive GWG and risk of ASD in offspring. (B) Inadequate GWG and risk of ASD in offspring. BMI: body mass index; GWG: gestational weight gain; OR: odds ratio; ASD: autism spectrum disorders.

Table 3. Plot of sensitivity analysis by excluding one study each time and the pooling estimate for the rest of the studies.

Sensitivity analysis	Excessive GWG					Inadequate GWG				
	I^2	*p*	OR	OR (95%CI)		I^2	*p*	OR	OR (95%CI)	
Dodds et al. (2011)	52	.01	1.28	1.05	1.56	72%	.94	0.99	0.75	1.31
Gardner et al. (2015)	15	.0004	1.3	1.13	1.5	27%	.63	0.95	0.78	1.16
Qiu et al. (2018)	52	.002	1.24	1.08	1.41	68%	.65	1.05	0.86	1.27
Shen et al. (2018)	45	.007	1.22	1.06	1.4	0	.009	1.15	1.03	1.28
Ziyu (2015)	0	.0004	1.16	1.07	1.26					

analysis of excessive GWG with normal maternal baseline BMI. High risk of ASD in offspring with Excessive GWG born of normal maternal baseline BMI was observed, while inadequate GWG was not.

Currently, several hypotheses have been proposed to explore the association of GWG and the risk of ASD in offspring. First, weight gain should be associated with a high-fat diet (Wrottesley et al. 2017). High fat diet can induce oxidative stress and inflammatory response in hippocampus of offspring, which causes dysregulation of serotonin synthesis in dopaminergic neurons (Bilbo and Tsang 2010; Lau 2013). Second, the effect of GWG on offspring's nervous system may result from the leptin resistance mechanism caused by obesity. Leptin plays an important role in maintaining normal reproductive function and foetal growth and development. Higher levels of leptin can lead to impaired brain development, which affects speaking capability, social activities and motor functioning (Farr et al. 2006). Finally, many animal studies reported that maternal high fat diet (MHFD) may induce a shift in microbial ecology in offspring, which may negatively impact social behaviour. Buffington et al. (2016) confirmed that the intestinal microbes of the offspring of MHFD mice during pregnancy were significantly altered, affecting offspring's autistic behaviour through oxytocin and dopamine reward systems.

To date, investigations into the relationship between GWG and autism are still generally dearth. The current study established the lack of quantitative studies. Specifically, only two studies (Gardner et al. 2015; Shen et al. 2018) analysed associations with GWG based on different pre-pregnancy BMI and offspring ASD. Dose–response analysis was not performed in the current work and this should be evaluated in future review studies. The evidence that excessive GWG is associated with higher risk of offspring ASD has clinical importance to some extent, especially in certain countries that overemphasise nutrient intake during pregnancy. Obstetrics practitioners should take note of the weight gain of pregnant women, and provide appropriate medical advice based on the guidelines. At the social level, more science based activities for weight management during pregnancy should be carried out to raise the awareness of scientific management of weight gain during pregnancy.

This meta-analysis has several strengths. First, this is the first systematic review and meta-analysis on the association between GWG and GWG and ASDs in offspring. Second, stratified analysis was carried out to investigate the robustness of the current findings, considering biological and methodological factors. In this context, it was revealed that the association persisted even after adjusting for maternal BMI, gestational age at birth, sex and parental history of

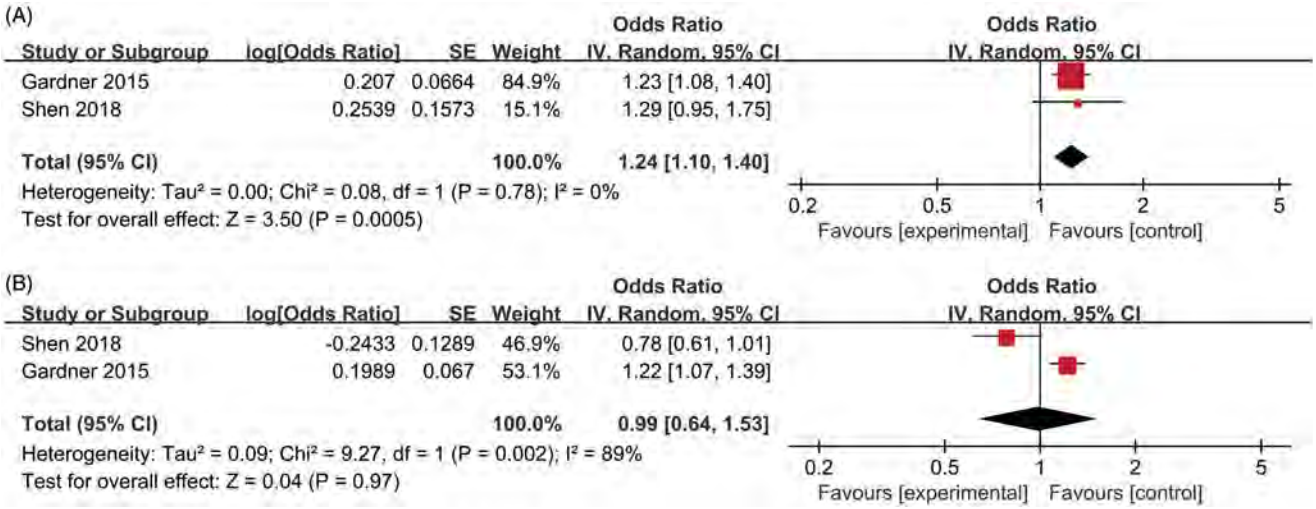

Figure 3. (A) Excessive GWG with normal maternal baseline BMI and risk of ASD in offspring. (B) Inadequate GWG with normal maternal baseline BMI and risk of ASD in offspring. BMI: body mass index; GWG: gestational weight gain; OR: odds ratio; ASD: autism spectrum disorders.

Table 4. Subgroup analysis by use of covariates, study design and GWG standard.

Subgroup meta-analysis	Excessive GWG				Inadequate GWG			
	No. of studies	OR (95%CI)	I^2	p	No. of studies	OR (95%CI)	I^2	p
Use of covariates								
Adjusted OR	4	1.24 (1.08, 1.41)	0	.0003	2	1.01 (0.75, 1.38)	84	.93
Unadjusted OR	3	1.35 (1.13, 1.61)	17	.0009	2	1.07 (0.85, 1.35)	0	.54
Study design								
Cohort	2	1.14 (1.05, 1.24)	0	.003	2	1.16 (1.04, 1.28)	0	.007
Case-control	3	1.44 (1.18, 1.75)	0	.0003	2	0.85 (0.69, 1.05)	0	.12
GWG standard								
IOM	4	1.28 (1.05, 1.56)	52	.01	3	0.99 (0.75, 1.31)	72	.94
Cut-off points	1	1.19 (1.02, 1.39)	N/A	.03	1	1.1 (0.87, 1.39)	N/A	.43

N/A: not applicable; GWG: gestational weight gain; OR: odds ratio.

psychiatric treatment, e.g. third, excessive or inadequate GWG (according to the IOM recommendations or appropriate cut-off points) was used as an explanatory variable and has been proven to be useful for other adverse pregnancy outcomes. It is noteworthy that the three Chinese studies included in the meta-analysis used IOM weight gain recommendations. Some studies have reported that IOM standards may not be applicable to certain Asian countries due to ethnic differences. Tat Xin et al. reported that the IOM GWG standard applies to the Singapore population (Tat Xin et al. 2014), but it is not suitable for the Korean population. Choi et al.'s study indicated that considerably higher and wider optimal GWG ranges than recommended by IOM are established to avoid adverse perinatal outcomes in Korean population (Choi et al. 2017). In January 2018, the national GWG guideline for Chinese women was published (Huang et al. 2018), and a universal recommendation with the IOM criteria may result in more misclassification and unnecessary weight gain among pregnant Chinese women in the future. Based on this, there may be a shift in results for studies of inappropriate GWG management and ASD; therefore, further studies should be conducted based on local appropriate recommendations. Some limitations in the current meta-analysis should be mentioned. First, the main limitation was that the standards of pre-pregnancy obesity and GWG used in the included studies for the meta-analysis were different. Three studies used WHO 1995 standards to define BMI, while two studies used the guidelines of Chinese adults overweight and obesity prevention. Dodd's study used '$\leq$7 kg' to define inadequate GWG and '$\geq$18 kg 'to define excessive GWG, other studies were conducted according to IOM Pregnancy Weight Guidelines. Nevertheless, the stratified analyses results did not change considerably. Second, three of the included studies were case-control studies. Case-control design may lead to selective bias and recall or memory bias. This limitation could partly explain the different results between case-control and cohort studies in the stratified analysis for children born to inadequate GWG mothers. Third, the confounding factors that were included in the study are different, which may have let to the inconsistent results. The inconsistency in adjustment for confounders across all studies is a limitation of this meta-analysis that cannot be quantified. Unfortunately, considering the data limitation, the effects of inconsistency in adjusting for confounders across all studies could not be quantified in the results of the meta-analysis.

This meta-analysis suggests that excessive GWG may be a risk factor for ASD in offspring. However, it was not concluded in the meta-analysis that the association between inadequate GWG and ASD in offspring according to Inconsistent results between cohort studies and control studies in subgroup meta-analysis. Further research based on a large population of prospective cohort studies, are

recommended to confirm the results. In addition, future replication studies in this area should have better control of confounding factors, and more accurate results measurement.

Author contributions

Zhao-Xu Tian and Ya-Ling Gao were responsible for the acquisition of data, analysis and interpretation of data, drafting the manuscript, and final approval. Man Wan, Yun Xie, Jie Liu, Bi-Fang Wu, Rui-Zhang Su were also responsible for the acquisition, analysis, and interpretation of data. Yi-Qun Hu and Li-Li Tian were responsible for the conception and design of the study, critical revision, and final approval.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was supported by the Natural Science Foundation of Fujian Province (Grant No. 2015J01534) and the Fujian Medical Innovation Project (2019-CXB-31).

ORCID

Yi-Qun Hu http://orcid.org/0000-0001-9157-7865

References

Bilbo SD, Tsang V. 2010. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. The FASEB Journal 24: 2104–2115.

Bilder DA, Bakian AV, Viskochil J, Clark EA, Botts EL, Smith KR, et al. 2013. Maternal prenatal weight gain and autism spectrum disorders. Pediatrics 132:e1276–e1283.

Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. 2016. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. Cell 165:1762–1775.

Choi SK, Lee G, Kim YH, Park IY, Ko HS, Shin JCJRB, et al. 2017. Determining optimal gestational weight gain in the Korean population: a retrospective cohort study. Reproductive Biology and Endocrinology: RB&E 15:67.

Cordner ZA, Tamashiro KL. 2015. Effects of high-fat diet exposure on learning & memory. Physiology and Behavior 152:363–371.

Diez MC, Gallardo F, Tortella G, Rubilar O, Navia R, Bornhardt C. 2014. Dietary intervention rescues maternal obesity induced behavior deficits and neuroinflammation in offspring. Journal of Neuroinflammation 11: 156.

Dodds L, Fell DB, Shea S, Armson BA, Allen AC, Bryson S. 2011. The role of prenatal, obstetric and neonatal factors in the development of autism. Journal of Autism and Developmental Disorders 41:891–902.

Farr SA, Banks WA, Morley JE. 2006. Effects of leptin on memory processing. Peptides 27:1420–1425.

Gardner RM, Lee BK, Magnusson C, Rai D, Frisell T, Karlsson H, et al. 2015. Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: results from a Swedish total population and discordant sibling study. International Journal of Epidemiology 44:870–883.

Hendrix RA, Rohrer JE, Danawi H, Refaat A. 2012. Autism spectrum disorders: a sibling case-control study of maternal prenatal body mass index. The International Journal of Childbirth Education 27:79.

Huang X, Tan H, Cai M, Shi T, Mi C, Lei JJBP, et al. 2018. Gestational weight gain in Chinese women – results from a retrospective cohort in Changsha. BMC Pregnancy and Childbirth 18:185.

Jo H, Schieve LA, Sharma AJ, Hinkle SN, Li RW, Lind JN. 2015. Maternal prepregnancy body mass index and child psychosocial development at 6 years of age. Pediatrics 135:E1198–E1209.

Lau D. 2013. What are the effects of maternal obesity on synaptic function in the maternal and offspring hippocampus? UWSpace. Available from: http://hdl.handle.net/10012/7635

Lavelle TA, Weinstein MC, Newhouse JP, Munir K, Kuhlthau KA, Prosser LA. 2014. Economic burden of childhood autism spectrum disorders. Pediatrics 133:e520–e529.

Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. 2018. Autism spectrum disorder. The Lancet 392:508–520.

Maher GM, O'Keeffe GW, Kearney PM, Kenny LC, Dinan TG, Mattsson M, et al. 2018. Association of hypertensive disorders of pregnancy with risk of neurodevelopmental disorders in offspring: a systematic review and meta-analysis. JAMA Psychiatry 75:809–819.

Matelski L, Van de Water J. 2016. Risk factors in autism: thinking outside the brain. Journal of Autoimmunity 67:1–7.

Qiu T, Guo BB, Wang LZ, Zhang H, Xu Y, Jiang XY. 2018. Association between overweight/obesity in parents and autism spectrum disorders in offspring. Zhongguo Dang Dai Er Ke Za Zhi 20:383–386.

Sanchez CE, Barry C, Sabhlok A, Russell K, Majors A, Kollins SH, et al. 2018. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obesity Reviews 19:464–484.

Shen YD, Dong HX, Lu XZ, Lian N, Xun GL, Shi LJ, et al. 2018. Associations among maternal pre-pregnancy body mass index, gestational weight gain and risk of autism in the Han Chinese population. BMC Psychiatry 18:11.

Stang A. 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology 25:603–605.

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343: d4002.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. 2008. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Group. JAMA 283(15):2008–2012.

Tat Xin E, John Carson A, Rahul M, Huishan K, Truls S, Thiam Chye T, et al. 2014. Determining optimal gestational weight gain in a multiethnic Asian population. Journal of Obstetrics and Gynaecology Research 40:1002–1008.

van der Burg JW, Sen S, Chomitz VR, Seidell JC, Leviton A, Dammann O. 2016. The role of systemic inflammation linking maternal BMI to neurodevelopment in children. Pediatric Research 79:3–12.

Williams K, Helmer M, Duncan GW, Peat JK, Mellis CM. 2010. Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. Child: Care, Health and Development 34:249–256.

Wrottesley SV, Pisa PT, Norris SA. 2017. The influence of maternal dietary patterns on body mass index and gestational weight gain in urban Black South African women. Nutrients 9:732.

Xiang AH, Wang X, Martinez MP, Walthall JC, Curry ES, Page K, et al. 2015. Association of maternal diabetes with autism in offspring. JAMA 313:1425–1434.

Ziyu L, Jianmin W, Xia L, Yan Z, Yuanyuan Q, Shengnan X, et al. 2015. Association between mothers' body mass index before pregnancy or weight gain during pregnancy and autism in children. Chinese Journal of Epidemiology 36:949–952.

Zwaigenbaum L, Penner M. 2018. Autism spectrum disorder: advances in diagnosis and evaluation. BMJ (Clinical Research Ed.) 361:k1674.