Contribution of Excessive Gestational Weight Gain to the Increased Risk of Autism Spectrum Disorder Occurrence in Offspring

Sorayya Kheirouri¹ and Tohid Farazkhah¹

Abstract

Background: According to epidemiological studies, the number of children affected by autism spectrum disorder (ASD) has elevated notably in recent years, which increases the importance of identifying and controlling modifiable risk factors of ASD.

Aim: We aim to explore the association of maternal gestational weight gain (GWG) with the risk of ASD in offspring.

Methods: This case-control study was conducted in Tabriz, Iran, from October 2019 to July 2020. Data of 426 children (208 with ASD and 218 healthy) were collected using medical records and face-to-face interviews with their mothers.

Results: Maternal GWG was significantly higher in the ASD group \( (P = .002) \). The percentage of inadequate (3.4% vs 0.5%) and excess (85.6% vs 56.0%) GWG was significantly higher in the ASD group \( (P < .001) \). Maternal \( (P < .001) \) and paternal \( (P = .004) \) ages were significantly lower in the ASD group compared with the healthy group. Boys were shown to be more affected by ASD than girls \( (P < .001) \). Results of multivariate regression indicated that maternal GWG \( \text{[OR (95% CI): 1.10 (1.03, 1.19), P = .005]} \), gestational age \( \text{[OR (95% CI): 1.21 (1.05, 1.41), P = .009]} \), maternal age \( \text{[OR (95% CI): 0.82 (0.73, 0.91), P < .001]} \), child male sex \( \text{[OR (95% CI): 3.82 (2.31, 6.30), P < .001]} \), and low education of father \( \text{[OR (95% CI): 4.96 (1.56, 15.72), P = .006]} \) were independently associated with increased risk of ASD.

Conclusion: The results indicate that maternal excessive GWG, maternal and gestational age, parental low education level, and male sex of infant may independently increase the risk of ASD in offspring.

Keywords
Autism spectrum disorder, gestational weight gain, maternal factors, birth weight, prenatal factors

Introduction

Autism spectrum disorders (ASD) is a neurodevelopmental condition characterized by impaired social interactions, abnormal language development, and stereotypic behavior and interests.⁵ ASD is estimated to affect approximately 1% of people globally.⁶ According to the latest report by the Centers for Disease Control and Prevention, the number of children affected by ASD has increased from 1 in 166 births in 2004 to 1 in 54 births in 2020.⁷ According to a national study in Iran, the prevalence of ASD was 6.26 in every 10,000 children under 5 years in 2012.⁸ The knowledge about the exact causes of ASD is still limited. According to previous studies, the etiology of ASD is multifactorial and many factors such as genetics,⁵,⁶ prenatal and perinatal factors,⁷,⁸ neuroanatomical abnormalities,⁹,¹⁰ and environmental factors¹¹ may play a role in the development of this disorder.

Gestational weight gain (GWG) is a modifiable factor related to maternal and neonatal health outcomes.¹² According to the literature, excessive GWG could increase the risk of maternal preeclampsia and macrosomia in infants.¹³,¹⁴ Also, risks of inadequate weight gain include low birth weight,
preterm birth, and failure to initiate breastfeeding. A recent review of more than 1 million women demonstrated that approximately 47% of pregnant women gained excessive weight and 23% of them gained inadequate weight during pregnancy. It has been suggested that gaining gestational weight outside the current recommended guidelines such as the Institute of Medicine (IOM) and clinical weight-gain recommendations may play a critical role in triggering the manifestations of ASD phenotypes in predisposing individuals during the prenatal period. Several studies reported an association between excessive GWG and ASD risk in offspring. However, findings regarding the association of inadequate GWG with the risk of ASD are more controversial. Because of inconsistent results of previous studies and the nonexistence of a similar study in Iran, we decided to conduct this study to investigate the association of GWG and other maternal and prenatal factors with the risk of ASD in offspring.

**Methods**

**Participants**

This case-control study was reviewed and approved by the ethics committee of the Tabriz University of Medical Sciences (ethical no: IR.TBZMED.REC.1398.1196; available online at http://ethics.research.ac.ir/IR.TBZMED.REC.1398.1196). This study was conducted in Tabriz, Iran, from October 2019 to July 2020. After receiving permission from the Welfare Organization, 208 children with ASD were selected from 4 autism centers (Raha, Sara, Hastibakhsh, and comprehensive autism center) in Tabriz city by convenient sampling method. The inclusion criteria for this group were as follows: children who were 3 to 10 years old and diagnosed by a psychiatric specialist for ASD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria. The exclusion criteria for this group were as follows: those who suffer from medical illnesses or other psychiatric disorders such as schizophrenia, attention deficit hyperactivity disorder (ADHD), intellectual disability disorder (IDD), specific learning disorders, developmental disorders of speech and language, or those who were twin or preterm births. Age-matched healthy children (n = 218) were also recruited as the control group from health centers. The inclusion criteria for this group were being apparently healthy with no symptoms of any disease and not taking any medications when the study was performed. The flowchart of sampling is provided in Figure 1.

**Data Collection**

A written informed consent was obtained from the parents of the children or their legal guardians. A trained researcher completed a structured questionnaire through a face-to-face interview with mothers of children regarding family socioeconomic status and information about psychiatric disorders of siblings. Medical records from an integrated health system were used for gathering all other required data including maternal and paternal age; prepregnancy body mass index (BMI); gestational age; GWG; type of delivery; prepregnancy disease and medication history; disease and medication during pregnancy; gestational supplement intake; duration of nausea or vomiting; vitamin B6 injection; maternal and paternal smoking status; infant’s gender, age, birth weight, birth order, feeding type in first 6 months of life; duration of exclusive breastfeeding; supplements intake; and medication intake. The questionnaire included demographic information about the family, medical history of the family, and information regarding the maternal prepregnancy and pregnancy conditions. Maternal GWG was categorized as excess, adequate, or inadequate according to the IOM recommendations, 2009, based on maternal prepregnancy BMI status defined by the WHO. The recommended amount of GWG is 12.5 kg to 18

![Figure 1. Flowchart of Study Participants](image-url)
kg, 11.5 kg to 16 kg, 7 kg to 11.5 kg, and 5 kg to 9 kg for women entering pregnancy with underweight BMI (≤18.5 kg/m²), normal weight (18.5 kg/m²-24.9 kg/m²), overweight (25 kg/m²-29.9 kg/m²) and obese (≥30 kg/m²), respectively. The socioeconomic status of families was assessed by questioning parents’ education and family income. Parent’s education was categorized as low (for illiterate or elementary education), moderate (for junior or senior high school education), and high (for university education). Also, family income was categorized as low (for less than 10 million rial income per month), moderate (for 10 to 30 million rial income per month), and high (for more than 30 million rial income per month). 

Statistical Analysis

Data were analyzed using SPSS version 16.0 software (SPSS Inc. IL., Chicago, USA). The chi-square test was used for comparing qualitative variables between the groups. To compare quantitative variables between the 2 groups, the normality of quantitative variables was first evaluated by one-sample Kolmogorov–Smirnov test, and then, the independent samples t test or Mann–Whitney U test was used for comparison of normally and nonnormally distributed data, respectively. Binary logistic regressions were conducted to calculate the odds ratio (OR) for the relationship between maternal prepregnancy and prenatal factors with the risk of ASD. The selected potential confounders were entered into the regression function as covariates. The significance level of all tests was $P < .05$ (2-tailed).

Results

Demographic Characteristics of Parents

Demographic characteristics of the children’s families are presented in Table 1. Maternal ($P = .001$) and paternal ($P = .004$) ages were significantly lower in the ASD group compared with the healthy group. The percentage of mothers who were younger than 20 years old at the time of conception was significantly higher in the ASD group than in the control group (6.3 vs 1.4; $P = .008$). The percentage of postterm (13.9 vs 5.5) deliveries was significantly higher in the ASD group ($P = .003$). Maternal GWG was significantly higher in the ASD group ($P = .002$). However, when the effect size (0.29) was considered, the difference was not clinically remarkable. Percentage of inadequate (3.4% vs 0.5%) and excess (85.6% vs 56.0%) GWG were significantly higher in the ASD group ($P < .001$). The number of mothers with a disease during pregnancy was

| Table 1. Demographic Characteristics of Parents and Sibling(s) |
|---------------------------------------------------------------|
| **–** | **ASD (n = 208)** | **Control (n = 218)** | **P Value** |
| Maternal age$^a$ (years) | 23.61 ± 2.99 | 24.57 ± 2.57 | <.001$^e$ |
| Maternal age$^b$ | | | .008$^e$ |
| <20 | 13 (6.3) | 3 (1.4) | |
| ≥20 | 195 (93.8) | 215 (98.6) | |
| Paternal age$^a$ (year) | 28.93 ± 3.99 | 30.09 ± 4.12 | .004$^e$ |
| Prepregnancy weight$^c$ (kg) | 57.62 ± 5.87 | 56.71 ± 6.38 | .510$^d$ |
| Maternal height$^a$ (cm) | 159.12 ± 5.28 | 158.28 ± 5.37 | .105$^d$ |
| Prepregnancy BMI$^b$ (kg/m²) | 22.77 ± 2.21 | 22.62 ± 2.26 | .510$^d$ |
| Gestational age$^b$ | | | .003 |
| Term | 179 (86.1) | 206 (94.5) | |
| Postterm | 29 (13.9) | 12 (5.5) | |
| GWG$^e$ (kg) | 17.41 ± 3.36 | 16.45 ± 3.07 | .002$^e$ |
| GWG categories according to IOM$^b$ | | | <.001$^e$ |
| Inadequate | 7 (3.4) | 1 (0.5) | |
| Adequate | 23 (11.1) | 95 (43.6) | |
| Excess | 178 (85.6) | 122 (56.0) | |
| Type of delivery$^b$ | | | .132$^e$ |
| Natural | 146 (70.2) | 138 (63.3) | |
| Cesarean | 62 (29.8) | 80 (36.7) | |
| Vacuum | 0 (0.0) | 0 (0.0) | |
| Forceps | 0 (0.0) | 0 (0.0) | |
| Prepregnancy disease history$^b$ | | | .381$^e$ |
| No disease | 180 (86.5) | 202 (92.7) | |
| DM$^f$ | 4 (1.9) | 2 (0.9) | |
| HTN$^g$ | 8 (3.8) | 3 (1.4) | |
| CVD$^h$ | 3 (1.4) | 3 (1.4) | |
| Thyroid disease | 1 (0.5) | 1 (0.5) | |
| Depression | 12 (5.8) | 7 (3.2) | |

(Table 1 continued)
|                                        | ASD (n = 208) | Control (n = 218) | P Value |
|----------------------------------------|---------------|------------------|---------|
| Prepregnancy medication<sup>b</sup>   |               |                  | .526<sup>e</sup> |
| No medication                          | 197 (94.7)    | 213 (97.7)       |         |
| Anti–DM                                | 4 (1.9)       | 2 (0.9)          |         |
| Anti–HTN                               | 4 (1.9)       | 1 (0.5)          |         |
| CVD related                            | 2 (1.0)       | 1 (0.5)          |         |
| Levothyroxine                          | 1 (0.5)       | 1 (0.5)          |         |
| Disease during pregnancy<sup>b</sup>  |               |                  | <.001<sup>e</sup> |
| No disease                             | 169 (81.3)    | 207 (95.0)       |         |
| DM                                     | 22 (10.6)     | 3 (1.4)          |         |
| HTN                                    | 13 (6.3)      | 4 (1.8)          |         |
| CVD                                    | 3 (1.4)       | 1 (0.5)          |         |
| Thyroid disease                        | 0 (0)         | 1 (0.5)          |         |
| Depression                             | 1 (0.5)       | 2 (0.9)          |         |
| Medication during pregnancy<sup>b</sup>|               |                  | .074<sup>e</sup> |
| No medication                          | 193 (92.8)    | 213 (97.7)       |         |
| Anti–DM                                | 6 (2.9)       | 2 (0.9)          |         |
| Anti–HTN                               | 7 (3.4)       | 2 (0.9)          |         |
| CVD related                            | 2 (1.0)       | 0 (0)            |         |
| Levothyroxine                          | 0 (0)         | 1 (0.5)          |         |
| Gestational supplement intake<sup>b</sup>|      |                  | 1.000<sup>e</sup>  |
| Folic acid                             | 208 (100.0)   | 218 (100.0)      |         |
| Iron                                   | 208 (100.0)   | 218 (100.0)      |         |
| Vitamin D                              | 208 (100.0)   | 218 (100.0)      |         |
| Duration of nausea or vomiting<sup>b</sup>|               |                  | .135<sup>e</sup> |
| Lasted for 3 months or less            | 145 (69.7)    | 166 (76.1)       |         |
| Lasted for more than 3 months          | 63 (30.3)     | 52 (23.9)        |         |
| Vitamin B<sub>6</sub> injection<sup>b</sup>|               |                  | .551<sup>e</sup>  |
| Yes                                    | 87 (41.8)     | 85 (39.0)        |         |
| No                                     | 121 (58.2)    | 133 (61.0)       |         |
| Maternal smoking status<sup>b</sup>   |               |                  |         |
| Current smoker                         | 1 (0.5)       | 0 (0.0)          | .305<sup>e</sup> |
| Former smoker                          | 2 (1.0)       | 1 (0.5)          | .535<sup>e</sup> |
| Paternal smoking status<sup>b</sup>   |               |                  | .412<sup>e</sup>  |
| Yes                                    | 22 (10.6)     | 18 (8.3)         |         |
| No                                     | 186 (89.4)    | 200 (91.7)       |         |
| Family size<sup>b</sup>               |               |                  | .251<sup>e</sup>  |
| ≤3                                     | 159 (76.4)    | 156 (71.6)       |         |
| >3                                     | 49 (23.6)     | 62 (28.4)        |         |
| Education of father<sup>b</sup>       |               |                  | .082<sup>e</sup>  |
| Low                                    | 16 (7.7)      | 8 (3.7)          |         |
| Moderate                               | 150 (72.1)    | 152 (69.7)       |         |
| High                                   | 42 (20.2)     | 58 (26.6)        |         |
| Education of mother<sup>b</sup>       |               |                  | .028<sup>e</sup>  |
| Low                                    | 24 (11.5)     | 10 (4.6)         |         |
| Moderate                               | 156 (75.0)    | 179 (82.1)       |         |
| High                                   | 28 (13.5)     | 29 (13.3)        |         |
| Family's economic status<sup>b</sup>  |               |                  | .174<sup>e</sup>  |
| Low                                    | 15 (7.2)      | 10 (4.6)         |         |
| Moderate                               | 53 (25.5)     | 44 (20.2)        |         |
| High                                   | 140 (67.3)    | 164 (75.2)       |         |
| Psychological disease of sibling(s)<sup>b</sup>|     |                  | .039<sup>e</sup>  |
| No disease                             | 201 (96.6)    | 217 (99.5)       |         |
| Autism                                 | 3 (1.4)       | 0 (0.0)          |         |
| ADHD<sup>a</sup>                       | 4 (1.9)       | 0 (0.0)          |         |
| Mentally disabilities                  | 0 (0.0)       | 1 (0.5)          |         |

**Note:** <sup>a</sup>expressed as mean (SD); <sup>b</sup>expressed as frequency (percent); <sup>c</sup>P value was reported based on independent samples t test; <sup>d</sup>P value was reported based on Mann–Whitney U test; <sup>e</sup>P value was reported based on chi-square.

**Abbreviations:** DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease; BMI, body mass index; GWG, gestational weight gain; ASD, autism spectrum disorder; IOM, Institute of Medicine; ADHD, attention deficit hyperactivity disorder.
significantly higher in the ASD group ($P < .001$). The percentage of mothers (11.5% vs 4.8%) with low education levels was significantly higher in the ASD group ($P = .028$). The number of siblings with psychiatric disorders was significantly higher in the ASD group ($P = .039$). Maternal prepregnancy weight, height, BMI, disease history, medication, maternal type of delivery, gestational supplement intake, medication during pregnancy, duration of nausea or vomiting, vitamin B6 injection, maternal and paternal smoking status, paternal education level, family size, and family economic status did not significantly differ between the 2 groups. None of the parents were taking alcohol.

**Demographic Characteristics of Children**

The demographic characteristics of children are presented in Table 2. Boys were shown to be more affected by ASD than girls ($P < .001$). Age, birth weight, birth order, feeding type in the first 6 months of life, duration of exclusive breastfeeding, and intake of supplements did not significantly differ between ASD and healthy children.

**Maternal and Prenatal Factors and ASD Risk**

Logistic regression was conducted to explore the relationship among maternal, prenatal, and neonatal factors with risk of ASD in the offspring (Table 3). Results of univariate analysis showed that GWG ($P = .003$), gestational age ($P = .01$), maternal age ($P = .001$), gestational diabetes ($P < .001$), gestational hypertension ($P = .01$), child male sex ($P < .001$), low education of father ($P = .03$), and mother ($P = .04$) were associated with increased risk of ASD in offspring.

However, results of multivariate analysis showed that maternal GWG, gestational age, maternal age, gestational diabetes, child male sex, and moderate education of father, and moderate education of mother were independently associated with increased risk of ASD. Each unit (1 kg) increase in GWG was associated with 10% [OR (95% CI): 1.10 (1.03, 1.19), $P = .005$] increased odds of ASD. Mothers with excess GWG were 7.00 times more likely to have a child with ASD ($P < .001$). Each unit (1 week) increase in gestational age was associated with 21% increased odds of ASD [OR (95% CI): 1.21 (1.05, 1.41), $P = .009$]. Each unit (1 year) increase in maternal age was associated with 18% decreased odds of ASD [OR (95% CI): 0.82 (0.73, 0.91), $P < .001$]. Postterm infants were 4.34 times more likely to be affected by ASD than term ones ($P = .001$). The risk of ASD in the male sex was 3.82 times more than female sex ($P < .001$). Fathers with low ($P = .006$) and moderate ($P = .01$) education were 4.96 and 2.11 times more likely to have a child with ASD, respectively.

| Table 2. Demographic Characteristics of Children |
|-----------------------------------------------|
| Gender$^a$ | ASD (n = 208) | Control (n = 218) | $P$ Value |
|---------|--------------|-----------------|----------|
| Male    | 164 (78.8)   | 118 (54.1)      | $< .001^b$ |
| Female  | 44 (21.2)    | 100 (45.9)      |          |
| Age$^c$ (year) | 6.86 ± 1.93 | 6.88 ± 1.86 | 0.91$^d$ |
| Birth weight$^c$ (kg) | 3.37 ± 0.46 | 3.28 ± 0.46 | 0.07$^d$ |
| Birth order$^e$ | – | – | 0.49$^e$ |
| First birth | 160 (76.9) | 157 (72.0) |          |
| Second birth | 41 (19.7) | 51 (23.4) |          |
| ≥ Third birth | 7 (3.4) | 10 (4.6) |          |
| Feeding type in first 6 months of life$^f$ | – | – | 0.32$^f$ |
| Breastfeeding | 166 (79.8) | 182 (83.5) |          |
| Infant formula | 42 (20.2) | 36 (16.5) |          |
| Duration of exclusive breastfeeding (n = 348)$^g$ | – | – | 0.91$^h$ |
| <4 months | 0 (0.0) | 0 (0.0) |          |
| 4–6 months | 40 (24.1) | 43 (23.6) |          |
| ≥6 months | 126 (75.9) | 139 (76.4) |          |
| Supplements | – | – |          |
| Folic acid | 208 (100.0) | 218 (100.0) | 1.00$^b$ |
| Iron | 208 (100.0) | 218 (100.0) | 1.00$^b$ |
| Vitamin D | 208 (100.0) | 218 (100.0) | 1.00$^b$ |
| Medications | – | – |          |
| None | 92 (44.2) | 218 (100.0) |          |
| Risperidone | 46 (22.1) | – |          |
| Ritalin | 24 (11.5) | – |          |
| Anticonvulsants | 46 (22.1) | – |          |

**Note:** expressed as frequency (percent); $^a$ $P$ value was reported based on chi-square; $^c$ expressed as mean ± SD; $^d$ $P$ value was reported based on independent samples t test.

**Abbreviation:** ASD, autism spectrum disorder.
### Table 3. Association of Maternal, Paternal, and Neonatal Factors with Risk of ASD in Offspring

|                                              | Risk of ASD                                                                 |
|----------------------------------------------|-----------------------------------------------------------------------------|
|                                              | Univariate Analysis | Multivariate Analysis |
|                                              | OR* (95% CI)         | P        | OR* (95% CI)         | P        |
| GWG (continuous)                             | 1.09 (1.03, 1.16)    | .003     | 1.10 (1.03, 1.19)    | .005     |
| GWG categories according to IOM              |                                                                             |
| Inadequate                                   | 28.91 (3.38, 246.78) | <.001    | 26.71 (2.33, 305.93) | .008     |
| Adequate                                     | 1.00 (reference)       | <.001    | 1.00 (reference)     | <.001    |
| Excess                                       | 6.02 (3.61, 10.04)    | .01      | 7.00 (3.86, 12.70)   | .009     |
| Gestational age (continuous)                 | 1.17 (1.03, 1.33)     | .01      | 1.21 (1.05, 1.41)    | .009     |
| Gestational age (categorized)                |                                                                             |
| Term                                         | 1.00 (reference)       | .004     | 1.00 (reference)     | .001     |
| Postterm                                     | 2.78 (1.37, 5.61)     | .01      | 4.34 (1.82, 10.33)   | .008     |
| Maternal age (continuous)                    | 0.88 (0.82, 0.94)     | .01      | 0.82 (0.73, 0.91)    | <.001    |
| Maternal age (year)                          |                                                                             |
| <20                                          | 4.77 (1.34, 17.01)    | .01      | 3.34 (0.76, 14.60)   | .10      |
| ≥20                                          | 1.00 (reference)       |          | 1.00 (reference)     |          |
| Prepregnancy BMI                             | 1.02 (0.94, 1.12)     | .001     | 1.09 (0.98, 1.21)    | .10      |
| Disease during pregnancy                     |                                                                             |
| No disease                                   | 1.00 (reference)       | 1.00 (reference) |
| DM                                           | 8.89 (2.64, 30.52)    | <.001    | 10.76 (2.73, 42.39)  | .001     |
| HTN                                          | 3.98 (1.27, 12.43)    | .01      | 3.14 (0.93, 10.53)   | .06      |
| CVD                                          | 3.67 (0.37, 35.64)    | .26      | 6.04 (0.56, 64.64)   | .136     |
| Thyroid disease                              | 0.00 (0.00, NA)       | 1.000    | 0.00 (0.00, NA)      | 1.000    |
| Depression                                   | 0.61 (0.05, 6.81)     | .69      | 1.05 (0.08, 12.90)   | .96      |
| Gender of child                              |                                                                             |
| Female                                       | 1.00 (reference)       | 1.00 (reference) |
| Male                                         | 3.15 (2.06, 4.83)     | <.001    | 3.82 (2.31, 6.30)    | <.001    |
| Birth weight                                 | 1.46 (0.96, 2.20)     | .07      | 1.12 (0.67, 1.87)    | .65      |
| Birth order                                  |                                                                             |
| First birth                                  | 1.00 (reference)       | 1.00 (reference) |
| Second birth                                 | 0.78 (0.49, 1.25)     | .31      | 1.47 (0.78, 2.76)    | .23      |
| ≥Third birth                                 | 0.68 (0.25, 1.85)     | .45      | 2.69 (0.72, 9.94)    | .13      |
| Feeding type in first 6 months of life       |                                                                             |
| Breastfeeding                                | 1.00 (reference)       | 1.00 (reference) |
| Infant formula                               | 1.27 (0.78, 2.09)     | .32      | 1.78 (0.98, 3.24)    | .057     |
| Education of father                          |                                                                             |
| Low                                          | 2.76 (1.08, 7.04)     | .03      | 4.96 (1.56, 15.72)   | .006     |
| Moderate                                     | 1.36 (0.86, 2.15)     | .18      | 2.11 (1.14, 3.89)    | .01      |
| High                                         | 1.00 (reference)       | 1.00 (reference) |
| Education of mother                          |                                                                             |
| Low                                          | 2.48 (1.00, 6.12)     | .04      | 0.79 (0.25, 2.49)    | .69      |
| Moderate                                     | 0.90 (0.51, 1.58)     | .72      | 0.37 (0.17, 0.82)    | .01      |
| High                                         | 1.00 (reference)       | 1.00 (reference) |
| Economic status of family                    |                                                                             |
| Low                                          | 1.75 (0.76, 4.03)     | .18      | 2.04 (0.80, 5.17)    | .13      |
| Moderate                                     | 1.41 (0.89, 2.23)     | .14      | 1.22 (0.71, 2.08)    | .46      |
| High                                         | 1.00 (reference)       | 1.00 (reference) |

Note: *adjusted for appropriate confounding factors (maternal age, prepregnancy BMI, gestational age, GWG, disease during pregnancy, child's gender, birth weight, birth order, feeding type in first 6 months, maternal and paternal education, and economic status).

Abbreviations: GWG, gestational weight gain; DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease; BMI, body mass index

**Discussion**

The results of this study showed that maternal excessive GWG, gestational and young maternal age, parental low education level, and male sex of infant were independently related to the augmented risk of ASD in offspring. In this study, we found that maternal excessive GWG could increase the risk of ASD in offspring. The finding agrees with the results of previous studies, which have all reported that maternal intense GWG may be related to enhanced risk of ASD in children. Logan et al indicated that excessive GWG leads to high levels of leptin in both cord blood and maternal...
In this study, maternal inadequate GWG was also associated with the risk of ASD in infants. Su et al. reported a significant association between maternal inadequate GWG and risk of ASD based on cohort studies, but not on case-control studies. Kheirouri and Alizadeh indicated no significant association between maternal inadequate GWG and risk of ASD in a systematic review study. In our study, although the P value was significant, because of the small number of participants included in the inadequate GWG group, the confidence interval was too wide which makes uncertainty greater and the effect size imprecise. Therefore, comprehensive studies are required by focusing more specifically on these groups of mothers with more samples.

This study showed that gestational age was positively associated with the risk of ASD in infants and postterm infants were more likely to be affected by ASD than term ones. Gardner et al. indicated that postterm births were not associated with autism risk, however, several more recent studies reported a higher risk of ASD in children born postterm. Increased fetal exposure to gestational complications like gestational diabetes or hypertension during prolonged intrauterine development is a possible mechanism for the association. Augmented risk of malnutrition because of placental failure and/or cesarean delivery might be other factors in increasing ASD risk in postterm infants. However, in this study, cesarean delivery did not associate with the risk of ASD.

In this study, a positive association was observed between the low education level of fathers and the increased risk of ASD in offspring. There are so few studies exploring this association. Larsson et al. and Sun et al. did not observe any association between parental education and the risk of ASD in offspring. Possible explanations for the negative association between high parental education and increased risk of ASD would be that parents with a high level of education pay more attention to prenatal care, reasonable parenting style, and a good family environment, which could rectify the poor performance of children with genetic susceptibility to ASD. Because the association between parental education and risk of autism in offspring has been little studied, more studies are needed to explore this association.

In this study, we found that mothers of younger ages were more likely to have a child with ASD. Previous studies have mostly reported an increased risk of ASD with advanced maternal age. In this work, the number of mothers over 35 years was too low (n = 2). In agreement with our findings, Sandin et al. in a cohort study from 5 countries including 5,766,794 children reported that both younger and older maternal age was associated with increased risk of ASD in offspring. Also, a comprehensive investigation found that in younger women the chance of having a child with autism was higher. Overall, fewer studies have been performed regarding maternal age and ASD with no clear cutoff points. Therefore, more studies are needed to confirm this association and its underlying mechanisms.

Limitations and Strengths

We could not conduct randomization and used convenient sampling method which could be affected by selection bias. Because this study was conducted in 4 autism and 4 health centers in Tabriz city of Iran, the results could not generalize to the community population. As we interviewed mothers to gather some data which we could not find in medical records such as family income, these data could be influenced by recall and/or response rate bias. Furthermore, the unavailability of data on other maternal comorbidities during pregnancy such as infections and respiratory or renal diseases was another limitation of this study. This study is possibly the first of its kind in Iran. We used reliable medical records for extracting all the quantitative variables such as maternal GWG and most of the qualitative variables like diseases and medication histories of participants.

Future Directions

Further studies are needed to investigate the role of epigenetic mechanisms and paternal obesity or BMI in increasing the risk of autism. Also, precise and well-designed studies are required to investigate: (a) the role of multiple mediating factors such as hormonal, inflammatory, neurobehavioral, and genetic variables in the GWG-ASD association; (b) the mechanisms underlying potential neurodevelopmental effects of maternal prepregnancy obesity and GWG; and (c) whether excessive GWG increases the odds of ASD in ASD children with or without intellectual disability.

Implications for Practice and/or Policy

These findings reveal the importance of evaluating GWG as a possible predictor of ASD and emphasize empowering health caregivers to help pregnant mothers to experience adequate GWG according to the IOM recommendation.

Conclusion

The results indicate that maternal excessive GWG, age, parental low education level, and male sex of infant may independently increase the risk of ASD in offspring.
Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
This study was financially supported by Tabriz University of Medical Sciences.

Statement of Informed Consent and Ethical Approval
Necessary ethical clearances and informed consent was received and obtained respectively before initiating the study from all participants.

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