Maternal and neonatal risk factors for autism spectrum disorder: A case-control study from Egypt

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Abstract

Background
The prevalence of autism spectrum disorder (ASD) has been increasing steadily in Egypt and worldwide. Detecting risk factors for ASD could help initiate screening and risk prevention approaches. Herein, this study aimed to detect several maternal and neonatal risk factors for ASD in Egypt.

Methods
In this case-control study, mothers of children with ASD who were visiting Beni-Suef University Hospital in Egypt (n = 268) were compared to mothers of children without ASD attending one primary school with a kindergarten (n = 504) regarding their preconception, conception, and postconcept ion characteristics. Data were collected using a self-administered questionnaire. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to investigate the possible associations between the collected data and the odds of ASD.

Results
In the multivariable-adjusted models, urban residence: OR (95% CI) = 2.33 (1.60–3.38), relative father: 2.63 (1.74–3.96), history of diabetes: 5.98 (1.99–17.97), previous abortion: 2.47 (1.20–13.38), assisted fertility: 4.01 (1.20–13.38), family history of ASD: 7.24 (2.00–26.24), multiple pregnancy: 11.60 (2.54–53.07), exposure to passive smoking during pregnancy: 2.95 (1.86–4.68), vaginal bleeding during pregnancy: 3.10 (1.44–6.67), hypertension with pregnancy: 3.64 (1.06–12.51), preterm labor: 2.64 (1.26–5.57), neonatal convulsions: 14.88 (5.01–44.20), and admission to neonatal intensive care unit 2.13: (1.21–3.74) were associated with the increased odds of ASD. On the other hand, the intake of vitamins during pregnancy: 0.09 (0.06–0.16) and C-section: 0.44 (0.27–0.70) were associated with the decreased odds of ASD.
Conclusion
This study detected several maternal and neonatal risk factors for ASD in Egyptian children.

1. Introduction
Autism spectrum disorder (ASD) is a term referring to a constellation of early-appearing deficits in social, emotional, and nonverbal communications in addition to strict or repetitive behaviors [1, 2]. The disorder, which has a global prevalence of 0.5% to 2% [3], results in a substantial social and economic burden [4, 5]. Since early diagnosis and behavioral intervention in ASD could effectively improve prognosis, detecting ASD risk factors to identify at-risk children should be encouraged [6].

While ASD is strictly linked to genetic factors [7–10], cumulating epidemiological evidence has suggested that maternal and neonatal factors could play important roles as well [11–30]. Yet, the majority of the epidemiological studies were conducted on Western populations [19–30]. Besides, a previous multi-ethnic study found that risk factors for ASD varied across races [23]. Another study detected noticeable differences in ASD risk factors across five countries [24]. Therefore, applying the findings of the Western studies to non-Western populations would be inaccurate. Further, most epidemiological studies assessed selected lifestyle or environmental factors and even reached inconsistent findings [19–30].

Egypt, on the other hand, has one of the highest fertility and population growth rates worldwide; 3.3 and 2.1%, respectively [31]; therefore, it can be speculated that the number of ASD patients in the country has been increasing accordingly. However, no previous studies have comprehensively studied the risk factors for ASD in Egypt.

In this context, we conducted a case-control study to investigate the potential associations of several maternal and neonatal risk factors with ASD using a sample from Egypt.

2. Methods
2.1. Study population
In this case-control study, mothers of children with ASD were compared to mothers of children without ASD. During the period between July 2019 and January 2021, mothers of children with ASD were recruited from Beni-Suef University Hospital where their children were receiving psychiatric, speech, phoniatric, and dietetic consultations. Beni-Suef University Hospital is a teaching hospital that offers primary, secondary, and tertiary healthcare services to the residents of Beni-Suef Governorate in South Egypt.

Out of 308 invited mothers of children with ASD, 268 accepted to participate with a response rate of 87%. To recruit mothers of children without ASD to serve as controls, invitation letters were sent in March 2020 to the mothers of children attending one public primary school with a kindergarten close to Beni-Suef University Hospital. Mothers who gave their written approvals received the study questionnaire. To minimize the potential impact of recall bias, we asked the participating mothers from the control group to report the data of the youngest living child only. Eventually, out of 1018 mothers invited, 718 gave their acceptance with an acceptance rate of 70.5%. Out of 718 questionnaires sent, 545 were sent back with responses, yet we removed 41 questionnaires for incomplete data (n = 38) or having other children with ASD (n = 3). No incentives were offered for participation.
2.2. ASD ascertainment

ASD, in this study, was diagnosed by psychiatric specialists, according to the American Psychiatric Association’s Diagnostic and Statistical Manual, Fifth Edition (DSM-5), when children had persistent deficits in each of the following communications: 1) social-emotional reciprocity, 2) nonverbal communicative behaviors, and 3) developing and understanding relationships in addition to at least two of the following types: 1) stereotyped movements or using of objects, 2) insistence on sameness, 3) restricted interests, and 4) hypo- or hyperreactivity to sensory inputs [1].

2.3. Assessment of risk factors

Data on risk factors were collected from mothers of children with and without ASD using a self-administered questionnaire in the Arabic language. The questionnaire was designed by the authors of this study after revising the literature and was composed of four sections. Section I included information about the child: name, age (number in years), sex (male or female), order (number), and age of ASD diagnosis (number in years) (in the ASD questionnaires only). Section II included data about the mother before conception: residence (urban or rural), job (yes or no), education (none, elementary or preparatory, high school or equal, or university and higher studies), the father of the child is a relative (yes or no), histories of hypertension, diabetes, bronchial asthma, and psychiatric diseases (yes or no, each), family history of ASD (yes or no), using assisted fertility (yes or no), and previous abortion (yes or no). Section III included data about the mother during conception: age at pregnancy (years), multiple pregnancy (yes or no), exposure to passive smoking and pesticides (yes or no, each), intakes of antibiotics and vitamins (yes or no, each), history of vaginal bleeding during pregnancy, diabetes with pregnancy, hypertension with pregnancy, and preterm labor (yes or no, each), and mode of delivery (normal or C-section). Section IV included data about the child after conception: low birthweight (yes or no), neonatal respiratory distress and convulsion (yes or no, each), and admission to neonatal intensive care unit (yes or no). Mothers who could not read or write and those who were not able to understand certain questions were asked to seek help from the study investigators who made their contact details available. It took most mothers 15–25 minutes to complete the questionnaire.

2.4. Statistical analysis

The logistic regression analyses were used to calculate the odds ratios (ORs) and their 95% confidence intervals (95% CIs) for maternal and neonatal risk factors among mothers of children with ASD compared with mothers of children without ASD. All associations were presented unadjusted (model I) and adjusted for sex and order of the child and preconception variables (model II). In addition to the first two models, every conception variable was adjusted further for other conception variables (model III), and every postconception variable was adjusted further for other postconception variables (model IV). Data were analyzed using the Statistical Package for Social Science (SPSS) released in 2013 (IBM SPSS Statistics for Windows, Version 22.0, IBM Corporation, Armonk, New York).

2.5. Ethical considerations

The Research Ethics Committee of the Faculty of Medicine, Beni-Suef University approved the study protocol. We conducted the study in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. The details, eligibility criteria, and aims of this
study were described for the included mothers who signed their written informed consent forms before participation.

3. Results

This study included mothers of 268 children with ASD (70.1% males, 29.9% females) and mothers of 504 children free of ASD (44.0% males and 56.0% females). The mean age of children with ASD was 8.82±3.47 years and that of the children without ASD was 6.42±1.95 years, and the mean age of ASD diagnosis was 4.68±2.03 years. In general, children in the ASD group were more likely to be males and the eldest of their siblings (p-value< 0.001) (Table 1).

Regarding the preconception variables, urban residence: OR (95% CI): 2.96 (2.17–4.02), higher education: 1.37 (1.02–1.85), relative father: 2.81 (1.99–3.98), positive histories of hypertension: 2.18 (1.13–4.19), diabetes: 6.76 (2.47–18.53), and bronchial asthma: 2.06 (1.09–3.87), previous abortion: 3.81 (2.57–5.66), assisted fertility: 9.54 (3.21–28.34), and family history of ASD: 14.20 (4.20–48.06) were associated with the increased odds of ASD in the unadjusted model. After adjusting for sex and order of the child and other preconception variables, urban residence: 2.33 (1.60–3.38), relative father: 2.63 (1.74–3.96), positive history of diabetes: 5.98 (1.99–17.97), previous abortion: 2.47 (1.56–3.91), assisted fertility: 4.01 (1.20–13.38), and family history of ASD: 7.24 (2.00–26.24) remained statistically significant (Table 2).

During conception, multiple pregnancy: 14.20 (4.20–48.06), exposure to passive smoking: 2.88 (2.11–3.93) and pesticides: 2.91 (1.17–7.20), vaginal bleeding during pregnancy: 6.19 (3.53–10.86), diabetes with pregnancy: 4.68 (2.11–10.36), hypertension with pregnancy: 3.62 (1.43–9.19), and preterm labor: 2.85 (1.68–4.84) were associated with the increased odds of ASD while vitamin intake: 0.10 (0.07–0.15) was associated with the decreased odds of ASD in the unadjusted model. After adjusting for sex and order of the child, preconception variables, and other conception variables, the following variables predicted ASD: multiple pregnancy: 11.60 (2.54–53.07), exposure to passive smoking: 2.95 (1.86–4.68), threatened abortion: 3.10 (1.44–6.67), hypertension with pregnancy: 3.64 (1.06–12.51), and preterm labor: 2.64 (1.26–5.57) while intake of vitamins: 0.09 (0.06–0.16) and C-section: 0.44 (0.27–0.70) were associated with lower odds of ASD (Table 3).

After conception, neonatal respiratory distress: 1.95 (1.20–3.19), neonatal convulsions: 9.97 (4.35–22.87), and admissions to neonatal intensive care unit: 4.13 (2.90–5.87) were associated with the increased odds of ASD in the unadjusted model, yet the association of neonatal respiratory distress with ASD disappeared in the adjusted models (Table 4).

Table 1. Characteristics of children.

| Characteristics                  | Cases   | Controls | P-value |
|----------------------------------|---------|----------|---------|
| Frequency                        | 268     | 504      | -       |
| Sex, %                           |         |          |         |
| Male                             | 70.1    | 44.0     | <0.001  |
| Female                          | 29.9    | 56.0     |         |
| Order, %                         |         |          |         |
| Eldest                           | 47.0    | 23.2     | <0.001  |
| Younger                          | 53.0    | 76.8     |         |
| Current age in years, mean ± Sd (range) | 8.82±3.47 (2–13) | 6.42±1.95 (3–12) | <0.001 |
| Age at diagnosis in years, mean ± Sd (range) | 4.68±2.03 (1–9) | -        | -       |

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4. Discussion

To the best of our knowledge, this is the first study to examine several maternal and neonatal risk factors for ASD in Egypt. We detected that urban residence, relative father, history of diabetes, previous abortion, assisted fertility, family history of ASD, multiple pregnancy, exposure to passive smoking during pregnancy, vaginal bleeding during pregnancy, hypertension with pregnancy, preterm labor, neonatal convulsions, and admission to neonatal intensive care unit were associated with the increased odds of ASD while intakes of vitamins during pregnancy and C-section were associated with the decreased odds of ASD.

It was also obvious, in our study, that male sex and being the first child were associated with ASD which agreed with most previous literature [22]; therefore, we controlled for both factors in all regression models to verify that the associations between the investigated preconception, conception, and postconception factors with ASD were independent of the sex of the child and...
his/her order. However, it should be noted that the association of ASD with birth order may be due to the study design (selection criteria for controls).

Of note, our manuscript studied several maternal and neonatal risk factors for ASD among a non-Western population and used a standardized method for ASD diagnosis; however,

### Table 3. Conception maternal predictors of autism spectrum disorder.

| Characteristics       | Cases % | Controls % | Model I | Model II | Model III |
|-----------------------|---------|------------|---------|----------|----------|
| Age at pregnancy      |         |            |         |          |          |
| <35 years             | 85.1    | 89.3       | 1       | 1        | 1        |
| ≥35 years             | 14.9    | 10.7       | 1.46 (0.94–2.27) | 1.60 (0.95–2.72) | 1.48 (0.78–2.80) |
| Multiple pregnancy    |         |            |         |          |          |
| No                    | 92.2    | 99.4       | 1       | 1        | 1        |
| Yes                   | 7.8     | 0.6        | 14.20 (4.20–48.06) | 11.49 (2.94–45.02) | 11.60 (2.54–53.07) |
| Exposure to passive smoking |     |          |         |          |          |
| No                    | 50.0    | 74.2       | 1       | 1        | 1        |
| Yes                   | 50.0    | 25.8       | 2.88 (2.11–3.93) | 3.16 (2.16–4.61) | 2.95 (1.86–4.68) |
| Exposure to pesticides|         |            |         |          |          |
| No                    | 95.5    | 98.4       | 1       | 1        | 1        |
| Yes                   | 4.5     | 1.6        | 2.91 (1.17–7.20) | 3.44 (1.27–9.37) | 2.72 (0.70–10.56) |
| Intake of antibiotics |         |            |         |          |          |
| No                    | 78.7    | 81.3       | 1       | 1        | 1        |
| Yes                   | 21.3    | 18.7       | 1.18 (0.82–1.70) | 0.77 (0.49–1.20) | 0.70 (0.41–1.20) |
| Intake of vitamins    |         |            |         |          |          |
| No                    | 48.1    | 8.3        | 1       | 1        | 1        |
| Yes                   | 51.9    | 91.7       | 0.10 (0.07–0.15) | 0.07 (0.04–0.12) | 0.09 (0.06–0.16) |
| Vaginal bleeding      |         |            |         |          |          |
| No                    | 81.3    | 96.4       | 1       | 1        | 1        |
| Yes                   | 18.7    | 3.6        | 6.19 (3.53–10.86) | 4.58 (2.41–8.67) | 3.10 (1.44–6.67) |
| Diabetes with pregnancy|       |            |         |          |          |
| No                    | 92.2    | 98.2       | 1       | 1        | 1        |
| Yes                   | 7.8     | 1.8        | 4.68 (2.11–10.36) | 2.88 (1.15–7.24) | 1.75 (0.57–5.39) |
| Hypertension with pregnancy |     |            |         |          |          |
| No                    | 95.1    | 98.6       | 1       | 1        | 1        |
| Yes                   | 4.9     | 1.4        | 3.62 (1.43–9.19) | 3.31 (1.11–9.85) | 3.64 (1.06–12.51) |
| Preterm labor         |         |            |         |          |          |
| No                    | 86.6    | 94.8       | 1       | 1        | 1        |
| Yes                   | 13.4    | 5.2        | 2.85 (1.68–4.84) | 2.83 (1.54–5.17) | 2.64 (1.26–5.57) |
| Mode of delivery      |         |            |         |          |          |
| Normal                | 31.0    | 26.8       | 1       | 1        | 1        |
| C-section             | 69.0    | 73.2       | 0.82 (0.59–1.13) | 0.57 (0.39–0.84) | 0.44 (0.27–0.70) |

Model I: Unadjusted  
Model II: Adjusted for sex and order of the child and preconception variables  
Model III: Adjusted for model II and other conception variables  

### Table 4. Postconception neonatal predictors of autism spectrum disorder.

| Characteristics                    | Cases % | Controls % | Model I | Model II | Model III | Model IV |
|------------------------------------|---------|------------|---------|----------|-----------|----------|
| Low birthweight                    |         |            |         |          |           |          |
| No                                 | 78.4    | 80.4       | 1       | 1        | 1         | 1        |
| Yes                                | 21.6    | 19.6       | 1.13 (0.79–1.63) | 0.95 (0.61–1.47) | 0.87 (0.50–1.50) | 0.82 (0.46–1.44) |
| Respiratory distress               |         |            |         |          |           |          |
| No                                 | 86.9    | 92.9       | 1       | 1        | 1         | 1        |
| Yes                                | 13.1    | 7.1        | 1.95 (1.20–3.19) | 1.41 (0.80–2.50) | 1.02 (0.50–2.11) | 0.77 (0.36–1.66) |
| Neonatal convulsions               |         |            |         |          |           |          |
| No                                 | 87.7    | 98.6       | 1       | 1        | 1         | 1        |
| Yes                                | 12.3    | 1.4        | 9.97 (4.35–22.87) | 8.21 (3.23–20.90) | 14.45 (4.83–43.29) | 14.88 (5.01–44.20) |
| Admission to neonatal intensive care unit |     |            |         |          |           |          |
| No                                 | 60.4    | 86.3       | 1       | 1        | 1         | 1        |
| Yes                                | 39.6    | 13.7       | 4.13 (2.90–5.87) | 2.99 (1.98–4.53) | 1.95 (1.14–3.34) | 2.13 (1.21–3.74) |

Model I: Unadjusted  
Model II: Adjusted for sex and order of the child and preconception variables  
Model III: Adjusted for model II and conception variables  
Model IV: Adjusted for model III and postconception variables
several limitations should be considered. First, the retrospective design of this study cannot imply causality; therefore, future prospective studies are needed to confirm our findings. Second, data on maternal and neonatal variables were collected using a self-administered questionnaire and were not linked to hospital records; consequently, the possibility of recall, information, and misclassification forms of bias is likely. For the same reasons, it was difficult to assess many conception and postconception conditions such as weight gain during pregnancy, placental and umbilical cord complications, and the Apgar score of the infants. Third, it could be speculated that our sample was biased towards severe ASD because we included mothers of children who were receiving medical consultations for different conditions related to ASD. Other less severe ASD cases might have been underrepresented. Fourth, we cannot exclude the possibility that the children of mothers in the control group might have undiagnosed children with ASD because we did not screen their children for ASD. Fifth, we had no data about the developmental and psychiatric disorders that can accompany ASD such as intellectual disability, developmental dyslexia, and depression. However, a previous study showed no differences in the risk factors for ASD between ASD children with and without comorbidities [23]. Sixth, some reported associations with ASD, particularly those that would rely on medical diagnoses, such as the history of hypertension, diabetes, asthma, and psychiatric disorder, could be attributed to higher access to medical care in mothers with ASD children. Seventh, since this study had an observational design, residual confounding could not be excluded.

In conclusion, we detected several maternal and neonatal risk factors for ASD in a cohort from Egypt. We believe that the findings of this study can help in future national screenings and educational programs. Longitudinal studies that link maternal and neonatal data of Egyptian mothers and their offspring to hospital records are warranted. Our study raised the potential for early identification of at-risk children who can benefit from interventions.

Supporting information

S1 File. SPSS file of the raw data.
(SAV)

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References
1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013. https://www.cdc.gov/ncbddd/autism/hcp-dsm.html
2. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018; 392(10146):508–520. https://doi.org/10.1016/S0140-6736(18)3129-2 PMID: 30078460
3. Chiarotti F, Venerosi A. Epidemiology of autism spectrum disorders: A review of worldwide prevalence estimates since 2014. Brain Sci. 2020; 10(5):274. https://doi.org/10.3390/brainsci10050274 PMID: 32370097
4. Leigh JP, Du J. Brief Report: Forecasting the economic burden of autism in 2015 and 2025 in the United States. J Autism Dev Disord. 2015; 45(12):4135–4139. https://doi.org/10.1007/s10803-015-2521-7 PMID: 26183723
5. Lavelle TA, Weinstein MC, Newhouse JP, Munir K, Kuhlthau KA, Prosser LA. Economic burden of childhood autism spectrum disorders. Pediatrics. 2014; 133(3):520–529. https://doi.org/10.1542/peds.2013-0763 PMID: 24515505
6. McEachin JJ, Smith T, Lovaas OI. Long-term outcome for children with autism who received early intensive behavioral treatment. Am J Ment Retard. 1993; 97(4):359–372. PMID: 8427693
7. Folstein S, Rutter M. Infantile autism: a genetic study of 21 twin pairs. J Child Psychol Psychiatry. 1977; 18(4):297–321. https://doi.org/10.1111/j.1469-7610.1977.tb00443.x PMID: 562353
8. Steffenburg S, Gilberg C, Hellgren L, Andersson L, Gilberg IC, Jakobsson G, et al. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. J Child Psychol Psychiatry. 1989; 30(3):405–416. https://doi.org/10.1111/j.1469-7610.1989.tb00254.x PMID: 2745591
9. Ciaranello AL, Ciaranello RD. The neurobiology of infantile autism. Annu Rev Neurosci. 1995; 18:101–128. https://doi.org/10.1146/annurev.ne.18.030195.000533 PMID: 7605057
10. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, et al. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med. 1995; 25:63–77. https://doi.org/10.1017/ s0033291700028099 PMID: 7792363
11. Eaton WW, Mortensen PB, Thomsen PH, Frydenberg M. Obstetric complications and risk for severe psychopathology in childhood. J Autism Dev Disord. 2001; 31:279–285. https://doi.org/10.1023/a:1010743203048 PMID: 11518482
12. Newschaffer CJ, Fallin D, Lee NL. Heritable and nonheritable risk factors for autism spectrum disorders. Epidemiol Rev. 2002; 24:137–153. https://doi.org/10.1093/epirev/mx010 PMID: 12762089
13. Croen LA, Grether JK, Selvin S. Descriptive epidemiology of autism in a California population: who is at risk? J Autism Dev Disord. 2002; 32:217–224. https://doi.org/10.1023/a:1015405914950 PMID: 12108623
14. Lauritzen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. J Child Psychol Psychiatry. 2005; 46:963–971. https://doi.org/10.1111/j.1469-7610.2004.00391.x PMID: 16108999
15. Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, et al. Advancing paternal age and autism. Arch Gen Psychiatry. 2006; 63:1026–1032. https://doi.org/10.1001/archpsyc.63.9.1026 PMID: 16953005
16. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology. 2002; 13:417–423. https://doi.org/10.1097/00001648-200207000-00009 PMID: 12094096
17. Glasson EJ, Bower C, Petterson B, De Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry. 2004; 61:618–627. https://doi.org/10.1001/archpsyc.61.6.618 PMID: 15184241
18. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olsen AV, Agerbo E, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 2005; 161:916–928. https://doi.org/10.1093/aje/kwi123 PMID: 15870155
19. Williams K, Helmer M, Duncan GW, Peat JK, Mellis CM. Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. Child Care Health Dev. 2008; 34(2):249–256. https://doi.org/10.1111/j.1365-2214.2007.00796.x PMID: 18257794

20. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torio G, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry. 2011; 68(11):1095–1102. https://doi.org/10.1001/archgenpsychiatry.2011.76 PMID: 21727249

21. Dodds L, Fell DB, Shea S, Armonson BA, Allen AC, Bryson S. The role of prenatal, obstetric and neonatal factors in the development of autism. J Autism Dev Disord. 2011; 41(7):891–902. https://doi.org/10.1007/s10803-011-1114-8 PMID: 20922473

22. Lyall K, Schmidt RJ, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. Int J Epidemiol. 2014; 43(2):443–464. https://doi.org/10.1093/ije/dyt282 PMID: 24518932

23. Getahun D, Fassett MJ, Pelletier MR, Wing DA, Xiang AH, Chiu V, et al. Association of perinatal risk factors with autism spectrum disorder. Am J Perinatol. 2017; 34(3):295–304. https://doi.org/10.1055/s-0036-1597624 PMID: 28099978

24. Bai D, Yip BHK, Windham GC, Sourander A, Francis R, Yoffe R, et al. Association of genetic and environmental factors with autism in a 5-Country Cohort. JAMA Psychiatry. 2019; 76(10):1035–1043. https://doi.org/10.1001/jamapsychiatry.2019.1411 PMID: 31314057

25. Sandin S, Schendel D, Magnusson P, Hultman C, Sureren P, Susser E, et al. Autism risk associated with parental age and with increasing difference in age between the parents. Mol Psychiatry. 2016; 21(5):693–700. https://doi.org/10.1038/mp.2015.70 PMID: 26055426

26. Connolly N, Anixt J, Manning P, Ping-lin D, Marsolo KA, Bowers K. Maternal metabolic risk factors for autism spectrum disorder-An analysis of electronic medical records and linked birth data. Autism Res. 2016; 9(8):829–837. https://doi.org/10.1002/aur.1586 PMID: 26824581

27. Burd L, Severud R, Kerbeshian J, Klug MG. Prenatal and perinatal risk factors for autism. J Perinat Med. 1999; 27(6):441–450. https://doi.org/10.1515/JPM.1999.059 PMID: 10732302

28. Brimacombe M, Ming X, Lamendola M. Prenatal and birth complications in autism. Matern Child Health J. 2007; 11(1):73–79. https://doi.org/10.1007/s10995-006-0142-7 PMID: 17053965

29. Cryan E, Byrne M, O’Donovan A, O’Callaghan E. A case-control study of obstetric complications and later autistic disorder. J Autism Dev Disord. 1996; 26(4):453–460. https://doi.org/10.1007/BF02172829 PMID: 8863095

30. Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. Pediatrics. 2001; 107(4): E63. https://doi.org/10.1542/peds.107.4.e63 PMID: 11335784

31. Egypt population. Worldometers. 2021. https://www.worldometers.info/world-population/egypt-population/