While Paul et al [46] reported that the median age of identification of autistic cases was 5.7 years, according to our result it was 2.8 years. This difference can be explained in the light of that there is often a wide variation in the age which children present for diagnosis or to obtain necessary therapy, in different socioeconomic groups. Katarzyna et al [47] reported that the earliest symptoms of autism often appear before a child's second birthday, but most children with autism are not diagnosed until they are in preschool or elementary school. Parametric survival models revealed that several factors were associated with a younger age of identification: being male, having an IQ of 70 or lower [46].

The possibility that autism is more common in offspring of older parents has generated considerable interest[48], our study showed that although there was no difference between mother age of autistic children and mothers of control group at time of delivery, father's age at the time of delivery was higher in cases (median 38) than in controls (median 33) and this was statistically significant. Our result is consistent with Reichenberg et al [49] illustrated that there was an association between advancing paternal age and risk of ASD. They concluded that offspring of 40 years men or older were 5.75 times more likely to have ASD compared with offspring of men younger than30 years, while advancing maternal age showed no association with ASD after adjusting for paternal age. Confirmation of such an association could have important public health implications in light of increasing trends in recent decades regarding paternal age among KSA community.

According to Cars score [31] 33% of our cases had sever degree of autism, 41% had moderate degree, and 25% had mild degree. In relation to IQ 55% of our patients presented with mild to severe mental retardation, 35.8% with below average mentality and 8.3% with normal mentality. This is in accordance with Baron-Cohen et al[50]. who reported that autistic children have spectrum of IQ ranged from 0 to 60.

Although many authors [42,51] had reported that most of parents of autistic children are non-consanguineous, our study showed that the majority of autistic parents (55%) was first degree consanguineous. Moreover, this study showed a statistically significant difference between cases and controls concerning family history of psychiatric disorders, as 39% of autistic children had positive family history of psychiatric disease compared to only 18.3% of controls. This is concordant with researchers[51,52] that discovered that parents of autistic children are twice as likely to have had psychiatric illness, and that rates of autism rose substantially if parents had suffered schizophrenia, depression or a range of other personality and psychiatric disorders.

Concordant to AL-Baz et al [42]results that reported family history of autism in 16% of cases versus 1% of control, our results revealed that 36.9% versus only 11.7% of families of cases of autistic patients and controls respectively had a positive family history of autism and this difference was statistically significant.

An association between general developmental impairments and maternal diabetes has been previously observed[53], more over a population-based study [54]in young children provided evidence that maternal metabolic conditions are a risk factor for autism, developmental delay without autistic symptoms, and impairments in several domains of development, particularly expressive language, after adjusting for sociodemographic and other characteristics. This current study showed that 30% of mothers of autistic children compared to only 12.5% of mothers of control group were diabetics, this difference was statistically significant.

A study conducted by Ronald[55] et al found associations between autism and factors such as tropical storms, family discord and women's self-reports of stress during pregnancy. Although our result is in concordant with this as 48.3% of mothers of autistic patients versus only 11.7% of controls were exposed to psychic trauma during pregnancy, it contradict the result of a recent epidemiological study[56] which found that experiencing a stressful event, such as the death of a family member or a severe illness, during pregnancy does not increase the risk of having a child with autism. In relation to smoking during pregnancy, it has been linked to numerous pregnancy complications and birth defects, such as low birth weight, preterm labor, congenital heart defects, and placental problems[57], no studies showed direct correlation between maternal smoking during pregnancy and autism. Researchers involved with the Center for Disease Control and Prevention's United States[58] autism surveillance program found that children with high-functioning autism, such as those with Asperger's Disorder, were more likely to be born to women who smoked during pregnancy. Our results revealed that 33.3% of mothers of autistic children were exposed to negative smoking during pregnancy compared to only 12.8% of controls and this was statistically significant, it is worth mentioning that due to cultural basis we cannot be sure whether mothers of autistic children were smokers or were really exposed to negative smoking as they stated.

Regarding natal and post-natal factors, a recent study[59] noted that pregnant women who have their labor started or sped up artificially are slightly more likely to have autistic children, putting an explanation that "infants destined to develop autism are less likely to send out the correct biochemical signals for normal progression of labor. Concerning our result although 26.7% of cases compared to 18.3% of controls were delivered by cesarean section, yet this difference was not statistically significant. In relation to birth weight and autism, 35% of cases compared to 20% of controls had low birth weight the difference were statistically significant. Birth weight is the net result of at least three factors: genetic growth potential, duration of the pregnancy, and rate of fetal growth[60]. As the genetic growth potential is unknown, and our study showed no significant difference between cases and controls in relation to length of gestation, therefore this indicates that our study shows a relation between being small for gestational age due to intrauterine growth retardation and not to preterm birth is associated with an increased risk of autism. These findings are consistent with

results of a recent population-based case-control study conducted in Finland 2013 [61] which concluded that low birth weight, is strongly related to childhood autism.

A meta-analysis review published in 2010[62] that examined Over 60 perinatal and neonatal factors showed association between abnormal presentation, in general specially breech presentation, fetal distress and an increased risk of autism and this is consistent with our result as 25% of cases versus 10% of controls had abnormal presentation, and 41.7% of cases compared to only 26.7% of controls were admitted to nursery due to fetal distress and this difference was statistically significant. It is worth mentioning that our study showed statistically significant difference between number of cases and controls admitted to nursery and as we know that preterm, small for gestational age, hyper bilurbinemia, and fetal distress are common causes of nursery admission, plus that there was no statistical difference between cases and controls in relation to preterm and hyper-bilirubinemia, so we can conclude that according to our result fetal distress, small for gestational age are two important risk factor for autism.

Regarding physical condition during first two years of life, there was no significant difference between cases and controls in relation to congenital anomalies, chronic illnesses, intake of antibiotics during first two years. Regarding the relation between children gastrointestinal disorders to autism: nested case-control study [63] using data from the UK General Practice Research Database found no evidence that children with autism were more likely than children without autism to have had defined gastrointestinal disorders at any time before their diagnosis of autism, this is inconsistent with our result that concluded that 25% of cases versus 12.5% of control had repeated gastro-enteritis, this difference was statistically significant.

Although there was no statistical significant difference between cases and controls in relation to motor mile stones, there was significant difference in relation to language development. This is inconsistent with an Egyptian study [42] that was conducted to determine possible risk factors of autism; they found statistically significant difference in all studied developmental milestones between autistic children and control group. Moreover McPartland [64] found that children with autism may be delayed in acquiring motor activity, such as bicycle riding. They may be poorly coordinated or have an abnormal gait or posture, poor hand writing.

In 28.3% of our patients the specific presenting symptom of autism was delayed speech, in 18.3% started with loss of eye contact, 13.3% the condition presented with inattention to mother in 10% symptoms started with preferring to play alone. In concordance with our results Noens et al[65], reported that about a third to a half of individuals with autism do not develop enough natural speech to meet their daily communication needs. Also Volkmar and klin[66] concluded that social impairments were recognizable in ASDs diagnosed children as poor eye contact, inability to utilize nonverbal gestures, and inability to play the same way as typically developing children. Other studies [42, 67] reported that children with autism presented a series of abnormal behaviors, including no social smile, no eye contact, no respond to own name and delay in language.

To conclude autism is one of five disorders that falls under the umbrella of Pervasive Developmental Disorders (PDD), a category of neurological disorders characterized by ‘‘severe and pervasive impairment in several areas of development.’[2,3,4]’ Despite a growing body of research, the etiology of autism remains unknown and highly uncertain[35]. According to our logestic regression they were consistent to results of recent studies that showed that high paternal and not maternal age[50], positive family history of psychiatric disorder[51,52] and autism among family members[42], maternal diabetes mellitus[54], exposure of mothers to stress [55] were associated with high risk of autism. Other risk factors male children, high maternal education consanguinity, abnormal presentation, low birth weight due to small for gestational age, nursery admission and repeated gastrointestinal disorders although not proven as independent risk factors for autism , these variables should be examined in future studies that use large population based birth cohorts with precise assessments of exposures and potential confounders.

Autism is a devastating condition with no known cure. The rising prevalence, coupled with the severe emotional and financial impact on the families, underscores the need for large, prospective, population-based studies with the goal of elucidating the early-life modifiable risk factors.

5. Recommendations

- Early detection of cases of autism through: National screening program (CHAT) for preschoolers and increase the awareness of populations and families by the early symptoms and signs of autism as delayed speech and loss of eye to eye contact.
- All children should be screened with standardized developmental tools at specific intervals (at the 9–18–24–30 months) for early detection of ASDs.
- Proper management of autistic children including behavior, educational, cognitive and pharmacotherapy through expanding and fortifying the autism specialized rehabilitation centers.

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References

[1] Kanner L. Autistic disturbances of affective contact. Nerv Child. 1943; 2: 217-250.
[2] F.R.Volkmar,A.Klin .Issues in the classification of autism and related conditions.F Volkmar, R Paul, A. Klin,D. Cohen, Handbook of autism and pervasive

developmental, neurobiology, and behavior, 3rded, 2005, Wiley, Hoboken,NJ,pp. 5-41
[3] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition(DSM-IV). Washington, DC: American Psychiatric Publishing; 1994
[4] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text Revision(DSM-IV-TR). Washington, DC: American Psychiatric Publishing; 2000
[5] Rutter M. Diagnosis and definition of childhood autism. J Autism Child Schizophr 1978;8:139-61
[6] Barid G, Simonoff E, Pickles S, Meldrum D, etal. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the special needs and Autism Project(SNAP). Lancet 2006;368:210-5
[7] CDC. Prevalence of autism spectrum disorders-Autism and Developmental Disabilities Monitoring Network, United States,2006. MMWR 2009:58(SS-10)
[8] CDC. Prevalence of autism spectrum disorders-Autism and Developmental Disabilities Monitoring Network,14 sites, United States,2008. MMWR 2012:61(No.SS-3
[9] Al-Zahrani A. Prevalence and clinical characteristics of autism spectrum disorders in school-age children in Taif-KSA. Int J Med SCI Public Health 2013; 2(3); 578-582
[10] Charman T. The prevalence of autism spectrum disorders. Recent evidence and future challenges. Eur Child Adolesc Psychiatry 2002; 11:249-56
[11] Wing L, Potter D. The epidemiological of autistic spectrum disorders: is the prevalence rising? Ment Retard Dev Disabil Res Rev 2002; 8:151-61
[12] Fombonne E. 2005. Epidemiological studies of pervasive Developmental disorders. In Handbook of Autism and Pervasive Developmental Disorders, ed. FVolkmar, R Paul, A Klin, D Cohen, pp. 42-69. Hoboken,NJ: Wiley
[13] Rutter M. Incidence of autism spectrum disorder: changes over time and their meaning. Acta Paediatr.2005;94:2-15
[14] Gurney JG, McPheeters ML, Davis MM. Parental report of health conditions and health care use among children with and without autism . Arch Pediatr Adolesc Med.2006;160(8):825-30
[15] Ghaziuddin M, Ghaziuddin N, GredenJ. Depression in persons with autism: implications for research and clinical area. J Autism Dev Disorders.2002;32(4):299-306
[16] Nazeer N, Ghaziuddin M. Autism Spectrum Disorders: Clinical Features and Diagnosis. Pediatric Clinics of North America:2012;59(1):19-25
[17] Risch N, Spiker D, Lotspeich L, etal A genomic screen of autism : evidence for a multilocus etiology. Am J Hum Genet. 1995;65:493-507
[18] Pickles A, Bolton P, Macdonald H, etal.. Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: a twin and family history study of autism. Am J Genet. 1995;57:717-726
[19] Richler J, Luyster R, Risi S, et al Is there a regressive phenotype of autism spectrum disorder associated with the measles-mumps rubella vaccine? A CPEA study. J Autism Dev Disorder. 2006;36(3):299-316
[20] Gardener H, Spiegelman D, Buka S. Perinatal and Neonatal Risk factors for Autism: A comprehensive Meta-analysis. Pediatrics. 2011;128(2):344-355
[21] Gardener H, Spiegelman D, Buka S. Prenatal risk factors for autism: a comprehensive meta-analysis. Br J Psychiatry. 2009;195(1):7-14
[22] Brian M. D'Onofrio, Martin E. Rickert, Emma Frans, Ralf Kuja-Halkola, Catarina Almqvist, Arvid Sjölander, Henrik Larsson, Paul Lichtenstein (2014). "Paternal Age at Childbearing and Offspring Psychiatric and Academic Morbidity". JAMA Psychiatry 71 (4): 432–438.
[23] Abel K, Dalman C, Svesson A, et al. Deviance in Fetal Growth and Risk of Autism Spectrum Disorder. Am J Psychiatry 2013; 170:391–398
[24] Liperopoulous C, Bassan H, Sullivan N. Positive screening for autism in Ex-preterm Infants: Prevalence and Risk Factors. Pediatrics Vol. 121 No 4 Aprail 1, 2008 pp. 758-765
[25] Bolton P, Pickles A, Harrington R. Season of birth : issues, approaches and findings for autism. J Child Psychol Psychiatry 1992, Vol 33,: 509-530
[26] Measles, mumps, and rubella (MMR) vaccine". Centers for Disease Control and Prevention. 22 August 2008. Archived from the original on 7 April 2008. Retrieved 2008-12-21.
[27] Institute of Medicine (US) Immunization Safety Review Committee (17 May 2004). Immunization Safety Review: Vaccines and Autism. Institute of Medicine of the National Academy of Sciences. PMID 20669467. Retrieved 13 June 2007.
[28] 28 – MMR The facts. NHS Immunisation Information. 2004. Retrieved 2007-09-19
[29] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
[30] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Publishing; 2000
[31] E. Schopler, R.J. Reichler, B.R. Renner The childhood autism rating scale (CARS): for diagnostic screening and classification of autism Irvington, New York (1986)
[32] Stanford-Binet International Scale. 4th ed. 2 years to adult, useful for handicapped children; 1986
[33] Kidd P. Autism, an extreme challenge to integrative medicine. Part I: the knowledge base Altern Med Rev, 7 (2002), pp. 292–316
[34] 34- Caronna E,, Milunsky J, Tager-Flusberg H. Autism spectrum disorders: clinical and research frontiers. Arch Dis Child 2008;93:518-523 doi:10.1136/adc.2006.115337
[35] 35- Freitag C M. The genetics of autistic disorders and its clinical relevance: a review of the literature. Mol Psychiatry, 12 (1) (2007), pp. 2–22
[36] 36- Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, et al. 1995. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol.

Med. 25:63–77
[37] 37- Libbey JE, Sweeten TL, McMahon WM, Fujinami RS. 2005. Autistic disorder and viral infections. J. Neurovirol. 11:1–10
[38] 38- Chakrabarti, E. Fombonne Pervasive developmental disorders in preschool children JAMA, 285 (24) (2001), pp. 3093–3099
[39] 39- Newschaffer CJ, Croen LA, Daniels J et al.. The epidemiology of autism spectrum disorders . Annu Rev Public Health. 2007 [Retrieved 2009-10-10];28:235–58. doi:10.1146/annurev.publhealth.28.021406.144007. PMID 17367287.
[40] 40- T.L. Arndt, C.J. Stodgel, P.M. Rodier. The tetralogy of autism. Int J Dev Neurosci, 23 (2–3) (2005), pp. 189–199
[41] 41- Epigenetics of autism spectrum disorders. Hum. Mol. Genet. (2006) 15 (suppl 2): R138-R150. doi: 10.1093/hmg/ddl213
[42] 42- El-Baz F, Ismael N, Nour El-Din S. Risk factors for autism: An Egyptian study. Egyptian Journal of Medical Human Genetics Volume 12, Issue 1, May 2011, Pages 31–38
[43] 43- Itzchak EB, Zachor DA, Assaf Harofeh. Male: female ratio is related to autism spectrum disorder in the family and to maternal age. Harofeh Medical Center, Zerifin, Israe. Franklin Hall B Level 4 (Philadelphia Marriott Downtown l); 2010.
[44] 44- Shu, F B, Lung, Y. Change The mental health in mothers with autistic children: a case –control study in Southern Taiwan kasohsing J Med Sci (6) (2000), pp. 308–314
[45] 45- King M, Bearman P. Socioeconomic Status and the Increased Prevalence of Autism in California. Am Sociol Rev. Apr 1, 2011; 76(2): 320–346.
[46] 46- Paul T, Maureen D, Matthew M, Craig N, S.M.etal.Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study. J Am Acad Child Adolesc Psychiatry, 48 (5) (2009), pp. 474–483
[47] 47- Katarzyna K, Rhea A, Fred V. Autism spectrum disorder in the second year: stability and change in syndrome expression J Child Psychol Psychiatry (2006)
[48] 48- Maureen S. Durkin, Matthew J. Maenner, Craig J. Newschaffer. Advanced Parental Age and the Risk of Autism Spectrum Disorder. Am J Epidemiol. 2008;168(11):1268-1276
[49] 49- Reichenberg A, Gross R, Weise M, et al. Advancing paternal age and autism. Arch Gen Psychiatry, 63 (9) (2006), pp. 1026–1032
[50] 50- Baron-Cohen S, Hoekstra R,, Knickmeyer R et al. The autism-spectrum quotient (AQ): adolescent version J Autism Dev Disord, 36 (2006), pp. 343–350
[51] 51- Al-Hifthy E, Ghaziuddin M Autism in Saudi Arabia: Presentation, Clinical Correlates and Comorbidity Transcultural Psychiatry June 2009 vol.
[52] 52- Daniels J, Forssen, U , Hultman C. Parental Psychiatric Disorders Associated With Autism Spectrum Disorders in the Offspring. Pediatrics Vol. 121 No. 5 May 1, 2008 pp. e1357 -e1362 oi:10.1542/peds.2007-2296
[53] 53- Rizzo TA, Dooley SL, Metzger BE, etal. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. Am J Obstet Gynecol. 1995;173(6):1753–1758
[54] 54- Krakowiak P, Walker C, Bremer A, Maternal Metabolic Conditions and Risk for Autism and Other Neurodevelopmental Disorders Pediatrics 2012;129;e1121;
[55] 55- Ronald A, Pennell CA, Whithouse A J. Prenatal Maternal stress associated with ADHD and Autistic traits in early childhood. Front Psychology 2010(6) DOI: 10.1371
[56] 56- Rai D, Golding J, Magnusson C et al. Prenatal and Early Life Exposure to Stressful Life Events and Risk of Autism Spectrum Disorders: Population-Based Studies in Sweden and England. PLOS ONE 2012
[57] 57- Ness RB, Grisso JA, Hirschinger N, et al. (February 1999). "Cocaine and tobacco use and the risk of spontaneous abortion". N. Engl. J. Med. **340** (5): 333–9
[58] 58- Centers for Disease Control and Prevention. 2007. Preventing Smoking and Exposure to -Secondhand Smoke Before, During, and After Pregnancy.
[59] 59- Gregay SG, Anthopolos R, Grotegut CA. Association of autism with increased or augmented childbirth in north Carolina birth record (1990-1998) and education research (1997-2007) daraisase. Jana Pediatrics 2013; 167(10): 959-66.
[60] 60- Larson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: parental factors, parental psychiatric history, and socioeconomic status. American Journal of Epidemiology 2005; 161:916-25.
[61] 61- Lampi KM, Lehtonen L, Swominen A, et al. Risk of autism spectrum disorders in low birth weight and small for gestational age infant. The Journal of Pediatric 2012; 161(5): 830-836.
[62] 62- Garderer H, Spicgelman D, Buka SL. Perinatal and nconaral risk factor for autism: a comprehensive meter-analysis. Pediatrics 2011; 128(2): 344-355.
[63] 63- Black C. Relation of childhood gastrointestinal disorders to autism: nested cases-worked study using data from UK general practice research database. BMJ 2002; 325: 419.
[64] 64- McParland JP. Asperger syndrome. Adolecs Med Clinic 2006; 17(3): 771-788.
[65] 65- Noens I, Berchelacer-Onnes V, Verporten R, et al. The com for: an instrument for the indication of augmuitive communication in people with autism and intellectual disability. J intellec disabl Res. 2006; 50(9): 261-632.
[66] 66- Volkmar FR, Klin A, Rubin E, et al. Autism and the pervasive developmental disorders. J Child Psychology and Psyctratry 35(5): 861-876.
[67] 67- Xicy, Ma HW, Hua TY, et al. Behavioral patterns of artistic children during infancy. Chunases J Contemy Pedar 2006: 6: 470-472