Sana'a University Journal of Medical and Health Sciences https://journals.su.edu.ye/index.php/jchm

Vol. 17 | No. 2 | Page 40 – 50 | 2023 | ISSN: 2958-7476

Doi: 10.59628/jchm.v17i2.292

Non-Genetic Factors in Schizophrenia in Yemen

Hassan Abdulwahab Al-Shamahy[1,2,*] , Sami Mohammed Abdo Hassan[1]

[1]Medical Microbiology and Clinical Immunology Department, Faculty of Medicine and Health Sciences, Sana'a University, Republic of Yemen

[2]Medical Microbiology department, Faculty of Medicine, Genius University for Sciences & Technology, Dhamar city, Republic of Yemen.

***Corresponding author:** *h.shmahe15@su.edu.ye*

ARTICLE INFO

Article history:
Received: May 4, 2023
Accepted: Aug 4, 2023
Published: Dec, 2023

KEYWORDS

1. Mental disorders
2. Non-Genetic Factors in Schizophrenia
3. Schizophrenia
4. Yemen

ABSTRACT

Background and objective: The way we think about schizophrenia today is profoundly different from the way this illness was seen in the twentieth century. We now know that the etiology of schizophrenia is multifactorial and reflects an interaction between genetic vulnerability and environmental contributors. Environmental risk factors such as pregnancy and birth complications, childhood trauma, migration, social isolation, urbanicity, and substance abuse, alone and in combination, acting at a number of levels over time, influence the individual's likelihood to develop the disorder. There are no studies on mental health in Yemen in general and schizophrenia in particular. Thus, the aim of this study was to study the non-genetic risk factors of schizophrenia. The specific objectives were to compare exposure to suspected risk factors for schizophrenia in a cohort of schizophrenia patients with those randomly selected from the community.

Methods: The researchers approached inpatient in Al-Amal Hospital for Psychiatric Diseases with a diagnosis of schizophrenia. Patients from this list were then randomly selected using the card-shuffling technique. Patients were included in the study if a review of their records confirmed a diagnosis of schizophrenia according to DSM IV criteria, they were ≥18 years old, and had attended the clinics between the period January 2021 and December 2021. Controls were from general population by selected randomly from the list of censuses by simple random selection from Sana'a governorate.

Results: Regarding associated risk factors of schizophrenia, there was significant association with low income (OR= 7.1), loss work (OR=57), smoking (OR=5.9) , Khat chewing (OR=12.4), birth complications (OR=7.2) , 1-6 Apgar scores (OR=1.8), older paternal age (OR=3.2), the spring birth (OR=2.2), and winter birth (OR=1.9), childhood trauma (OR=1.9), cannabis (OR=7.4), hypertension(OR=4.7) , and diabetics (OR=6.6).

Conclusion: Future research in Yemen should also explore potential protective factors in groups at risk for psychotic disorders. A new area of research should involve big data and predictive models, by replacing traditional paper notes with electronic patient records.

CONTENTS

4. Discussion

1. **Introduction:**

Schizophrenia is a [1] mental illness manifested by persistent or recurrent [2] psychotic episodes. The main symptoms include hallucinations (usually hearing voices), disorganized thinking, and delusions [3]. Additional symptoms include decreased emotional expression, social withdrawal, and apathy [2]. Symptoms typically develop progressively, onset during youth, and in a lot of cases never solve [3, 4]. Much research has shown that schizophrenia has a well-established genetic component, which can now be estimated using the polygenic risk score for schizophrenia [5,6]. In the the ground-breaking meta-analysis of genome-wide association study (GWAS) of schizophrenia, 108 loci associated with schizophrenia were identified [6]. The implicated sites include genes required in regulation of calcium channels, dopamine synthesis, neurotransmitter glutamate receptors and immunity. However, these studies and following GWAS studies clarify only a minority of the variation in liability for schizophrenia across populations. This reflects the fact that a large proportion of the responsibility for the occurrence of schizophrenia and the severity of the condition may be due to interactions between genes and the environment [7] or to epigenetic mechanisms that reflect the influence of environmental factors. Indeed, mounting evidence suggests that non-genetic risk factors not only contribute to disease, but also suggest ways in which we might find potential subgroups of people at higher risk and thus impact clinical management [7].

From the time when early 2011, Yemen has been live through political instability and war. The population of Yemen in general and Sana'a in particular suffer from an insecure pace of life and may suffer from psychological and physical stress that can affect their mental health. It is clear that there are limited studies in Yemen that study and discuss infectious diseases [8-20], immunological diseases, antimicrobial resistance, etc. [21-23], but unfortunately there are no studies on mental health in Yemen in general and schizophrenia in particular. Thus, the aim of this study was to study non-genetic factors of developing schizophrenia in Sana'a. The specific objectives were to compare exposure to suspected risk factors for schizophrenia in a cohort of schizophrenia patients with those randomly selected from the community.

2. Materials And Methods

Study sample

The researchers approached inpatient in Al-Amal Hospital for Psychiatric Diseases with a diagnosis of schizophrenia. Patients from this list were then randomly selected using the card-shuffling technique. Patients were included in the study if a review of their records confirmed a diagnosis of schizophrenia according to DSM IV criteria, they were ≥18 years old, and had attended the clinics between the period January 2021 and December 2021. Controls were from general population by selected randomly from the list of censuses by simple random selection from Sana'a governorate. The comparator (control) was selected by simple random sampling in order to make statistical conclusions about the population. It also helps ensure high internal validity: randomization is the best way to minimize the influence of potentially confounding variables. In this way, the basic requirements were prepared for this, as a complete list of each member of the population was obtained in Sana'a Governorate. The random selection was done by computer, after which each of the 110 selected residents was contacted or reached. Data was collected from them by telephone or access to them.

Data analysis: Descriptive statistics were computed as mean and frequencies (count and percentages). The two-tailed paired *t*-test was used to compare continuous characteristics (age) between the groups. Comparisons between schizophrenia cases and healthy control (outcome variable) with respect to patient

characteristics (age, gender, highest level of education, employment status, poor adherence, income, substance abuse, etc were examined by the use of contingency tables (chi-squared test with Yates correction and Fisher's exact test, ORs). All analyses were calculated by the Epi-Info version 7 (CDC, USA).

Ethical Consideration: Ethical approval No:1699 dated January 1, 2021 was taken from the Medical Ethics and Research Committee of the Faculty of Medicine and Health Sciences, Sana'a University. The trial was according to the ethical guidelines of the review committee.

3. Results

Regarding associated risk factors of schizophrenia, there was significant association with low income in which odds ratio was 7.1, 95% CI=3.5-14.3 and p <0.001, loss work (OR=57, 95% CI=24.8 - 133 and p <0.001), smoking (OR=5.9, 95% CI=3.1 – 11.1 and p <0.001), Khat chewing (OR=12.4, 95% CI= 6.3 – 24.7 and p <0.001), birth complications (OR=7.2, 95% CI=1. 6 – 32.8 and p <0.001), 1-6 Apgar scores (OR=1.8, 95% CI=1.1 – 3.3 and p=0.04), older paternal age (OR=3.2, 95% CI=1.5-6.8, and p <0.001), the spring birth (OR=2.2, 95% CI=1.2-4.2, and p =0.01), and winter birth (OR=1.9, 95% CI=1.1-3.4, and p =0.02), parental socioeconomic status (OR=7.1, 95% CI=3.5-14.3, and p <0.001), childhood trauma (OR=1.9, 95% CI=1.1-3.4, and p=0.02), cannabis (marijuana) use in adolescence (OR=7.4, 95% CI=1.0-61, and p =0.03), hypertension(OR=4.7, 95% CI=1.3-17.2, and p =0.009), and diabetics (OR=6.6, 95% CI=1.4-30.2, and p =0.005) (Table 1-5).

4. DISCUSSION

In terms of risk factors for schizophrenia, schizophrenia is defined as a neuro-developmental disorder without precise boundaries, or a single cause, and is thought to develop from interactions of the genetic environment with the respective vulnerability factors [6, 24, 25]. These risk factor relations are multifaceted, as they can engage abundant and diverse abuses from pregnancy into adulthood [25]. Genetic predisposition by itself, without the interaction of environmental factors, would not make possible the progress of schizophrenia [25]. The genetic component means that prenatal brain development is disturbed, and environmental influence influences postnatal brain development [26]. Facts illustrate that genetically susceptible children are more probable to be influenced by environmental risk factors [26]. In the current study, there was an association between obstetric complications and the development of schizophrenia with an associated odds ratio of 7.2, 95% CI = 1. 6 - 32.8 and p < 0.001, also 1–6 Apgar scores were significantly associated with schizophrenia (OR = 1.8, 95% CI = 1.1–3.3 and p = 0.04), these results are consistent with the studies by Cannon et al. [27], Dalman et al. [28], Mittal et al. [29] and Kotlicka-Antczak et al. [30]; as obstetric complications have been well documented as a risk factors for schizophrenia; and an increased susceptibility to schizophrenia has been associated with emergency caesarean section, bleeding during pregnancy, pre-eclampsia [29], low birth weight, and the use of forceps for delivery [31-33].

In the current study an association between advancing parental age and developing schizophrenia was associated with an associated OR of 3.2, with 95% CI = 1.5–6.8, and p < 0.001. This finding is similar to that previously reported in which increased paternal age, from ages above 34 and older was associated with schizophrenia [34–38]. An attractive theory suggests that an age-related increase in sporadic de novo mutations in male germ cells may play a role [39–41]. However, this was ruled out by a study from Denmark indicating that delayed marriage and reproduction may be due to the personality traits of the fathers [42]. A less consistent pattern of outcomes emerged with regard to maternal age at birth and risk of schizophrenia in the offspring. In one study, age younger than 19 years old and older than 40 years old [43] appeared to increase the risk. However, in another cohort study, the risk was shown to be reduced in offspring of

mothers older than 30 years of age [44]. Lopez Castroman and others. (2010) found only a significant linear association with maternal age [45].

In the current study, an association between trauma and the development of schizophrenia had an associated OR of 1.9, with a 95% CI = 1.1–3.4, and p was 0.02 with trauma and social adversities in various forms, both during childhood and adulthood, have been widely investigated as potential risk factors for schizophrenia. Varese and colleagues report, in a meta-analysis of case-control, prospective, and cross-sectional studies, that there is strong evidence that childhood adversity (defined as sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying) is associated with an increased risk of psychosis in adulthood (overall odds ratio = 2.78) [46]. There is an association between permanent separation from or death of one or both parents and psychosis [47] and abuse, bullying, and psychosis [48]. A strong association was found between childhood trauma and schizophrenia symptoms, with childhood trauma associated with the most severe forms of positive symptoms in adulthood, particularly hallucinations [49], and affective symptoms [50]. Life events proximal to disease onset, defined as situations that lead to positive or negative changes in personal circumstances and/or have a threat component, were investigated [51]. One of the last 10 years review and meta-analysis of the relationship between life events and psychosis suggested a three-fold increase in the odds of life events in the period prior to the onset of psychosis, the time period under study ranging from 3 months to 3.6 years [52].

In the current study, there was an association between low parental socioeconomic status and the development of schizophrenia where the associated OR was 7.1, with 95% CI = 3.5–14.3, and P was <0. 001.This finding is consistent with previous reports in which some reports link social inequality at birth to schizophrenia. It has been reported that socioeconomic status (usually measured by parental occupation) is associated with an increased risk of developing psychosis [53]. However, while some findings are positive, there are a number of conflicting studies that show no association between psychosis and low social class at birth or even an association with high social class [54]. Signs of isolation/denial, alone and cumulative, are also associated with psychosis [24]. Patients with first-episode psychosis are more likely to live alone; being single or unemployed; live in rented accommodation, in crowded conditions; and having income below the official poverty level, not only at first contact with psychiatric services but up to 5 years before the onset of psychosis, with odds nearly twofold increased. World Health Organization (WHO) studies have reported that despite better access to biomedical treatment, higher rates of chronic disability and dependency in schizophrenia occur in high-income countries than in low-income countries and suggest that something essential for recovery is missing in the tissue. social [25].

In the current study there was no association between urban residence and development of schizophrenia as its associated OR was 1.1, with 95% CI = 0.63–1.8, and P was 0.78. This is in contrast to previous reports by Marcellis et al. [55], Krabbendam et al. [56] and van Os et al. [57], as growing up and/or living in an urban environment is often associated with an increased risk of developing schizophrenia or psychosis in general. A meta-analysis including a total of 47,087 cases of psychosis shows a pooled odds ratio for psychosis in the urban setting compared to the rural setting of 2.39 (95% CI 1.62–3.51) [58]. Changing the place of residence in childhood from a rural to an urban environment doubles the risk of developing schizophrenia [59], and the more years a child spends in an urban area, the higher the risk [60]. Many explanations have been proposed such as increased exposure to prenatal influenza [61], maternal obstetric complications [62], Toxoplasma infection [63], cannabis use [64], social deprivation, income inequality, and social fragmentation but none of which have been

verified. Moreover, while the largest multicentre study of first-episode psychosis patients to date (the EU-GEI study) confirmed heightening in northern European cities including London, Amsterdam, and Paris, the effect of heightening intensity is not so evident in southern European settings [65].

In the current study, there was an association between cannabis and use of other substances such as khat and smoking with the development of schizophrenia where the associated OR was 5.9, (95% CI = 3.1 - 11.1 and $p < 0.001$) for smoking, and khat chewing had an associated OR of 12.4 (95% CI = 6.3). -24.7, $p < 0.001$), and for cannabis (marijuana) use in adolescence it was 7.4 (95% CI = 1.0–61, $p = 0.03$). These results are consistent with the fact that drug use before seizures or during a psychotic episode is highly prevalent in psychotic patients [66]. There is good evidence that psychostimulants (such as amphetamines and cocaine) can induce psychosis [67]. There have also been some suggestions that alcohol misuse and psychosis may be linked [68], and the last five years, a meta-analysis has raised the question whether tobacco use could be a risk factor for psychosis [69]. However, much greater evidence points to an important role in the aetiology and pathogenesis of cannabis use. Prospective epidemiological studies consistently report an association between cannabis use and schizophrenia [70-72], with an estimated two- to three-fold increased risk [70]. A dose-response relationship between the extent of use and the risk of developing psychosis was presented in a meta-analysis [73]. The association is strongest in individuals who used cannabis previously [71], who used high-potency cannabinoids (THC) or frequently [70]. In fact, the EU-GEI study found that if high-potency cannabis was no longer available, about 12% of first-episode psychosis cases could be prevented across 11 sites in Europe, rising to 30% in London and 50% in Amsterdam [74]. The age at which cannabis use begins appears to be related to the age at onset of psychosis [75] while continued cannabis use after the first episode is associated with a lower prognosis [76], higher relapse rates, longer hospitalizations, and more severe positive symptoms [77].

5. Conclusion

Future research in Yemen should also explore potential protective factors in groups at risk for psychotic disorders. A new area of research should involve big data and predictive models, by replacing traditional paper notes with electronic patient records. It is likely that in the near future schizophrenia will require a host of new diagnostic approaches, including measures of genetic risk, environmental risk factors, and brain imaging.

Acknowledgments

Full thanks for the generous support of the Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen.

Conflict Of Interest

No conflict of interest associated with this work.

Author's Contributions

This article is part of a research conducted by Dr. Sami Mohammed Abdo Hassan for his Ph.D., who carried out clinical and laboratory works with the assistance and supervision of Professor Hassan Al-Shamahy. Both contributed to the evaluation of clinical and laboratory findings, data analysis, and writing of the manuscript.

6. References

[1] 1.WHO (2022). "ICD-11: 6A20 Schizophrenia". World Health Organization. Retrieved 23 November 2022.

[2] Owen MJ, Sawa A, Mortensen PB. (2016). "Schizophrenia". The Lancet. **388** (10039): 86–97. doi:10.1016/S0140-6736(15)01121-6.

[3] Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (5th ed.) (2013). Arlington, VA: American Psychiatric Association. 2013. pp. 99–105. ISBN 978-0-89042-555-8.

[4] US National Institute of Mental Health (2022)."Schizophrenia". Health topics. US National Institute of Mental Health. April 2022. Retrieved 22 November 2022.

[5] International Schizophrenia C, Purcell SM, Wray NR, Stone JL, Visscher PM, O'DonovanMC, *et al*. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder.

Nature. 2009;460(7256):748–52. *doi: 10.1038/nature08185*.

[6] Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421–7.

[7] van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophr Bull. 2008;34(6):1066–82 . *doi: 10.1093/schbul/sbn117* .

[8] Al-Khamesy KSA, Al-Shehari MM, Al-Moyed KAA, Atf-allah JYY, Al-Shamahy HA, Al-Hadad AM (2022). Prevalence and risk factors of latent tuberculosis among healthcare workers in Sana'a city, Yemen using whole blood interferon-γ release assay. Universal J Pharm Res; 7(5):1-7. *https://doi.org/10.22270/ujpr.v7i5.833*

[9] Al-kadassy AM, Al-Ashiry AFS, and Al-Shamahy HA (2019). Sero-epidemiological study of hepatitis B, C, HIV and treponema pallidum among blood donors in Hodeida city- Yemen. Universal J Pharm Res; 4(2): 1-8. *https://doi.org/10.22270/ujpr.v4i2.256*

[10] AL-Shamahy HA (2000). Prevalence of Hepatitis B surface antigen and Risk factors of HBV infection in a sample of healthy mothers and their infants in Sana'a, Yemen. Ann Saudi Medicine; 20: 464-467. *https://doi.org/10.5144/0256-4947.2000.464*

[11] Al-Shamahy HA, Rabbad IA, Al-Hababy A. Hepatitis B virus serum markers among pregnant women in Sana'a, Yemen. Ann Saudi Med 2003; 23:87-89. *https://doi.org/10.5144/0256-4947.2003.87*

[12] Al-Shamahy HA, Hanash SH, Rabbad IA, Al-Madhaji NM, Naser SM (2011). Hepatitis B vaccine coverage and the immune response in children under ten years old in Sana'a, Yemen. Sultan Qaboos Univ Med J; 11(1):77-82. Epub 2011.

[13] Amran OAA, Al-Shamahy HA, Al Hadad AM, Jaadan BM 92019). Explosion of hepatitis B and C viruses among hemodialysis patients as a result of hemodialysis crisis in Yemen. Universal J Pharm Res; 4(5):1-8. *https://doi.org/10.22270/ujpr.v4i5.311*

[14] Hanash SH, Al-Shamahy HA, Bamshmous MHS (2019). Prevalence and genotyping of hepatitis C virus in hemodialysis patients and evaluation of HCV-core antigen test in screening patients for dialysis in Sana'a city, Yemen. Universal J Pharm Res; 4(2): 14-18. *https://doi.org/10.22270/ujpr.v4i2.251*

[15] Rabbad IA, Al-Somainy AAM, Al-Shamahy HA, Nasser SM (2014). Prevalence of hepatitis G virus infection among chronic hepatitis B, chronic hepatitis C and HIV patients in Sana'a, Yemen. J Chin Clin Med; 5 (11), 654-658 . *https://doi.org/10.3855/jidc.3796*

[16] Alqaisi NANS, AL-Mekhlafi AM, Al-Shamahy HA, *et al*. (2021). Toxoplasmosis in pregnant women in Yemen: The immune status and potential risk factors. Universal J Pharm Res; 6(2):1-6. *https://doi.org/10.22270/ujpr.v6i2.570*

[17] Abu-Hurub AS, Okbah AA, Al-Dweelah HMA, Al-Shamahy HA, *et al*. (2022). Prevalence of visceral leishmaniasis among adults in Sana'a city-Yemen. Universal J Pharm Res ; 7 (2):1-6. *https://doi.org/10.22270/ujpr.v7i2.745*

[18] Alastot E, Al-Shamahy HA (2018). Prevalence of leptospirosis amongst slaughterhouse workers and butchers in Sana'a city-Yemen. Universal J Pharm Res; 3(2):17-20. *https://doi.org/10.22270/ujpr.v3i2.133*

[19] *A*l-Eryani SA, Alshamahi EYA, Al-Shamahy HA, *et al*. (2021). Prevalence and risk factors for trachoma among primary school children in Sana'a city, Yemen. Universal J Pharm Res; 6(4):1-6. *https://doi.org/10.22270/ujpr.v6i4.636*

[20] Al-Hrazi RMA, Al-Shamahy HA, Jaadan BM (2019). Determination of rifampicin mono-resistance *Mycobacterium tuberculosis* in the National tuberculosis control programme in Sana'a city-Yemen: A significant phenomenon in war region with high prevalence tubercloisis. Universal J Pharm Res; 4(3):1-6. *https://doi.org/10.22270/ujpr.v4i3.266*

[21] Alhasani AH, Al-Akwa AA, Al-Shamahy HA, Al-deen HMS, Al-labani MA (2020). Biofilm formation and antifungal susceptibility of candida isolates from oral cavity after the introduction of fixed orthodontic appliances. Universal J Pharm Res; 5(4):1-6. *https://doi.org/10.22270/ujpr.v5i4.435*

[22] Al-dossary OAI, Al-Kholani AIM, AL-Haddad KA, Al-Najhi MMA, Al-Shamahy HA, Al-adhami IAA, Aldhorae K (2022). Interleukin-1β levels in the human gingival sulcus: Rates and factors affecting its levels in healthy subjects. Universal J Pharm Res; 7(5):42-48. *https://doi.org/10.22270/ujpr.v7i5.838*

[23] Al-Mansor MI, Al-Moyed KAA, Al-Shehari MM, Al-Shamahy HA, Al-gunaid EA, Al-Haddad AM (2022). Association of epstein-barr virus with systemic lupus erythematosus by limited materials: Patient characteristics and clinical manifestations in Yemen. Universal J Pharm Res; 7(5):49-56. *https://doi.org/10.22270/ujpr.v7i5.839*

[24] Mulvany F, O'Callaghan E, Takei N, Byrne M, Fearon P, Larkin C. Effect of social class at birth on risk and presentation of schizophrenia: case-

control study. BMJ. 2001;323(7326):1398–401. *doi: 10.1136/bmj.323.7326.1398*

[25] Morgan C, Kirkbride J, Hutchinson G, Craig T, Morgan K, Dazzan P, *et al*. Cumulative social disadvantage, ethnicity and first-episode psychosis: a case-control study. Psychol Med. 2008;38(12):1701–15. *doi: 10.1017/S0033291708004534*

[26] Jablensky A, Sartorius N.What did the WHO studies really find? Schizophr Bull. 2008;34(2):253–5. *doi: 10.1093/schbul/sbm151*

[27] Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry. 2002;159(7):1080–92. *doi: 10.1176/appi.ajp.159.7.1080.*

[28] Dalman C, Thomas HV, David AS, Gentz J, Lewis G, Allebeck P. Signs of asphyxia at birth and risk of schizophrenia. Populationbased case-control study. Br J Psychiatry. 2001;179:403–8. *doi: 10.1192/bjp.179.5.403.*

[29] Mittal VA, Ellman LM, Cannon TD. Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications. Schizophr Bull. 2008;34(6):1083–94. *doi: 10.1093/schbul/sbn080.*

[30] Kotlicka-AntczakM, Pawelczyk A, Rabe-Jablonska J, Smigielski J, Pawelczyk T. Obstetrical complications and Apgar score in subjects at risk of psychosis. Journal of psychiatric research. 2014;48(1):79–85. *doi: 10.1016/j.jpsychires.2013.10.004*

[31] Hultman CM, Sparen P, Takei N, Murray RM, Cnattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. BMJ. 1999;318(7181):421–6. *doi: 10.1136/bmj.318.7181.421.*

[32] Abel KMWS, Susser ES, Dalman C, Pedersen MG, Mortensen PB, Webb RT. Birth weight, schizophrenia, and adult mental disorder: is risk confined to the smallest babies? Arch Gen Psychiatry. 2010;67(9):923–30. *doi: 10.1001/archgenpsychiatry.2010.100.*

[33] Lahti M, Eriksson JG, Heinonen K, Kajantie E, Lahti J,Wahlbeck K, *et al*. Maternal grand multiparity and the risk of severe mental disorders in adult offspring. PloS one. 2014;9(12):e114679. *https://doi.org/10.1371/journal.pone.0114679*

[34] Hubert A, Szoke A, Leboyer M, Schurhoff F. Influence of paternal age in schizophrenia. Encephale. 2011;37(3):199–206. *doi: 10.1016/j.encep.2010.12.005*.

[35] Buizer-Voskamp JE, Laan W, Staal WG, Hennekam EA, Aukes MF, Termorshuizen F, *et al*. Paternal age and psychiatric disorders: findings from a Dutch population registry. Schizophr Res. 2011;129(2-3):128–32. *doi: 10.1016/j.encep.2010.12.005*.

[36] Brown AS, Schaefer CA, Wyatt RJ, Begg MD, Goetz R, Bresnahan MA, *et al*. Paternal age and risk of schizophrenia in adult offspring. Am J Psychiatry. 2002;159(9):1528–33. *doi: 10.1176/appi.ajp.159.9.1528.*

[37] Perrin M, Harlap S, Kleinhaus K, Lichtenberg P, Manor O, Draiman B, *et al*. Older paternal age strongly increases the morbidity for schizophrenia in sisters of affected females. Am J Med Genet B Neuropsychiatr Genet. 2010;153B(7):1329–35. *https://doi.org/10.1002/ajmg.b.31116*

[38] Sipos A, Rasmussen F, Harrison G, Tynelius P, Lewis G, Leon DA, *et al*. Paternal age and schizophrenia: a population based cohort study. BMJ. 2004;329(7474):1070. *doi: 10.1136/bmj.38243.672396.55*.

[39] Malaspina D, Corcoran C, Fahim C, Berman A, Harkavy- Friedman J, Yale S, *et al*. Paternal age and sporadic schizophrenia: evidence for de novo mutations. Am J Med Genet. 2002;114(3): 299–303. *doi: 10.1002/ajmg.1701.*

[40] Crow JF. Development. There's something curious about paternalage effects. Science (New York, NY). 2003;301(5633):606–7. *doi: 10.1126/science.1088552*.

[41] Torrey EF, Buka S, Cannon TD, Goldstein JM, Seidman LJ, Liu T, *et al*. Paternal age as a risk factor for schizophrenia: how important is it? Schizophr Res. 2009;114(1-3):1–5. *doi: 10.1016/j.schres.2009.06.017*.

[42] Petersen L, Mortensen PB, Pedersen CB. Paternal age at birth of first child and risk of schizophrenia. Am J Psychiatry. 2011;168(1):82–8. *doi: 10.1176/appi.ajp.2010.10020252.*

[43] Nosarti C, Reichenberg A, Murray RM, Cnattingius S, Lambe MP, Yin L, *et al*. Preterm birth and psychiatric disorders in young adult life. Arch Gen Psychiatry. 2012;69(6):E1–8. *doi: 10.1001/archgenpsychiatry.2011.1374.*

[44] Haukka JK, Suvisaari J, Lonnqvist J. Family structure and risk factors for schizophrenia: case-sibling study. BMC psychiatry. 2004;4:41.

[45] Lopez-Castroman J, Gomez DD, Belloso JJ, Fernandez-Navarro P, Perez-Rodriguez MM, Villamor IB, *et al*. Differences in maternal and paternal age between schizophrenia and other psychiatric disorders. Schizophr Res. 2010;116(2-3):184–90. *doi: 10.1016/j.schres.2009.11.006.*

[46] Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, *et al*. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and

cross-sectional cohort studies. Schizophr Bull. 2012;38(4):661–71. *doi: 10.1093/schbul/sbs050.*

[47] Agid O, Shapira B, Zislin J, Ritsner M, Hanin B, Murad H, *et al*. Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. Mol Psychiatry. 1999;4(2):163–72. *doi: 10.1038/sj.mp.4000473.*

[48] Arseneault L, Cannon M, Fisher HL, Polanczyk G, Moffitt TE, Caspi A. Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. Am J Psychiatry. 2011;168(1):65–72. *doi: 10.1176/appi.ajp.2010.10040567.*

[49] Read J, van Os J, Morrison AP, Ross CA. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. Acta Psychiatr Scand. 2005;112(5):330–50. *doi: 10.1111/j.1600-0447.2005.00634.x.*

[50] Matheson SL, Shepherd AM, Pinchbeck RM, Laurens KR, Carr VJ. Childhood adversity in schizophrenia: a systematic meta-analysis. Psychol Med. 2013;43(2):225–38. *doi: 10.1017/S0033291712000785.*

[51] Bebbington P,Wilkins S, Jones P, Foerster A,Murray R, Toone B, *et al*. Life events and psychosis. Initial results from the Camberwell Collaborative Psychosis Study. Br J Psychiatry. 1993;162:72–9. *doi: 10.1192/bjp.162.1.72.*

[52] Beards S, Gayer-Anderson C, Borges S, Dewey ME, Fisher HL, Morgan C. Life events and psychosis: a review and meta-analysis. Schizophr Bull. 2013;39(4):740–7. *doi: 10.1093/schbul/sbt065.*

[53] Castle DJ, Scott K, Wessely S, Murray RM. Does social deprivation during gestation and early life predispose to later schizophrenia? Soc Psychiatry Psychiatr Epidemiol. 1993;28(1):1–4. *doi: 10.1007/BF00797825*.

[54] Makikyro T, IsohanniM, Moring J, Oja H, Hakko H, Jones P, *et al*. Is a child's risk of early onset schizophrenia increased in the highest social class? Schizophr Res. 1997;23(3):245–52. *doi: 10.1016/s0920-9964(96)00119-3*.

[55] Marcelis M, Navarro-Mateu F, Murray R, Selten JP, Van Os J. Urbanization and psychosis: a study of 1942-1978 birth cohorts in The Netherlands. Psychol Med. 1998;28(4):871–9. *doi: 10.1017/s0033291798006898*.

[56] Krabbendam L, van Os J. Schizophrenia and urbanicity: a major environmental influence-conditional on genetic risk. Schizophr Bull. 2005;31(4):795–9. *doi: 10.1093/schbul/sbi060.*

[57] van Os J, Hanssen M, Bijl RV, Vollebergh W. Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. Arch Gen Psychiatry. 2001;58(7):663–8. *doi: 10.1001/archpsyc.58.7.663.*

[58] Vassos E, Pedersen CB, Murray RM, Collier DA, Lewis CM. Meta-analysis of the association of urbanicity with schizophrenia. Schizophr Bull. 2012;38(6):1118–23. *doi: 10.1093/schbul/sbs096*

[59] Marcelis M, Takei N, van Os J. Urbanization and risk for schizophrenia: does the effect operate before or around the time of illness onset? Psychol Med. 1999;29(5):1197–203. *doi: 10.1017/s0033291799008983.*

[60] March D, Hatch SL, Morgan C, Kirkbride JB, Bresnahan M, Fearon P, *et al*. Psychosis and place. Epidemiologic reviews. 2008;30:84–100. *doi: 10.1093/epirev/mxn006.*

[61] Westergaard T, Mortensen PB, Pedersen CB,Wohlfahrt J,Melbye M. Exposure to prenatal and childhood infections and the risk of schizophrenia: suggestions from a study of sibship characteristics and influenza prevalence. Arch Gen Psychiatry. 1999;56(11):993–8. *doi: 10.1001/archpsyc.56.11.993*.

[62] Eaton WW, Mortensen PB, Frydenberg M. Obstetric factors, urbanization and psychosis. Schizophr Res.2000;43(2-3):117–23. *doi: 10.1001/archpsyc.56.11.993.*

[63] Torrey EF, Yolken RH. The urban risk and migration risk factors for schizophrenia: are cats the answer? Schizophr Res. 2014;159(2-3):299–302. *doi: 10.1001/archpsyc.56.11.993.*

[64] Lewis G, David A, Andreasson S, Allebeck P. Schizophrenia and city life. Lancet. 1992;340(8812):137–40. *doi: 10.1016/0140-6736(92)93213-7.*

[65] Jongsma HE, Gayer-Anderson C, Lasalvia A, Quattrone D, Mule A, Szoke A, *et al*. Treated incidence of psychotic disorders in the multinational EU-GEI study. JAMA Psychiatry. 2018;75(1):36–46. *doi: 10.1001/jamapsychiatry.2017.3554.*

[66] Wade D, Harrigan S, Edwards J, Burgess PM, Whelan G, McGorry PD. Patterns and predictors of substance use disorders and daily tobacco use in first-episode psychosis. Aust N Z J Psychiatry. 2005;39(10):892–8. *doi: 10.1080/j.1440-1614.2005.01699.x.*

[67] Sara GE, Large MM, Matheson SL, Burgess PM, Malhi GS, Whiteford HA, *et al*. Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation. Aust N Z J Psychiatry. 2015;49 (2): 106–17. *doi: 10.1177/0004867414561526.*

[68] Koskinen J, Lohonen J, Koponen H, Isohanni M, Miettunen J. Prevalence of alcohol use disorders in schizophrenia-a systematic review and meta-

analysis. Acta Psychiatr Scand. 2009;120(2):85–96. *doi: 10.1111/j.1600-0447.2009.01385.x.*

[69] Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. Lancet Psychiatry. 2015;2(8):718–25. *doi: 10.1016/S2215-0366(15)00152-2*.

[70] Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ. 2002;325(7374): 1199. *doi: 10.1016/S2215-0366(15)00152-2*.

[71] Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002;325(7374):1212– *doi: 10.1136/bmj.325.7374.1212*

[72] van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol. 2002;156(4):319–27. *doi: 10.1093/aje/kwf043*.

[73] Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Metaanalysis of the association between the level of cannabis use and risk of psychosis. Schizophr Bull. 2016;42(5):1262–9. *doi: 10.1093/schbul/sbw003*.

[74] Di FortiM, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, *et al*. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry. 2019;6(5):427–36. *doi: 10.1016/S2215-0366(19)30048-3*.

[75] Galvez-Buccollini JA, Proal AC, Tomaselli V, Trachtenberg M, Coconcea C, Chun J, *et al.* Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. Schizophr Res. 2012;139(1-3):157–60. *doi: 10.1016/j.schres.2012.06.007*.

[76] Alvarez-JimenezM, Priede A, Hetrick SE, Bendall S,Killackey E, Parker AG, *et al*. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr Res. 2012;139(1-3):116–28. *doi: 10.1016/j.schres.2012.05.007*.

[77] Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, *et al*. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry. 2016;3(3):215–25. *doi: 10.1016/S2215-0366(15)00363-6 .*

RESULTS

Table 1: Age and Gender Distribution of schizophrenic patients and the control in Sana'a City, Yemen

Characters	Cases n=110		Control n=110	
	Number	percentage	Number	percentage
Gender				
Female	5	4.9	29	26.4
Male	105	95.5	81	73.6
Age groups				
20 – 29 years	44	40	78	70.9
30-39 years	48	43.6	18	16.4
40 – 49 years	6	5.5	14	12.7
≥ 50 years	12	10.9	0	0
Total	**110**	**100**	**110**	**100**
Mean age	33.7 years		28.6 years	
SD	9.6 years		7.5 years	
Median	33 years		27 years	
Mode	35 years		28ears	
Min	20 years		18 years	
Max	75 years		48 years	

Table 2: Complications related to pregnancy and childbirth as risk factors for developing schizophrenia

Characters	Cases n=110		Control n=110		*OR*	*95% CI*	X^2	*P*
Birth complications								
Yes	13		2		7.2	1.6-32.8	8.6	0.003
No	97		108					
Birth weight								
Normal	71		67		1.2	0.67-2	0.31	0.57
Low	39		43		0.85	0.4-1.4	0.31	0.57
Apgar scores								
1-6	41		27		1.8	1.1-3.3	4.2	0.04
7-10	69		83		0.54	0.3-0.9	4.2	0.04
paternal age								
older	29		11		3.2	1.5-6.8	9.9	<0.001
Younger	81		99		0.31	0.14-0.6	9.9	<0.001
Maternal smoking during pregnancy								
Yes	38		27		1.6	0.9-2.9	2.6	0.1
No	72		83					
season of birth								
The Spring	35		19		2.2	1.2-4.2	6.3	0.01
The Summer	21		39		0.42	0.22-0.79	7.4	0.006
The autumn	18		29		0.54	0.28-1.05	3.3	0.07

Table 3: Trauma and Social Adversities factors as associated risk factors of schizophrenia development

Characters	Cases n=110		Control n=110		*OR*	*95% CI*	X^2	*P*
parental socioeconomic status								
High	10	9.1	16	14.5	0.58	0.25-1.3	1.5	0.21
Moderate	2	1.8	38	41.8	0.035	0.008 0.15	39	<0.001
Low	98	89.1	56	50.9	7.1	3.5-14.3	33.8	<0.001
childhood trauma								
Yes	41		26		1.9	1.1-3.4	4.8	0.02
No	69		84					
cannabis (marijuana) use in adolescence								
Yes	7		1		7.4	1.0-61	4.6	0.03
No	103		109					
Hypertension	13	11.8	3		4.7	1.3-17.2	6.7	0.009
Diabetics	12	10.9	2		6.6	1.4-30.2	7.6	0.005

Table 4: Marital status, residency, and economic factors as associated risk factors of schizophrenia development

Characters	Cases n=110		Control n=110		*OR*	*95% CI*	X^2	*P*
Marital status								
Married	59	53.6	52	47.3	1.2	0.75-2.1	0.89	0.34
Single	51	46.4	58	52.7	0.77	0.45-1.3	0.89	0.34
Residency								
Rural	49	44.5	51	46.4	0.92	0.54-1.58	0.073	0.78
Urban	61	55.5	59	53.6	1.1	0.63-1.8	0.073	0.78
Economic status								
Housing								
Own	88	80	51	46.4	4.6	2.5-8.4	26.7	<0.001
Rent	22	20	59	53.6	0.21	0.11-0.3	26.7	<0.001
Income								
High	10	9.1	16	14.5	0.58	0.25-1.3	1.5	0.21
Moderate	2	1.8	38	41.8	0.035	0.008-0.15	39	<0.001
Low	98	89.1	56	50.9	7.1	3.5-14.3	33.8	<0.001
Loss of work								
Yes	92	83.6	10	9.1	57	24.8-133	126	<0.001
No	16	14.6	100	90.9				

Table 5: Habits as associated risk factors of schizophrenia development

Characters	Cases n=110		Control n=110		*OR*	*95% CI*	X^2	*P*
Smoking								
Yes	59	53.6	18	16.4	5.9	3.1-11.1	33.5	<0.001
No	51	46.4	92	83.6				
Khat chewing								
Yes	96	87.3	39	35.5	12.4	6.3-24.7	62	<0.001
No	14	12.7	71	64.5				
cannabis (marijuana) use in adolescence								
Yes	7		1		7.4	1.0-61	4.6	0.03
No	103		109					