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Genetic, Environmental and psychosocial Risk Factors for Psychotic Disorders: A Case–Control Study in Damascus, Syria

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Abstract

Introduction:

Schizophrenia is a chronic neurodevelopmental disorder characterized by positive, negative, and cognitive symptoms, leading to substantial disability and premature mortality. Affecting approximately 1% of the global population, it typically manifests in late adolescence or early adulthood. Its etiology involves complex interactions between genetic susceptibility and environmental exposures, including obstetric complications, prenatal stress, urbanicity, migration, and substance use. Despite extensive international research, data from Syria remain limited. This study aimed to investigate genetic, environmental and psychosocial risk factors associated with psychotic disorders in a Syrian population.

Methodology:

A case–control study was conducted at Al-Mouwasat University Hospital, Damascus, Syria, between October 2022 and October 2023. The study included 100 patients with psychotic disorders and 100 first- or second-degree relatives without psychotic disorders, aged 18–65 years. Data were collected through structured interviews covering sociodemographic characteristics, psychiatric and medical history, obstetric complications (Lewis–Murray Scale), socioeconomic status, and medication adherence (MARS). Categorical and continuous variables were analyzed using chi-square and Mann–Whitney/Kruskal–Wallis tests, respectively. Spearman correlation and binary logistic regression were performed, with statistical significance set at $p < 0.05$.

Results

Maternal prenatal stress was significantly more prevalent among cases than controls (32% vs 14%) and was associated with increased odds of psychotic disorder (OR = 2.89, 95% CI: 1.43–5.85). Cases also demonstrated significantly higher rates of obstetric complications. Rural-to-urban transition was more common among cases, whereas general migration and parental age at childbirth were not significantly associated. In multivariable analysis, employment status was independently protective, while rural-to-urban transition remained a significant risk factor.

Conclusion

Psychotic disorders among Syrian adults are influenced by prenatal and social factors, particularly maternal stress during pregnancy and rural-to-urban transition, while employment appears protective. These findings underscore the importance of early identification, maternal mental health support, and social interventions to reduce risk and improve outcomes.

Introduction

Schizophrenia is a chronic and disabling mental disorder that imposes a substantial burden on individuals, families, and society. It is characterized by a combination of psychotic, negative and cognitive symptoms. Psychotic or positive symptoms include delusions, hallucinations, and markedly disorganized speech or behavior. Negative symptoms involve diminished motivations, social withdrawal, and reduced emotional expression. In addition, individuals with schizophrenia commonly experience cognitive impairments, particularly in executive functioning, memory, and processing speed [1].

Schizophrenia affects approximately 1% of the global population and is recognized as one of the top ten causes of health burden in the world [2]. Schizophrenia is typically diagnosed in the late teens to early thirties, and tends to emerge earlier in males (late adolescence – early twenties) than females (early twenties – early thirties) [3].

Many individuals with schizophrenia do not achieve full recovery. Even those with favorable outcomes face profound, life-long impacts, including social isolation, stigma, and reduced opportunities for close relationships. Schizophrenia was associated with a weighted average of 14.5 years of potential life lost, and was higher for men than women [4]. Contributing factors to the increased mortality risk include, arterial hypertension, diabetes mellitus, and high cholesterol and triglycerides, in addition to an unhealthy lifestyle including smoking, physical inactivity, poor diet, substance abuse [5].

Schizophrenia is considered a neurodevelopmental disorder with no single cause. Instead, it arises from complex interactions between genetic and environmental vulnerability factors. These risk factors can interact from prenatal stages through adulthood, producing cumulative effects that shape the course of the disorder [6].

Regarding risk factors, the genetic basis of schizophrenia involves numerous susceptibility genes, each exerting only a small individual effect. Advances in whole-genome sequencing and modern DNA amplification methods enabled the detection of these susceptibility loci. Among the most extensively investigated genetic alterations are single nucleotide polymorphisms (SNPs) and copy number variations (CNVs), including small nucleotide deletions [7]. Among the CNVs associated with schizophrenia, the most thoroughly investigated is the 22q11.2 deletion syndrome, which is estimated to increase the risk of developing the disorder by roughly 25-fold [8].

Twin studies consistently estimate that the heritable risk for schizophrenia lies between 70% and 80%, underscoring a substantial genetic component [9]. In parallel, increasing paternal age has emerged as a significant risk factor, potentially through de novo mutations in germ cells: epidemiological evidence shows that offspring of older fathers face a significantly higher risk of schizophrenia [10].

Although genetic factors contribute substantially to schizophrenia, environmental exposures play a key role in shaping disease risk and expression. Environmental insults, such as obstetric complications

(OCs), cannabis use, urban upbringing, migration, and childhood trauma, have been consistently implicated in increasing the risk of developing psychosis [11–14].

Despite the wealth of international literature, there remains a lack of localized evidence addressing the combined influence of genetic, environmental, and psychosocial risk factors for schizophrenia in Syria. Most existing studies have been conducted in Western populations, where cultural, environmental, and healthcare contexts differ significantly from those in Syria. Schizophrenia has a relatively low prevalence, and large population-based studies would be logistically challenging and resource-intensive; therefore, a case–control study design is particularly suitable in this setting. By comparing individuals diagnosed with schizophrenia (cases) to those without the disorder (controls), this approach efficiently allows the investigation of multiple genetic, environmental, and social risk factors within a manageable sample size. Generating evidence specific to the Syrian population will provide a clearer understanding of the determinants of schizophrenia and support the development of more effective preventive and therapeutic strategies.

Methods

Study Setting and Design

The study was conducted in the psychiatric outpatient clinic and psychiatry department of Al-Mouwasat University Hospital in Damascus, Syria. Data were collected over a one-year period from October 2022 to October 2023.

Participants

The case group comprised patients with a confirmed diagnosis of a psychotic disorder—including schizophrenia, schizophreniform disorder, delusional disorder, schizoaffective disorder, or acute psychotic episode—based on DSM-5 criteria. The control group consisted of first- or second-degree relatives of case participants who had no lifetime history of any psychotic disorder.

Eligible participants were aged 18–65 years. Exclusion criteria included age <18 or >65 years, intellectual disability, suspected organic or substance-induced psychosis, or a diagnosed mood disorder. The final sample included 200 participants, with 100 cases and 100 controls. Using relatives as controls may reduce independence for familial risk factors and is acknowledged as a potential limitation.

The sample size was calculated for an unmatched case-control study based on the expected prevalence of the main risk factor among controls and the minimum odds ratio considered clinically significant. Assuming a prevalence of 20% for the exposure in controls, a two-sided α of 0.05, and 80% power, the required sample size was approximately 98 participants per group. We recruited 100 participants in the case group and 100 in the control group. This sample size allows for the detection of moderate to large association while accounting for potential missing or incomplete data.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Damascus University, according to the Faculty Council Decision No. 3551 dated 28/08/2022.

All participants provided written informed consent after receiving detailed information about the study objectives and procedures.

Data Collection

Data were collected using a random sampling method through structured interviews conducted by a psychiatrist. The interviews gathered detailed information on socio-demographic characteristics, psychiatric and medical history, and exposure to potential risk factors, including parental age at birth, season of birth, maternal stress during pregnancy, rural-to-urban transition, history of migration or travel, and other relevant clinical variables.

Assessment of Obstetric Complications

Obstetric complications were evaluated using the Lewis–Murray Scale, a standardized instrument commonly employed in psychiatric research to document prenatal, perinatal, and neonatal complications. The scale assesses pregnancy-related events (e.g., maternal illness, bleeding, pre-eclampsia), labor and delivery complications (e.g., fetal distress, prolonged labor, assisted delivery), and neonatal conditions (e.g., hypoxia, low birth weight, prematurity). Each item is coded as present, absent, or uncertain, and higher total scores reflect a greater burden of obstetric complications. The Lewis–Murray Scale is widely used in schizophrenia research, particularly for evaluating early-life hypoxic and perinatal risk factors [15].

Socioeconomic Status

Socioeconomic status was determined using the **Irish Classification of Occupations**, which categorizes individuals into six socioeconomic classes based on occupational status [16].

Stress during pregnancy

Maternal stress during pregnancy was assessed among the participants' mothers. Stress exposure was defined as the experience of one or more major life stressors during pregnancy, including the death of a spouse, divorce, exposure to violence, serious physical illness or injury, marital separation, imprisonment of the husband, remarriage, significant changes in the health of a family member, or the death of a close relative.

Medication Adherence

Adherence to treatment within the case group was evaluated via the Medication Adherence Rating Scale (MARS). The MARS is a 10-item questionnaire with a binary (yes/no) response format, where each "yes" response contributes one point to a total score. Higher scores reflect greater medication adherence. The

assessment period specifically covered the seven days prior to data collection [17]. Medication adherence was evaluated to see if other case variables had an effect on medication adherence.

Statistical analyses were performed using SPSS version 25. Descriptive statistics summarized participant characteristics. Categorical variables were compared using Pearson's chi-square. While continuous variables were analyzed with the Mann–Whitney U or Kruskal–Wallis tests due to non-normal distributions. Spearman's correlation assessed associations between continuous variables. Binary logistic regression was used to identify independent predictors of psychotic disorder. A two-tailed p value < 0.05 was considered statistically significant.

Results

Descriptive Analysis of Study Results

The case and control groups were comparable in terms of sex distribution, with males comprising 54% of participants in each group. Mean age was also similar between cases (31.86 ± 12.36 years) and controls (31.60 ± 12.94 years). Differences were observed in marital status, as a higher proportion of cases were single compared with controls (58% vs. 44%), whereas marriage was more common among controls (56% vs. 26%). Divorced (12%) and widowed (4%) participants were identified exclusively in the case group.

With regard to educational attainment, basic education was the most frequently reported level in both groups (54% of cases and 48% of controls). However, university-level education was more prevalent among controls than cases (38% vs. 26%). Employment status also differed between the groups, with unemployment being more common among cases (54%), while the majority of controls were employed (66%).

The socio-demographic characteristics of the study participants are summarized in **Table 1**.

Variable	Category	Cases (n=100)	Controls (n=100)
Sex	Male	54 (54%)	54 (54%)
	Female	46 (46%)	46 (46%)
Age (years)	Mean ± SD	31.86 ± 12.36	31.60 ± 12.94
	Range	17–60	17–64
Marital status	Single	58 (58%)	44 (44%)
	Married	26 (26%)	56 (56%)
	Divorced	12 (12%)	0 (0%)
	Widowed	4 (4%)	0 (0%)
Education	Basic	54 (54%)	48 (48%)
	University	26 (26%)	38 (38%)
	Secondary	16 (16%)	10 (10%)
	Illiterate	4 (4%)	4 (4%)
Employment	Employed	46 (46%)	66 (66%)
	Unemployed	54 (54%)	34 (34%)

Table 1: Socio-Demographic Characteristics of Cases and Controls.

Participants' places of residence were similarly distributed across groups. The largest proportions originated from Rural Damascus (38% of cases and 32% of controls) and Damascus city (26% in both groups). All remaining locations, each representing 2% or less of the total sample, were grouped under the category "Other" for clarity (Table 2).

Residence	Cases (n=100)	Controls (n=100)
Rural Damascus	38 (38%)	32 (32%)
Damascus	26 (26%)	26 (26%)
Deir ez-Zor	10 (10%)	2 (2%)
Lebanon	2 (2%)	8 (8%)
As-Suwayda	4 (4%)	4 (4%)
Rural Aleppo	4 (4%)	2 (2%)
Other (≤2%)	16 (16%)	26 (26%)

Table 2: Distribution of Residence among Cases and Controls

Assessment of socioeconomic status revealed comparable patterns between the two groups. In both the case and control groups, the majority of participants were classified within Class 3 (42% and 46%, respectively), followed by Class 2 (20% in each group). The complete distribution across all socioeconomic classes is presented in Table 3.

social class scale	Control Group (n=100)	Cases Group (n=100)
Class 1 (**Professional occupations)**	12 (12%)	14 (14%)
Class 2 (Managerial and technical occupations)	20 (20%)	20 (20%)
Class 3 (Non-manual occupations)	46 (46%)	42 (42%)
Class 4 (Skilled manual occupations)	12 (12%)	14 (14%)
Class 5 (Semi-skilled manual occupations)	6 (6%)	6 (6%)
Class 6 (Unskilled manual occupations)	4 (4%)	4 (4%)

Table 3: Distribution of Social Class Status among Controls and Cases according to Irish Census-derived Social Class Scale.

Regarding family history of illnesses, 36% of case participants reported a history of physical diseases, while 10% reported no family history of illness. Psychotic disorders were reported among first-degree relatives in 24% of cases, and among second-degree relatives in 16% of cases. A family history of non-psychotic psychiatric disorders was reported in 14% of cases. Family history of psychiatric disorders was not independently analyzed for the control groups, as controls were biologically related to cases, and reported histories could overlap with the cases themselves.

With regard to diagnostic profile, the majority of participants in the control group had no psychiatric disorder (86%). In the case group, schizophrenia was the most prevalent diagnosis, accounting for 78% of cases, followed by schizophreniform disorder (14%). The remaining diagnoses included delusional disorder, schizoaffective disorder, and acute psychotic episodes. A detailed diagnostic breakdown for both groups is presented in Table 4.

Diagnosis	Case Group (n=100)
Schizophrenia	78 (78%)
Schizophreniform Disorder	2 (2%)
Schizoaffective Disorder	6 (6%)
Acute Psychotic Episode	14 (14%)
	Control Group (n=100)
Borderline Personality Disorder	6 (6%)
Generalized Anxiety Disorder	6 (6%)
Trichotillomania	2 (2%)
No psychiatric Diagnosis	86 (86%)

Table 4: Diagnostic Profile of Participants in the Control and Case Group.

Psychiatric comorbidities were identified in 20% of the case group. The most frequently observed comorbidity was generalized anxiety disorder (8%), followed by obsessive–compulsive disorder (4%). Other comorbid conditions, each occurring in 2% of participants, are summarized in Table 5.

Comorbidity	Number
None	80 (80%)
Generalized Anxiety Disorder	8 (8%)
Obsessive–Compulsive Disorder	4 (4%)
Substance Misuse	2 (2%)
Borderline Personality Disorder	2 (2%)
Hypochondriasis	2 (2%)
Conversion Disorder	2 (2%)

Table 5: Distribution of Psychiatric Comorbidities among Cases.

The duration of the current psychotic episode among cases was categorized into three intervals: ≤1 month, 1–6 months, and >6 months. The largest proportion of patients reported an episode duration of ≤1 month (38%), followed by durations of 1–6 months (34%), while episodes lasting >6 months accounted for 28% of the sample.

With respect to seasonal onset, episodes most frequently began during autumn (32%), followed by winter (30%), summer (20%), and spring (18%).

Inferential Analysis

Maternal age at childbirth did not differ significantly between cases and controls (mean ± SD: 26.78 ± 6.14 vs 25.64 ± 6.75 years, respectively; Mann–Whitney U = 4442.0, Z = –1.37, p = 0.172). Similarly, paternal age at childbirth was comparable between the two groups (mean ± SD: 34.44 ± 6.78 vs 32.98 ± 7.06 years, respectively; Mann–Whitney U = 4418.0, Z = –1.43, p = 0.154).

The association between psychotic disorders and season of birth was analyzed using a Pearson chi-square test. As shown in **Table 6**, the highest proportion of cases was observed among individuals born in winter 32 (32%) followed by spring 28 (28%). However, the difference in birth season distributions between cases and controls was not statistically significant (Pearson $\chi^2 = 7.13$, df = 3, p = 0.068).

In the odds ratio analysis, individuals born in winter and spring demonstrated modestly higher odds of being a case compared with those born in autumn and summer (OR = 1.45, 95% CI: 1.08–1.94). Conversely, birth in autumn or summer was associated with lower odds of being a case (OR = 0.70, 95% CI: 0.52–0.92). Although these findings suggest a seasonal trend toward increased risk among winter and spring births, the overall association did not reach statistical significance and should therefore be interpreted with caution.

Season of Birth	Controls n (%)	Cases n (%)	OR	95% CI
Winter	22 (40.7%)	32 (59.3%)	1.45	1.08-1.94
Spring	20 (41.7%)	28 (58.3%)		
Summer	30 (55.6%)	24 (44.4%)	0.7	0.52-0.92
Autumn	28 (63.6%)	16 (36.4%)		

Table 6: Distribution of Cases and Controls by Season of Birth.

Maternal exposure to psychological stress during pregnancy differed significantly between cases and controls. A substantially higher proportion of cases (32%) reported maternal stress exposure during gestation compared with controls (14%). This difference was statistically significant on chi-square analysis ($\chi^2 = 9.15$, df = 1, p = 0.002).

Further analysis using binary logistic regression showed that offspring whose mothers experienced stress during pregnancy had nearly threefold higher odds of developing a psychotic disorder compared with those whose mothers did not report stress exposure (OR = 2.89, 95% CI: 1.43–5.85, p = 0.003). These findings suggest a strong association between prenatal maternal stress and the occurrence of psychotic disorders in offspring.

This study examined the association between psychotic disorders and obstetric complications using the Lewis–Murray Scale. The mean Lewis–Murray score was higher among cases (1.04 ± 1.56; range: 0–6; n = 100) than controls (0.62 ± 1.19; range: 0–4; n = 100). A Mann–Whitney U test demonstrated that this difference was statistically significant (U = 4288.0, Z = −2.13, p = 0.033), indicating a greater burden of obstetric complications among cases compared with controls.

Rural-to-urban transition was significantly more frequent among cases than controls (67.9% vs. 32.1%). Pearson's chi-square analysis showed a statistically significant association between rural-to-urban transition and psychotic disorders ($\chi^2 = 9.92$, df = 1, p = 0.002).

In contrast, general migration or travel did not differ significantly between cases and controls. A total of 36% of cases reported a history of migration or travel compared with 24% of controls, while 64% of cases and 76% of controls reported no such history. Although migration or travel was more commonly reported among cases, this difference did not reach statistical significance (Pearson $\chi^2 = 3.43$, df = 1, p = 0.064).

Factors Associated with Medication Adherence

Among cases, medication adherence assessed using the Medication Adherence Report Scale (MARS) was examined in relation to several potential risk factors. No significant correlations were observed between medication adherence scores and either maternal or paternal age. Adherence scores also did not differ significantly according to season of birth.

Medication adherence was significantly higher among participants whose mothers experienced lower levels of psychological stress during pregnancy compared with those exposed to higher maternal stress (mean rank = 58.29 vs. 45.73, respectively; Mann–Whitney U = 782.0, Z = −2.36, p = 0.018). In contrast, no significant association was observed between medication adherence and obstetric complications as measured by the Lewis–Murray scale (p = 0.143).

Participants who experienced a rural-to-urban transition demonstrated significantly higher medication adherence (mean rank = 58.29) compared with those who did not relocate (mean rank = 45.73). However, no significant difference in adherence was found among participants with a history of general migration or travel (p = 0.539).

These results are summarized in **Table 7**.

Predictor	Test	N	Statistic	p-value	Interpretation
Maternal age at birth	Spearman correlation	100	ρ = 0.003	0.976	No significant association
Paternal age at birth	Spearman correlation	100	ρ = 0.023	0.823	No significant association
Season of birth	Kruskal–Wallis H	100	H = 6.62 df = 3	0.085	No significant difference
Maternal stress during pregnancy	Mann-Whitey U	100	U=782.0 Z= -2.36	0.018	Higher adherence among participants whose mothers experienced less stress during pregnancy
Obstetric complications (Lewis–Murray)	Spearman correlation	100	ρ = −0.147	0.143	No significant association
Rural-to-urban transition	Mann–Whitney U	100	U = 882.0 Z = −2.20	0.028	Lower adherence among participants who moved
History of migration/travel	Mann–Whitney U	100	U = 1,070.0 Z = −0.62	0.539	No significant difference

Table 7: Summary of Relationships between Risk Factors and Medication Adherence (MARS Scale).

Logistic regression was performed to identify independent predictors of psychotic disorder (case status). Employment and rural-to-urban transition emerged as significant predictors: employed participants had lower odds of being cases compared with unemployed participants (OR = 0.244, 95% CI: 0.094–0.632, p = 0.004), while participants who transitioned from rural to urban areas had higher odds of being cases (OR = 2.747, 95% CI: 1.272–5.929, p = 0.010).

Other variables, including history of migration or travel, age, sex, maternal and paternal ages, season of birth, and obstetric complications measured by the Lewis–Murray scale, were not statistically significant. Notably, exposure to stress (OR = 1.269, 95% CI: 0.990–1.627, p = 0.060) showed trends toward increased risk but did not reach significance.

The results are summarized in **Table 8**.

Predictor	B	S.E.	Wald	p-value	OR (Exp(B))	95% CI for OR
Employment	-1.412	0.486	8.433	0.004	0.244	0.094–0.632
Rural-to-urban transition	1.010	0.393	6.623	0.010	2.747	1.272–5.929
History of migration/travel	0.025	0.424	0.003	0.953	1.025	0.447–2.353
Age	0.001	0.015	0.003	0.959	1.001	0.972–1.030
Sex	-0.670	0.487	1.891	0.169	0.512	0.197–1.330
Maternal age at birth	0.013	0.036	0.142	0.707	1.014	0.945–1.087
Paternal age at birth	0.056	0.033	2.807	0.094	1.058	0.991–1.129
Lewis–Murray score	0.201	0.125	2.599	0.107	1.222	0.958–1.561
Season of birth (overall)	–	–	5.546	0.136	–	–

Table 8: Logistic Regression Analysis of Sociodemographic and Obstetric Factors Associated with Psychotic Disorder.

Discussion

In the present study, the mean age at onset of psychotic disorder was 31.86 ± 12.36 years, which is higher than that reported in large epidemiological studies, where the median age of onset is approximately 25 years with a peak around 20.5 years [18]. This difference likely reflects delayed help-seeking and late diagnosis. In contexts such as Syria, several studies document limited availability of mental health services, shortages of trained professionals, and barriers to accessing care — including low awareness and social stigma — that contribute to substantial treatment gaps and delayed presentation to clinical services [19].

The proportion of single individuals was higher in the case group, with cases having 2.84 times the odds of being single than the control group. This likely reflects the social impairments associated with psychotic disorders. Meta-analytic evidence suggests that deficits in emotion processing in these conditions are linked to lower social competence and fewer close relationships, which may contribute to the higher prevalence of single status among affected individuals.[20]

Unemployment was higher in the case group than in controls (54% vs 34%), likely reflecting the occupational impairment that schizophrenia and related psychoses impose. Existing literature documents that psychosocial dysfunction, cognitive deficits, and stigma contribute to reduced employability and sustained job loss among patients with psychosis [21]. This occupational disadvantage further entrench social isolation, financial hardship, and poorer clinical outcomes, creating a vicious cycle that hampers recovery.

Basic education was the most prevalent level in both groups (54% of cases and 48% of controls). Although lower educational attainment has been reported among patients with schizophrenia [22], the similar distribution observed in controls suggests that this pattern likely reflects the educational structure of the source population rather than an illness-specific effect.

Because the controls in this study were first- or second-degree relatives of the cases, the rates of psychotic disorders among first- and second-degree relatives were similar (40% in cases vs. 44% in controls). This suggests that the occurrence of schizophrenia should not be attributed solely to genetic liability, but rather reflects a multifactorial etiology in which polygenic risk interacts with environmental exposures [23].

No significant association was found between parental age at birth and the occurrence of psychotic disorders. Maternal age did not significantly influence the risk of schizophrenia in logistic regression analyses. Similarly, the proportion of fathers aged ≥ 35 years was comparable between cases (46%) and controls (42%), with no statistically significant difference ($\chi^2 = 0.325$, df = 1, $p = 0.569$). These results contrast with findings from a Dutch population registry study, which reported an increased risk of schizophrenia associated with paternal age over 35 years. [24].

Psychiatric comorbidities were observed in 20% of patients, with generalized anxiety disorder (8%) and obsessive–compulsive disorder (4%) being the most frequent. It was not determined whether these comorbid symptoms preceded or followed the onset of psychosis.

The economic status of both groups was comparable, which is expected given the kinship relation between them. The majority of participants belonged to social class III according to the Irish occupational classification. This observation contrasts with established global epidemiological patterns, which generally report a higher prevalence of psychotic disorders among individuals from lower social classes—a relationship often attributed to increased exposure to socioeconomic stressors, material deprivation, and other risk factors associated with disadvantaged socioeconomic status [25].

In our sample, winter births were more frequent among cases than controls (32% vs. 20%), as were spring births (28% vs. 20%). Overall, 60% of cases were born during the winter–spring period, consistent with the previously reported winter–spring birth excess for schizophrenia in the Northern Hemisphere [26]; however, this association did not reach statistical significance in our study ($p = 0.069$).

Exposure to maternal stress during pregnancy was reported more frequently among cases than controls (32% vs. 14%) and was significantly associated with an increased risk of psychotic disorders ($p = 0.002$). Logistic regression indicated that prenatal stress was associated with nearly a threefold higher odds of developing psychosis. This finding is consistent with a Qatari study, which also reported a significant association between schizophrenia and prenatal stress ($p < 0.001$) [27], further supporting the potential role of maternal stress as an important environmental risk factor for psychotic disorders.

Our findings, showing a significant association between obstetric complications and psychotic disorders (p = 0.033), with risk increasing according to the severity of complications, are consistent with those reported by Verdolini et al. (2023). In contrast, Margari et al. (2011) found no significant difference in pre- and perinatal complications between cases and controls (p = 0.43); however, they reported that postnatal complications, such as infections or hospitalization, were associated with an increased risk of psychotic disorders (p = 0.03).

Possible mechanisms underlying the impact of prenatal stress and obstetric complications on the development of psychotic disorders include Hypothalamic-pituitary-adrenal axis over activation; when maternal stress elevates cortisol, which crosses the placenta and overstimulates fetal glucocorticoid receptors in the hippocampus, amygdala and pre-frontal cortex, impairing neurogenesis and stress-regulation circuits [28]. Moreover, Many OCs produce acute oxygen deprivation that reduces neurotrophic signaling, leading to gray-matter loss, white-matter tract deficits and cortical thinning-findings repeatedly linked to schizophrenia [29].

Urban migration was associated with a three-fold increased risk of psychotic disorders. This aligns with evidence from Swedish population-based studies showing that being born in or residing in urban areas increases schizophrenia risk compared with rural settings, an effect often attributed to heightened social stressors and environmental exposures [30].

The occurrence of psychotic disorders was higher among individuals with a history of migration or travel; however, this association did not reach statistical significance (p = 0.064). In contrast, Stilo and Murray (2019) reported significantly elevated rates of schizophrenia and other psychotic disorders among migrants and refugees, particularly those originating from developing countries. The discrepancy may be partly explained by differences in study populations, as our sample was limited to first-generation migrants and did not include refugees or second-generation migrants. These findings highlight the need for more nuanced research examining migration-related risk across different migrant generations and contexts [31].

In this study, medication adherence was significantly higher among participants who had transitioned from rural to urban areas compared with those who had not relocated. This suggests that moving to urban settings may confer advantages for treatment adherence, potentially through better access to healthcare services, improved social support networks, or increased exposure to adherence-promoting health information. Additionally, adherence was significantly higher among participants whose mothers experienced lower stress during pregnancy, indicating that early-life maternal stress may have a lasting impact on patients' engagement with treatment.

Conclusion and Recommendations

This study highlights several factors associated with psychotic disorders among Syrian adults. Cases were more likely to be single, have experienced maternal stress during pregnancy, undergone rural-to-urban transition, and reported higher obstetric complications compared with controls. Employment was

found to be protective, while parental age, season of birth, and general migration or travel showed no significant association. Medication adherence was higher among participants reporting lower maternal stress exposure during pregnancy and those who had relocated from rural to urban areas. These findings underscore the role of social, prenatal, and environmental factors in the occurrence and management of psychotic disorders in this population.

Based on the findings of this study, several measures are recommended to address psychotic disorders in the Syrian population. Efforts should focus on early identification and intervention, including community awareness programs to reduce stigma and encourage timely help-seeking. Maternal health programs should integrate mental health support and stress reduction strategies during pregnancy, given the association between prenatal maternal stress and psychotic disorders. Additionally, initiatives to improve social functioning and employment opportunities for individuals with psychotic disorders could help mitigate social impairment. Special attention should also be given to populations undergoing rural-to-urban transition, ensuring access to mental health services. Finally, further research with larger, population-based samples is warranted to confirm these findings, explore genetic contributions, and better understand causal pathways.

Study Limitations

This study has several limitations. The case-control design allows for the identification of associations but cannot establish causality, and the retrospective collection of the data may be subject to recall bias, particularly for variables such as maternal stress and obstetric complications. The relatively small sample size may reduce the power to detect associations for less common exposures, and some measures, including medication adherence and Lewis–Murray obstetric complication scores, rely on self-report or proxy reporting, which may introduce measurement bias.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Damascus University, according to the Faculty Council Decision No. 3551 dated 28/08/2022.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Patient and Public Involvement:

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Authors' contributions

NA: conceived and designed the study, drafted the initial manuscript**,** contributed to data collection and ensured data quality,

AA: conducted data analysis, and led the revision process**.**

YL: provided overall supervision of the study design, and offered revisions to the manuscript.

All authors reviewed and approved the final version of the manuscript for submission.

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