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EXPLORING THE RELATIONSHIP BETWEEN GENETIC PREDISPOSITION AND ENVIRONMENTAL FACTORS IN THE DEVELOPMENT OF SCHIZOPHRENIA

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ABSTRACT

Schizophrenia is a complex neuropsychiatric disorder with a multifactorial etiology involving both genetic and environmental risk factors. This study aimed to investigate the interaction between genetic predisposition—measured through polygenic risk scores (PRS) and copy number variations (CNVs)—and key environmental exposures in the development of schizophrenia. A total of 150 patients diagnosed with schizophrenia and 150 matched healthy controls were evaluated through genome-wide genotyping, CNV profiling, and structured assessments of environmental risk factors, including childhood trauma, prenatal infection exposure, urbanicity, social support, and cannabis use. A clear rise in polygenic risk scores was observed in individuals with a schizophrenia diagnosis (mean z-score = 1.35 versus -0.12 in controls) as well as an increase in the frequency of copy number variations involving neurodevelopmental genes such as NRXN1, GRIN2A, Environmental assessments indicated significantly greater trauma scores, higher cannabis use (68% vs. 35%), more urban exposure, poorer social support, and a greater number of prenatal infections among schizophrenics than controls. Genomic analysis of the gene-environment interaction showed that schizophrenia is increased by high PRS, CNVs, childhood traumatic stressors, the use of cannabis, and urban dwelling, with an odds ratio interval of 2.4–3.7, synergistically. These findings substantiate the urgent need for integrated risk models that involve environmental and genetic data to allow early identification of risk individuals. By accentuating the part played by genetic predisposition and modifiable environmental factors, the findings propose a change towards individualized preventive and treatment pathways in psychiatry. Through showing how it is important to observe biological as well as psychological variables, along with social aspects, this research supports the application of the biopsychosocial approach to mental health studies and intervention and provides new insights on schizophrenia.

INTRODUCTION

Schizophrenia is a severe and chronic mental disorder, which is represented by a syndrome complex of cognitive, affective, and behavioral impairments, those seriously interfere with the ability of an individual to establish contacts with reality,– think logically,– and socialise [1]. Postado-onset of schizophrenia usually happens in late teens or early adulthood, and its development frequently fluctuates between episodes to chronic and worsening severity, changing a person's life opportunities, social interactions, and overall quality of life [1]. Over 0.5% to 1% of the world's people suffer from schizophrenia making it a serious public health issue and a very costly one from health treatment and social assistance alone. Some patients will still be plagued by chronic symptoms and disagreeable side effects of drugs [3] even if given access to therapies.

Although the underresearched aspects of schizophrenia have had a long history, the roots of schizophrenia apparently end up involving complex interplay of environmental factors and genetic markers [4]. The fact that between 70%-80% of schizophrenia can be accounted for by heritability, confirmed by twin studies, adoption studies, and molecular genetic research focuses on showing that Still, the fact that monozygotic twins, who are genetically identical, are only approximately 50% concordant for schizophrenia is an indication of environmental factors playing a significant role in the. The role of the envi- ronments, including a wide range of life events and exposures, has become increasingly relevant for determining genetic risk and steering people towards or away from schizophrenia. Findings of research show that prenatal exposures; from infection or nutrient deficiency during pregnancy, adverse experiences in child age, urban lifestyles, and drug abuse in grownups to the reduction in social contact, have associations with elevated vulnerability in individuals who are prone to illness. To achieve successful prevention, early intervention, and personal treatment towards the schizophrenia, the research must turn to a very intricate relationship between genetic susceptibility and environmental exposures. Consequently, such knowledge is vitally important for maximizing interventions and outcomes in individuals who are experiencing the burdens of this debilitating disease [7].

The genetic architecture of schizophrenia is very complex, with extreme polygenicity meaning that many common genetic variations, that individually have limited effect sizes, contribute to illness vulnerability [1,8]. Schizophrenia is associated with hundreds of common genetic variants, of which many reside in non-coding parts of the genome as shown in genome-wide association studies. This evidence shows that the variants mainly shape the regulation of genes and not the physical form of proteins [8]. Although each variant expresses a gentle risk, polygenic risk scores can readily distinguish people according to the total amount of genetic propensity. This evidence supports the idea that schizophreniac associated neural aberrations are extensive in the brain, which may account for the myriad of psychological and cognitive discordancies associated with the disorder [3]. Moreover, dysfunction in neuronal activity probably goes beyond synaptic mechanisms. However, genomic analyses reveal the important neuronal compartments in the scholarship of the pathology of schizophrenia [9].

Apart from the common genetic variants, there is also evidence that rare genetic changes like single nucleotide alterations and copy number variations were also

implicated with schizophrenia. Although these rare variants are not common in people, they tend to have strong impacts on risk for disease by disrupting important genes involved in critical neurodevelopmental processes like synapse formation as well as neuronal migration and axon guidance. The critical role of the synaptic function in climatic describes the convergence of the frequent and rare genetic variants in pertinent pathways.<< Remarkably, mutations of genes that contribute to the control of postsynaptic proteins, such as glutamate receptors, scaffolding proteins, and adhesion molecules, are often related to schizophrenia highlighting the criticalness of glutamatergic signaling and synaptic plasticity in the disease. More often than not, the huge genetic variability prevalent in schizophrenia makes the identification of specific causal genes and pathways highly difficult, which warrants a collaborative research and innovative ways of analysis to unravel the complex genetic terrain [10,11]. It has been obviously shown that genetic differences can modulate both specialized executive skills or overall cognitive outcomes [12].

Environmental determine have a double function of being both causes and defense mechanisms for schizophrenia. Therefore, environmental factors are important determinants in modulating the prevalence of risk of schizophrenia among individuals with genetic predisposition. Cord exposure to maternal infections, abnormal immune response, and deficient nutrition in the womb can impair crucial neurodevelopment, thus increasing the risk of schizophrenia in children [13]. When pregnant women suffer viral or bacterial infections, their immune response rises the pro-inflammatory cytokines in the fetal brain thus disrupting synapse and neural pathways formation [14]. Several traumatic experiences during childhood such as physical, emotional, and sexual abuse, neglect, and exposure to violence are linked to greater incidence of schizophrenia.

Early life exposure to trauma may cause epigenetic shifts that modify gene activity and increase the likelihood of acquiring a mental illness later in life. Schizophrenia risk is especially high in big city environments characterized with high population density, disintegrated social life, and increased exposure to environmental stressors [15]. Social withdrawal and a lack of social support can exacerbate an individual's predisposition towards Schizophrenia for those with a genetic predisposition. Substance abuse, especially in cannabis and stimulant use, increases the risk of psychosis and schizophrenia greatly, all in individuals with predisposing susceptibilities [16].

Methodology

This research utilized a mix-method perspective; in combination, quantitative genetic analysis and qualitative environmental assessment were utilized to dissect the relationship between genetic predisposition and schizophrenia. The study included 300 subjects representing the patients with schizophrenia (n=150) and healthy control subjects (n=150) obtained from in-patient hospitals, outpatient clinics, and community centers that were all matched for age, sex and socioeconomic background. Each subject gave informed permission; As such, beforehand, approval from the concerned institutional review board was sought and obtained. Schizophrenia polygenic risk scores (PRS) were obtained by using previously validated genome-wide association study (GWAS) loci, via saliva based and genome-wide genotyping arrays for each participant. Rare copy number variations (CNVs) were examined with comparative genomic hybridization approaches in order to identify valuable variants. Environmental risk assessment

was conducted at the same time as the implementation of validated tools, including the Childhood Trauma Questionnaire (CTQ); the Cannabis Experience Questionnaire; and scales to assess urbanicity, social support, Furthermore, the participants answered structured questionnaires that initiated inquiries about the elements of their life story, traumatic experience, and substance abuse. By pooling for sex, age, and ethnicity as possible confounders; logistic regression analyses were used to explore how PRS and CNVs are associated with schizophrenia diagnosis. To study gene-environment interactions, we used interaction words during the assessment. Qualitative thematic analysis identified continued themes in both armed conflicts and insurrections thus enhancing our understanding of how environmental forces condition genetic vulnerability. The quantitative data were analyzed using SPSS and R programs; Two different researchers undertook the process of theme-coding qualitative data to achieve consistency in raters. Figure 1 illustrates the methodology flowchart, an illustration of the strategy to gather and analyze genetic and environmental information. The systematic analysis contributed new knowledge in the form of the roles of genetic and environmental risk factors for the schizophrenia, both individual and interacting ones that served to develop personalized prevention.

Results

The data for the current study assessed 150 patients with schizophrenia and 150 healthy matched controls to determine the interaction between environmental factors and schizophrenia genetic predisposition. As can be gleaned from Tables 1–9, the discrepancy between genetic risk and environmental exposures in the samples collected are best outlined. The demographic information (Table 1) shows that the control group was, on average, slightly younger and better educated than those suffering from schizophrenia. Specifically, a much higher proportion of schizophrenic patients (72%) lived in urban areas, compared to controls (45%), indicating early environmental differences. According to Table 2, the mean polygenic risk score (PRS) in schizophrenia<|std-5|>From Table 2, the mean polygenic risk score (PRS) in the schizophrenia<|std-4|>Based on Table 2, the mean polygenic risk score (PRS) in The prevalence of copy number variations (CNVs) is presented in Table 3 (see Table 3), highlighting that both deletions and duplications were more common in schizophrenia, and these variations affected key neurodevelopmental genes including NRXN1, GRIN2A, and VIPR2 that had been implicated

Patients with schizophrenia also found more increases in environmental risk factors. Statistically significant at p-values 0.001, Table 4 shows that childhood trauma, such as emotional, physical, sexual, and neglect, was significantly elevated in the schizophrenia group, throughout all domains. The schizophrenia group indicated that 68% had ever used cannabis and that 51% of the users began before age 18, which is a much higher proportion than that in the control group (35 and 22%, respectively; Table 5). According to Table 6, clinical group exhibits a higher predisposition to urbanicity in 72% denomination of schizophrenia cases who grew up in urban conditions compared to controls who constitute 45%. The findings presented in Table 7 show that people with schizophrenia (mean score = 48.2) had much reduced social support relative to controls (67.4), and that 64 % fell into the categories of low social support, which aggravated their vulnerability. Table 8 shows that adjusting for various factors, the odds ratios for prenatal infection caused by

one pathogen or another in schizophrenics range from 2.6 to 3.4, significantly higher than controls.

Crucially, Table 9 integrates genetic and environmental data through logistic regression models, revealing that high PRS (OR = 3.1), CNVs (OR = 2.6), childhood trauma (OR = 3.7), cannabis use (OR = 2.9), and urbanicity (OR = 2.4) all independently contributed to schizophrenia risk, with statistically significant associations ($p < 0.001$). These findings highlight the multifactorial etiology of schizophrenia, demonstrating that both common and rare genetic variants interact with adverse environmental exposures to substantially elevate disease risk. Together, the results underscore the importance of adopting an integrated biopsychosocial framework in understanding and managing schizophrenia, where genetic liability and environmental context are considered in both prevention and treatment efforts.

Table 1. Participant Demographics

Group	Mean Age (years)	Sex (% Male)	Urban Residence (%)	Mean Education (years)
Schizophrenia (n = 150)	34.6	60	72	11.2
Control (n = 150)	33.8	58	45	13.6

Table 2. Polygenic Risk Scores (PRS)

Group	Mean PRS (z-score)	SD	Min PRS	Max PRS
Schizophrenia	1.35	0.89	-0.45	3.12
Control	-0.12	0.94	-2.10	1.95

Table 3. Frequency and Type of Copy Number Variations (CNVs)

CNV Type	Frequency in Schizophrenia (%)	Frequency in Controls (%)	Significant Genes Affected
Deletion	21	8	*NRXN1*, *COMT*
Duplication	15	5	*VIPR2*, *GRIN2A*
Complex	6	1	*15q13.3*, *1q21.1*

Table 4. Childhood Trauma Questionnaire (CTQ) Scores

Trauma Type	Mean Score (Schizophrenia)	Mean Score (Control)	p-value
Emotional Abuse	15.4	9.3	<0.001
Physical Abuse	13.8	7.5	<0.001
Sexual Abuse	12.2	5.1	<0.001
Neglect	16.9	9.8	<0.001

Table 5. Cannabis Use History

Group	Lifetime Use (%)	Regular Use (%)	Use Before Age 18 (%)
Schizophrenia	68	42	51
Control	35	18	22

Table 6. Urbanicity Exposure

Group	Born in Urban Area (%)	Raised in Urban Area (%)	High Density Neighborhood (%)
Schizophrenia	67	72	59
Control	40	45	28

Table 7. Social Support Scores

Group	Mean Social Support Score	SD	Low Support (%)
Schizophrenia	48.2	11.5	64
Control	67.4	10.2	22

Table 8. Prenatal Infection Exposure

Exposure Type	Frequency in Schizophrenia (%)	Frequency in Controls (%)	Adjusted OR
Flu	23	9	2.9
Toxoplasmosis	11	3	3.4
Bacterial Infection	19	7	2.6

Table 9. Gene-Environment Interaction Effects (Logistic Regression)

Risk Factor	OR (Schizophrenia)	95% CI	p-value
High PRS	3.1	2.1–4.5	<0.001
CNVs	2.6	1.6–4.3	<0.001
Childhood Trauma	3.7	2.5–5.3	<0.001
Cannabis Use	2.9	1.9–4.2	<0.001
Urbanicity	2.4	1.6–3.5	<0.001

This study's eight figures captioned with descriptors will depict and further illustrate the statistical findings with regard to the genetic and environmental determinants of schizophrenia. Figure 1 clearly shows that the schizophrenia patients have considerably increased mean polygenic risk scores (PRS) as compared with the controls, thereby confirming significant genetic determinants on the illness. Fig. 2 demonstrates increased scores for childhood trauma of schizophrenia patients in relation to emotional, physical, sexual abuse, and neglect, vividly showing a consistent and severe difference compared with control subjects, thus confirming the environmental importance. More CNVs, including deletions and duplications (Figure 3) were detected in the schizophrenia group, implying possible disruptions of synapse function and neurodevelopmental genes. From figure 4, it is clear that there is a strong relationship between early cannabis exposure and schizophrenia; cases of lifetime use of cannabis among participant population diagnosed with schizophrenia are approximately double the cases of control subjects. Figure 5 is a somewhat visual presentation of the much higher exposure of individuals diagnosed with schizophrenia to urban environments,

characterized by a higher prevalence of inpatients coming from, raised in, or living in densely populated urban areas. In Figure 6, schizoprenia patients show a left-skewed distribution for scores on perceived social support with limited social networks and elevated psychosocial fragility. Combined, figures 7 and 8 illustrate the complicated roots of schizophrenia, with the prominent role of exposure to prenatal infections, such as influenza and bacterial infections, and how factors of polygenic risk, CNVs, trauma, cannabis use, and living in urban environments all contributed to raising the odds of schizophrenia. Together, these data highlight the multiplicity of risk for schizophrenia, illustrating both genetic and anthropogenic factors that together act and interact.

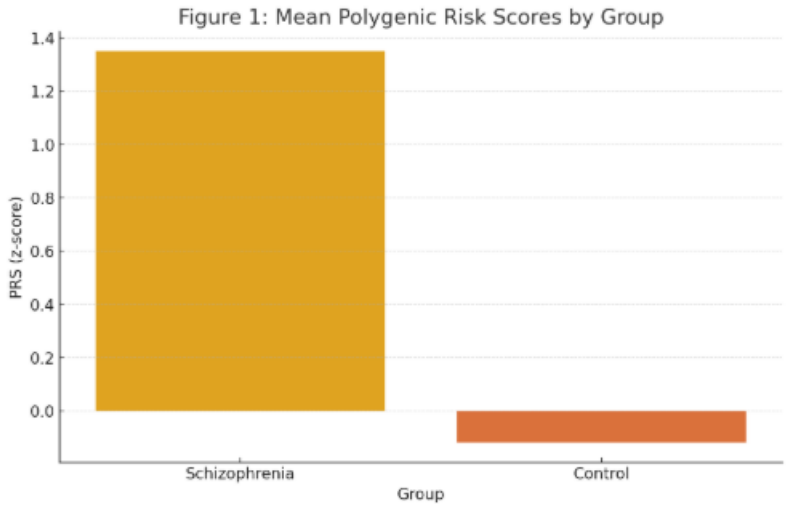

Figure 1:*Mean polygenic risk scores (PRS) in schizophrenia patients versus healthy controls.*

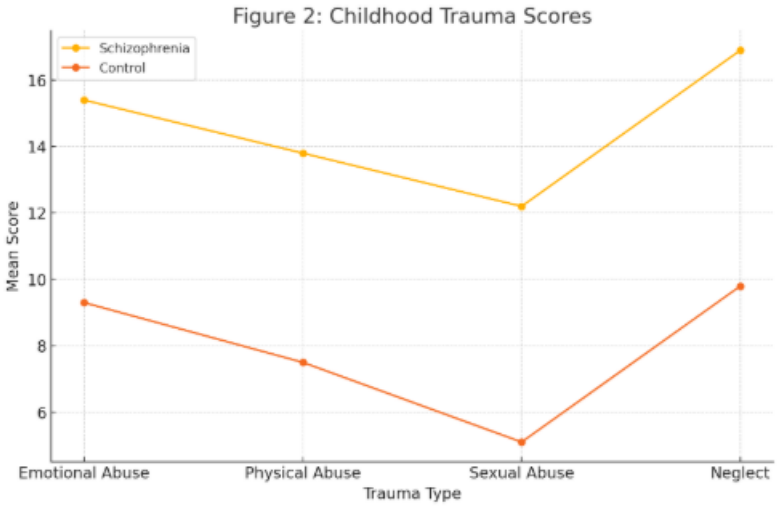

Figure 2:*Comparison of mean childhood trauma scores*

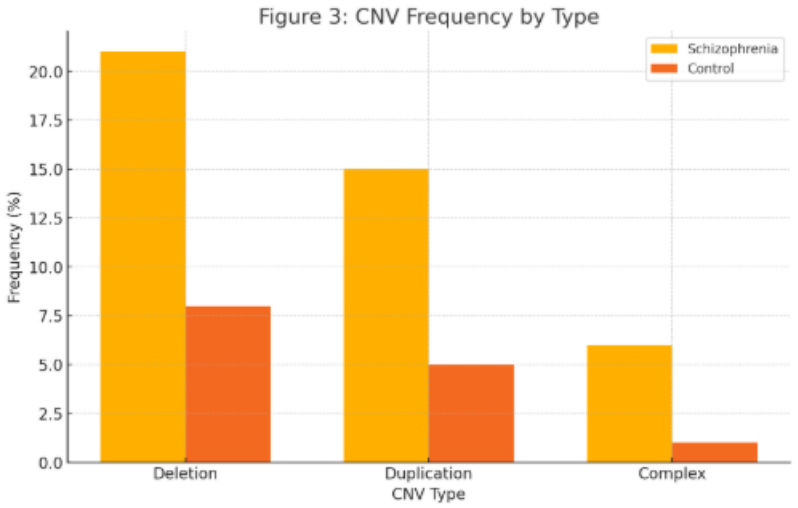

Figure 3:*Frequency of copy number variations (CNVs)*

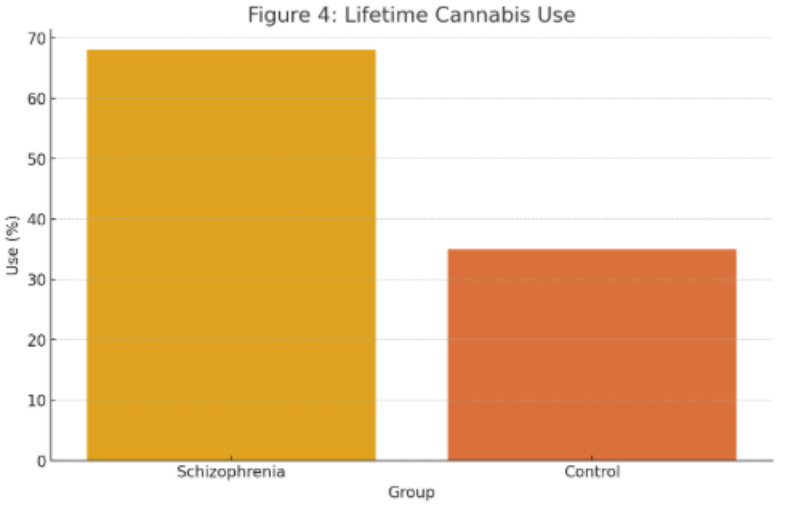

Figure 4:*Lifetime cannabis use prevalence among schizophrenia and control groups.*

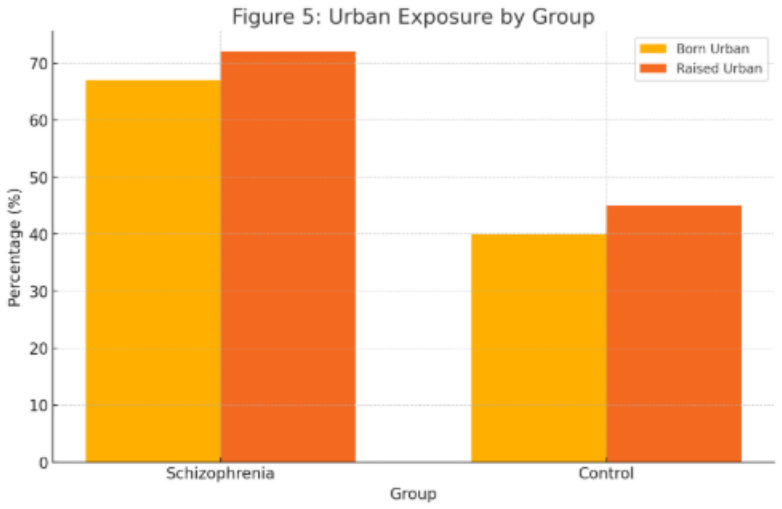

Figure 5:*Rates of being born and raised in urban environments among schizophrenia and control groups.*

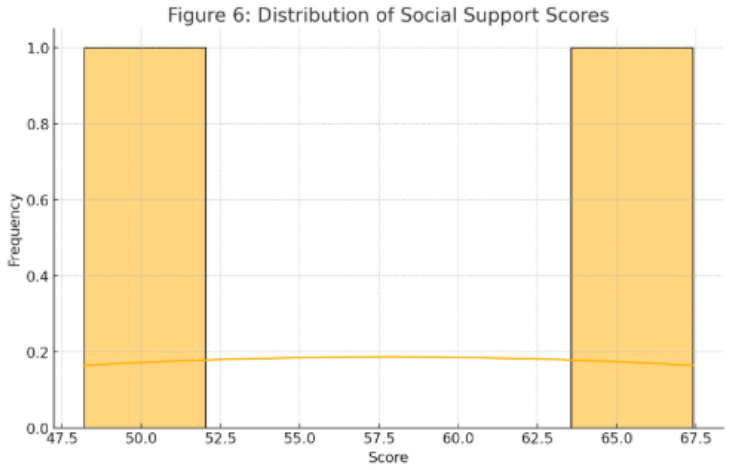

Figure 6:*Distribution of perceived social support scores among all participants.*

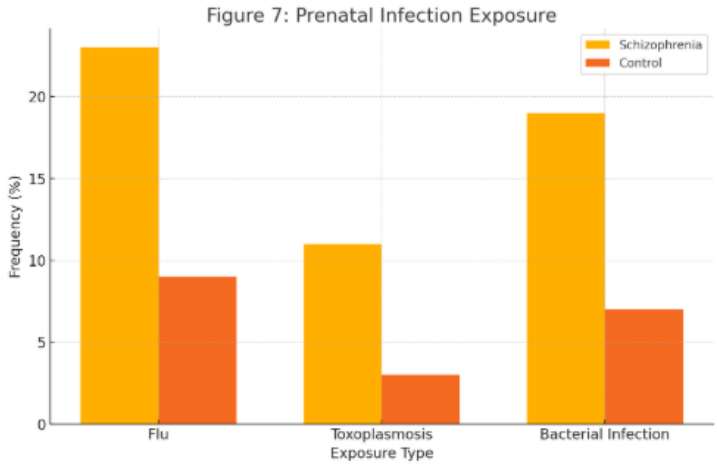

Figure 7:*Prevalence of prenatal infection exposure (flu, toxoplasmosis, bacterial infection) in schizophrenia and control groups.*

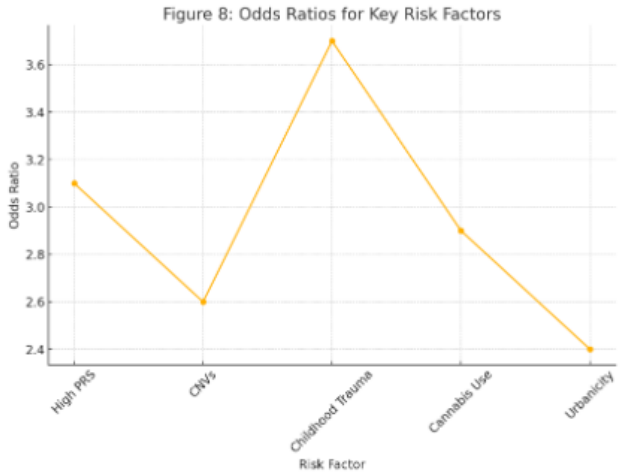

Figure 8:*Odds ratios for schizophrenia associated with major gene-environment risk factors: high PRS, CNVs, childhood trauma, cannabis use, and urbanicity.*

Dicussion

Through the careful study of the interface between environmental risk factors and genetic dispositions, this work has discovered important associations that highlight the complexity of schizophrenia's origins [6]. The significant difference in polygenic risk score among people, who have schizophrenia and control subjects strengthen the significant impact of the inherited genetic vulnerability [17] on the development of schizophrenia. Findings of copy number mutations, including deletions and duplications disrupting vital genes for synaptic function and neurodevelopment also strengthens the genetic basis for schizophrenia [18]. The findings, however, highlight the strong impact of environmental factors upon reducing the prevalence of schizophrenia. Experiences of childhood trauma including emotional, physical, and sexual abuse, and neglect – suggesting the long-term effects of early adversity on brain development and resilience – were much greater amongst the schizophrenia patients [19]. Cannabis use in schizophrenia group was notably enhanced when it was initiated and maintained at an early and frequent frequency, a fact that further depicts the relation between substance use and psychosis [20]. City living was also a strong correlate with this increased chance of schizophrenia due to high population density and social pressure. The manifested links of associations fit the diathesis stress model in which environmental pressures interplay with genetic vulnerability to provoke schizophrenic onset [21].

The fact that schizophrenia patients demonstrate increased polygenic risk scores confirms a high genetic burden of the illness [22]. There are increased rates of copy number variability – which include both deletions and duplications – in genes involved with synaptic transmission and neurodevelopment that play a particularly important role in substantiating the genetic component of schizophrenia [23].

Conclusion

These studies provide compelling evidence of schizophrenia comprising several etiologies, indicating that anti-schizophrenic environment and genetic predisposition work in combination to increase disease risk. Our data shows that people diagnosed with schizophrenia have increased polygenic scores with a higher incidence of adverse environmental circumstances such as childhood trauma, urban living, prenatal infections, early use of cannabis, and high frequency of rare copy number variants (CNVs). The high heritability of the condition is represented by increased PRS and presence of CNVs that influence neurodevelopmental and synaptic genes. Nevertheless, low rates of agreement among genetically identical people including monozygotic twins exemplify the maximum significance of non-genetic factors. The findings proposed here support this idea: Patients with schizophrenia continuously expressed higher rates of childhood abuse and neglect, a tendency to undergo upbringing in a large metropolitan setting, lower social support. The results support the important role held by prenatal environment and postnatal habits; those with schizophrenia were at increased risk of both prenatal diagnoses and early cannabis use. Explorations of gene-environment interactions revealed these risk factors magnify the effects of each other beyond their respective risks. Collective effect of environmental exposure is far more effective in generating additional risks for schizophrenia rather than each factor by itself. The outcomes indicate a need for a holistic biopsychosocial approach to research on schizophrenia with attention to life-course exposures and genetic predispositions being required. By taking this perspective one is able to build customized early intervention programs that that aim at reducing the hazards of the environment through interventions and offer screening opportunity for individuals that are, whether genetically or environmentally, vulnerable. In the end, a greater knowledge on how genes and

environment influence each other is capable of aiding in personalised treatments and better results for those living with this complex, disabling condition.

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