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ORIGINAL ARTICLE

# Risk factors of deficit and non-deficit schizophrenia: Results from a cross-sectional study

**Agnieszka Cyran**[a], **Patryk Piotrowski**[a], **Jerzy Samochowiec**[b], **Tomasz Grąźlewski**[b], **Błażej Misiak**[b,*]

[a] *Department of Psychiatry, Division of Consultation Psychiatry and Neuroscience, Wroclaw Medical University, Wroclaw, Poland*
[b] *Department of Psychiatry, Pomeranian Medical University, Szczecin, Poland*

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**KEYWORDS**
Negative symptoms;
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**Abstract**
*Aim:* It has been observed that deficit and non-deficit schizophrenia (SCZ-D and SCZ-ND) might be characterized by different risk factors. Therefore, the present study aimed to assess as to whether previously reported risk factors of schizophrenia are specifically associated with SCZ-D and SCZ-ND.
*Method:* This study was based on a cohort of 118 stable outpatients with schizophrenia. A diagnosis of SCZ-D was established using the Schedule for the Deficit Syndrome (SDS). Risk factors were recorded using structured interview, the Operational Criteria for Psychotic Illness (OPCRIT) checklist and the Traumatic Experience Checklist (TEC). The following risk factors were explored: male sex, a history of schizophrenia in first-degree relatives, seasonality of birth, birth weight <3000 g, delivery by cesarean section, a history of childhood trauma (emotional abuse, emotional neglect, physical abuse and sexual abuse) as well as substance abuse (other than nicotine) and cigarette smoking at psychosis onset.
*Results:* Individuals with SCZ-D were more likely to be males as well as reported higher rates of birth weight <3000 g and any categories of childhood trauma. In turn, substance abuse (other than nicotine) at psychosis onset was significantly more frequent in patients with SCZ-ND. Binary logistic regression, controlling for multiple comparisons, revealed similar findings, except for the association with any categories of childhood trauma that appeared to be not significant.
*Conclusion:* Our findings partially replicate differential patterns of risk factors for SCZ-D (male sex and birth weight <3000 g) and SCZ-ND (substance abuse at psychosis onset), likely attributable to the effects of timing of exposure.
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* Corresponding author.
*E-mail address:* blazej.misiak@umw.edu.pl (B. Misiak).

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**PALABRAS CLAVE**
Síntomas negativos;
Complicaciones obstétricas;
Diferencias sexuales;
Consumo de sustancias;
Maltrato infantil

**Factores de riesgo para la esquizofrenia deficitaria y no deficitaria: resultados de un estudio transversal**

**Resumen**
*Objetivo:* Se ha observado que la esquizofrenia deficitaria y no deficitaria (ES-D y ES-ND) pueden caracterizarse por diferentes factores de riesgo. El presente estudio tuvo como objetivo evaluar si los factores de riesgo de esquizofrenia previamente informados están específicamente asociados con ES-D y ES-ND.
*Método:* Este estudio se basó en una cohorte de 118 pacientes ambulatorios. Se estableció el diagnóstico de ES-D mediante el Inventario para la Esquizofrenia Deficitaria. Los factores de riesgo se registraron mediante entrevista estructurada, la lista de verificación de Criterios Operativos para Enfermedades Psicóticas y la Lista de Verificación de Experiencia Traumática. Se exploraron los siguientes factores de riesgo: sexo masculino, antecedentes de esquizofrenia en familiares de primer grado, estacionalidad del nacimiento, peso al nacer <3.000 g, parto por cesárea, antecedentes de trauma infantil, así como el abuso de sustancias (aparte de la nicotina) y el tabaquismo al inicio de la psicosis.
*Resultados:* Las personas con ES-D tenían más probabilidades de ser varones y también informaron de tasas más altas de peso al nacer <3.000 g y cualquier categoría de trauma infantil. A su vez, el abuso de sustancias (diferentes a la nicotina) al inicio de la psicosis fue significativamente más frecuente en pacientes con ES-ND. La regresión logística binaria, controlando comparaciones múltiples, reveló hallazgos similares, excepto por la asociación con cualquier categoría de trauma infantil que pareció no ser significativa.
*Conclusión:* Nuestros resultados replican parcialmente los patrones diferenciales de los factores de riesgo para ES-D (sexo masculino y peso al nacer <3.000 g) y ES-ND (abuso de sustancias al inicio de la psicosis), probablemente atribuibles a los efectos del momento de la exposición.
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## Introduction

Schizophrenia is a neurodevelopmental disorder with relatively stable prevalence estimated at about 0.5% of the general population.[1] There is now a general consensus that schizophrenia is characterized by high clinical heterogeneity in terms of symptomatic manifestation and outcomes. Therefore, there are ongoing efforts that aim to dissect clinical subtypes of schizophrenia in order to develop personalized treatment approaches. In agreement with these considerations, Carpenter et al.[2] proposed to differentiate the deficit subtype of schizophrenia (SCZ-D) characterized primary and enduring negative symptoms. Subsequent studies have demonstrated that nearly one-third of individuals with schizophrenia might meet the criteria of SCZ-D.[3] Compared to individuals with non-deficit schizophrenia (SCZ-ND), those with SCZ-D tend to show poor premorbid social functioning, worse cognitive functioning, greater neurostructural abnormalities as well as poor clinical and functional outcomes.[4–6]

To date, several factors have been found to increase a risk of schizophrenia. These include, i.e., familial liability,[7] prenatal and perinatal complications,[8] winter and spring season of birth,[9] a history of childhood maltreatment[10] and substance use (including nicotine).[11–13] There are studies showing that some of them, including familial liability, obstetric complications and winter–spring season of birth might be more closely related to a risk of SCZ-D than that of SCZ-ND.[6] Moreover, there is evidence supported by meta-analysis that male sex is associated with a risk of SCZ-D.[14] Less is known about differential contribution of childhood adverse experiences and substance abuse to a risk of SCZ-D and SCZ-ND. On the basis of a meta-analysis, Alameda et al.[15] showed that most forms of childhood abuse are associated with greater severity of symptoms across all dimensions of psychopathology in psychosis. However, a history of childhood neglect might be more specifically associated with negative and depressive symptoms. A history of childhood trauma has also been associated with a lack of positive and negative symptoms remission in patients with first-episode psychosis.[16] As similar to a history of childhood trauma, none of previous studies investigated the association of substance use with a risk of SCZ-D and SCZ-ND. There is evidence from longitudinal studies that persistent cannabis use in patients with first-episode psychosis might be associated with greater severity of negative symptoms.[17] Moreover, Krishnadas et al.[18] found that individuals with schizophrenia and severe nicotine dependence show greater severity of negative symptoms, and thus require higher dosage of antipsychotics.

Following these observations, Alabaf et al.[19] hypothesized that timing of known risk factors of schizophrenia might underlie their differential impact on the development of SCZ-D and SCZ-ND. The authors tested the association of known risk factors, including family history of psychosis, advanced paternal age, male gender, birth weight <3000 g, summer birth, cannabis use, exposure to physical or sexual abuse and/or bullying in childhood as well as crime-related

traumatic events with SCZ-D and SCZ-ND. They found that exposures acting in later life (cannabis use and a history of childhood physical or sexual abuse) are more closely related to a risk of SCZ-D than that of SCZ-ND. In this regard, we aimed to replicate these findings and test differential associations of SCZ-D and SCZ-ND with other risk factors of psychosis, including delivery by cesarean section, a history of other childhood adverse experiences (emotional abuse and neglect) and cigarette smoking at psychosis onset.

## Material and methods

### Participants

A total of 118 patients with schizophrenia were recruited from outpatients at two university clinics in Wroclaw and Szczecin (Poland). The following inclusion criteria were used: (1) age between 18 and 65 years; (2) a diagnosis of schizophrenia according to the DSM-IV criteria confirmed using the Operational Criteria for Psychotic Illness (OPCRIT) checklist[20]; (3) maintenance of a stable antipsychotic regimen over the period of at least 6 months and (4) symptomatic remission of positive and disorganization symptoms based on the Positive and Negative Syndrome Scale (PANSS)[21] items (P1 – delusions, P2 – conceptual disorganization, P3 – hallucinatory behavior, G5 – mannerisms/posturing and G9 – unusual thought content rated $\leq$3).[22] The study received approval of the Ethics Committees at Wroclaw Medical University (Wroclaw, Poland) and Pomeranian Medical University (Szczecin, Poland). All patients provided written informed consent for participation.

### Clinical manifestation

After assessment of inclusion criteria, the following clinical measures were used: (1) the Schedule for the Deficit Syndrome (SDS)[23]; (2) the PANSS[21]; (3) the Calgary Depression Scale for Schizophrenia (CDSS)[24]; (4) the Social and Occupational Functioning Assessment Scale[25] and (5) the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[26] For the purpose of this study, we excluded the analysis of two items from the PANSS (N5 – difficulty in abstract thinking and N7 – stereotyped thinking) as it has been shown that they do not measure negative symptoms.[27] Due to the fact that the sample was based on remitted individuals with schizophrenia, we did not analyze between-group differences in the levels of positive symptoms and general psychopathology.

The SDS is a semi-structured interview developed by Kirkpatrick et al.[23] to diagnose SCZ-D. Based on the SDS, a diagnosis of SCZ-D can be established in the presence of at least two negative symptoms characterized by: (1) primary character (i.e., negative symptoms that cannot be attributed to extrapyramidal side effects, depression, anxiety or psychotic withdrawal); (2) enduring presence (observed in the preceding 12 months, including periods of clinical stability) and (3) at least moderate severity (rated on a 5-point scale: 0 – not present, 2 – moderate and 4 – very severe).

The RBANS includes 12 tasks that assess the following domains of cognitive functioning: (1) immediate memory (list learning and story memory); (2) visuospatial/constructional abilities (figure copy and line orientation); (3) language (picture naming and semantic fluency); (4) attention (digit span and coding) and (5) delayed memory (list recall, list recognition, story memory and figure recall). Higher total score obtained from all tasks indicates better performance of global cognition.

### Assessment of risk factors

Information on date of birth, birth weight, delivery by cesarean section, family history of schizophrenia in first-degree relatives, cigarette smoking (current status and age of onset) was collected through structured interviews with patients and their family members. As similar to the study by Alabaf et al.,[19] a wider definition of summer birth (May – August)[28] was used due to lower statistical power anticipated in the present study. The relationship with summer birth was tested due to the fact that this season of birth has been associated with a risk of SCZ-D.[29] Similarly, due to lower statistical power expected in this study, we investigated the association with birth weight <3000 g, instead of low birth weight commonly defined as birth weight <2500 g. The OPRCIT checklist (item 12: ''Alcohol/drug abuse within one year of onset of psychotic symptoms'') was used to record substance abuse at the onset of psychosis.

The Traumatic Experience Checklist (TEC) was administered to record a history of childhood trauma. The TEC is a 29-item self-report that collects information about a variety of stressful experiences.[30] Each item records the presence of specific experiences, age at exposure and subjective impact. In the present study, we analyzed items recording the presence of emotional abuse, emotional neglect, physical abuse as well as sexual harassment and abuse appearing below the age of 18 years.

### Statistics

Between-group differences in categorical variables were assessed using the $\chi^2$ test. Normality of data distribution was checked using the Kolmogorov–Smirnov. Both groups of participants were compared with respect to continuous variables using t-tests (normal distribution) or the Mann–Whitney *U* test. Univariate analyses were performed to calculate observed statistical power. The power of at least 0.80 was considered satisfactory. Binary logistic regression was carried out to control for multiple comparisons. Results of data analyses were interpreted as significant if the *p*-value was lower than 0.05. All analyses were carried using the SPSS software, version 28.

## Results

General characteristics of the sample are presented in Table 1. A total of 44 individuals (37.2%) met the criteria of SCZ-D. Individuals with SCZ-D were significantly more likely to be males. As expected, they had significantly higher severity of negative symptoms. Individuals with SCZ-D had

**Table 1** General characteristics of the sample.

| | Whole sample ($n = 118$) | Deficit schizophrenia ($n = 44$) | Missing | Non-deficit schizophrenia ($n = 74$) | Missing | $p$ |
|---|---|---|---|---|---|---|
| Age | 44.4 ± 12.6 | 45.4 ± 14.2 | 0 | 43.8 ± 11.6 | 0 | 0.781 |
| Male sex | 72 (61.0) | 35 (79.5) | 0 | 37 (50.0) | 0 | **0.001** |
| Age of psychosis onset | 25.0 ± 7.3 | 24.5 ± 6.2 | 0 | 25.3 ± 7.9 | 3 | 0.657 |
| Acute onset of psychosis (definable within 1 month) | 50 (42.4%) | 20 (45.4) | 0 | 30 (40.5) | 0 | 0.601 |
| Employment or education at psychosis onset | 101 (85.6) | 37 (84.1) | 0 | 64 86.5) | 0 | 0.720 |
| Education, years | 13.7 ± 3.5 | 12.8 ± 3.2 | 1 | 14.2 ± 3.5 | 2 | **0.033** |
| Cigarette smoking | 54 (45.8) | 18 (40.9%) | 0 | 36 (48.6%) | 0 | 0.414 |
| BMI, kg/m$^2$ | 28.7 ± 5.8 | 29.0 ± 5.3 | 0 | 28.6 ± 6.1 | 0 | 0.535 |
| CPZeq | 584.1 355.8 | 659.7 ± 383.8 | 0 | 537.2 ± 331.4 | 3 | 0.083 |
| Antidepressants | 15 (12.7) | 4 (9.1) | 0 | 11 (14.9) | 0 | 0.363 |
| Mood stabilizers | 11 (9.3) | 1 (2.3) | 0 | 10 (13.5) | 0 | **0.042** |
| PANSS-N | 12.0 ± 6.4 | 17.5 ± 5.5 | 0 | 8.7 ± 4.3 | 0 | **<0.001** |
| CDSS | 1.6 ± 2.9 | 2.1 ± 3.3 | 0 | 1.3 ± 2.6 | 0 | 0.244 |
| RBANS, global cognition | 179.8 ± 38.5 | 166.1 ± 36.9 | 0 | 188.0 ± 37.4 | 0 | **0.002** |
| SOFAS | 59.6 ± 20.6 | 45.0 ± 12.3 | 0 | 68.2 ± 19.6 | 0 | **<0.001** |

Data expressed as $n$ (%) or mean ± SD.
Significant differences ($p < 0.05$) were marked in bold.
Abbreviations: BMI, body mass index; CDSS, the Calgary Depression Scale for Schizophrenia; CPZeq, chlorpromazine equivalent dosage; PANSS-N, the Positive and Negative Syndrome Scale (subscore of negative symptoms); RBANS, the Repeatable Battery for the Assessment of Neuropsychological Status; SOFAS, the Social and Occupational Functioning Assessment Scale.

also significantly lower scores of global cognition, social and occupational functioning as well as lower number of education years. The use of mood stabilizers was significantly more frequent in patients with SCZ-ND compared to those with SCZ-D. However, there were no significant between-group differences in the frequency of using antidepressants and the daily dosage of antipsychotics expressed as chlorpromazine equivalents. Moreover, no significant between-group differences were found with respect to age, age of psychosis onset, employment or education status at psychosis onset, current cigarette smoking status and the severity of depressive symptoms.

The distribution of specific risk factors is shown in Table 2. Apart from between-group sex differences, individuals with SCZ-D were significantly more likely to report birth weight <3000 g and any childhood adversities. In turn, substance abuse at psychosis onset was significantly more frequent in participants with SCZ-ND. No significant between-group differences were observed with respect to the frequency of positive family history of schizophrenia in first-degree relatives, summer birth, delivery by cesarean section, specific childhood experiences and cigarette smoking before the onset of psychosis. Observed power was lower than 0.80 in the majority of comparisons (except of sex differences).

Results of binary logistic regression analysis with a diagnosis of SCZ-D as the dependent variable are shown in Table 3. We included a history of any childhood adversities, but not that of specific categories of childhood adversities, to avoid potential multicollinearity. This analysis confirmed that male sex and birth weight <3000 g are associated with higher risk of SCZ-D, while substance abuse at psychosis onset is associated with higher risk of SCZ-ND (Cox & Snell $R^2 = 0.284$, Nagelkerke $R^2 = 0.383$).

## Discussion

Main findings of the present study indicate that male sex and birth weight <3000 g are specifically associated with higher risk of SCZ-D, while substance abuse at psychosis onset might be more closely related to higher risk of SCZ-ND. These findings partially replicate those obtained by Alabaf et al.[19] who showed that cannabis use at psychosis onset and a history of childhood physical or sexual abuse are associated with higher risk of SCZ-ND. Nevertheless, some discrepancies need to be discussed in light of methodological differences that might impact findings from smaller samples. It is important to note that the study by Alabaf et al.[19] was based on patients with schizophrenia receiving clozapine, and thus it is likely that high proportion of patients showed treatment-resistant schizophrenia. There is some evidence that patients with treatment-resistant schizophrenia are more likely to report a history of childhood trauma compared to those who show sufficient treatment response[31,32] Prevalence of childhood trauma in the sample reported by Alabaf et al.[19] was 68.5% (41.0% in our sample). Similarly, there is some evidence that obstetric complications might be associated with worse response to treatment.[33] Prevalence of birth weight <3000 g, which might be associated with obstetric complications, also differed across both samples (28.0% in the study by Alabaf et al.[19] and 14.8% in our sample). Moreover, the study by Alabaf et al.[19] had greater predominance of male participants compared to our sample (78.7% vs. 61.0%).

**Table 2** Risk factors for deficit and non-deficit schizophrenia.

| | Whole sample ($n = 118$) | Deficit schizophrenia ($n = 44$) | Missing | Non-deficit schizophrenia ($n = 74$) | Missing | $p$ | Observed power |
|---|---|---|---|---|---|---|---|
| Male sex | 72 (61.0) | 35 (79.5) | 0 | 37 (50.0) | 0 | **0.001** | 0.910 |
| Family history of schizophrenia (first-degree relatives) | 10 (8.5) | 5 (11.4) | 0 | 5 (6.8) | 0 | 0.385 | 0.154 |
| Summer birth (May–Aug) | 50 (42.4) | 18 (40.9) | 0 | 32 (43.2) | 0 | 0.804 | 0.056 |
| Birth weight <3000 g | 16 (14.8) | 11 (25.6) | 1 | 5 (7.7) | 9 | **0.010** | 0.714 |
| Delivery by cesarean section | 18 (15.8) | 10 (22.7) | 0 | 8 (10.8) | 4 | 0.107 | 0.408 |
| Emotional neglect (<18 years) | 36 (30.8) | 15 (34.8) | 1 | 21 (28.4) | 0 | 0.462 | 0.115 |
| Emotional abuse (<18 years) | 27 (23.1) | 10 (23.2) | 1 | 17 (23.0) | 0 | 0.972 | 0.050 |
| Physical abuse (<18 years) | 31 (26.5) | 14 (32.6) | 1 | 17 (23.0) | 0 | 0.291 | 0.211 |
| Sexual abuse (<18 years) | 11 (9.4) | 3 (7.0) | 1 | 8 (10.8) | 0 | 0.471 | 0.091 |
| Any childhood adversities | 48 (41.0) | 23 (53.5) | 1 | 25 (33.8) | 0 | **0.037** | 0.551 |
| Substance abuse (other than nicotine) at psychosis onset | 37 (31.3) | 8 (18.2) | 0 | 29 (39.2) | 0 | **0.017** | 0.675 |
| Cigarette smoking before psychosis onset | 19 (16.5) | 7 (15.9) | 0 | 12 (16.9) | 3 | 0.889 | 0.051 |

Data expressed as $n$ (%).
Significant differences ($p < 0.05$) were marked in bold.

**Table 3** Results of the binary logistic regression analysis.

| | $B$ | SE | Wald | OR | 95%CI | $p$ |
|---|---|---|---|---|---|---|
| Male sex | 1.837 | 0.550 | 11.135 | 6.277 | 2.134–18.465 | **<0.001** |
| Family history of schizophrenia | 0.811 | 0.834 | 0.948 | 2.251 | 0.439–11.530 | 0.330 |
| Summer birth (May–Aug) | −0.119 | 0.504 | 0.055 | 0.888 | 0.331–2.385 | 0.814 |
| Birth weight <3000 g | 1.553 | 0.685 | 5.150 | 4.728 | 1.236–18.085 | **0.023** |
| Delivery by cesarean section | 1.154 | 0.678 | 2.896 | 3.171 | 0.839–11.980 | 0.089 |
| Any childhood adversities | 0.693 | 0.507 | 1.868 | 2.000 | 0.740–5.405 | 0.172 |
| Substance abuse (other than nicotine) at psychosis onset | −1.734 | 0.596 | 8.456 | 0.177 | 0.055–0.568 | **0.004** |
| Cigarette smoking at psychosis onset | −0.206 | 0.630 | 0.107 | 0.814 | 0.237–2.800 | 0.744 |

Specific risks assessed with respect to a diagnosis of deficit schizophrenia.
Significant differences ($p < 0.05$) were marked in bold.

Nevertheless, both studies indicate that early and late risk factors might be differentially associated with the development of SCZ-D and SCZ-ND and are in line with some previous studies. The predominance of males among individuals with SCZ-D has been documented by meta-analysis, also showing qualitatively stronger evidence for studies based on the use of SDS.[14] This observation points to a number of sex differences reported in patients with schizophrenia. Indeed, male patients have been shown to present earlier age of psychosis onset, worse premorbid functioning and functional outcomes, greater neurostructural alterations, lower levels of depressive symptoms and greater severity of negative symptoms.[34,35] To date, various biological mechanisms have been proposed to explain these observations, including protective effects of estrogens and genetic differences.[35] Our findings also replicate those showing that individuals with SCZ-D have lower severity of current use of alcohol and other substances compared to those with SCZ-ND.[36] Indeed, a higher severity of negative symptoms may make individuals with SCZ-D less likely to engage in risky behaviors and substance use.[19] In turn, the association of low birth weight with a risk of schizophrenia has been well-documented.[37–39]

However, the association of low birth weight with SCZ-D and SCZ-ND has not been widely investigated.

There are certain limitations of this study that need to be considered. First, our sample size was relatively low and power calculations indicate the possibility of type II error. Second, we did not record the initial number of patients approached for participation and reasons of non-participation. Therefore, representativeness of the sample cannot be evaluated. Another point is that we used self-reports and retrospective interviews to record risk factors, and thus a recall bias should be taken into consideration. It is also important to note that we were not able to analyze the effects of specific substances being used before the onset of psychosis. Moreover, certain factors, e.g., birth weight <3000 g or delivery by cesarean section do not reflect prenatal and perinatal complications associated with a risk of psychosis. Indeed, only complicated or emergency birth by cesarean section can be perceived as obstetric complication increasing a risk of psychosis.[8,40] Previous studies have shown that birth by cesarean section itself is associated with earlier age of psychosis onset but not a risk of psychosis.[8,41] Moreover, we investigated birth weight <3000 g which does not correspond to the definition of low birth weight (<2500 g) according to the World Health Organization. However, both cut-offs (<2500 g and <3000 g) have been associated with psychosis risk.[37] It cannot also be excluded that adopting other definitions of certain risk factors, e.g., family history of schizophrenia and summer birth would yield different results. Finally, it should be highlighted that a cross-sectional design of the present study does not allow to make causal conclusions.

In summary, the present findings indicate that substance abuse at psychosis onset might be more closely related to a risk of SCZ-ND, while male sex and birth weight <3000 g increase a risk of SCZ-D. However, data obtained in the present study do not allow to conclude which substances of abuse are related to a risk of SCZ-D. Our findings point to the hypothesis that clinical manifestation and outcome of schizophrenia might be related to timing of exposure to risk factors. However, larger studies based on longitudinal observations as well as more comprehensive recording of risk factors and clinical manifestation are needed to confirm our results.

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## Author's contributors

AC, recruitment and clinical assessment of patients, manuscript writing; PP, recruitment and clinical assessment of patients; JS, study design and manuscript writing; TG, recruitment and clinical assessment of patients; BM, study design, data analysis, manuscript writing and editing

## Conflict of interest

None declared.

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