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RESEARCH LETTER

Environmental Factors in the Etiology of Mental Disorders in the Czech Republic: Final Results

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We researched the environmental factors in the etiology of mental disorders in the Czech Republic.

A novel avenue of research assesses the sum of an individual's environmental exposures to create their polyenviromic risk score (PERS). An individual's PERS is calculated as follows: first, the odds ratio for each evidence-based environmental risk factor is obtained based on literature; next, the presence or absence of each environmental risk factor is determined for the participant and the log of the odds ratio for each environmental risk factor is multiplied by either 1 (risk factor is present) or 0 (risk factor is absent); these values are summed and then divided by the total number of risk factors assessed. In this way, environmental risk factors are aggregated. This attitude was created by Padmanabhan et al, and we only adopted this mathematical procedure.[1]

The aim of our study was to investigate the lifetime presence of both environmental risk factors and protective variables in patients with psychosis or a mood disorder (PSYCH+MOOD), compared with patients with an anxiety disorder (ANX). We used this group configuration because the genetic backgrounds of psychoses and mood disorders overlap, but are distinct from anxiety disorders. We tested the main hypothesis that the PERS and polyenviromic protective score differ between the PSYCH +MOOD and ANX groups. This hypothesis is based on the presumption that heritability is higher in psychoses and mood disorders compared with anxiety disorders.

Our preliminary results which included 94 patients with psychosis or a mood disorder and 52 with anxiety disorder, were published in Neuropsychiatric Disease and Treatment.[2] Neither the polyenviromic risk score nor the polyenviromic protective score differed significantly between the PSYCH+MOOD and ANX groups ($p = 0.149$ and $p = 0.466$, respectively).

Additionally, we accumulated more research data to increase the validity of our results. We used the same methods to assess participants who were either hospitalized or treated at the outpatient office of the Department of Psychiatry, University Hospital at Hradec Kralove or Olomouc, Czech Republic. We maintained the same inclusion and exclusion criteria. We now present the final data of our study below:

Both the PSYCH+MOOD and ANX groups included 200 participants each. Their demographic and clinical characteristics are summarized in Table 1.

The diagnostic stratification for the PSYCH+MOOD group was as follows: a single episode of major depression (n = 56), schizophrenia (n = 54), recurrent major depressive disorder (n = 36), bipolar disorder (n = 28), brief psychotic disorder (n = 18) and delusional disorder (n = 8). For the ANX group, the diagnostic classification was as follows: generalized anxiety disorder (n = 102), acute stress reaction (n = 43), panic disorder (n = 22), neurasthenia (n = 13), somatization disorder (n = 8), agoraphobia (n = 6), post-traumatic stress disorder (n = 3), social phobia (n = 2) and undifferentiated somatoform disorder (n = 1). Psychiatric comorbidity was found in 36 patients in the PSYCH+MOOD group (all of them had personality disorders) and in 51 in the ANX group (33 with another anxiety disorder and 18 with

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Table 1 Demographic and Clinical Characteristics

Variable	PSYCH+MOOD Group (n = 200)	ANX Group (n = 200)	Test Values t/chi-square/M-W-U	p value	Test
Age (years)	46.0 ± 14.0 (18–76)	44.0 ± 14.0 (18–79)	18715.5	0.267	Mann–Whitney *U*-test
Sex (M/F ratio)	67/133	54/146	2.002	0.157	Chi-square test
Body mass index (kg/m^2)	27.2 ± 6.0 (15–68) median 26.1	26.0 ± 6.3 (14–61) median 25.0	17410.5	0.037	Mann–Whitney *U*-test
Education			2.16	0.540	Chi-square test
Primary	14 (7.0%)	21 (10.5%)			
Secondary	148 (74.0%)	142 (71.0%)			
Tertiary	38 (19.0%)	37 (18.5%)			
Currently employed	116 (58.0%)	132 (66.0%)	2.52	0.112	Chi-square test
Disability pension	115 (57.5%)	76 (38.0%)	15.653	0.001	Chi-square test
Marital Status			2.894	0.235	Chi-square test
Single	83 (41.5%)	68 (34.0%)			
Married	76 (38.0%)	80 (40.0%)			
Divorced/Widowed	41 (20.5%)	52 (26.0%)			
Currently living with a partner	158 (79.0%)	156 (78.0%)	0.059	0.808	Chi-square test
Childless	71 (35.5%)	55 (27.5%)	2.966	0.085	Chi-square test
Duration of illness (years)	12.6 ± 10.2 (1–44)	8.9 ± 9.6 (1–43)	1797.5	0.008	Mann–Whitney *U*-test
Currently hospitalized	184 (92.0%)	198 (99.0%)	1.694	0.553	Fischer's exact test
Number of previous hospitalizations	3.4 ± 4.4 (0–19)	1.1 ± 1.9 (0–9)	1594.5	0.0003	Mann–Whitney *U*-test
Psychotropic medication				<0.0001 in all four groups	Chi-square test
Antipsychotics	153 (76.5%)	54 (27.0%)	31.699		
Antidepressants	121 (60.5%)	188 (94.0%)	15.766		
Anxiolytics	44 (22.0%)	118 (59.0%)	17.864		
Mood stabilizers	59 (29.5%)	0 (0%)	18.325		

Abbreviations: ANX, anxiety disorder; F, female; M, male; M-W-U, Mann–Whitney *U*-test; PSYCH+MOOD, psychosis or a mood disorder.

personality disorders). We did not enroll participants with PSYCH+MOOD disorders and ANX comorbidity or vice versa into our study. The typically prescribed antipsychotics were olanzapine, quetiapine, risperidone, aripiprazole and clozapine. The most frequently prescribed antidepressants were es/citalopram, sertraline, fluoxetine, venlafaxine, mirtazapine and trazodone. The most frequently prescribed anxiolytics were clonazepam, alprazolam, bromazepam, oxazepam, and pregabalin, and the mood stabilizers prescribed included lithium, valproate and lamotrigine. If antipsychotics were prescribed to patients with ANX, it was typically quetiapine 25–50 mg/day as a sedative.

Among the individual risk factors, we found that obstetric complications less frequently occurred in the PSYCH +MOOD group than in the ANX group (8.5% in the PSYCH+MOOD group vs 16.1% in the ANX group; chi-square =

5.237; p = 0.022; chi-square test). There were no significant between-group differences in any other risk factor or in any of the three protective factors. The polyenviromic risk score (PERS) and the polyenviromic protective score did not significantly differ between the groups (Table 2).

This nonsignificant difference in total environmental risk/protective factors between the PSYCH+MOOD and ANX groups corresponds with our preliminary results and means that the timing of the exposures and the possible combinations of factors should also be evaluated.[2,3]

Several neural substrates mediate the influence of environmental factors on the development of mental disorders. For example, post-traumatic stress disorder is related to abnormal dynamics in the hypothalamus-pituitary-adrenal axis activation. Prefrontal cortex, amygdala and hippocampus are implicated in stress processing, mood regulation and psychosis. In depression, the crosstalk between inflammation, metabolic pathways and neural circuits can affect neural network activity. Moreover, epigenetic modifications regulate gene expression patterns linked to psychiatric phenotypes.[4] Parkinson's disease with changes affecting the whole basal ganglia network, accompanied with cognitive and social functioning alterations is linked to oxidative stress, reduced antioxidant capacity and apoptosis.[5] Oxidative stress and inflammation in the brain can be addressed by lifestyle adjustments.[6] Ginkgo biloba with its bioactive compounds (terpenoids, polyphenols, organic acids, flavonoids) is associated with anti-inflammatory, antioxidant, and neuroprotective properties.[7] Antioxidants are able to improve or stabilize cognitive functions, memory, and Alzheimer's disease. They are also effective in the healthy population to prevent cognitive degeneration. An important intermediary between the nervous and enteric systems is the gut-brain axis.[8] At the genetic level, serotonin and dopamine influenced by their relevant gene polymorphisms (5-HTTLPR in serotonin, COMT in dopamine) have an impact on fear-induced bradycardia expression, related to fear conditioning, important for example in anxiety disorders.[9] These findings are substantial for understanding the biological plausibility of polyenviromic risk scores and their relationship in predicting mental health outcomes.

Other important studies relevant to environmental factors in the etiology of mental disorders were also published. Uzun et al evaluated the relationship between psychopathology and environmental factors in psychiatric diseases by nonrecursive modeling.[10] Based on their research into a study group with 378 participants (the mean age was 37.3; 61.6% were women) using four assessment scales, the International Classification of Diseases ICD-10 and the Clinical Global Impression Scale, the authors came to the conclusion that childhood trauma and age were found as significant variables for self-esteem, childhood trauma for perceived support, and disease severity and diagnosis in individual and social functionality. Baz et al compared early maladaptive schemas in obsessive-compulsive disorder patients (n = 42), their siblings (n = 24), and controls (n = 42) using the Young Schema Questionnaire Short Form-3 and the Yale-Brown Obsession-Compulsion Scale in the patients.[11] The authors found similarities between maladaptive schemas in the obsessive-compulsive disorder patients and their healthy siblings, whilst differences between the siblings and the healthy

Table 2 Polyenviromic Risk Score and Polyenviromic Protective Score

Variable	PSYCH+MOOD group (n = 200)	ANX group (n = 200)	Test values: t/chi-square/M-W-U	p value	Test
Polyenviromic risk score	Mean 0.0520 SD 0.0282 Median 0.0504 Minimum 0.0000 Maximum 0.1390	Mean 0.0546 SD 0.0296 Median 0.0513 Minimum 0.0000 Maximum 0.1466	19127.5	0.45	Mann–Whitney *U*-test
Polyenviromic protective score	Mean −0.0461 SD 0.0168 Median −0.0436 Minimum −0.0688 Maximum 0.0000	Mean −0.0447 SD 0.0157 Median −0.0436 Minimum −0.0621 Maximum 0.0000	18572.5	0.159	Mann–Whitney *U*-test

Abbreviations: ANX, anxiety disorder; M-W-U, Mann–Whitney *U*-test; PSYCH+MOOD, psychosis or a mood disorder; SD, standard deviation.

controls were detected. These results suggest a genetic basis for the early maladaptive schemas in obsessive-compulsive disorder.

Our study has several limitations. First, the cross-sectional design makes it impossible to establish causality, so our results are related more to prediction than to causation.[12] We applied the cross-sectional design because our study was the first attempt to survey the topic. A longitudinal design can be the logical next step to explain causality. Second, the mentally ill participants' assessment of past stressful life events and their significance may have been influenced by recall bias.[13] Third, we only used self-reported data, we did not measure any biological marker of chronic stress like hair and nail cortisol, telomere length or mitochondrial DNA copy number.[14] Fourth, almost all the study participants were hospitalized; therefore, the study groups may not be representative of all patients with the same diagnoses. The study population was subject to a selection bias. No healthy control subjects were analyzed. Fifth, our study only included participants from the Czech Republic, which has a relatively homogenous ethnicity and demographic characteristics; therefore, the results may not be generalizable to other countries where international migration is high. Additionally, we did not examine the genetic and epigenetic characteristics of the study participants. Our results may have been influenced by confounding variables such as socioeconomic factors, which is not addressed in the study. A general problem is that protective environmental factors in mental disorders have been understudied so far, so we did not have the use of them in our research. Their role in the development of intervention strategies may be significant in the future. Nevertheless, the fact that we applied the summarizing and complex concept of assessing environmental risk/protective factors in the etiology of mental disorders is the main advantage of our study.[1] This is similar to the trend in psychiatric genetics, where polygenic risk scores are calculated. Polygenic risk scores may be used to estimate an individual's lifetime genetic risk of disease, but the current discriminative ability is low in the general population. Clinical implementation of polygenic risk score may be useful in cohorts where there is a higher prior probability of disease, for example, in early stages of diseases to assist in diagnosis or to inform treatment choices.[15] As of the PERS, the state of affairs can become analogous in the future.

We conclude that the use of polyenviromic risk/protective scores may be helpful in the prevention and provision of personalized treatment of mental disorders. However, several issues in the methodology need to be resolved.

Ethical Statement

The authors state that all procedures in this study complied with the World Medical Association Declaration of Helsinki. All procedures involving patients were approved by the Ethics Committee of University Hospital in Hradec Kralove (approval number 201903) and the Ethics Committee of University Hospital in Olomouc (approval number 25/19). Written informed consent was obtained from all participants.

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Disclosure

The authors report no conflicts of interest in this work.

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