

Environmental Factors in the Etiology of Mental Disorders in the Czech Republic

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Background: Both genetic and environmental factors are important in etiology of mental disorders. Calculating polyenviromic risk/protective scores provides an updated perspective in research on the environmental causes of psychiatric disorders. We aimed to compare environmental risk and protective factors in patients with psychosis or a mood disorder (PSYCH+MOOD) and those with an anxiety disorder (ANX).

Methods: We administered the internationally accepted questionnaire from the EUropean Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study, enriched with mood and anxiety disorder-relevant measures, to patients at two large university hospitals in the Czech Republic.

Results: Ninety-four PSYCH+MOOD patients (average age 42.5 years; 46 males) and 52 ANX patients (average age 47.2 years; 17 males) participated. Neither polyenviromic risk score nor polyenviromic protective score differed significantly between PSYCH+MOOD and ANX groups ($p = 0.149$; $p = 0.466$, respectively).

Conclusion: Scientific validity of the polyenviromic risk/protective score construct must still be demonstrated in large psychiatric samples, ideally in prospective studies. Nevertheless, researchers have already started to investigate environmental factors in the etiology of mental disorders in their complexity, similarly to polygenic risk scores.

Keywords: anxiety disorders, environmental factors, mood disorders, schizophrenia, stress

Plain Language Summary

- Environmental factors, which may be biological, psychological, societal or spiritual, are important in etiology of mental disorders.
- Assessment of environmental factors may contribute to prevention and treatment of psychiatric disorders.
- A summarizing evaluation of environmental etiological factors using polyenviromic risk/protective scores is an updated approach.
- We examined polyenviromic risk/protective scores in 146 psychotic, mood or anxiety disorder patients hospitalized in two large university hospitals in the Czech Republic.
- Polyenviromic risk/protective scores did not differ significantly between the sample with psychoses/mood disorders versus the group with anxiety disorders.
- Our results emphasize the need for further research of environmental factors in the etiology of mental disorders in their complexity, similarly to polygenic risk scores.

Introduction

The lifetime prevalence of mental disorders is estimated at 12.0–47.4%.¹ A substantial portion of mental disorders are chronic or lifelong, including substance addictions,² schizophrenia,³ bipolar disorder,⁴ recurrent major depression⁵ and obsessive-compulsive disorder.⁶ If we aim at full, lifelong remission, therapeutic outcomes are far from satisfactory. One reason for this

is that we do not understand mental disorders' etiology well, so therapy cannot be causal. In almost all mental disorders, both genetic and environmental etiological factors are needed to induce clinical symptoms.⁷ This is why "exposome" (which is the sum of significant environmental triggers) is studied. A novel avenue of research assesses the sum of an individual's environmental exposures to create their polyenviromic risk score (PERS).⁸ 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.⁸ In this way, environmental risk factors are aggregated. Thus, the PERS is adapted from the formula used to calculate polygenic risk scores.⁹ It is also useful to study mental disorders as cumulative groups, rather than as individual diagnostic entities. This is because etiological factors overlap among disorders, meaning that higher-level, broad categorical constructs may be more appropriate targets of etiological research than specific diagnoses.¹⁰ Furthermore, both environmental risk factors and those that are protective should be assessed.¹¹ The polyenviromic protective score is calculated like the PERS.

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.^{12,13} 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.^{9,14} Schizophrenia, bipolar disorder and major depressive disorder are closely and causally linked; thus, using a broad mental illness category that encompasses major mood and psychotic disorders may be appropriate in research investigations.¹⁰

Materials and Methods

Study Sample

The PSYCH+MOOD group had International Classification of Diseases 10th Revision (ICD-10) F2 or F3 disorder diagnoses. The ANX group had ICD-10 F4 disorder diagnoses.

Participants were either hospitalized or treated at the outpatient office of the Department of Psychiatry, University Hospital at Hradec Kralove or Olomouc, Czech Republic. Their mental condition was stable (ie, without medication changes or clinical state deterioration within the past two weeks). The inclusion criteria were as follows: F2, F3 or F4 ICD-10 diagnosis; no concomitant F0, F1, F5 or F7 ICD-10 diagnosis; age 18–65 years; male or female; and willingness to participate in research. The main rationale for the selection of F2, F3 and F4 diagnostic groups is the fact that they are markedly represented in the adult population of psychiatric patients and the difference in the etiological involvement of environmental risk/protective factors in F2+F3 vs F4 may be striking.¹³ By using the above mentioned inclusion criteria, we strove to minimize the distorting effect of other diagnoses with a different etiology.

Measures

Psychiatric Examination

Each patient's ICD-10 diagnosis was confirmed by a professor of psychiatry (L. H. or K. L.). The diagnoses were based on clinical interviews; the Composite International Diagnostic Interview (CIDI) or the Mini International Neuropsychiatric Interview (MINI) were not applied. The psychiatric assessment included the family (genetic) history, the personal history (somatic diseases, childhood and adolescence, education, occupational history, marital and sexual history, social and economic history, psychoactive substance abuse, hobbies, premorbid personality, legal problems, military service and plans for the future), the history of the present mental disorder and its treatment, and the assessment of the present psychopathology (*status praesens psychicus*) as described in the literature.¹⁵

Stressful Life Events and Other Environmental Factors Questionnaire

We used the internationally accepted questionnaire from the EUropean Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study.¹⁶ This questionnaire covers the individual's entire life, including obstetric complications, childhood adversities and serious stressful events in adulthood. Response options are YES/NO.

We enriched the EU-GEI questionnaire with variables that were not present in the original version, but for which literature-based effect sizes are known (ie, for schizophrenia,¹⁷ mood disorders^{18,19} and anxiety disorders²⁰). To allow between-groups comparisons, we asked every participant about the each variables, even if it was not relevant in some cases.

Environmental risk factors for schizophrenia:

- advanced paternal age (>40 years) at conception (odds ratio 1.47),²¹
- presence of obstetric or perinatal complications (odds ratio 3.66),²²
- whether the participant was born in the winter or spring (odds ratio 1.21),²³
- upbringing in an urban area (odds ratio 1.19),²⁴
- childhood history of physical abuse, sexual abuse or neglect (odds ratio 2.66),²⁵
- death of a parent when the participant was a child (odds ratio 2.70),²⁶
- history of cannabis abuse (odds ratio 1.37),²⁷ and
- being a member of an ethnic minority (odds ratio 1.40).²⁸

Environmental risk factors for mood disorders:

- serious chronic somatic disorder (odds ratio 1.53),²⁹
- traumatic brain injury (odds ratio 2.00),³⁰
- low level of physical activity (odds ratio 1.12),³¹
- obesity (odds ratio 1.40),³²
- alcohol abuse (odds ratio 2.04),¹⁸
- smoking (odds ratio 1.50),³³
- presence of any job-related stress (odds ratio 1.77),³⁴
- serious stressful events in adulthood (odds ratio 2.85),¹⁹
- migration (odds ratio 2.94),³⁵ and
- living a solitary lifestyle (odds ratio 2.90).³⁶

Environmental risk factor for anxiety disorders:

- low level of physical activity (odds ratio 1.12).²⁰

We also asked each participant about all protective environmental factors for which a literature-based effect size is known for our study populations (ie, mood^{37,38} and anxiety³⁹ disorders). We did not inquire about environmental protective factors for schizophrenia because there is no convincing evidence of them.⁴⁰

Environmental protective factors for mood disorders:

- Mediterranean diet (odds ratio 0.84),⁴¹
- sufficient physical activity (odds ratio 0.88),³⁸ and
- good social support (odds ratio 0.74).⁴²

Environmental protective factors for anxiety disorders:

- Mediterranean diet (odds ratio 0.84),⁴³ and
- sufficient physical activity (odds ratio 0.88).²⁰

Statistics

We used SPSS software, version 23 (IBM Corp., Armonk, NY, USA). We compared the two patient groups on continuous measures using the Mann–Whitney *U*-test and two-sample Student's *t*-test. Categorical measures were compared by chi-squared test or Fisher's exact probability test. Chi-square post-hoc tests with Bonferroni correction were used to analyze the difference between the PSYCH+MOOD and ANX groups in the marital status in more detail. Kruskal–Wallis test was used to compare the three patient groups (PSYCH vs MOOD vs ANX) on total PERS and polyenviromic protective score. Distribution normality was tested by the Shapiro–Wilk test. We used the Pearson's correlation coefficient to establish possible intercorrelations between individual environmental risk or protective factors. The Spearman's correlation coefficient was applied to detect a possible association of the polyenviromic risk/protective score with the duration of illness.

The alpha level required for statistical significance was 0.05 in all cases. The polyenviromic risk/protective score was calculated for each participant, as suggested by Padmanabhan.⁸

Results

Demographic and Clinical Data

Ninety-four patients were included in the PSYCH+MOOD group and fifty-two subjects were involved in the ANX group. Their demographic and clinical characteristics are presented in Table 1.

Diagnostic stratification for the PSYCH+MOOD group was: single episode of major depression (*n* = 24), schizophrenia (*n* = 23), bipolar disorder (*n* = 22), recurrent major depressive disorder (*n* = 14), brief psychotic disorder (*n* = 8) and delusional disorder (*n* = 3). For the ANX group: generalized anxiety disorder (*n* = 25), panic disorder (*n* = 11), agoraphobia (*n* = 5), somatization disorder (*n* = 5), neurasthenia (*n* = 3), post-traumatic stress disorder (*n* = 1), acute stress reaction (*n* = 1) and undifferentiated somatoform disorder (*n* = 1). Psychiatric comorbidity was found in 19

Table 1 Demographic and Clinical Characteristics

Variable	PSYCH+MOOD Group (<i>n</i> = 94)	ANX Group (<i>n</i> = 52)	Test Values <i>t</i> /chi-Square/M-W <i>U</i>	<i>p</i> value	Test
Age (years)	42.5 ± 12.9 (18–74)	47.2 ± 13.9 (21–74)	−2.061	0.041	Student's <i>t</i> -test
Gender (M/F ratio)	46/48	17/35	3.601	0.058	Chi-square test
Body mass index (kg/m ²)	28.1 ± 6.8 (17–68) median 26.8	25.5 ± 5.1 (14–43) median 24.8	1710.5	0.007 for median	Mann–Whitney <i>U</i> -test
Education			0.901	0.852	Fischer's exact test
Primary	8 (8.5%)	3 (5.8%)			
Secondary	61 (64.9%)	37 (71.2%)			
University	25 (26.6%)	12 (23.1%)			
Currently employed	56 (59.6%)	34 (65.4%)	0.379	0.538	Chi-square test
Disability pension	48 (51.1%)	21 (40.4%)	1.532	0.216	Chi-square test
Marital status			6.741	0.034	Chi-square test
Single	46 (48.9%)	14 (26.9%)	6.702	Post-hoc	Post-hoc
Married	35 (37.2%)	27 (51.9%)	2.957	0.029	Chi-square test with
Divorced/Widowed	13 (13.8%)	11 (21.2%)	1.307	0.258	Bonferroni correction
				0.759	
Currently living with a partner	76 (80.9%)	51 (98.1%)	8.776	0.003	Chi-square test
Childless	46 (48.9%)	9 (17.3%)	14.264	0.0001	Chi-square test

(Continued)

Table 1 (Continued).

Variable	PSYCH+MOOD Group (n = 94)	ANX Group (n = 52)	Test Values t/chi-Square/M-W U	p value	Test
Duration of illness (years)	12.7 ± 10.1 (1–43)	9.0 ± 9.5 (1–41)	1797.5	0.008	Mann–Whitney U-test
Currently hospitalized	91 (96,8%)	52 (100%)	1.694	0.553	Fischer's exact test
Number of previous hospitalizations	3.2 ± 4.3 (0–18)	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	72 (76.6%)	15 (28.8%)	31.699		
Antidepressants	58 (61.7%)	48 (92.3%)	15.766		
Anxiolytics	20 (21.3%)	29 (55.8%)	17.864		
Mood stabilizers	27 (28.7%)	0 (0%)	18.325		

PSYCH+MOOD patients (all of them personality disorders) and in 16 ANX patients (another anxiety disorder n = 9, personality disorders n = 7). The PSYCH+MOOD subjects with an ANX comorbidity and vice versa were not included in our study.

Antipsychotics typically prescribed were olanzapine, risperidone, quetiapine, aripiprazole, clozapine and lurasidone. The most frequent antidepressants were es/citalopram, fluoxetine, sertraline, venlafaxine, mirtazapine, vortioxetine and trazodone. The most frequent anxiolytics were clonazepam, oxazepam, bromazepam, alprazolam, pregabalin and hydroxyzine. Mood stabilizers included lithium, valproate and lamotrigine. If antipsychotics were prescribed to ANX patients, the typical medication was quetiapine 25–50 mg/day as a sedative.

Risk and Protective Environmental Factors

Among the individual risk factors, we found that compared with the ANX group, PSYCH+MOOD patients less frequently experienced obstetric complications (5.4% in PSYCH+MOOD vs 19.6% in ANX; chi-square = 7.149; p = 0.008; Chi-square test), were more frequently obese (29.8% in PSYCH+MOOD vs 13.7% in ANX; chi-square = 4.658; p = 0.031; Chi-square test) and more frequently experienced job-related stress (56.4% in PSYCH+MOOD vs 36.5% in ANX; chi-square = 5.275; p = 0.022; Chi-square test). There were no significant between-group differences on any other risk factors, or on any of the three protective factors. PERS and polyenviromic protective score did not differ significantly between the groups (PERS: PSYCH+MOOD 0.057±0.03; median 0.054 vs ANX 0.051±0.032; median 0.044, Mann–Whitney U = 2091; p = 0.149, Mann–Whitney U-test, Figure 1; polyenviromic protective score: PSYCH+MOOD –0.045±0.02; median –0.044 vs ANX –0.046±0.014; median –0.044, Mann–Whitney U = 2284; p = 0.466, Mann–Whitney U-test, Figure 2).

Figure 1: Distribution of data was shown graphically by a box and whisker plot. In a box and whisker plot the ends of the box are the upper and lower quartiles, the median is marked by a horizontal line inside the box; the whiskers are the two lines outside the box that extend to the highest and lowest observations. Outliers and extremes are shown as separately plotted points and stars.

Figure 2: Distribution of data was shown graphically by a box and whisker plot. In a box and whisker plot the ends of the box are the upper and lower quartiles, the median is marked by a horizontal line inside the box; the whiskers are the two lines outside the box that extend to the highest and lowest observations. Outliers and extremes are shown as separately plotted points and stars.

We detected the following moderately severe positive intercorrelations between environmental risk factors: Death of a parent in childhood and ethnic minority (r = 0.427; p < 0.0001), ethnic minority and traumatic brain injury (r = 0.489; p < 0.0001) in the PSYCH+MOOD group; serious chronic somatic disorder and job-related stress (r = 0.487; p = 0.0003), death of a parent in childhood and abuse in childhood (r = 0.477; p = 0.0004) in the ANX category. Other

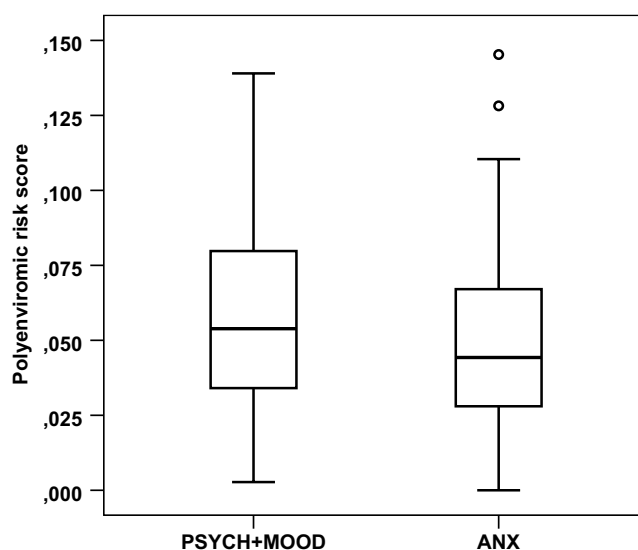


Figure 1 Polyenviromic risk score.

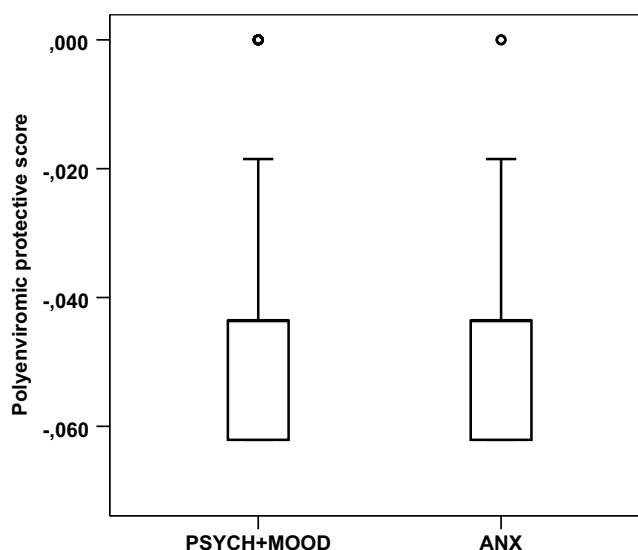


Figure 2 Polyenviromic protective score.

intercorrelations between environmental risk factors or between environmental protective factors in both study groups were only weak or absent.

PERS was significantly associated with the duration of illness in the ANX group (Spearman's correlation coefficient 0.287, $r = 0.287$; $p = 0.039$), but not in the PSYCH+MOOD subjects (Spearman's correlation coefficient -0.036 , $r = -0.036$; $p = 0.732$). Polyenviromic protective score was associated with the duration of illness in neither the ANX participants (Spearman's correlation coefficient 0.001, $r = 0.001$; $p = 0.996$), nor the PSYCH+MOOD patients (Spearman's correlation coefficient -0.042 , $r = -0.042$; $p = 0.690$).

When we compared the three patient groups (PSYCH vs MOOD vs ANX) on total PERS and polyenviromic protective score, there were no significant differences (chi-square = 2.120; $p = 0.346$ for PERS; chi-square = 1.089; $p = 0.580$ for protective factors; Kruskal–Wallis test; detailed data not shown).

Discussion

We found that compared with the ANX group, PSYCH+MOOD patients were more frequently obese, single, childless, had a longer duration of illness and were more frequently hospitalized in spite of the fact that the ANX participants were generally older. That PSYCH+MOOD patients experience difficult, unsatisfactory lives from the medical, psychological, societal and economic perspectives has been described extensively.¹⁶ Our results correspond with this knowledge.

The more frequently experienced job-related stress in the PSYCH+MOOD group compared with the ANX patients may be attributable to cognitive deficit, which is present in psychoses⁴⁴ as well as in mood disorders.^{45,46} On the other hand, our finding that obstetric complications were more frequent in the ANX participants compared with the PSYCH+MOOD group is atypical,²² and may be due to our insufficient explanation of this issue to the study participants before the research. The individual risk/protective factors had a different statistical weight (odds ratio), as stated in the Methods section.

PERS and polyenviromic protective score did not differ significantly between the groups.

This nonsignificant PSYCH+MOOD vs ANX difference in overall environmental risk/protective factors herein underlines the need to also assess factors' exposure timing and unique combinations.¹⁰

We were unable to establish the effect size of the polyenviromic risk score because the individual odds ratios as stated in the Methods section come from different studies with different study populations. Generally, we do not doubt that the magnitude of the polyenviromic risk score is biologically/clinically meaningful, simply because the heritability of mental disorders is far from 100% (heritability based on twin studies: schizophrenia 70%, mood disorders 53%, anxiety disorders 30–60%).^{14,47} In the polyenviromic protective score, the knowledge is still inconclusive because protective factors of mental disorders have only recently been studied, and there is a lack of research data.

The detected moderately severe positive intercorrelations between individual environmental risk factors in the PSYCH+MOOD as well as ANX study subjects may lead to speculations, for example why being a member of an ethnic minority may be associated with the death of a parent in childhood or with experiencing a traumatic brain injury, but these findings should be at least replicated in an independent sample, before any reliable hypothesis is postulated.

Our finding that PERS was significantly associated with the duration of illness in the ANX group but not in the PSYCH+MOOD subjects may be explained by the fact that the longer exposition to adverse life events results in their more intensive influence on the individual's psyche. This effect is more striking in anxiety disorders, whilst the background of psychoses and mood disorders is rather genetic/biological.

The only previous PERS-based study was performed by Padmanabhan et al.⁸ They examined whether an aggregate score reflecting exposure to nine environmental risk factors could predict conversion to psychosis in a pilot group of 83 young participants with high familial schizophrenia risk. They found that higher PERS was significantly associated with conversion to psychosis (OR = 1.97; $p = 0.009$), supporting the notion that an aggregate index of environmental risk may be a helpful predictor in that population. We are the second team to use the "PERS" to study the etiology of mental disorders.

The review by Serafini et al.⁴⁸ suggests that even if bipolar disorder and unipolar depressive disorder both belong to mood disorders, they are partially different from each other in brain morphological abnormalities. Reductions in the volume of basal ganglia and the hippocampus appear more specific for pediatric unipolar depression, whereas reduced corpus callosum volume and increased rates of deep white matter hyperintensities are more specific for pediatric bipolar disorder. With this knowledge in mind, scientists should be aware that some etiopathogenetic differences may be present within the same broad diagnostic category, which might also be true for environmental triggering factors. In addition to this, a part of mental disorders including their causes may be quite undetected and thus not studied. For example, Pompili et al.⁴⁹ state that above 2% of the alleged traffic accidents are suicidal behavior in reality.

Our study is not without limitations. We did not assess intercorrelations among, and time frames for exposure to individual environmental factors as suggested by Uher et al.¹⁰ Our cross-sectional design precludes deducing cause and effect.⁵⁰ Assessing past stressful life events may have been influenced by recall bias, and the significance of these incidents was evaluated only subjectively, without use of any biological marker. Recall bias occurs when participants in a study are systematically more or less likely to recall and relate information on exposure depending on their outcome status, or to recall information regarding their outcome dependent on their exposure.⁵¹ Potential diagnostic biomarkers of

chronic stress include cortisol, adrenocorticotrophic hormone, brain-derived neurotrophic factor, catecholamines, glucose, hemoglobin A1c, triglycerides, cholesterol, prolactin, oxytocin, dehydroepiandrosterone sulfate, C-reactive protein, interleukin-6 and interleukin-8.⁵² Environmental risk factors like cannabis abuse may have dose-dependent effects that were not considered herein. Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk for psychosis.⁵³ Our small sample size may have provided insufficient statistical power; thus, replication with larger samples is needed. We were unable to ascertain odds ratios for each environmental risk and protective factor within each relevant diagnosis using the PERS simply because the data have yet to be identified, and we used a single representative odds ratio for each risk/protective factor if the data were available. Nearly all of our participants were hospitalized and thus may not be representative of all patients who meet the same ICD-10 criteria. These results from the Czech Republic, where there is a relatively homogenous ethnic demographics, may not generalize to other countries where international migration is higher. It is typical in the Czech Republic to live in a relatively small city (ie, fewer than 20,000 residents) or villages; thus, we considered being raised in Prague (1.3 million residents) to reflect a “childhood in an urban area”. This may also limit generalization of our results to countries with similar urban stratifications.

No genetic variant and no environmental exposure on its own is a sufficient cause of mental illness. The most likely scenario is that both genetic and environmental factors jointly contribute to the causation of mental illness. This phenomenon has been described as a gene-environment interaction.¹⁰ We did not examine genetic background of the study participants, which is a shortcoming of our research.

The main advantage of our study is the application of a summarizing and complex concept of the assessment of environmental risk/protective factors in the etiology of mental disorders. This is a logical step in research, because the evaluation of individual environmental variables in isolation brought only a limited scientific benefit. In this way, we come after a similar trend in psychiatric genetics, where polygenic risk scores are already calculated.

We also expect that our sample may represent the whole of the Czech Republic well because a) Hradec Kralove is in Bohemia and Olomouc is in Moravia (two major sections of the country) and b) only 5.5% of the inhabitants are foreigners,⁵⁴ none of whom were included in this sample.

Conclusions

Our results may be helpful toward prevention and personalized treatment of mental disorders. Some environmental risk factors are modifiable, including childhood abuse, smoking and illicit drug abuse, thus physicians should be especially aware of these. Further, environmental protective factors like a healthy diet can also be more intensively encouraged and supported. Further research should focus on the scientific validity of the polyenviromic risk/protective score construct, within large, diverse psychiatric cohorts, ideally using a prospective design. The scientific take-home message of our work is that researchers have started to consider environmental factors in the etiology of mental disorders in their complexity, as polyenviromic risk/protective scores, similarly to polygenic risk scores which have already been applied before.

Abbreviations

ANX, anxiety disorder; BMI, body mass index; CIDI, Composite International Diagnostic Interview; EU-GEI, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; ICD-10, International Classification of Diseases 10th Revision; MINI, Mini International Neuropsychiatric Interview; MOOD, mood disorder; OR, odds ratio; PERS, polyenviromic risk score; PSYCH, psychosis.

Data Sharing Statement

The anonymized data that support the findings of this study are available upon reasonable request from the corresponding author (L.H.). The data are not publicly available because they contain information that could compromise the privacy of research participants.

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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Authors' Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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