Association of Polygenic Risk Scores for Schizophrenia with Psychosis-Proneness Indicators in the General Population: A Narrative Review

Связь оценок полигенного риска шизофрении с показателями предрасположенности к психозу в общей популяции: нарративный обзор литературы

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Review

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ABSTRACT

BACKGROUND: Schizotypy (ST) and psychotic-like experiences and negative symptoms (PENS) are commonly used phenotypes in high-risk and early intervention research for schizophrenia and other non-affective psychoses. However, the origin of these phenotypes in the general population is poorly understood and their association with the genetic predisposition to psychoses has not yet been proven.

AIM: The aim of this study is to answer the question of whether data on the relations of ST and PENS with polygenic risk scores for schizophrenia (SZ-PRS) support the hypothesis that these phenotypes are subclinical manifestations of genetic liability for schizophrenia.

METHODS: Literature describing these relations in the general population was analyzed. The literature search was performed in the PubMed database using the following keywords in English: ((“schizotyp*” OR “psychotic-like experiences” OR “psychosis proneness” OR “psychotic experiences”) AND (”polygenic risk” OR “genetic liability” OR “polygenic score”)); the search in eLIBRARY.RU was conducted using the Russian words for “schizotypy”, “schizotypal features”, “psychotic experiences”, “psychotic experience”, “psychotic symptoms”, and “polygenic risk”, covering publications from 2009 to 2024.

RESULTS: Of the identified records, 45 publications were found eligible. No expected positive correlations of SZ-PRS with common ST measures have been observed. For PENS, the results are inconsistent. Overall, SZ-PRS correlate more often with the PENS general factor and negative symptoms than with psychotic experiences *per se*.

CONCLUSION: The literature does not provide convincing evidence of the association between SZ-PRS and ST/PENS. The search for the substantive psychological meaning of polygenic vulnerability to psychosis captured by SZ-PRS should be expanded to other personality processes and traits.

АННОТАЦИЯ

ВВЕДЕНИЕ: Шизотипия (ШТ), а также переживания, сходные с психотическими и негативными симптомами (ППНС), — это фенотипы, широко используемые в исследованиях высокого риска и ранних вмешательств при шизофрении и других неаффективных психозах. Однако происхождение этих фенотипов в общей популяции остается недостаточно изученным, а их связь с генетической предрасположенностью к психозам пока не доказана.

ЦЕЛЬ: Рассмотреть достоверность гипотезы о том, что ШТ и/или ППНС являются субклиническими проявлениями генетической предрасположенности к шизофрении, на основе анализа данных литературы о взаимосвязи психометрической ШТ и ППНС с оценками полигенного риска шизофрении в общей популяции.

МЕТОДЫ: Был проведен анализ литературных источников, в которых описаны эти взаимосвязи в общей популяции. Поиск литературы осуществлялся в базах данных PubMed и eLIBRARY.RU с использованием следующего поискового запроса: ((«schizotyp*» OR «psychotic-like experiences» OR «psychosis proneness» OR «psychotic experiences») AND («polygenic risk» OR «genetic liability» OR «polygenic score»)); а также соответствующих русскоязычных терминов «шизотипия», «шизотипические черты», «психотические переживания», «психотический опыт», «психотические симптомы» и «оценка полигенного риска». Поиск охватывал публикации за период с 2009 по 2024 год.

РЕЗУЛЬТАТЫ: Из записей, выявленных в ходе поиска, было отобрано 45 публикаций, соответствующих критериям включения. Ожидаемые положительные корреляции между оценкой полигенного риска шизофрении и распространенными показателями ШТ установлены не были. Результаты оценки ППНС неоднозначны. В целом оценка полигенного риска шизофрении чаще коррелируют с общим фактором ППНС и негативными симптомами, чем с психотическими переживаниями как таковыми.

ЗАКЛЮЧЕНИЕ: Литературные данные не предоставляют убедительных доказательств связи между оценкой полигенного риска шизофрении и ШТ/ППНС. Чтобы лучше понять основное психологическое содержание полигенной предрасположенности к психозу, отражаемой оценкой полигенного риска шизофрении, следует расширить поиск и учитывать другие личностные процессы и характеристики помимо ШТ и ППНС.

Keywords: *schizophrenia; schizotypy; psychotic-like experiences; PLEs; PENS; polygenic risk scores*
Ключевые слова: *шизофрения; шизотипия; психотические переживания; PLEs; PENS; оценка полигенного риска*

INTRODUCTION

Schizophrenia is a chronic disabling disorder in which polygenic predisposition plays an important role [1]. Early intervention is assumed to reduce the risk of psychosis in individuals with genetic vulnerability to the disease. Approaches to identifying vulnerable individuals in non-clinical samples are based on the idea of a psychoses-proneness continuum, with psychotic patients at one end and individuals from the general population with schizophrenia-like traits or experiences at the other [2–4].

Schizotypy (ST) is an early concept of the "schizophrenic genotype" subclinical expression [3]. ST represents a constellation of personality traits resembling positive, negative, and disorganized symptoms of schizophrenia. These traits can manifest as several personality disorders or as normal personality variants [5]. In the latter case, they are measured mainly with questionnaires for schizotypal personality and are called psychometric ST. Psychotic-like experiences (PLEs) are another conceptualization of schizophrenia liability [4]. PLEs are defined as subclinical psychotic symptoms (delusions and hallucinations) in the absence of illness/in a non-clinical population/in individuals who do not seek psychiatric help [4]. The prevalence of PLEs in the population is about 8%, with the highest frequency in childhood (up to 17%) [4]. Recently, it has been proposed to supplement the PLEs with cognitive disorganization and negative dimensions, this wider concept being referred to as psychotic experiences and negative symptoms (PENS) [6].

The development of molecular genetic technologies in the last decades has made it possible to directly assess the relationship between genetic liability to schizophrenia and psychosis-proneness indicators [7–11].

The methodologies include calculating genetic correlations between schizophrenia and ST/PENS based on genome-wide association studies (GWAS) of these traits and assessing associations of ST/PENS with polygenic risk scores for schizophrenia (SZ-PRS). SZ-PRS is the sum of schizophrenia risk alleles in an individual genome, weighted by the strength of the association of each allele with the disease [7]. The weights are effect sizes derived from GWAS conducted by the Psychiatric Genomics Consortium (PGC) [7–10].

A systematic review, considering the comprehensive genome-wide data on PENS obtained by 2018, concluded that PENS in the general population are genetically associated with schizophrenia and that the negative dimension in addition shares genetic influences with major depression [6]. Regarding the relations of PENS with SZ-PRS, the review's authors found 10 relevant studies, and four of them reported significant associations, though the proportion of variance in PENS explained by SZ-PRS did not exceed 1%. The results obtained for different age groups and with different instruments were more consistent for the negative dimension than for PLEs. Notably, only one of the reviewed papers concerned ST [6]. Since then, new large-scale studies of both ST and PENS, some of which used SZ-PRS based on the summary statistics of the latest and most powerful schizophrenia GWAS (PGC3 GWAS [10]), have been conducted but not reviewed.

The aim of this study was to answer the question of whether data on the relations of ST and PENS with polygenic risk scores for schizophrenia support the hypothesis that these phenotypes are subclinical manifestations of genetic liability for schizophrenia. Developing an accurate picture of the relationship between genetic liability to schizophrenia and ST/PENS is of importance for the conceptualization of psychosis-proneness and might help to advance the prevention of psychotic disorders.

METHODS

Eligibility criteria

Inclusion criteria:

The review included articles, containing the empirical research on the relationship in the general population of psychometric Schizotypy and psychotic-like experiences and negative symptoms with SZ-PRS.

Information sources

The literature search was performed in the PubMed and eLIBRARY.RU databases.

Search strategy

The search in PubMed was conducted using the following keywords: (("schizotyp*" OR "psychotic-like experiences" OR "psychosis proneness" OR "psychotic experiences") AND ("polygenic risk" OR "genetic liability" OR "polygenic score")) published from 01 Jan. 2009 to 30 Dec. 2024. The lower time threshold was chosen because the GWAS-based PRS concept in 2009 [7]. The search in eLIBRARY.RU was conducted using the Russian words for "schizotypy", "schizotypal features", "psychotic experiences", "psychotic experience", "psychotic symptoms", and "polygenic risk". Reference of the identified papers were manually examined to find additional relevant articles.

Selection process

The primary screening of potentially relevant articles was conducted by reviewing their titles and abstracts and performing a preliminary assessment if they meet the eligibility criteria. The selected articles were listed for further review of their full texts and selection of relevant studies that met all the planned inclusion and exclusion criteria. Exclusion criteria were as follows: 1) clinical samples or samples of psychotic patients' relatives; 2) the use of basic personality traits (e.g., openness to experience) as a proxy of ST/PENS; 3) the use of SZ-PRS as a modifying factor without presenting data on the direct effects of SZ-PRS on ST/PENS; 4) conference proceedings, dissertation thesis, or preprints. No restrictions were imposed on the language of publication or the age of the subjects. Works with overlapping or even almost identical samples from the same projects were not excluded to demonstrate the level of in/consistency of the results and since different publications of the same project could report on different aspects of ST/PENS.

The resulting publications were then selected for analysis based on the following inclusion criteria: 1) research articles; 2) articles contained data on the association of SZ-PRS with ST or PENS measured in individuals from the general population using questionnaires or diagnostic interviews; 3) SZ-PRS based on GWAS conducted in 2009 or later; 4) articles published in peer-reviewed scientific journals.

Data analysis

From the publications selected for consideration, the author extracted information on: 1) available demographic characteristics of the sample (age, sex, ethnicity, relatedness between subjects); 2) the way of measuring ST/PENS;

3) GWAS to build SZ-PRS; 4) the presence of a statistically significant relationship between ST/PENS and SZ-PRS; 5) associations between ST/PENS and PRS for other mental illnesses or psychological traits.

RESULTS

Characteristics of articles

The search in PubMed returned 87 articles, of which 35 met the criteria, and one relevant publication (our own [12]) was found in the eLIBRARY.RU database. The investigation of the references lists yielded another 9 articles. Thus, 45 publications were selected for analysis, of which 9 investigated the associations of SZ-PRS with ST, 4 — ST and PENS, and 32 — with PENS (Table S1 in the Supplementary).

Of the eligible studies [12–56], most were carried out within a several large longitudinal projects, which had the genome-wide data for their participants. They mainly included individuals of European ethnicity, used PGC2 GWAS [8] for SZ-PRS calculation and were balanced by sex of participants. Of the instruments assessing ST, the most popular (5 out of 13 publications) was the Schizotypal Personality Questionnaire (SPQ, or its short form SPQ-B) measuring cognitive-perceptual (positive), interpersonal (negative), and disorganized dimensions of ST. PENS were primarily evaluated with project-specific interviews and questionnaires exploring selected items from common clinical diagnostic instruments [26–39]. The exception was the Community Assessment of Psychic Experience (CAPE) questionnaire consisting of positive, negative, and depressive scales, which is a widely used international instrument for assessing PENS [13, 20–23, 31–33, 42–46, 48, 49]. The main difference between the instruments measuring ST and PENS was that the former addressed stable characteristics (personality traits), and the later evaluated states (whether there were PENS, how often, and whether this experience was distressing). In addition, the PENS items were formulated more psychopathologically, i.e. they concerned symptoms. However, there was no clear boundary between the PENS and ST indices either in terms of the temporal stability of characteristics or in terms of their content. In particular, the CAPE has been created using items from clinical scales (the Present State Examination, Scale for the Assessment of Negative Symptoms, Subjective Experience of Negative Symptoms, and Calgary Depression Scale) but also assesses stable characteristics of a person (e.g., magical thinking), and its positive and negative scales significantly correlate with similar scales from the Structured Interview for Schizotypy, Revised (SIS-R) [13].

Association of polygenic risk scores for schizophrenia with schizotypy

The first study of self-reported ST using the GWAS-based SZ-PRS was performed on two samples of Greek conscripts [14]. The first sample completed SPQ and the Perceptual Aberrations Scale (PAS). Instead of the expected positive correlations of the SZ-PRS with ST indicators, the authors found negative ones that reached the level of significance for the positive and disorganized ST [14]. When retesting 121 people from the original cohort of 875 conscripts in 18 months, these relationships disappeared, which the authors explained by a decrease in distress in the conscripts. In the second sample, the Schizotypal Personality Scale (STA) was applied to assess paranoid and magical thinking and unusual experiences; in addition, trait anxiety was measured with the State-Trait Anxiety Inventory (STAI). SZ-PRS did not correlate with ST indicators but associated with anxiety [14].

Subsequent studies also failed to find positive correlations of SZ-PRS with standard measures of the SPQ or other ST questionnaires [12, 15–20]. A recent publication [21] has reported an association of SZ-PRS with the positive dimension of the Multidimensional Schizotypy Scale (MSS) in men. However, there were no associations of SZ-PRS with either the MMS positive dimension in women and in the combined group, or with the MSS negative dimension in either group.

Some of the above-mentioned studies attempted to develop non-standard ST indicators with which the SZ-PRS could correlate [16, 18, 19]. Nenadić et al. [18] explored an uncorrelated 4-factor model of the SPQ-B to avoid the influence of neuroticism on the responses and did not reveal a relationship between the ST factors and SZ-PRS. Docherty et al. [16] conducted a factor analysis of the SPQ-B in the entire sample of more than 9,000 participants and in groups of men and women and found that in men the first factor was associated with SZ-PRS. This factor included four items reflecting difficulties in social interaction. The first factor extracted in female group consisted of items from various SPQ-B scales and did not correlate with SZ-PRS. Tiego et al. [19] used factor analysis and the Item Response Theory to construct a bifactor model of ST based on 12 different scales. The model consisted of 9 specific factors

(delusions, hallucinations, etc.) and three higher-order factors (general, positive and negative ones). SZ-PRS correlated positively with the delusions factor and the decreased social interest and involvement factor, without sex differences. These correlations were not mediated by the higher-order factors.

Two projects — European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI) and Genetic Risk and Outcome for Psychosis (GROUP) — applied the interview (SIS-R) to assess ST. The first study was on participants from the GROUP cohort and found positive correlations of SZ-PRS with the SIS-R positive factor [13]. However, in a replication study of GROUP and EU-GEI data, the correlations of SZ-PRS with all analyzed SIS-R indicators (total score, positive and negative factors) turned out to be negative, and in the larger sample (EU-GEI) they reached the level of significance for the total score and the positive scale [22]. Of importance, in unaffected relatives of psychotic patients from the same projects, SIS-R scores positively correlated with SZ-PRS [13, 22]. Later, for the EU-GEI sample a bifactor model was developed that included a general factor and three specific factors (cognitive-perceptual, paranoid and negative), and the expected positive correlation of SZ-PRS with the general factor was observed; the associations with specific factors were not assessed in this work [23].

Also worth mentioning is the study of Schaefer et al. [24] carried out on samples of twins at the age of 24 and 34 years using the Personality Inventory for DSM-5 Psychoticism scale (the total score of psychoticism and subscales: unusual beliefs and experiences, eccentricity, perceptual dysregulation). The authors found correlations between SZ-PRS and all indicators of psychoticism, even when the cannabis use during adolescence was controlled for. Of note, the items of this instrument were formulated in a more psychopathological manner than those of ST personality questionnaires.

To summarize, despite some positive results, the pooled data indicate the absence of significant, reproducible relationships between the psychometric ST and SZ-PRS in the general population. At the same time, some studies [12, 14, 16, 18] have found positive correlations of standard and non-standard ST indicators with PRS of emotional dysregulation (neuroticism, anxiety, depression), which might suggest the influence of genetically determined negative affectivity on the self-reported ST.

Association of polygenic risk scores for schizophrenia with psychotic experiences and negative symptoms

Childhood and youth

Of significant interest is the relation of genetic predisposition to schizophrenia with PENS in youth, i.e., in individuals who are approaching or at the age of maximum risk for developing psychosis. This relation has been examined in several research projects [25–46].

Two USA longitudinal studies evaluated PLEs in youth using diagnostic interviews. In the Adolescent Brain Cognitive Development (ABCD) middle childhood (9–10 years) cohort, SZ-PRS correlated with the presence of distressing PLEs but not with the total number of PLEs, while the total number of PLEs correlated positively with cross-disorder (psychiatric) PRS and negatively with education PRS [25]. These findings were taken to suggest that among the PLEs, only the most severe psychotic experiences might reflect genetic liability to schizophrenia. However, Hernandez et al. [26] revealed no difference in SZ-PRS between children (aged 9–12) from the ABCD project who had and had no severe and/or distressing PLEs. Then Ku et al. [27], having assessed not only the severity but also the recurrence of PLEs over 4 years after the first examination, found in this cohort a positive correlation of SZ-PRS with the presence of distressing recurring PLEs, but not with transient ones, which was partly consistent with the initial hypothesis of Karcher et al. [25]. In the Philadelphia Neurodevelopmental Cohort (PNC), no association was found between the presence of PLEs and SZ-PRS or PRS for emotional traits in youth (8–22 years) of either European or African American descent; at the same time, the presence of PLEs, especially in children under 12 years of age, was associated with PRS for attention deficit hyperactivity disorder (ADHD) [28, 29].

In the UK Avon Longitudinal Study of Parents and Children (ALSPAC), PLEs (delusions, hallucinations, thought interference) were assessed using the Psychosis-Like Symptoms interview (PLIKSi) or a corresponding questionnaire (PLIKS-Q), and negative symptoms were measured with the CAPE negative scale [30–34]. No association was found between SZ-PRS and PLEs measured at 12, 18, and 20 years [30–32]. SZ-PRS correlated with negative symptoms, as well as with anxiety disorders at age 16 [31]. Later, the data of 16-year-old participants were examined applying two models of PENS: a model of four correlated factors (positive, negative, depressive and anxious) and a bifactor model with a general factor and four specific ones [33]. In the

correlated model, SZ-PRS were significantly positively associated with all factors. In the bifactor model, there were positive correlations of SZ-PRS with the general and negative factors. In addition, the general factor was associated with PRS for neuroticism. It was also shown that individuals with different severity and age trajectories of PENS did not differ in SZ-PRS [34]. Of interest, the latter study showed a high comorbidity of PENS with generalized anxiety disorder and depressive episode, reaching 80% in the group with multiple recurring PENS [34].

Another UK project, the Twins Early Development Study (TEDS), assessed 16-year-old twins using the Specific Psychotic Experiences Questionnaire (SPEQ: paranoia, hallucinations, cognitive disorganization, grandiosity, and anhedonia) and parental assessment of negative symptoms [35–38]. No positive correlations were found between SZ-PRS and the presence, severity or age dynamics of PENS components [35–38]. However, associations were observed between PENS and PRS for other mental illnesses and traits, mainly depression PRS and education PRS [37, 38]. Similarly, in the sample of the UK Environmental Risk (E-Risk) Longitudinal Twin Study, the number of PENS at 12–18 years was significantly associated with depression PRS, and only at the trend level — with SZ-PRS [39]. In contrast, in the Child and Adolescent Twin Study in Sweden (CATSS), there were positive correlations between PLEs and SZ-PRS [40]. Notably, the authors did not screen the sample for schizophrenia due to the young age (18 years) of the subjects. In a meta-analysis of data from the three mentioned projects (TEDS, ALSPAC and CATSS) published by 2019, Pain et al. [41] obtained significant associations of SZ-PRS with cognitive disorganization, anhedonia and negative symptoms. Associations of SZ-PRS with hallucinations and delusions were significant only in the subgroup of adolescents who had these PLEs: the higher the SZ-PRS, the more pronounced delusions and hallucinations were. Anhedonia and negative symptoms, in addition, correlated positively with depression PRS, while delusions and hallucinations were negatively associated with PRS for bipolar disorder (BD) [41].

The CAPE-based results are also mixed. In Brazilian children and adolescents, no association was found between SZ-PRS and the scores of this questionnaire, which was slightly modified in the context of this study [42]. In adolescents and young adults from the European projects IMAGEN and Dutch Utrecht Cannabis Cohort (UCC), different authors obtained correlations of SZ-PRS with different CAPE indicators. Marchi et al. [43] found positive associations of SZ-PRS with CAPE total scores in the UCC sample, which included a significant number of individuals who used cannabis (the latter is a risk factor for PLEs), but failed to replicate this association in the IMAGEN sample. Elkrief et al. [44] found positive associations of SZ-PRS with CAPE total scores in both samples. Regarding the CAPE scales, however, it turned out that in the IMAGEN sample SZ-PRS correlated with the positive and depressive scales, while in the UCC sample — with the negative and depressive ones. Previously, Velthorst et al. [45] found a positive correlation of the CAPE positive symptoms scale with the SZ-PRS in a subsample of UCC, but the authors did not report on the use of the other CAPE scales. In the IMAGEN subsample aged 21–22 years, SZ-PRS predicted the higher versus low CAPE total scores both directly (a significant direct effect in a mediation analysis) and indirectly, through age-related dynamics of personality traits and victimization (significant indirect effects); however, in a large replication sample of adolescents from another project, only the indirect effects were confirmed [46].

In sum, studies of children and young people have not yielded convincing evidence in favor of a relationship between SZ-PRS and delusional and hallucinatory experiences. In some cases, associations of SZ-PRS with the PENS general factor and negative symptoms have been observed.

Broad age groups of adults

A significant portion of the PENS studies was conducted on broad age groups of predominantly adult individuals (16–65 years). The research of Derks et al. [47] included 148 people of 18–50 years (the initial stage of the GROUP sample recruitment) and did not find correlations of SZ-PRS with PENS. Mas-Bermejo et al. [20, 21] observed no significant correlations between SZ-PRS and the CAPE indicators in Spanish students aged 18–62. Of the GROUP and EU-GEI studies mentioned in the ST section, the first study of the GROUP cohort reported no significant correlations of SZ-PRS with the CAPE measures [13], while the replication study of both cohorts found negative correlations [22]. However, subsequent EU-GEI publications reported positive correlations of SZ-PRS with the CAPE positive scale [48] and with the positive, negative, depressive [49] and general factors of the CAPE bifactor model [23, 49].

Some studies considered the relationship of PENS with the context in which they occurred. Thus, Johnson et al. [50]

assessed cannabis-related PENS in individuals of European and African descent who were ascertained for addictive disorders. The authors found positive associations of SZ-PRS with all symptoms measured by the Semi-Structured Assessment for the Genetics of Alcoholism interview (paranoia, depression-anhedonia, decreased social contacts, and cognitive difficulties), except for hallucinations. In a replication sample consisting predominantly of individuals with opioid dependence, the associations did not reach significance.

In the longitudinal Dutch project NEMESIS-2, Hasmi et al. [51] tested the hypothesis that PLEs occurring outside the context of non-psychotic mental disorders (mood, anxiety and drug use disorders) might not be of interest for predicting the development of psychosis. Using a clinical interview, they assessed the occurrence of 20 delusional and hallucinatory symptoms in people from the general population during a 9-year follow-up period, then dividing the symptoms into isolated ones and those observed in the context of non-psychotic disorders. The authors compared individuals with the isolated PLEs and with PLEs in the context of non-psychotic disorders to controls without PLEs on the frequency of high SZ-PRS (from the upper quartile of the SZ-PRS distribution). In accordance with the hypothesis, only the group with non-psychotic disorders differed from the controls.

Pries et al. [52] examined suspiciousness, fear of losing control, racing and pervasive thoughts, and difficulties to express thoughts in a Belgian sample of 593 people aged 15–35 using the ecological momentary assessment. The authors also assessed everyday stress. The symptoms studied correlated with childhood trauma and everyday stress, but not with SZ-PRS. The authors found only a weak positive effect of the interaction of SZ-PRS and childhood trauma on psychotic symptoms. At the same time, SZ-PRS correlated positively with positive emotions and were not associated with negative affect or stress reactivity.

Several publications presented the relationships between SZ-PRS and PLEs in an UK BioBank cohort, which included people over 40 years old, i.e., those who had already passed the age of risk [53–56]. Of the almost half a million biobank sample, 157,387 people completed the UKB online Mental Health Questionnaire (MHQ). The MHQ included one question each on the presence and frequency of visual and auditory hallucinations, persecutory delusions, and delusions of reference [53]. Additionally, the distress associated with each symptom was assessed. The findings regarding correlations between PLEs and SZ-PRS in the entire group, which included not only healthy individuals but also individuals who had previously sought psychiatric help, were mixed [53, 54]. When studying only healthy unrelated individuals of British or Irish decent, Legge et al. [55] observed positive correlations of SZ-PRS with the presence of each symptom, with the strongest associations being found for distressing experiences and persecutory delusions. Similar data were obtained by the authors using PRS for BD, depression, ADHD, and autism, which suggest a nosologically non-specific relationship between PLEs and genetic liability to mental disorders. Later, Barbu et al. [56] confirmed the association of PLEs with SZ-PRS for this sample, based on the latest and more powerful GWAS of schizophrenia (PGC3 GWAS).

In summary, there is inconsistency of data regarding the association of SZ-PRS with PENS in adults from the general population. It is important to note the discrepancy between the results obtained by using different factor models of the same instruments in practically the same or overlapping samples.

DISCUSSION

Since the introduction of PRS, numerous studies have been conducted on the contribution of SZ-PRS to the phenotypic manifestations of psychosis-proneness in the form of ST or PENS. Their results do not provide convincing evidence of the association between SZ-PRS and the studied phenotypes. No expected positive correlations of SZ-PRS with common ST measures have been observed. The findings regarding PENS are more complicated. Among the few positive results, there are more correlations of SZ-PRS with the general factor of PENS and negative symptoms than with positive ones. An exception is the findings for individuals over 40 years old, for whom a significant relationship between SZ-PRS and PLEs is shown [55]. However, these results have been obtained within one biobank and may be subject to population stratification bias. Of note, in the absence of the reproducible relation with SZ-PRS, the psychosis-proneness indicators correlate with PRS for other disorders and traits, particularly PRS for major depressive disorder and neuroticism. As discussed earlier [12, 16], this is partly expected given the high prevalence of symptoms of depression and anxiety in the population, their potential to bias self-reports, and twin studies linking schizotypy and neuroticism. However, further research that takes into account sex differences is needed to provide

a mechanistic understanding of the relationship between neuroticism and susceptibility to psychosis. In addition, the PRS-based findings overlap with other types of genetic data (genetic correlations, Mendelian randomization) from some projects described above. According to the latter: 1) ST does not show significant genetic commonality with schizophrenia, but is genetically associated with depression; 2) genetic correlations of PENS with major depressive disorder are higher than with schizophrenia; 3) PENS in adolescence are not genetically associated with PENS and ST in adulthood; and 4) genetic associations of PENS with schizophrenia and depression are higher in adulthood than in adolescence [57].

The lack of associations between SZ-PRS and the psychosis-proneness indicators might be partly explained by the studies' methodologies. Most investigations used data collected within multi-center longitudinal projects aimed at answering different research questions. Due to this, the studies have shortcomings associated with sample compositions. In particular, cohorts of some projects included related individuals (siblings/twins), which was not always controlled for. The UK Biobank research applied minimal phenotyping. A significant number of studies included heavily overlapping samples. Finally, some studies included individuals across a broad age range. Age might be critical for the phenotypic expression of genetic susceptibility to psychosis. However, the broad age range hardly fully explains the lack of correlations between PENS and SZ-PRS, since such correlations have not been observed in the majority of studies with strict age cutoffs.

Also this review has some limitations, including the analysis of only two databases and the lack of co-authors to discuss the process and results of the literature search. Future quantitative assessment based on meta-analysis should provide more rigorous evidence of the presence or absence of correlations between SZ-PRS and PENS than the qualitative one and could clarify the reasons for the heterogeneity of the results related to the sample composition and measurement instruments used.

CONCLUSION

The available results allow to draw preliminary conclusions about the relationship between SZ-PRS and behavioral indicators of predisposition to psychosis, refute previously stated hypotheses and provide grounds for new ones that should be tested in future studies. First, they do not confirm that the current ST assessment is adequate for identifying individuals at risk for psychosis and necessitate a revision of existing ST measurement instruments. Second, it has been previously suggested that psychosis vulnerability scores may be an expression of both a specific psychotic factor and a general (transdiagnostic) psychopathological factor *p* [2, 58]. The combined data, and especially the data obtained using the bifactor models of ST and PENS, support the idea of a transdiagnostic genetic nature of ST/PENS and the hypothesis that the *p* factor may to some extent be a consequence of genetically determined negative emotionality/affective dysregulation. At the same time, they do not confirm the association of a specific psychotic factor with SZ-PRS. Next, only the most severe, recurring and distressing psychotic experiences appear to reflect genetic liability to schizophrenia, which calls into question the idea of a genetic continuum of ST and psychotic experiences in non-clinical and clinical populations. Further, given the discrepancy between the data obtained for youth and late adulthood, it can be assumed that the nature of ST and PENS in different age groups is different. Finally, the lack of correlations between SZ-PRS and ST/PENS echoes the lack of correlations between SZ-PRS and specific clinical characteristics of schizophrenia [59]. Thus, the search for the substantive psychological meaning of polygenic vulnerability to psychosis captured by SZ-PRS should be expanded to personality processes and characteristics other than ST and PENS.

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Supplementary data

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