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# Schizophrenia polygenic risk score: zooming-in on early, non-psychotic developmental expressions of vulnerability

## Summary

*Polygenic Risk Scores (PRS) are proxy values generated combining multiple genetic markers into a single score indicative of specific lifetime risk for a disease. The PRS approach has been increasingly implemented in psychiatry, especially for the study of schizophrenia. Although the majority of studies on PRS focused on possible associations with overt clinical features in patients with already diagnosed schizophrenia spectrum disorders, an emerging trend involves early phenotypic expression of genetic risk for schizophrenia in the general population. This article offers an update on this emerging trend, focusing on how the genetic risk for schizophrenia is early expressed at an endophenotypic level, through a broad range of soft non-psychotic neurocognitive and behavioral manifestations. These features might be integrated with other prediction paradigms, such as familial-high-risk, neurodevelopmental and clinical staging models, to empower and refine early detection strategies.*

**Key words**
Polygenic Risk • Schizophrenia • Phenotype • Neurodevelopment • Early detection

## Introduction

Polygenic Risk Scores (PRS), i.e. proxy values generated combining multiple genetic markers into a single score indicative of specific lifetime risk for a disease [1,2], are becoming increasingly popular as research and translational tools in somatic medicine and in psychiatry [3,4]. Within psychiatry, PRS define cumulative risk profiles based on the identification of genetic variants related to psychiatric disorders, obtained through genome-wide association studies (GWAS). This approach has proven particularly promising in schizophrenia, although the etiopathogenetic complexity (and the multiple genotype-environment (GxE) interactions) involved in the development of its spectrum conditions remain largely unknown [5].

Most studies on schizophrenia-related PRS (s-PRS) mainly focused on testing and assessing possible associations between with overt (or emergent) clinical features in patients with already diagnosed schizophrenia spectrum disorders. In this perspective, a recent study [6] reported that s-PRS was associated with general psychopathology at the Positive and Negative Syndrome Scale (PANSS) and with anxiety at the Hamilton Anxiety Rating Scale rather than with positive or negative symptoms in a sample of patients with first-episode of psychosis. Other studies focused on the association between s-PRS and psychopathological liability in the adult general population; in fact, another recent study [7] reported that s-PRS was associated in youth (18-22 age range) with phenotypic expressions involving anxiety, depression, nicotine use, trauma and family history of psychological disorders.

Empirical evidence on the effects of s-PRS at different levels of analysis and in different populations (general vs. clinical) was recently reviewed [8],



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and studies centered on s-PRS, published until March 2016 seem to converge on four main issues.

1. Pleiotropy between schizophrenia and other psychiatric disorders. Genetic risk for schizophrenia in the general population has a phenotypic effect at the psychopathological level not only related to schizophrenia spectrum disorder manifestations, but also to other non-schizophrenic manifestations, such as bipolar disorder, schizoaffective disorder and anxiety. Interestingly, s-PRS studies suggest possible relationships and overlaps between disorders [9]: for example, in bipolar disorder s-PRS is associated with mood-incongruent psychotic symptoms [10] and is inversely associated with lithium response [11].
2. Less common-variant genetic overlap between schizophrenia and cognition than with other psychopathology. Available studies found an inverse relationship between s-PRS and global measures of cognition [12-14]. No robust empirical data are available on the association between s-PRS and specific cognitive functions; interestingly, recent studies found effects of s-PRS on neural activations during specific cognitive tasks such as reward processing [15], working memory [16] and memory encoding [17]. Considering the inverse association between s-PRS and cognition, an apparent counterfactual finding that needs replication regards the lack of association between s-PRS and primary school achievement [18]; however, it could be hypothesized that the age of assessment could influence this possible relationship, therefore the effects of s-PRS on school achievement need to be evaluated along the academic course.
3. Small variance explained by currently available s-PRS for all phenotypes (presumably limited by the fact that PRS do not capture Copy Number Variants or rare Single Nucleotide Polymorphism contributions to variance).
4. Early phenotypic expression of genetic risk for schizophrenia in the general population through a broad range of soft (i.e. non-psychotic) neurocognitive and behavioral features during development. Vulnerability to schizophrenia spectrum conditions is manifested through a phenotypic cloud that incorporates cognitive-emotional, interpersonal and socio-functional features presumably more relevant for the emergence of negative symptoms and social impairments than for the onset of positive psychotic experiences [19-21].

The latter point represents the specific focus of this review, that expands conclusions of the cited review [8] including recent additional empirical findings that might be useful to complete the phenotypic puzzle and enrich our understanding of the dynamic mosaic of early developmental expressions related to s-PRS in the general population.

## s-PRS and vulnerability (endo)phenotypes

In the last two years, several empirical contributions investigated phenotypic effects in infancy and childhood of s-PRS in the general population. Jansen and colleagues [22] indicated a selective association of s-PRS with higher internalizing scores at Child Behavior Checklist at all ages, as well as with higher externalizing scores at age 3 and 6. Moreover, looking at the syndromic subscales, s-PRS was positively associated with higher emotional reactivity at age 3, all internalizing subscales (emotional reactivity, anxiety/depression, somatic complaints, withdrawal) at age 6, and Thought Problems (a proxy score for psychosis-proneness and soft positive symptoms) at age 10.

Nivard et al. [23] reported a strong association of s-PRS with childhood (age 7 to 10) and adolescent (age 12 to 15) depression, a weaker association with Oppositional Defiant Disorder/Conduct Disorder (ODD/CD) at age 7, and a steeper increase in the association from childhood to adolescence for Attention Deficit/Hyperactivity Disorder and ODD/CD. Riglin et al. [24] reported an association of s-PRS with Performance IQ, speech intelligibility and fluency, and headstrong behavior at age 7-9, and with social difficulties and behavioural problems at age 4. In a subsequent study [25] of the same group, s-PRS was prospectively associated with broadly-defined emotional difficulties constantly from childhood (age 7) to mid-life adulthood (age 42) through six points of assessment, differently from depression-PRS that was associated with emotional difficulties only in the last assessment. Moreover, a higher s-PRS was associated with non - optimal overall infant neuromotor development between 2 and 5 months in a recent study by Serdarevic et al. [26].

Overall, despite contingent differences in experimental settings and designs, these recent empirical findings encourage an updated perspective on the neurodevelopmental antecedents of schizophrenia [19-21]. From a developmental perspective, phenotypic effects of s-PRS are not only early and substantial, but they are also detectable at a behavioral level from the perinatal period (age 2-5 months) [26] through infancy (age 3-4) [22 24], childhood (age 7-9 years) [25] and adulthood [7 27].

These findings on the phenotype cohere with preliminary findings on the endophenotypes, as suggested by the reported association between s-PRS and neurodevelopmental features. The effects of s-PRS on cortical gyrification calculated at structural neuroimaging have been investigated in two independent and healthy general populations [28]: a higher s-PRS was significantly associated with a lower local gyrification index in the

bilateral inferior parietal lobes, where case-control differences have been reported in previous studies on schizophrenia. Similar findings were reported also by Neils et al. [29], who compared subjects at high familial risk of schizophrenia who remained well, with those who developed sub-diagnostic symptoms, or who developed schizophrenia with healthy controls. Authors tested whether individuals at high familial risk of schizophrenia carried an increased burden of trait-associated alleles using s-PRS, as well as the extent to which s-PRS was associated with gyral folding in the frontal and temporal lobes. Authors found that individuals at high familial risk of schizophrenia who developed the disorder carried a significantly higher s-PRS compared to those at high-risk who developed sub-diagnostic symptoms or remained well and to healthy controls; furthermore, within the high-risk cohort, there was a significant and positive association between s-PRS and bilateral frontal gyrification. These findings that S-PRS impacts on early neurodevelopment to confer greater gyral folding as detected in young adulthood are in line with early phenotypic effects.

Finally, a recent report [30] showed an interaction between the environment and genetics. In fact, parental behaviours can influence offspring developmental outcomes, supporting the hypothesis that PRS predict variation in characteristics beyond the target trait, including characteristics that are considered to be environmental. For example, the offspring genetic risk for schizophrenia is positively associated with paternal age: children whose father is over 45 at their birth have on average a genetic risk score for schizophrenia over one quarter standard deviation higher than children whose father is under the age of 26 at their birth. This finding may have implications for schizophrenia, in which several early environmental risk factors may play a trigger role for the atypical neurodevelopment.

## Discussion: translational implication of s-PRS for early detection

The s-PRS approach applied in child-adolescent cohorts from the general population may provide an innovative opportunity to understand how the presumed genetic predisposition to schizophrenia is manifested in developmental time, attempting to disentangle the respective contribution of genetic and environmental risk factors along neurodevelopmental stages. This may be particularly helpful in the childhood premorbid period, in which neurobiological (schizotaxic [31 32]) vulnerability expresses itself in a mixed bag of unspecific phenotypic features (e.g. motor, cognitive, behavioral and social impairments), that might be rather difficult to ponder in terms of potential for psychopathological progression and prognostic trajectory [20 21]. Therefore, fine-grained empirical findings based on s-PRS, detailing the age-dependent stream of vulnerability phenotypes could have significant translational implications for the early detection of psychotic risk.

The construct of clinical high-risk state for psychosis (CHR) [33] – broadly conceived as a mental state at imminent risk of progressing into frank psychosis – has progressively evolved to capture the clinically subthreshold phase of psychosis, indexing people presenting with putatively prodromal symptoms. Early intervention mental health services for CHR may play a key role in preventing or delaying psychosis [34 35], but only a small proportion of those who develop psychosis is followed since prodromal stages in such services [36]. Consequently, programs for the detection of a larger proportion of subjects at risk of psychosis should strive to intervene earlier in the longitudinal trajectory of psychosis development [37]. Although the CHR/prodromal state and the subsequent risk of conversion to psychosis might appear, from a clinical and behavioral viewpoint, as early symptomatic stages, they nonetheless plausibly represent rather advanced/late stages from a neurodevelopmental perspective [38 39]. According to the neurodevelopmental hypothesis of schizophrenia [39], as well as for the clinical staging model [40], psychosis conceivably represents the last long-term stages of an altered neurodevelopmental process. Such process, although usually manifested in late adolescence/early-adulthood, is often antedated from the early years of life, by subtle expressions of biological vulnerability. Therefore, the goal of an early detection of psychotic risk in the premorbid period should be based on these subtle expressions of biological vulnerabilities, rather than on hypothetical early direct expressions of psychotic risks, as psychotic experiences, that has a modest and relative unspecific predictive power in youth [41]. At the same time, this goal is hampered by the poor knowledge of those early phenotypic expressions of biological vulnerability that are more specific for a longitudinal psychotic risk: in this perspective, a developmental view, corroborated by s-PRS finding could further increase our understanding of specific age-dependent GxE interactive [5] effects across neurodevelopment on both domain-general (e.g. cognitive and motor deficits) and domain-specific features of premorbid and prodromal stages (e.g. anomalies of subjective experiences, attenuated positive and negative symptoms) of psychosis. For example, motor functioning appears an intriguing specific domain of expression of the biological vulnerability to psychosis, as supported by distinct empirical paradigms, including the s-PRS paradigm [26], familial high-risk studies [42 43], and longitudinal birth-cohort studies [44 45]. These studies globally show that motor manifestations: 1) emerge al-

ready in premorbid stages, in terms of later achievement of motor milestones and poor motor coordination (i.e., dyspraxia); 2) persist in prodromal stages in terms, for example, of neurological soft signs [46 47]; 3) become more pronounced in psychotic clinical stages of schizophrenia (including drug-naïve individuals), due to distinct pathophysiological mechanisms, in terms of catatonia, chorea, dystonia, bradykinesia, tics, and stereotypies [48]. Interestingly, impairments in basic neurophysiological mechanisms as corollary discharges [49] may have a pathogenetic role both for early motor impairment and its maintenance as well as for specific longitudinal liability to psychosis [50], in terms of potential triggers for anomalous self-experiences, representing trait-like non-psychotic anomalies of subjective experience that have been recursively corroborated as schizophrenia spectrum vulnerability phenotypes [51].

In conclusion, studies based on the s-PRS paradigm are in their infancy and appear to have currently a limited explanatory power, as exemplified by the small variance explained for all phenotypes; although findings of s-PRS studies may have significant clinical implications for the early detection paradigm if integrated with empirical findings derived from other empirical paradigms, such as familial-high risk studies and longitudinal birth cohort studies, investigating phenotypic manifestations along the neurodevelopmental trajectory/clinical staging of psychosis. In particular the PRS paradigm may corroborate the value of early non-psychotic vulnerability phenotypes, as they emerge along development, for an early detection of psychotic risk. This is particularly important for childhood and early-adolescence premorbid stages, in which the psychopathological trajectories towards positive psychotic symptoms (i.e. the current gold standard for clinical high-risk stratification [33]) are still inchoate. At the same time, if psychosis prediction should be progressively antedated from prodromal stages, typically occurring in adolescence/young adulthood, to childhood premorbid stages, this has implications for the organization and the allocation of resources of mental health services, usually strictly distinct in Childhood and Adolescence Mental Health Services (CAMHS) and Adult Mental Health Services (AMH) [52].

## Conflict of Interest

The authors have no conflict of interests.

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