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Psychosis risk and development: What do we know from population-based studies?

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Abstract

Recent years have seen an advent in population-based studies in children, adolescents, and adults that examine the prevalence, etiology, and developmental trajectories of diverse subclinical psychopathological symptoms that pose a risk for the later development of severe mental illnesses. It is increasingly recognized that most categorically defined psychiatric disorders (i) occur on a spectrum or continuum, (ii) show high heterogeneity and symptom overlap, and (iii) share genetic and environmental risk factors.

Here, we discuss neurodevelopmental underpinnings of psychosis spectrum symptoms and review brain morphometric and functional alterations, as well as genetic liability for psychosis, in individuals experiencing psychotic symptoms (PS) in the general population. With regard to brain structure and function, findings of qualitatively similar alterations in individuals experiencing subthreshold PS and those with overt psychotic disorders support the notion of a psychosis continuum. However, genetic and epidemiological studies have emphasized the overlap of PS and other psychiatric illnesses. In particular, PS during adolescence appear to be a non-specific precursor of different psychopathological outcomes.

Given the evidence presented in this review, we argue that findings from population-based studies are appropriate to guide policy-making to further emphasize public health efforts. Broadly accessible mental health programs are promising to make a difference in the field of adolescent mental health. However, the specific efficacy of these programs warrants further study, and caution is advised to not over-pathologize potentially transient occurrence of mental health problems.

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Recent years have seen an advent in population-based studies that examine the prevalence, etiology, and developmental trajectories of diverse subclinical psychopathological symptoms that pose a risk for the later development of severe mental illnesses. It is increasingly recognized that most categorically defined psychiatric disorders (i) occur on a spectrum or continuum (1) that is not necessarily normally distributed (2), (ii) show high heterogeneity and symptom overlap, and (iii) share genetic and environmental risk factors (3,4). Therefore, population-based studies of psychopathology in youth assess a broad spectrum of symptoms as well as genetic risk, cognitive and general functioning, socioeconomic, and environmental factors to yield a more complete understanding of symptom etiology and development. Pediatric population-based studies with longitudinal study designs may be helpful for defining normative growth charts of diverse disease dimensions that in turn may aid in developing individual risk predictions (5).

Here, we review different aspects of population-based studies with regard to the psychosis spectrum; we discuss neurodevelopmental underpinnings of psychosis spectrum symptoms, brain morphometric and functional alterations in individuals experiencing psychotic symptoms in the general population, and the role of genetic liability for psychosis.

Given the overwhelming evidence offered by this body of recent work that even subclinical psychotic symptoms pose a risk for severe mental illnesses, we highlight promising strategies that facilitate access to mental health services for adolescents, a group highly vulnerable to mental health problems. Even though further research is needed, in particular to understand risk and resilience factors for longitudinal symptom progression, policy-making should take available data into account to further reduce mental health stigma and to invest in prevention and early intervention programs.

The psychosis spectrum and clinical staging models

Despite the longstanding conceptualization of a continuum of psychotic symptoms (PS), this is not reflected in current diagnostic manuals (6-9). Recent findings in both help-seeking individuals experiencing PS, and studies on PS in the general population have further emphasized this notion (10). Presumably, the psychosis continuum is characterized by qualitatively similar PS that vary in levels of conviction and duration, ranging from subclinical schizotypal symptoms to severe psychosis spectrum disorders such as schizophrenia. PS, as typically studied in population-based cohorts, include positive symptoms such as hallucinations and delusions. Sometimes negative symptoms such as flat affect are also considered when establishing subclinical psychosis categories (see (11,12)) for detailed discussion on psychometric issues).

The concept of a psychosis continuum has further facilitated the adoption of a clinical staging model (3,13). Symptoms typically observed in the general population refer to stage 1a, nonspecific general psychopathologies such as depressive and anxiety symptoms

alongside subthreshold PS, and stage 1b with more specific PS, i.e., commonly termed clinical- or ultra-high risk state (14). Stage 0 in this model is defined by a genetic risk through a positive family history of severe mental illness and other states are characterized by above-threshold PS (stage 2), persistence of symptoms (stage 3), and severe, non-remitted psychotic disorders (stage 4). Importantly, individuals do not necessarily change stages with time but may remain in their initially assigned stage. Similarly, studies on clinical high-risk (CHR) cohorts specifically examining conversion to full-blown psychosis, i.e., changes of clinical stages, find low transition rates of approximately 20-35% over 2 years (15,16). Furthermore, the clinical staging model is primarily based on retrospective studies and requires further prospective validation.

The fact that the majority of individuals with a first episode of psychosis have not sought help before their 'psychotic break' highlights the necessity to broaden the target symptoms and audience of early intervention strategies for psychosis spectrum disorders. Population-based studies have become an important strategy to validate the concept of a psychosis continuum, and may be helpful to tailor future primary prevention strategies to the general population by examining longitudinal trajectories of PS development across childhood and adolescence to detect early predictors (5,17).

Studies on PS in the general population can further be viewed as an alternative to the CHR approach, an enrichment sampling focused on *help-seeking* individuals fulfilling certain diagnostic criteria (14,18). Studies applying CHR criteria to date have focused primarily on psychosis spectrum outcomes (19). Given that clinical ascertainment is required, CHR cohorts may not reflect the broader population experiencing PS, which may at least partially explain higher pluripotentiality (i.e., risk of developing any kind of psychiatric disorder) of PS observed in population-based studies relative to CHR samples (20,21).

Are psychotic symptoms a public health concern?

Similar to overt psychotic disorders, PS in the general population (prevalence: 5.8% (22)) are often accompanied by cognitive impairments (23), reduced quality of life (24), higher rates of substance use, functional disability, suicidality (25-28), and alterations in brain structure and function (29-34), rendering PS an important public health issue. In accordance with a clinical staging model, PS pose an elevated risk for the later development of overt mental illness; not only severe psychosis spectrum disorders (35) but also depression, anxiety disorder, and bipolar disorder (3,36), amplifying the significance as a public health concern. However, recent epidemiological and genetic findings highlight the complex relationship between PS and severe mental illnesses (36-38): overt psychotic disorders may exhibit diverse psychopathological precursors and similarly, PS in childhood and adolescence do not always foreshadow persistent psychosis and/or schizophrenia later in life. For example, in the Philadelphia Neurodevelopmental Cohort (PNC) a positive predictive value of 0.51 was reported for initial screening of PS (39), but in a small Irish youth sample childhood PS had a positive predictive value of >0.59 for adolescent externalizing and internalizing problems (40).

Population-based longitudinal studies on subclinical/ subthreshold PS in children and adolescents offer promise for identifying disease biomarkers that predict progression to overt mental illness (41). Ultimately, these efforts aim at improving early identification of at-risk youth in order to improve long-term functional outcomes. Risk factors for subthreshold PS and overt psychotic disorders, include genetic risk, both family history (42,43) and high-impact copy number variations (CNVs) such as 22q11.2 deletion syndrome (44,45), exposure to drugs as well as childhood adversities/trauma, obstetric complications, and socioeconomic difficulties, including ethnic minority and immigrant status (46). Importantly, all forms of prevention, i.e., universal, selective, and indicated (47), can be tailored to these risk factors (17). For example, universal prevention targets the general population and could involve destigmatization and anti-bullying campaigns to improve mental well-being overall. Selective preventions for people with increased risk for developing psychiatric disorders (stage 0) could be implemented in clinics by providing services for families of patients with severe mental illnesses, and indicated prevention is aimed at improving outcome in CHR individuals (stages 1a and 1b) (17).

Overall, general population studies allow for larger and unbiased samples, without typical confounders in clinical populations such as medication and illness duration. Such studies can therefore inform and shape policy making for preventive measures of severe mental illnesses. Table 1 provides an overview of population-based studies cited in this review.

Early neurodevelopmental factors associated with psychotic symptoms

Do psychotic symptoms in childhood and adolescence predict psychosis?

A pressing question, requiring longitudinal study, is whether subclinical PS in youth in the general population are in fact associated with the onset of overt psychosis later in life. One such study is the Dunedin Multidisciplinary Health and Development study, a birth cohort study out of New Zealand that followed the initial cohort (N=1,037) over 38 years. A recent follow-up of this cohort reported that PS at age 11 were associated not only with a diagnosis of schizophrenia at age 38 (relative risk (RR) 7.24) but also with diagnoses of Post-Traumatic Stress Disorder (RR 3.03), substance dependence (RR 1.91), depression (RR 1.50), and anxiety (RR 1.47). Higher rates of PS at age 11 further predicted suicide/ suicide attempts at age 38, even when controlling for other psychiatric disorders at age 11 (RR 2.58) (35) [the 15-year follow-up study of the Dunedin cohort at age 26 reported very similar findings (48)]. It is important to note, however, that PS were assessed with the Diagnostic Interview Schedule for Children (DISC-C (49)), an instrument that includes only 5 questions on positive PS.

The Avon Longitudinal Study of Parents and Children (ALSPaC), with over 13,000 study participants, includes a total of 68 assessment points between birth and age 18. Niarchou et al. (50) reported that, similar to results from the Dunedin cohort, PS at age 12 were predictive of a psychotic disorder at age 18 (odds ratio (OR) 12.7). Interestingly, non-specific symptoms such as depersonalization and sub-psychotic unusual experiences were predictive of a psychotic disorder and depression at age 18 (51). Even though, ALSPaC also assessed only positive PS, the semi-structured PLIKSi instrument covers the three major

domains of positive PS, i.e., hallucinations, delusions, and bizarre thinking, and therefore reflects a broader spectrum of PS (52).

Overall, in the general population it appears that PS during childhood and adolescence increase the risk of later development of a broad range of psychiatric illnesses (pluripotentiality). PS in help-seeking individuals fulfilling CHR criteria may be more specific in terms of predicting psychosis onset (53) even though rates of co-occurring non-psychotic disorders are also higher in these cohorts relative to the general population (54).

Etiology

Although their etiology is not well understood, PS throughout life are often preceded and accompanied by emotional and behavioral problems, which in turn are often associated with (early) life adversities. Findings from the ALSPaC sample further confirmed previously described risk factors. In particular, early neurodevelopmental problems such as autism spectrum symptoms, asphyxia during birth, lower IQ, and delayed early motor development were specifically associated with PS in adolescence (4). Bolhuis et al. (Generation R study, N=3,984 (55,56)) highlighted emotional and behavioral problems at age 3 and 6 as the earliest significant predictors of PS at age 10. These encompassed depressive symptoms, aggressive behavior, anxiety, sleep difficulties, attention problems, and somatic complaints. Interestingly, emotional and behavioral problems also partially explained the association between previously described risk factors such as autistic traits and childhood adversities and PS, rendering it likely that emotional problems are a core risk factor or precursor for later PS. Further, the authors hypothesize that PS can manifest differently across the lifespan, ranging from emotional problems in early childhood to subclinical PS in late childhood and adolescence, and severe mental illness in adulthood. However, difficulties in validly assessing PS in younger children could lead to a distortion of the true association between childhood emotional problems and PS (55,57,58). A twin study (Twins Early Development Study [TEDS] and Longitudinal Experiences And Perceptions [LEAP], N ~ 5,076) further supports an association between childhood emotional and behavioral problems and adolescent PS by showing a modest genetic overlap across these phenotypes (59). Further, lack of certain personal resources such as low optimism, low self-esteem, and high avoidance, in addition to emotional problems, have been reported as significant predictors of PS during adolescence (60).

Early life stress and childhood adversities are associated with emotional and behavioral problems not only in childhood and adolescence but across the lifespan (61,62). In the largest population-based study to date, the World Health Organization Mental Health Survey (N= 23,998), McGrath and colleagues confirmed that childhood adversities are associated with an at least two-fold increased risk for developing PS, in a dose-response relationship (63). Childhood adversities characterizing ‘maladaptive family functioning’ (parental mental illness and substance abuse, family violence, physical and sexual abuse, neglect) posed a somewhat stronger association with later onset of PS than ‘other childhood adversities’ (parental death, divorce or loss, economic adversity). Interestingly, when adjusting for other mental illnesses with onset prior to PS, the association between childhood adversities and PS onset during adolescence became non-significant. This finding suggests that childhood

adversities are not only a risk factor for adolescent-onset PS, but also other psychopathological symptoms with onset prior to adolescence, which in turn may lead to PS.

Finally, an often-discussed risk factor for the consecutive development of PS is cannabis use; longitudinal results from the Netherlands Mental Health and Incidence Study (N=7,076) reported that baseline cannabis use predicted PS at follow-up (OR 2.76) (64). Recent publications conclude that the evidence for this association is sufficient for policy makers to take this risk into consideration when further discussing legalizing cannabis (65,66).

Genetic liability for psychotic symptoms in the general population

Recently, genetic studies have made great progress in elucidating the genetic architecture of severe mental illnesses. In the majority of cases, risk for severe mental illnesses appears to be attributable to the cumulative impact of multiple genes, where each gene individually explains only a small amount of variance, but the sum of risk alleles across all identified variants accounts for up to 18% of variance in schizophrenia diagnosis (67,68). As such, investigation of polygenic risk scores (PRS), based on effect sizes of common variants associated with schizophrenia (68) and other disorders (69) has become increasingly common in population-based studies.

Studies applying PRS (based on adults with established diagnoses) to developmental cohorts have recently emerged. For example, in the ALSPaC cohort schizophrenia PRS was significantly associated with negative symptoms (OR 1.21) and anxiety (OR 1.17) during adolescence, but not with positive symptoms, again suggesting that the genetic basis of PS may present differently across development (70). In line with behavioral studies, Riglin et al. highlighted associations between schizophrenia PRS and diverse problems of childhood development at ages 7 to 9, such as lower IQ (OR 1.13) and poor social (OR 1.08) and language skills (OR 1.10) (71).

A recent study combined three major population-based cohorts [ALSPaC, TEDS (72), and CATSS (Child and Adolescent Twin Study in Sweden (73)], identifying significant associations between schizophrenia PRS and different symptom domains: hallucinations and paranoia (when excluding individuals who scored zero), anhedonia, cognitive disorganization, and parent-rated negative symptoms (74). Interestingly, bipolar disorder PRS was also significantly associated with hallucinations and paranoia, even when including individuals who scored zero on this scale. PRS for major depression was further associated with anhedonia and parent-reported negative symptoms. In a follow-up study taking a multivariate factor analytic approach, Jones et al. found schizophrenia PRS was significantly associated with multiple psychopathology factors (positive symptoms, negative symptoms, depression, and anxiety) (38). However, these specific effects vanished when including a general psychopathology factor, suggesting that psychopathology during adolescence may be explained with one broad factor.

PS during adolescence are rather non-specific and pose risk for a variety of severe mental illnesses. Loohuis and colleagues therefore utilized a novel multi-trait approach (75) including PRS of a broad range of psychiatric disorders, including neurodevelopmental

disorders as well as brain and cognitive traits, to assess the association between these genetic risk factors and PS in youth. Interestingly, the ADHD PRS was the only significant predictor of PS in youth of European-American ancestry in the PNC (here N = 7,225), even after removing individuals endorsing any ADHD symptoms to avoid confounds related to phenotypic overlap (75). This finding was replicated in a sample of help-seeking CHR individuals. Further, the association between PS and ADHD PRS was age-dependent, such that the association was strongest in younger children (< 12 years old). It is noteworthy that for individuals < 12 years only collateral information on psychopathology was available, which could affect the results.

In addition to polygenic risk (i.e., common risk variants), recent exome sequencing studies have also found that rare and ultra-rare variants contribute to the genetic risk of schizophrenia (76,77).

Overall, findings from these studies highlight the complex association between genetic risk and PS during adolescence. While such symptoms may be non-specific, and presage later severe mental illnesses, polygenic risk may be indexing global psychopathology as well as risk for specific diagnostic entities. Importantly, because PRS are currently derived from almost entirely European cohorts, their application to non-European ethnic groups is problematic (78); collection of ethnically diverse samples is a research imperative. Further, while PRS are far from clinical utility in the general population, as ever-increasing GWAS size improves the strength of these associations, these risk scores may approach clinical utility in enriched populations in the near future (e.g., (79)).

Alterations in brain structure and function associated with psychotic symptoms

Examples of publicly available population-based datasets in youth that include multimodal imaging and neurocognitive assessments are the PNC (80) and the Adolescent Brain Cognitive Development study (ABCD, (81)). These samples offer unprecedented opportunities for the neuroscience community to study complex brain-behavior interactions during development. In particular, longitudinal data will allow for unique investigations of developmental trajectories. Given the young age of ABCD participants at study baseline (ages 9-10 (81)) it has the potential to capture earliest signs of emotional and behavioral problems associated with subsequent severe mental illnesses. Table 2 summarizes large-scale epidemiological cohorts with multimodal imaging.

The PNC has led to a wealth of new findings regarding structural and functional brain alterations in youth experiencing PS; 1,445 youth aged 8 to 21 years were recruited from the greater Philadelphia area and underwent genotyping, multimodal imaging, and neuropsychological testing. This sample was not ascertained for specific neuropsychiatric problems and includes multi-ethnic youth from various socio-economic backgrounds. Exclusion criteria were limited, and included significant medical problems, intellectual disability, neurological and/or endocrine conditions, and general MRI contraindications (80).

Importantly, all studies on PS in the PNC applied the same diagnostic criteria, offering comparability across studies (39,82). Furthermore, neuroimaging data were acquired with a single MRI scanner, reducing artifacts and heterogeneity due to scanner and study site variability.

Brain Morphometry

Gray and white matter morphology have been investigated in detail in the PNC. Reductions in local gray matter volume in youth experiencing PS relative to typically developing youth were observed in bilateral medial temporal lobes, and were also associated with PS severity (32). Further, a significant age by group interaction suggested that these local reductions in gray matter volume only became apparent in mid-adolescence in youth experiencing PS. This pattern of volume reductions in medial temporal regions mirrors a wealth of such findings not only in individuals with chronic schizophrenia, but also in individuals with first-episode psychosis as well as in individuals at clinical high-risk (CHR) for developing psychosis (83,84). Given that the medial temporal lobe in this study (32) included both the amygdala as well as parahippocampal cortex, this finding was followed up with a more detailed parcellation of the temporal lobe: whereas decreased volume of the left amygdala was associated with positive PS, decreased volume of the left entorhinal cortex was correlated with impaired cognition as well as more severe negative and disorganized symptoms (34), suggesting that variation in these brain structures may contribute to distinct symptom domains.

Jalbrzikowski et al. subsequently investigated whole-brain morphology differences in cortical thickness, surface area, and subcortical volume in PS youth in this cohort, relative to both youth with bipolar mood symptoms and typically developing youth (85). This study found thalamic volume reductions that were specific to PS. Again, these findings parallel those observed in individuals with overt psychosis and those at CHR (86), highlighting the role of the thalamus in neural system disruptions in psychosis. In terms of white matter microstructure, youth with PS also exhibited reduced fractional anisotropy in the retrolenticular internal capsule and the superior longitudinal fasciculus (SLF), possibly reflecting altered axonal diameter and/or myelination (87). Development of the SLF was associated with cognitive maturation in typically developing youth, an effect that was absent in youth experiencing PS.

Overall, alterations of brain morphology observed in these non-clinically ascertained cohorts of youth experiencing subthreshold PS can be interpreted as further evidence for a psychosis continuum, given qualitatively similar alterations observed in individuals with overt illness and those at CHR for psychosis.

Functional Brain Alterations

In terms of functional MRI, task-based brain function and resting state functional connectivity have both been investigated in population-based studies of PS. In the PNC, two MRI paradigms have been acquired: an n-back task probing different working memory loads and an emotion identification task. Working memory is viewed as a function of higher cognitive/ executive functioning consistently shown to be impaired in schizophrenia (88).

Similarly, a wealth of evidence exists for impaired emotional processing in schizophrenia (89). Wolf et al. found reduced activation in the executive control network in response to increasing working memory demands, concomitant with worse performance, in PS youth relative to typically developing peers (33). Amygdala activation in response to threatening facial expressions was increased in PS youth compared to unaffected youth and was also positively correlated with positive symptom severity (33).

Utilizing data from the IMAGEN study that included longitudinal fMRI and measures of PS at follow-up, Papanstasiou et al. observed increases in right frontal activation during reward anticipation and feedback of win from age 14 to 19 that was associated with PS at age 19; this increase over time was not observed in youth who did not report PS. The authors speculate whether this finding could be a possible compensatory mechanism. However, given that PS were not assessed at age 14, results are to be interpreted with caution.

Resting-state fMRI has become a popular tool to study how distant brain areas are functionally connected. Unlike task-based fMRI, it is less susceptible to performance and vigilance differences between groups, which facilitates interpretation of group differences.

Again, the PNC has allowed large-scale investigation of functional connectivity across development. With regard to static functional connectivity (i.e., average connectivity across the resting-state scan), Satterthwaite et al. showed that PS youth exhibited similar patterns of dysconnectivity to patients with overt psychosis. In particular, they observed hyperconnectivity within the default-mode network (DMN) and reduced functional connectivity within the executive control network (31). However, in one of the largest pediatric population-based samples (ABCD; N = 3,434) Karcher et al. recently reported *hypo*connectivity within the DMN and within the executive control networks that is associated with increased PS in 9- to 11-year old children (90). These differences in observed hypo- vs. hyperconnectivity may be attributable to age differences between the two studies. Nevertheless, there has been a similar dissonance in adult cohorts with overt psychosis, where both hypo- and hyperconnectivity of the DMN and executive control networks has been described (91,92).

In an elegant follow-up study that applied multivariate sparse canonical correlation analysis to the PNC resting state data, Xia and colleagues corroborated that in fact the *segregation* between the DMN and executive control networks is a common feature across multiple psychopathology dimensions, but the psychosis dimension shows the strongest effect (93). Moreover, a recent study of this cohort that investigated dynamic properties of functional connectivity, i.e., time-varying patterns of whole-brain connectivity, found that previously described dysconnectivity between the DMN and executive control networks in youth experiencing PS is time-dependent, and only occurs during certain periods of a resting-state scan, whereas dysconnectivity in visual and sensorimotor areas is much more pervasive (94).

The Human Connectome Project (HCP) is an adult cohort in which resting-state fMRI as well as self-reported PS were acquired. Here, PS were significantly inversely correlated with cognitive abilities, an effect that was partially mediated by global efficiency of the executive control network, a measure of network integration (95). With regard to dynamic functional

connectivity in the HCP, it has recently been shown that adults experiencing PS spend more time in a dynamic state, i.e., a distinct time-varying connectivity pattern, characterized by reduced connectivity within the DMN (29); a finding that mirrors previous results in studies on individuals with overt psychosis (96).

Summary

Overall, structural and functional brain imaging results on PS in the general population, in adult as well as youth samples, exhibit high overlap with findings obtained from individuals with overt psychosis and those at CHR for developing psychosis. Studies in CHR samples have shown that neuroanatomical biomarkers can predict conversion to overt psychosis and improve prognostic accuracy (97). Although not yet at the point of clinical utility, in the future such biomarkers may also identify individuals with subthreshold PS and altered brain structure and/ or function that may be at increased risk for progression of PS and onset of overt illness. Presumably, these individuals would benefit the most from prevention strategies such as psychosocial interventions, although this hypothesis has yet to be empirically tested.

Longitudinal imaging studies with comprehensive assessment of broad psychopathology, cognition, and socioeconomic/environmental measures are needed to answer important questions of early precursors, symptom development and progression.

Public health implications

Even though pediatric (including adolescent) population neuroscience is still in its infancy, studies overwhelmingly find that PS in childhood and adolescence pose a risk factor for later development of overt psychiatric illness, and are overall associated with reduced functioning and quality of life. Many early intervention specialty programs offer a coherent multimodal treatment framework for clients, including psychopharmacological treatment, psychotherapy and psychoeducation as well as vocational counseling (‘one-stop-shop’ (98)). Meta-analytic results suggest that multidisciplinary therapies can delay or prevent transition to overt psychosis (99,100). Low risk psychosocial interventions targeting functioning have been shown to be effective in CHR youth; such approaches are likely to be also effective in a broader audience (101-105). These results find consideration in the recently published guidelines of the European Psychiatric Association (106) where a dual treatment consisting of cognitive behavioral therapy and pharmacological treatment yields recommendation grade *A* (‘meta-analysis, systematic review, or RCTs with very low risk for bias’) for adult CHR individuals. For children and adolescents experiencing PS, as targeted by pediatric population neuroscience, the expert recommendation is specific psychological interventions to improve functioning and close monitoring of PS.

PS are often preceded by non-specific behavioral and emotional problems in childhood related to increased adversity and trauma. Since these precursors in themselves pose a risk for development of diverse psychopathologies, we argue – as others before us (107,108) – that these childhood-onset problems offer another promising target for population-based preventive interventions. However, causal mechanisms from abnormal neurodevelopment to subsequent psychopathology are not yet understood and require further longitudinal

research. Since only a minority of individuals with PS access appropriate mental health services, it will be important to implement services appropriate to a broad audience, for example in schools. It will be essential to identify those individuals at highest risk, and to reduce the number of false positives in order to provide cost effective services and to reduce stigma. Individual risk calculators developed and tested in CHR cohorts may not work as well when broadening the target audience. With sufficient longitudinal data, questionnaires such as the Psychosis Questionnaire, Brief Version (109) may be amenable for community samples, and may be used to develop risk calculators for youth in the general population.

Given the evidence presented here and results from the Outreach and Support in South London and Headspace initiatives (110-112), we argue that findings from population-based studies are adequate for guiding policy-making toward further emphasis on public health efforts, although more systematic research is needed in this area. Destigmatization initiatives for mental illness have been shown to be effective in reducing discrimination and stigma (113-115), and broadly accessible mental health programs like Headspace and Jigsaw are promising to make a difference in the field of adolescent mental health (112,116). However, the specific efficacy of these programs warrants further study, and caution is advised to not over-pathologize potentially transient occurrence of mental health problems.

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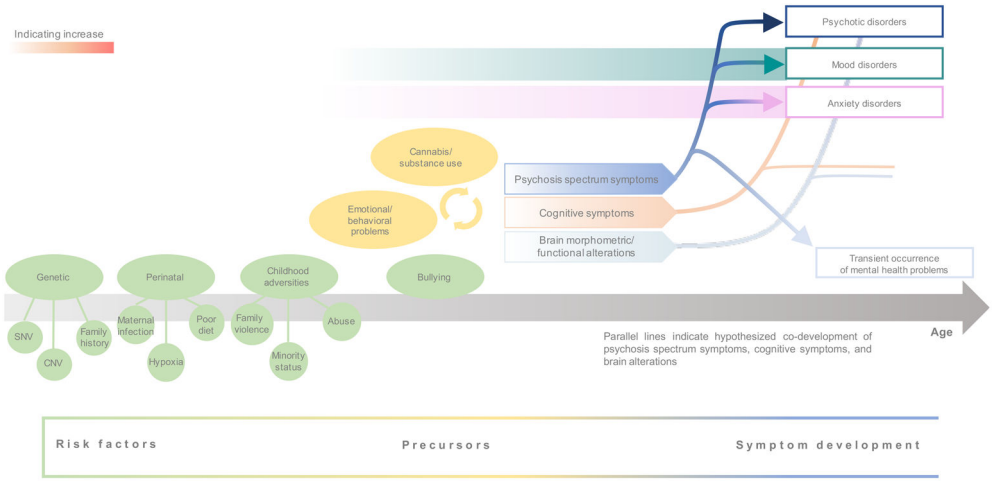

Figure 1:

Schematic of hypothesized development of psychosis spectrum symptoms, associated risk factors and precursors

Table 1:

Overview of population-based survey studies, sample sizes, and instrument used to assess PS symptoms

Study	Sample size	Psychopathology instrument relevant to PS	Longitudinal (y/n)
Avon Longitudinal Study of Parents and Children	13,988 *	PLIKSi	y
Dunedin Multidisciplinary Health and Development Study	1,037	DISC-C/DIS	y
WHO Mental Health Survey	23,998	CIDI	n
Netherlands Mental Health and Incidence Study	7,076	CIDI/SCID-III	y
Environmental-Risk Longitudinal Twin Study	2,232	SIPS	Y
Mental Health in the General Population (WHO)	38,694	MINI	n
My World Survey – Second Level	6,062	APSS	n
Twins Early Development Study + Longitudinal Experiences and Perceptions	5,537 – 5,076	SPEQ	y
The Child and Adolescent Twin Study in Sweden	17,220	K-SADS-PL	y

* sample size may vary due to bolstering of the initial sample; ALSPaC and Dunedin will include MRI in subsequent follow-ups.

PLIKSi – Psychosis-like Symptoms interview (45), DISC-C – Diagnostic Interview Schedule for Children (42), CIDI – Composite International Diagnostic Interview, SCID-III – Structured Clinical Interview for DSM-III-R, SIPS – Structured Interview for Prodromal Symptoms (108), MINI – Mini International Neuropsychiatric Interview (109), APSS – Adolescent Psychotic-like Symptom Screener (110), SPEQ – Specific Psychotic Experiences Questionnaire (111), K-SADS-PL – Schedule for Affective Disorders and Schizophrenia for School-age Children – present and lifetime version (112)

Table 2:

Overview of population-based neuroimaging studies

Study	Sample size	MRI modalities (not exhaustive)	Longitudinal (y/n)	Publicly available (y/n)
PNC	1,445[+]	Resting BOLD, task fMRI (emotion identification, n-back), structure (MPRAGE T1), DTI	n[*]	y
ABCD	11,878	Resting BOLD, task fMRI (MID, stop-signal, emotional n-back), structure (T1, T2), DTI	y[**]	y
HCP-D	1,350	Task fMRI (guessing task, go/ no go task, emotion identification), structure (T1, T2),	n	y
IMAGEN	~2,000	Resting BOLD, task fMRI (face/ emotion processing, MID, stop-signal, global cognition)	y	n
GenR	1,070	Resting BOLD, structure (T1), DTI	y	n
Saguenay Youth Study	1,029	Structure (T1, T2)	n	n
Nathan Kline Institute-Rockland Sample	>1,000	Resting BOLD, task fMRI (visual checkerboard, neurofeedback tasks), DTI	y	y

[*] longitudinal data are currently not publicly available

[**] longitudinal data release anticipated in summer 2020

[+] The PNC neuroimaging sample has a sample size of N = 1,445; however, the entire sample includes 9,421 individuals that completed the neurocognitive and psychopathology assessment

PNC – Philadelphia Neurodevelopmental Cohort, ABCD – Adolescent Brain Cognitive Development, HCP-D – Human Connectome Project Development (113), IMAGEN (114), GenR – Generation R (115), Saguenay Youth Study (116, 117), Nathan Kline Institute-Rockland Sample (NKI-RS (118); MRI – magnetic resonance imaging, MPRAGE – magnetization-prepared rapid acquisition with gradient echo, DTI – Diffusion Tensor Imaging