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Counterpoint. Early Intervention for Psychosis Risk Syndromes: Minimizing Risk and Maximizing Benefit

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Abstract

Background: Malhi et al. in this issue critique the clinical high risk (CHR) syndrome for psychosis.

Method: Response to points of critique.

Results: We agree that inconsistency in CHR nomenclature should be minimized. We respectfully disagree on other points. In our view: a) individuals with CHR and their families need help, using existing interventions, even though we do not yet fully understand disease mechanisms; b) substantial progress has been made in identification of biomarkers; c) symptoms used to identify CHR *are* specific to psychotic illnesses; d) CHR diagnosis is not "extremely difficult"; e) the pattern of progression, although heterogenous, is discernible; f) "psychosis-like symptoms" are common but are not used to identify CHR; and g) on the point described as 'the real risk,' CHR diagnosis does not frequently cause harmful stigma.

Discussion: Malhi et al.'s arguments do not fairly characterize progress in the CHR field nor efforts to minimize stigma. That said, much work remains in areas of consistent nomenclature, mechanisms of disease, dissecting heterogeneity, and biomarkers. With regard to what the authors term the "real risk" of stigma associated with a CHR "label," however, our view is that avoiding words like "risk" and "psychosis" reinforces the stigma that both they and we mean to oppose. Moreover, patients and their families benefit from being given a term that describes what is happening to them.

Malhi, Bell, Hamilton, and Morris in this issue (Malhi et al., 2020) present a critique of early intervention (EI) in psychiatry that is directly relevant to the clinical high risk (CHR) syndrome for psychosis. The main points of their argument are that EI paradigms like those involving the CHR syndrome: 1) have little chance to benefit patients because we do not understand the mechanisms of disease, 2) have been developed without reliable biomarkers for etiology and progression, 3) use non-specific symptoms to identify patients as at-risk, 4)

are based on a diagnosis that is extremely difficult to make, 5) identify a disorder with no discernible pattern of progression, 6) identify patients as at-risk based on symptoms that are common in non-psychotic individuals, 7) are characterized by confusion and inconsistency that hinders research and practice, 8) are investigated by researchers who may have become complacent, and 9) may harm patients more often than we realize by creating stigma and overall may do more harm than good. We address each of the individual points in turn.

1. Must we fully understand disease mechanisms before we try to help?

Malhi et al. assert that we do not understand the causes and pathophysiology of psychiatric illness to the extent we do medical illnesses such as ischemic heart disease, which we will not dispute. We do not dispute either that “much remains unknown about the biology, aetiology and progression of these syndromes”; however, in our view it does not follow that “the application of early intervention for psychiatric disorders is clearly hamstrung.” Just as molecular understanding of ischemic heart disease was not absolutely necessary to recommend dietary improvements and exercise, we can help many individuals who meet CHR criteria by providing professional feedback, monitoring, and treatment as needed, even if the jury remains out on exact molecular mechanisms that map onto psychosis. The Figure illustrates our view of the current state of disease models in CHR.

2. Is there an absence of reliable biomarkers for etiology and progression of psychosis?

Although what the authors mean by reliable is unclear, it is in fact the case that there are few FDA-registered biomarkers in neurology and none in psychiatry (or in CHR); however, Malhi et al. have pessimistically interpreted a snapshot taken during a period of rapid progress. For example, genomic insights into etiology (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Sekar et al., 2016) and risk prediction for psychosis using polygenic scores (Perkins et al., 2020) is at a similar state of development as for cardiovascular disease (Khera et al., 2018). Moreover, there is a robust literature on biological correlates of progression to psychosis that, when combined with genomic prediction, represent significant progress toward stratification and treatment biomarkers. To give but a few examples, imaging (Anticevic et al., 2015; Bernard et al., 2017; Cannon et al., 2015; Cao et al., 2019; Wang et al., 2016), electrophysiology (Bodatsch et al., 2011; Fryer et al.; Hamilton et al., 2019a; Hamilton et al., 2019b; Hay et al.; Kim et al., 2018; Mathalon et al., 2016; Perez et al., 2014; Ramyead et al., 2019; Tang et al., 2019; van Tricht et al., 2010), motor performance (Dean et al., 2018), natural language processing (Bearden et al., 2011; Bedi et al., 2015; Corcoran et al., 2018; Rezaii et al., 2019), and body fluid (Labad et al., 2015; Perkins et al., 2015; Pruessner et al., 2013; Walker et al., 2013) biomarkers in CHR all map onto psychosis-relevant clinical outcomes, to the point that several biomarker meta-analyses are available (see recent umbrella review (Fusar-Poli et al., in press)). Based on these findings, the US National Institute of Mental Health has found it timely to take the next step toward mature stratification biomarkers to dissect the heterogeneity of CHR course (US NIMH, 2019a, b).

3. Are the symptoms used to identify CHR not specific to psychotic illnesses?

Patients who meet CHR criteria do not all progress to psychosis or to any single psychiatric diagnosis. This is very much analogous to patients with mild cognitive impairment (MCI) who may progress to Alzheimer's disease, Lewy body or vascular dementia, some combination, or who might not progress at all. In fact, the 15% rate of conversion from CHR to psychosis at one year in a recent meta-analysis (Salazar de Pablo et al., 2020)is comparable to the annualized conversion rate from MCI to dementia in specialist centers (9.6%/year (Mitchell and Shiri-Feshki, 2009)) and to the annualized rate of progression from prediabetes to diabetes (5–10%/year (Tabak et al., 2012)).

Malhi et al.'s statement that the CHR field uses non-specific symptoms such as functional decline and change in subjective experience to *identify* patients as at-risk is misleading. The vast majority of patients (95% in a recent meta-analysis (Fusar-Poli et al., 2016a)) are identified based on specific positive psychotic symptoms that are either not severe enough or frequent enough to meet thresholds for psychotic disorder. Furthermore, CHR symptoms are specific to prediction of new/incident psychotic disorders, while there is no evidence they predict onset of any non-psychotic disorder (Fusar-Poli et al., 2017b; Schultze-Lutter et al., 2012; Webb et al., 2015; Woods et al., 2018).

For the remaining 5%, functional decline does *contribute* to identification but is not sufficient: a more specific genetic risk for psychosis is also required, which soon may no longer be dependent on family history alone but based on personalized genomic analysis. We also note that some CHR assessment instruments such as the Comprehensive Assessment of At Risk Mental State (CAARMS) do require functional decline for a CHR status, but again that is never the only requirement and nearly all patients also report specific symptoms.

Malhi et al. are correct that this 5% subgroup is not only rare but also associated with a lower risk of conversion to psychosis (Fusar-Poli et al., 2016a; Fusar-Poli et al., 2020) and different treatment needs. We agree and observe that the field is moving in the direction of reducing heterogeneity as suggested by the authors. The DSM-5 CHR criteria did not include this subgroup (American Psychiatric Association, 2013), and the European Psychiatric Association has recommended removing it (Schultze-Lutter et al., 2015). These patients do have treatment needs, however, and additional work is needed on their classification.

4. Is CHR diagnosis extremely difficult?

We first note that the CHR syndrome is either a research diagnosis or an innovative clinical one, not one endorsed as independently codable either in DSM-5 or ICD-10. Its status in DSM-5 (as Attenuated Psychosis Syndrome, APS) is somewhat ambiguous, described both as a "Condition for Further Study" (page 783) and also as one of four examples under the codable "Other Specified Schizophrenia Spectrum and Other Psychotic Disorder" (page 122) (American Psychiatric Association, 2013).

Malhi et al. are mistaken to characterize the CHR diagnosis as “extremely” difficult, either in the research or in the DSM-5 context. An extremely difficult diagnosis would have poor inter-rater reliability (IRR), but IRR for the CHR classification has *not* been poor. For the research diagnosis, a recent book chapter collected 23 IRR reports on the CHR research diagnosis for one assessment measure, the Structured Interview for Psychosis-risk Syndromes (SIPS) (Woods et al., 2019). Of the 17 reporting kappa as the reliability statistic, the median was 0.88, well into the excellent range. Diagnostic IRR for the CAARMS was similar (Kollias et al., 2015; Miyakoshi et al., 2009; Paterlini et al., 2019). IRR for the diagnostic positive symptoms in the recent NAPLS-3 study was 0.89 across 40 raters (Addington et al., in press).

In the DSM-5 context, the available data are sparser, and clinicians do require training to distinguish CHR from patients with no pathological attenuated psychotic symptoms and from those with frank psychosis (Miller et al., 2003). However, in a small sample from the DSM-5 field trials the reliability of the CHR diagnosis was right in the middle of the tested disorders, identical to that for schizophrenia (Clarke et al., 2013; Fusar-Poli et al., 2014; Regier et al., 2013). In another study, clinicians received a 30-minute training on DSM-5 APS before conducting unstructured diagnostic interviews. IRR was in the acceptable range (Woods et al., 2012).

That said, we do not mean to imply that the CHR diagnosis is a simple one. General clinical diagnostic experience is required, and care and sufficient time must be taken in specific training and implementation.

5. Does psychotic disorder lack a discernible pattern of progression?

Malhi et al. assert that “psychiatric illnesses do not appear to have a discernible pattern of progression in severity.” In the case of CHR, the evidence for a pattern of progression is actually quite strong, beginning with nonspecific symptoms such as anxiety and depression, followed by negative symptoms, and then by the more specific positive symptoms (Hafner et al., 1993). Most of the evidence on the early course comes from retrospective studies, since prospective population cohort studies can yield relatively few cases (Poulton et al., 2000). Ultimately newer such efforts like the Philadelphia Neurodevelopmental Cohort (Calkins et al., 2014) and the Adolescent Brain Cognition and Development study (Volkow et al., 2018) may be positioned to confirm the retrospective model.

From a prospective point of view, the course of CHR clearly shows considerable heterogeneity, with positive symptoms, functioning, cognition, and negative and affective symptoms all following partly independent trajectories (e.g. (Allswede et al., 2020)) that will continue to be dissected in the future (US NIMH, 2019a, b).

6. Are psychosis-like symptoms relatively common among non-psychotic individuals?

“Psychosis-like” symptoms or experiences (PLEs) are assessed by self-report. Malhi et al. recapitulate a common error (Schultze-Lutter et al., 2018) by conflating PLEs with the

clinician-assessed attenuated positive symptoms used to diagnose CHR, which unlike PLEs employ an experienced and trained clinician to distinguish pathological from non-pathological experiences. Studies comparing self-report vs interview methods consistently find that rates of attenuated positive symptoms in the CHR range on structured interview are much lower than rates of PLEs (Fusar-Poli et al., 2017a; Granö et al., 2016; Schultze-Lutter et al., 2018a; Schultze-Lutter et al., 2014b). Thus while PLEs are common, they typically do not achieve contemporaneous clinical significance and do not necessarily map directly to the CHR designation; their frequency does not invalidate CHR diagnostic assessment. In the report cited by Malhi et al. (Yung et al., 2006), fully 98.6% of new enrollees in a youth mental health clinic self-reported one or more PLEs at least sometime during their lives. By contrast, a recent review (Woods et al., 2019) of similar clinical samples that employed SIPS structured interviews found a median CHR diagnosis prevalence of 20.3%. That PLEs are not used to diagnose CHR in no way invalidates their value in general population studies of the psychosis continuum.

7. Is confusion and inconsistency hindering CHR research and practice?

Malhi et al. discuss three examples of different nomenclature used to capture youth and young adults at-risk for psychosis: Ultra High Risk (UHR), At-Risk Mental State (ARMS), and Clinical High Risk (CHR), and they comment that at least the term CHR is used in somewhat different ways across research groups, with for example some groups including the basic symptoms approach as fitting under CHR. On this last specific point, we note that many studies are careful to report results for basic symptoms separately (Ruhrmann et al., 2010b; Schultze-Lutter et al., 2014a; Schultze-Lutter et al., 2018b). Leaving that point, Malhi et al. state that this inconsistency of terminology complicates meta-analyses, both for rates of conversion to psychosis and for treatment outcome. A recent meta-analysis, however, did not find an effect of instrument on conversion outcomes (Fusar-Poli et al., 2015a). Similarly, a recent treatment meta-analysis did not find any effect for type of CHR instrument (Davies et al., 2018).

On the other hand, the two most frequently used at-risk instruments (the SIPS and CAARMS), although similar in many respects including in the assessment of attenuated positive symptoms, do differ in important details (Fusar-Poli et al., 2016b; Miller et al., 2003; Schultze-Lutter et al., 2013). For example, the SIPS but not the CAARMS excludes patients whose at-risk symptoms are better explained by another disorder, and the CAARMS but not the SIPS excludes patients who do not have poor or declining functioning. Moreover, there are few studies employing both instruments to evaluate the degree of overlapping identification. If nonoverlap is substantial it could introduce noise into meta-analyses that could indeed hamper detection of therapeutic signal, even if outcome differences are not statistically significant across platforms. Malhi et al. call for action to provide more clarity and consensus regarding the definition of terms. We agree with them, and several of us have recently (February, 2020) participated in a conference sponsored by US NIMH with precisely this aim. Substantial preliminary progress was made in several areas, and participants committed to continue the work over the next months.

It is unfortunate, but seems to be a general principle, that achieving uniform terminology can take time. Things are not so different in diabetes, where “prediabetes,” criticized on precisely the same grounds as “prodromal,” nonetheless appears to be gaining traction as the consensus term (Tabak et al., 2012), even though the World Health Organization and International Diabetes Foundation have preferred “intermediate hyperglycemia” (WHO and IDF, 2006), the International Expert Committee of the American Diabetic Association “high risk state of developing diabetes” (Nathan et al., 2009), and ICD-10 “abnormal glucose (R73.09)” (Dugan and Shubrook, 2017). Psychiatry has similar issues in general with DSM and ICD differences in the definition of mental disorders.

8. Have CHR researchers become complacent?

Malhi et al. speculate that the field may be possessed of “a false sense that accurate identification of prodromal psychosis is possible and has already been achieved,” which in turn “may foster complacency amongst researchers.” While we do feel some progress has been made in identifying which individuals with CHR are at higher and lower risk with clinically-based risk calculators (Cannon et al., 2016; Carrión et al., 2016; Osborne and Mittal, 2019; Zhang et al., 2018), we note that the previously mentioned US funding announcements (US NIMH, 2019a, b) carried the express purpose of pursuing a deeper understanding and prediction of the various CHR outcomes. Responses were received from researchers working on five continents. These initiatives run counter to the Malhi et al. worry about researcher complacency. In fact, the field has already redoubled efforts to improve CHR ascertainment through risk stratification (Koutsouleris et al., 2018) and CHR outcome delineation through trajectory mapping (Allswede et al., 2020).

9. Does the CHR ‘label’ cause harmful stigma?

Malhi et al. are concerned that CHR diagnostic practices may harm patients more often than we realize by creating stigma and may even do more harm than good. There is no question that stigma is harmful or that psychiatric patients face stigma; similarly, there can also be no question that stigmatizing patients is unacceptable and inconsistent with the ethical principle of *non-maleficence* (Beauchamp and Childress, 2013) or “first do no harm.”

More salient questions, however, are whether, how often, and in what ways does sharing an assessment of risk for psychosis with patients and families produce harmful stigma, and whether and how often disclosure offers benefits consistent with the competing ethical principles (Beauchamp and Childress, 2013) of *beneficence* and *autonomy*. In general we believe that Malhi et al. have overstated and over-emphasized the stigma-related risks associated with a CHR diagnosis, while overlooking evidence that sharing a CHR diagnosis can be helpful. In addition, we emphasize that empathic discussion during disclosure can minimize risks and maximize benefits.

9.1 Overstating the Risks of a CHR Diagnosis

Malhi and colleagues assert that discussing a diagnosis of CHR “has been associated with” significant stress among young people and “often leads to shame, diminished life expectations, and increased social withdrawal.” The authors cite three papers in support,

from 2002, 2005, and 2014 (Corcoran et al., 2005; Rusch et al., 2014; Warner, 2002). We submit that these three reports do not adequately summarize the current state of the field nor speak directly to whether the CHR diagnosis itself "has been associated with" or "often leads to" harm. Two of these papers are early essays that offer cautionary opinion but no empirical data (Corcoran et al., 2005; Warner, 2002). The remaining paper focuses on the effects of stigma and not on whether any psychiatric diagnosis made by the CHR clinic was a cause (Rusch et al., 2014).

Empirical studies not cited by Malhi et al. find substantially less reason for alarm and report that: 1) stigma associated with the CHR diagnosis is lower among patients than among professionals caring for them (Kim et al., 2017), 2) stigma is more likely due to the patient's experience of symptoms rather than to the clinician's diagnosis (Yang et al., 2015), 3) stigma is associated with CHR symptoms even when no diagnosis is attached (Anglin et al., 2014), and 4) stigma associated with the CHR diagnosis is similar to that associated with non-psychotic diagnoses when the CHR diagnosis is explained (Lee et al., 2016). One qualitative study describes anticipatory fear of the stigma associated with a psychosis diagnosis *before* seeking help at a CHR clinic, which of course does not speak to effects of the clinic's CHR diagnosis (Baron et al., 2019). A final study, like one previously mentioned(Rusch et al., 2014), did not discuss whether their clinic informed its patients they met the clinic's criteria for CHR, or the process for informing them, or whether the stigma ratings were made before or after that process (Pyle et al., 2015).

9.2 Evidence that sharing a CHR diagnosis can be helpful

Malhi et al. do not mention the possibility that disclosure of a CHR diagnosis can be helpful. Before reviewing the published evidence we wish to share our experience, evaluating thousands of individuals with CHR in 26 international clinics beginning in 1998, that disclosure of the CHR diagnosis is far more often helpful than hurtful. Each of our clinics is very much aware of the possibility of stigma and remains alert for it, continuously refining its disclosure practices to further minimize the likelihood of a stigmatizing outcome. Our group has also published several recent conceptual papers weighing ethical, legal, and practical benefits and costs of disclosure, including careful consideration of adolescent and young-adult population-specific factors, and in each instance, the preponderance of evidence has favored disclosure (Carol and Mittal, 2018; Corcoran and Landa, 2018; Corcoran, 2016; Millman and Schiffman, 2018; Mittal et al., 2015).

The published empirical evidence also supports the likelihood of benefit rather than harm from the disclosure of CHR diagnosis. A qualitative study from a CHR clinic in Basel reported that the majority of patients worried there was "something wrong with them" *before* coming to the clinic. Eight of eleven patients felt relieved to have symptoms validated and named as a condition by a professional (Uttinger et al., 2018). Another qualitative study of six individuals with CHR reported that the overall consensus was one of wanting to be informed about their condition (Welsh and Tiffin, 2012). For one patient the diagnosis confirmed that other people have similar difficulties and helped him normalize his experiences. Another reasoned that if the condition has been recognized and has a name then mental health services should be able to help. A quantitative study at one of our sites

described the effects on stigma of informing patients of the CHR diagnosis and its risk implications a mean of 11.5 months after disclosure. Disclosure evoked constructive emotions such as feeling understood, hopeful, and relieved (Yang et al., 2015). Lastly, a qualitative study from another of our sites found that "knowing what it means to be at-risk (or knowing their diagnosis) was reported by some participants as a way to feel validated, face their problems, and move forward" (McIlwaine, 2019).

These empirical data are fully consistent with our collective experience and speak to the ethical principle of *beneficence* (Beauchamp and Childress, 2013), or the intent to help patients. In addition, we note that sharing an assessment that a young person meets criteria for the CHR syndrome can send a message of hope to a distressed patient and/or their parents by preventing the mislabeling of attenuated positive symptoms as full psychosis or schizophrenia.

Another benefit of disclosing the CHR diagnosis is honoring the ethical principle of *autonomy* (Beauchamp and Childress, 2013), essentially that patients have the right to know information relevant to their health. There was a time when patients were not told they had cancer, with rates of nondisclosure in some countries as high as 80% (Benowitz, 1999). In one study, while only 54% of patients were told by their doctor they had cancer, 86% wished they had been told (Seo et al., 2000). Currently, withholding information from patients without their knowledge or consent is generally considered ethically unacceptable (American Medical Association, 2020). In our view, the AMA guidance clearly applies to the CHR syndrome since it is associated with very real morbidity (Fusar-Poli et al., 2015b; Ruhrmann et al., 2010a; Woods et al., 2001; Woods et al., 2010) in addition to its very real risk of progression to frank psychosis (Salazar de Pablo et al., 2020).

9.3 Empathic discussion and disclosure of diagnosis minimizes risks and maximizes benefits.

Malhi et al. do not mention the importance of the context and process of diagnostic disclosure in CHR. In terms of context it is important to recognize that CHR clinics do not conduct screenings in settings like schools and then notify people of their risk without their consent. Instead, CHR individuals typically seek out the clinic for help, and the help they are seeking typically includes answers to questions like "what is going on?" -- in essence a request for diagnosis.

In terms of the process of disclosure, we agree with published recommendations from two of our sites (Corcoran, 2016; Mittal et al., 2015) that conveyance of diagnostic and prognostic information should be tailored to each individual, especially when the patient is a minor. It is important to take time with young people and their families, providing clear and easy-to-understand information, soliciting and answering questions, and doing all these things on an ongoing basis. We agree with Malhi et al. that the CHR diagnostic impression should be presented as tentative. In fact, we would go further and state that a brief summary of the scientific basis for the diagnosis should be shared with patients and families, including that it remains innovative and has an ambiguous status in DSM-5, when consistent with their interests in this information and their capacities to understand it. It is generally not necessary to use professional nomenclature to convey the diagnosis and risk, but instead less formal

language such as “your symptoms are the kind that can sometimes turn into serious mental illness and the kind we try to help here” is often better, followed if the patient or family request by explanation that the kind of serious mental illness is psychosis and including more technical terminology and details. In these discussions, it is also important to convey the varying courses/outcomes that have been reported in the literature: that symptoms can remit, persist, or worsen, and that we currently have no way to distinguish those possibilities with certainty for any given individual.

Similar practices of diagnostic disclosure were described early in the existence of one of our longest-standing clinics (McGlashan et al., 2001). These practices and experiences are also similar to those of the world’s first CHR clinic, which found that young people “accept this sort of ‘label’ with little anxiety if it is explained that they are at risk of psychosis but that psychosis is not inevitable, and that treatment will be provided in an attempt to reduce risk and prevent onset of psychotic disorder” (Yung et al., 2010). In our view, such communication with patients and families about a CHR diagnosis is consistent with both best practice and ethical guidance from the AMA: to encourage the patient to specify preferences regarding communication of medical information; to honor a patient’s request not to receive certain medical information; and to tailor disclosure to meet the patient’s needs and expectations in keeping with the individual’s preferences (American Medical Association, 2020). In the context of this kind of empathic discussion, we believe the evidence strongly supports the view that the benefits of tailored disclosure of the CHR diagnosis to help-seeking patients outweigh the risks.

Finally, as another example of harm, Malhi et al. cite a survey of CHR clinics in the UK showing some implementation gaps between practice guidelines and actual practice. Implementation gaps are hardly unique to CHR. Moreover, details in the cited paper reveal that the antipsychotic use reported in the survey is never stated to be routine first-line use, and may even refer to selective use after conversion.

10. CONCLUSION

Overall, Malhi et al.’s arguments do not fairly characterize the state of progress in the CHR field nor efforts to minimize stigma by empathic discussion with patients and families about the meanings of psychiatric diagnosis and of risk. Despite their various points of critique, which we address above, Malhi et al. do not go so far as to conclude, however, that early intervention with CHR is sufficiently hamstrung and ethically precarious that we should stop trying to intervene early for patients such as those with CHR. Instead they recommend that “it is important that the claims of early intervention for psychosis be viewed tentatively.” We can certainly support that recommendation, because medical and psychiatric practice should always be open to re-evaluation and change, exactly as should each patient’s individual diagnosis and treatment plan. But ceasing and desisting would clearly be a mistake: we do help many individuals with CHR already by carefully assessing them, by sharing our impressions with them in an empathically-tailored fashion, and by monitoring and providing symptomatic treatment. The wait for clear understanding of disease mechanism could be a long one, and in the meantime substantial preventable suffering will have occurred. In the future we hope additional work in the CHR field will provide new, safe, and phase-specific

treatments for deployment in clinics worldwide that have learned how to ethically and compassionately locate and serve patients in the community. In the end, successful treatment--which requires research on the clinical entity--is one of the most important tools against stigma.

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Conflict of interest

Dr. Woods reports that he has received sponsor-initiated research funding support from Teva, Boehringer-Ingelheim, Amarex, and SyneuRx. He has consulted to Boehringer-Ingelheim, New England Research Institute, and Takeda. He has been granted US patent no. 8492418 B2 for a method of treating prodromal schizophrenia with glycine agonists. Dr. Hyman serves on the board of directors for Voyager Therapeutics, and on scientific advisory boards for Janssen, BlackThorn Therapeutics, F-Prime Capital, and Brave Neuroscience. He is also the Board Chair for the nonprofit Charles A. Dana Foundation and a consultant for Q-State Biosciences, and has received research funding from the Stanley Family Foundation. Other authors report no disclosures.

References

Addington J, Lu L, Kali B, Bearden CE, Cadenhead KS, Cornblatt BA, Keshavan M, Mathalon DH, McGlashan TH, Perkins DO, Seidman LJ, Stone WS, Tsuang MT, Walker EF, Woods SW, Cannon TD, in press. North American Prodrome Longitudinal Study (NAPLS 3): Methods and baseline description. Schizophrenia Research.

Allswede DM, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, Mathalon DH, McGlashan T, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Cannon TD, 2020. Characterizing covariant trajectories of individuals at clinical high risk for psychosis across symptomatic and functional domains. American Journal of Psychiatry 177(2), 164–171.

American Medical Association, 2020. AMA Principles of Medical Ethics, https://www.amaassn.org/system/files/2019-06/code-of-medical-ethics-chapter-2.pdf

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association, Arlington, VA.

Anglin DM, Greenspoon MI, Lighty Q, Corcoran CM, Yang LH, 2014. Spontaneous labelling and stigma associated with clinical characteristics of peers ‘at-risk’ for psychosis. Early Intervention in Psychiatry 8(3), 247–252. [PubMed: 23594363]

Anticevic A, Haut K, Murray JD, Repovs G, Yang GJ, Diehl C, McEwen SC, Bearden CE, Addington J, Goodyear B, Cadenhead KS, Mirzakhanian H, Cornblatt BA, Olvet D, Mathalon DH, McGlashan TH, Perkins DO, Belger A, Seidman LJ, Tsuang MT, van Erp TGM, Walker EF, Hamann S, Woods SW, Qiu ML, Cannon TD, 2015. Association of Thalamic Dysconnectivity and Conversion to Psychosis in Youth and Young Adults at Elevated Clinical Risk. Jama Psychiatry 72(9), 882–891. [PubMed: 26267151]

Baron J, Salvador M, Loewy R, 2019. Experience of associative stigma in parents of adolescents at risk for psychosis. Early Interv Psychiatry 13(4), 761–766. [PubMed: 29575746]

Bearden CE, Wu KN, Caplan R, Cannon TD, 2011. Thought Disorder and Communication Deviance as Predictors of Outcome in Youth at Clinical High Risk for Psychosis. Journal of the American Academy of Child and Adolescent Psychiatry 50(7), 669–680. [PubMed: 21703494]

Beauchamp TL, Childress JF, 2013. Principles of Biomedical Ethics, 7th ed. Oxford University Press, USA.

Bedi G, Carrillo F, Cecchi GA, Slezak DF, Sigman M, Mota NB, Ribeiro S, Javitt DC, Copelli M, Corcoran CM, 2015. Automated analysis of free speech predicts psychosis onset in high-risk youths. npj Schizophrenia 1, 15030.

Benowitz S, 1999. To Tell the Truth: A Cancer Diagnosis in Other Cultures Is Often a Family Affair. JNCI: Journal of the National Cancer Institute 91(22), 1918–1919. [PubMed: 10564674]

Bernard JA, Orr JM, Mittal VA, 2017. Cerebello-thalamo-cortical networks predict positive symptom progression in individuals at ultra-high risk for psychosis. Neuroimage-Clinical 14, 622–628. [PubMed: 28348953]

Bodatsch M, Ruhrmann S, Wagner M, Mueller R, Schultze-Lutter F, Frommann I, Brinkmeyer J, Gaebel W, Maier W, Klosterkoetter J, Brockhaus-Dumke A, 2011. Prediction of Psychosis by Mismatch Negativity. Biological Psychiatry 69(10), 959–966. [PubMed: 21167475]

Calkins ME, Moore TM, Merikangas KR, Burstein M, Satterthwaite TD, Bilker WB, Ruparel K, Chiavacci R, Wolf DH, Mentch F, Qiu H, Connolly JJ, Sleiman PA, Hakonarson H, Gur RC, Gur RE, 2014. The psychosis spectrum in a young U.S. community sample: Findings from the Philadelphia Neurodevelopmental Cohort. World Psychiatry 13(3), 296–305. [PubMed: 25273303]

Cannon TD, Chung Y, He G, Sun DQ, Jacobson A, van Erp TGM, McEwen S, Addington J, Bearden CE, Cadenhead K, Cornblatt B, Mathalon DH, McGlashan T, Perkins D, Jeffries C, Seidman LJ, Tsuang M, Walker E, Woods SW, Heinssen R, North Amer Prodrome Longitudinal, S., 2015. Progressive Reduction in Cortical Thickness as Psychosis Develops: A Multisite Longitudinal Neuroimaging Study of Youth at Elevated Clinical Risk. Biological Psychiatry 77(2), 147–157. [PubMed: 25034946]

Cannon TD, Yu C, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, Heinssen R, Jeffries CD, Mathalon DH, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Kattan MW, 2016. An individualized risk calculator for research in prodromal psychosis. American Journal of Psychiatry 173(10), 980–988.

Cao H, Chung Y, McEwen SC, Bearden CE, Addington J, Goodyear B, Cadenhead KS, Mirzakhanian H, Cornblatt BA, Carrión R, Mathalon DH, McGlashan TH, Perkins DO, Belger A, Seidman LJ, Thermenos H, Tsuang MT, van Erp TGM, Walker EF, Hamann S, Anticevic A, Woods SW, Cannon TD, 2019. Progressive reconfiguration of resting-state brain networks as psychosis develops: Preliminary results from the North American Prodrome Longitudinal Study (NAPLS) consortium. Schizophrenia Research.

Carol EE, Mittal VA, 2018. What are the implications of psychosis risk syndrome label? A diathesis-stress conceptualization. Journal of Ethics in Mental Health 10, 1–20.

Carrión RE, Cornblatt BA, Burton CZ, Tso IF, Auther AM, Adelsheim S, Calkins R, Carter CS, Niendam T, Sale TG, Taylor SF, McFarlane WR, 2016. Personalized prediction of psychosis: External validation of the NAPLS-2 psychosis risk calculator with the EDIPPP project. American Journal of Psychiatry 173(10), 989–996.

Clarke DE, Narrow WE, Regier DA, Kuramoto SJ, Kupfer DJ, Kuhl EA, Greiner L, Kraemer HC, 2013. DSM-5 Field Trials in the United States and Canada, Part I: Study Design, Sampling Strategy, Implementation, and Analytic Approaches. American Journal of Psychiatry 170(1), 43–58.

Corcoran C, Landa Y, 2018. Ethical Issues in Psychosis Screening and Prevention. Journal of Ethics in Mental Health 10, 1–13.

Corcoran C, Malaspina D, Hercher L, 2005. Prodromal interventions for schizophrenia vulnerability: the risks of being “at risk”. Schizophr Res 73(2–3), 173–184. [PubMed: 15653260]

Corcoran CM, 2016. Ethical and epidemiological dimensions of labeling psychosis risk. AMA Journal of Ethics 18(6), 633–642. [PubMed: 27322997]

Corcoran CM, Carrillo F, Fernández-Slezak D, Bedi G, Klim C, Javitt DC, Bearden CE, Cecchi GA, 2018. Prediction of psychosis across protocols and risk cohorts using automated language analysis. World Psychiatry 17(1), 67–75. [PubMed: 29352548]

Davies C, Cipriani A, Ioannidis JPA, Radua J, Stahl D, Provenzani U, McGuire P, Fusar-Poli P, 2018. Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. World Psychiatry 17(2), 196–209. [PubMed: 29856551]

Dean DJ, Walther S, Bernard JA, Mittal VA, 2018. Motor clusters reveal differences in risk for psychosis, cognitive functioning, and thalamocortical connectivity: evidence for vulnerability subtypes. Clinical psychological science 6(5), 721–734. [PubMed: 30319928]

Dugan J, Shubrook J, 2017. International Classification of Diseases, 10th Revision, Coding for Diabetes. Clin Diabetes 35(4), 232–238. [PubMed: 29109613]

Fryer SL, Bachman P, Belger A, Carrion R, Duncan E, Johannesen J, Niznikiewicz M, Roach B, Addington J, Cadenhead K, Mathalon D, Year. Experience-dependent Strengthening of Auditory Prediction Signals in Youth at Clinical High Risk for Psychosis: Effects of Clinical Outcome and Conversion, Early Intervention in Psychiatry, Boston, 10.1111/eip.12722

Fusar-Poli P, Cappucciati M, Borgwardt S, Woods SW, Addington J, Nelson B, Nieman DH, Stahl DR, Rutigliano G, Riecher-Rössler A, Simon AE, Mizuno M, Lee TY, Kwon JS, Lam MML, Perez J, Keri S, Amminger P, Metzler S, Kawohl W, Rössler W, Lee J, Labad J, Ziermans T, An SK, Liu CC, Woodberry KA, Braham A, Corcoran C, McGorry P, Yung AR, McGuire PK, 2016a. Heterogeneity of psychosis risk within individuals at clinical high risk: A meta-analytical stratification. JAMA Psychiatry 73(2), 113–120. [PubMed: 26719911]

Fusar-Poli P, Cappucciati M, Rutigliano G, Lee TY, Beverly Q, Bonoldi I, Lelli J, Kaar SJ, Gago E, Rochetti M, Patel R, Bhavsar V, Tognin S, Badger S, Calem M, Lim KO, Kwon JS, Perez J, McGuire P, 2016b. Toward s Standard Psychometric Diagnostic interview for Subjects at Ultra High Risk of Psychosis: CAARMS versus SIPS. Psychiatry Journal (Hindawi) 7146341.

Fusar-Poli P, Cappucciati M, Rutigliano G, Schultze-Lutter F, Bonoldi I, Borgwardt S, Riecher-Rossler A, Addington J, Perkins D, Woods SW, McGlashan TH, Lee J, Klosterkotter J, Yung AR, McGuire P, 2015a. At risk or not at risk? Meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. World Psychiatry 14, 322–332. [PubMed: 26407788]

Fusar-Poli P, Carpenter W, Woods S, McGlashan T, 2014. Attenuated psychosis syndrome: ready for DSM-5.1? Annual review of clinical psychology 10, 155–192.

Fusar-Poli P, Raballo A, Parnas J, 2017a. What Is an Attenuated Psychotic Symptom? on the Importance of the Context. Schizophrenia Bulletin 43(4), 687–692. [PubMed: 28039421]

Fusar-Poli P, Rocchetti M, Sardella A, Avila A, Brandizzi M, Caverzasi E, Politi P, Ruhrmann S, McGuire P, 2015b. Disorder, not just state of risk: Meta-analysis of functioning and quality of life in people at high risk of psychosis. British Journal of Psychiatry 207(3), 198–206.

Fusar-Poli P, Rutigliano G, Stahl D, Davies C, De Micheli A, Ramella-Cravaro V, Bonoldi I, McGuire P, 2017b. Long-term validity of the At Risk Mental State (ARMS) for predicting psychotic and non-psychotic mental disorders. European Psychiatry 42, 49–54. [PubMed: 28212505]

Fusar-Poli P, Salazar de Pablo G, Correll CU, Meyer-Lindenberg A, Millan MJ, Borgwardt S, Galderisi S, Bechdolf A, Pfennig A, Kessing LV, van Amelsvoort T, Nieman DH, Domschke K, Krebs MO, Koutsouleris N, McGuire P, Do KQ, Arango C, 2020. Prevention of Psychosis: Advances in Detection, Prognosis, and Intervention. JAMA Psychiatry.

Fusar-Poli P, Salazar de Pablo G, Correll CU, Meyer-Lindenberg A, Millan MJ, Borgwardt S, Galderisi S, Bechdolf A, Pfenning A, Kessing LV, van Amelsvoort T, Nieman DH, Domschke K, Krebs M-O, Koutsouleris K, McGuire P, Do KQ, Arango C, in press. Prevention of psychosis: advances in detection, prognosis and intervention. JAMA Psychiatry.

Granö N, Kallionpää S, Karjalainen M, Roine M, Ranta K, Heinimaa M, 2016. Discrepancy between self-reported and interviewed psychosis risk symptoms: Auditory distortions are the most reliably reported symptom by self-report. Early Intervention in Psychiatry 10(2), 129–136. [PubMed: 24861468]

Hafner H, Maurer K, Loffler W, Riecher-Rossler A, 1993. The influence of age and sex on the onset and early course of schizophrenia. Br J Psychiatry 162, 80–86. [PubMed: 8425144]

Hamilton HK, Roach BJ, Bachman PM, Belger A, Carrion RE, Duncan E, Johannesen JK, Light GA, Niznikiewicz MA, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Cannon TD, Mathalon DH, 2019a. Association between P300 Responses to Auditory Oddball Stimuli and Clinical Outcomes in the Psychosis Risk Syndrome. JAMA Psychiatry 76, 1187–1197. [PubMed: 31389974]

Hamilton HK, Woods SW, Roach BJ, Llerena K, McGlashan TH, Srihari VH, Ford JM, Mathalon DH, 2019b. Auditory and Visual Oddball Stimulus Processing Deficits in Schizophrenia and the Psychosis Risk Syndrome: Forecasting Psychosis Risk With P300. Schizophrenia bulletin 45(5), 1068–1080. [PubMed: 30753731]

Hay RA, Roach BJ, Attygalle SS, Cadenhead K, Carrion R, Bachman P, Johannesen J, Duncan E, Belger A, Niznikiewicz M, Mathalon D, 2013. Mismatch Negativity Abnormalities Are Associated with Poorer Functioning in Youth at Clinical High Risk for Psychosis: Evidence from the NAPLS Study. Biological Psychiatry 73(9), 272S-272S.

Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, 2018. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nature genetics 50(9), 1219–1224. [PubMed: 30104762]

Kim M, Lee TH, Yoon YB, Lee TY, Kwon JS, 2018. Predicting remission in subjects at clinical high risk for psychosis using mismatch negativity. Schizophrenia bulletin 44(3), 575–583. [PubMed: 29036493]

Kim SW, Polari A, Melville F, Moller B, Kim JM, Amminger P, Herrman H, McGorry P, Nelson B, 2017. Are current labeling terms suitable for people who are at risk of psychosis? Schizophrenia Research 188, 172–177. [PubMed: 28117104]

Kollias C, Kontaxakis V, Havaki-Kontaxaki B, Simmons MB, Stefanis N, Papageorgiou C, 2015. Inter-rater reliability of the Greek version of CAARMS among two groups of mental health professionals. Psychiatriki 26(3), 217–222. [PubMed: 26480226]

Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S, Rosen M, Ruef A, Dwyer DB, Paolini M, Chisholm K, Kambeitz J, Haidl T, Schmidt A, Gillam J, Schultze-Lutter F, Falkai P, Reiser M, Riecher-Rössler A, Upthegrove R, Hietala J, Salokangas RKR, Pantelis C, Meisenzahl E, Wood SJ, Beque D, Brambilla P, Borgwardt S, 2018. Prediction Models of Functional Outcomes for Individuals in the Clinical High-Risk State for Psychosis or with Recent-Onset Depression: A Multimodal, Multisite Machine Learning Analysis. JAMA Psychiatry 75(11), 1156–1172. [PubMed: 30267047]

Labad J, Stojanovic-Pérez A, Montalvo I, Solé M, Cabezas Á, Ortega L, Moreno I, Vilella E, Martorell L, Reynolds RM, 2015. Stress biomarkers as predictors of transition to psychosis in at-risk mental states: roles for cortisol, prolactin and albumin. Journal of psychiatric research 60, 163–169. [PubMed: 25466832]

Lee EH, Hui CL, Ching EY, Lin J, Chang WC, Chan SK, Chen EY, 2016. Public Stigma in China Associated With Schizophrenia, Depression, Attenuated Psychosis Syndrome, and Psychosis-Like Experiences. Psychiatr Serv 67(7), 766–770. [PubMed: 26975519]

Malhi GS, E., B., Hamilton A, Morris G, 2020. Early intervention for risk syndromes: What are the real risks? Schizophrenia Research.

Mathalon DH, Hamilton H, Bachman P, Belger A, Carrion R, Duncan E, Johannesen J, Niznikiewicz M, Cadenhead K, 2016. Mismatch Negativity and Repetition Positivity Predict Transition to Psychosis in Clinical High Risk Individuals. International Journal of Psychophysiology 100(108), 37.

McGlashan TH, Miller TJ, Woods SW, 2001. Pre-onset detection and intervention research in schizophrenia psychoses: current estimates of benefit and risk. Schizophr Bull 27(4), 563–570. [PubMed: 11824483]

McIlwaine S, 2019. “Now, at least, I have a direction”: a qualitative study examining the service-related needs of young people identified as having a clinical high-risk state for psychosis, https://escholarship.mcgill.ca/downloads/s7526h57b?locale=en

Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J, McFarlane W, Perkins DO, Pearlson GD, Woods SW, 2003. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull 29(4), 703–715. [PubMed: 14989408]

Millman ZB, Schiffman J, 2018. False-positives and Clinical Heterogeneity among Youth at Clinical High-risk for Psychosis: Clinical and Ethical Implications for Assessment and Treatment. Journal of Ethics in Mental Health 10, 1–19.

Mitchell AJ, Shiri-Feshki M, 2009. Rate of progression of mild cognitive impairment to dementia–meta-analysis of 41 robust inception cohort studies. Acta Psychiatrica Scandinavica 119(4), 252–265. [PubMed: 19236314]

Mittal VA, Dean DJ, Mittal J, Saks ER, 2015. Ethical, Legal, and Clinical Considerations when Disclosing a High-Risk Syndrome for Psychosis. Bioethics 29(8), 543–556. [PubMed: 25689542]

Miyakoshi T, Matsumoto K, Ito F, Ohmuro N, Matsuoka H, 2009. Application of the comprehensive assessment of at risk mental states (CAARMS) to the Japanese population: Reliability and validity of the Japanese version of the CAARMS. Early intervention in psychiatry 3(2), 123–130. [PubMed: 21352185]

Nathan DM, Nathan DM, Balkau B, Bonora E, Borch-Johnsen K, Buse JB, Colagiuri S, Davidson MB, DeFronzo R, Genuth S, Holman RR, Ji L, Kirkman S, Knowler WC, Schatz D, Shaw J, Sobngwi E, Steffes M, Vaccaro O, Wareham N, Zinman B, Kahn R, Int Expert C, 2009. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. Diabetes Care 32(7), 1327–1334. [PubMed: 19502545]

Osborne KJ, Mittal VA, 2019. External validation and extension of the NAPLS-2 and SIPS-RC personalized risk calculators in an independent clinical high-risk sample. Psychiatry Research 279, 9–14. [PubMed: 31279247]

Paterlini F, Pelizza L, Galli G, Azzali S, Scazza I, Garlassi S, Chiri LR, Poletti M, Pupo S, Raballo A, 2019. Interrater reliability of the authorized Italian version of the Comprehensive Assessment of At-Risk Mental States (CAARMS-ITA). Journal of Psychopathology 25, 24–28.

Perez VB, Woods SW, Roach BJ, Ford JM, McGlashan TH, Srihari VH, Mathalon DH, 2014. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: Forecasting psychosis risk with mismatch negativity. Biological Psychiatry 75(6), 459–469. [PubMed: 24050720]

Perkins DO, Jeffries CD, Addington J, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Mathalon DH, McGlashan TH, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Heinssen R, 2015. Towards a Psychosis Risk Blood Diagnostic for Persons Experiencing High-Risk Symptoms: Preliminary Results From the NAPLS Project. Schizophrenia Bulletin 41(2), 419–428. [PubMed: 25103207]

Perkins DO, Olde Loohuis L, Barbee J, Ford J, Jeffries CD, Addington J, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Mathalon DH, McGlashan TH, Seidman LJ, Tsuang M, Walker EF, Woods SW, 2020. Polygenic risk score contribution to psychosis prediction in a target population of persons at clinical high risk. American Journal of Psychiatry 177(2), 155–163.

Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H, 2000. Children's self-reported psychotic symptoms and adult schizophreniform disorder: A 15-year longitudinal study. Archives of General Psychiatry 57(11), 1053–1058. [PubMed: 11074871]

Pruessner M, Béchard-Evans L, Boekestyn L, Iyer SN, Pruessner JC, Malla AK, 2013. Attenuated cortisol response to acute psychosocial stress in individuals at ultra-high risk for psychosis. Schizophrenia research 146(1–3), 79–86. [PubMed: 23510595]

Pyle M, Stewart SL, French P, Byrne R, Patterson P, Gumley A, Birchwood M, Morrison AP, 2015. Internalized stigma, emotional dysfunction and unusual experiences in young people at risk of psychosis. Early Interv Psychiatry 9(2), 133–140. [PubMed: 25775264]

Ramyead A, Roach B, Hamilton H, Addington J, Bachman P, Bearden C, Belger A, Cadenhead K, Cannon T, Carrion R, 2019. O33. EEG Alpha Event-Related Desynchronization Deficits Predict Conversion to Psychosis in Individuals With the Psychosis Risk Syndrome. Biological Psychiatry 85(10), S119.

Regier DA, Narrow WE, Clarke DE, Kraemer HC, Kuramoto SJ, Kuhl EA, Kupfer DJ, 2013. DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses. American Journal of Psychiatry 170(1), 59–70.

Rezaii N, Walker E, Wolff P, 2019. A machine learning approach to predicting psychosis using semantic density and latent content analysis. npj Schizophrenia 5(1), 1–12. [PubMed: 30643138]

Ruhrmann S, Schultze-Lutter F, Klosterk√∂tter J, 2010a. Probably at-risk, but certainly ill - Advocating the introduction of a psychosis spectrum disorder in DSM-V. Schizophrenia Research 120(1–3), 23–37. [PubMed: 20400269]

Ruhrmann S, Schultze-Lutter F, Salokangas RKR, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heniz A, Morrison A, Lewis S, Graf von Reventlow H, Klosterkotter J, 2010b. Prediction of psychosis in adolescents and adults at high risk: Results from the Prospective Euroean Prediciton of Psychosis Study. Archives of General Psychiatry 67(3), 241–251. [PubMed: 20194824]

Rusch N, Corrigan PW, Heekeren K, Theodoridou A, Dvorsky D, Metzler S, Muller M, Walitza S, Rossler W, 2014. Well-Being Among Persons at Risk of Psychosis: The Role of Self-Labeling, Shame, and Stigma Stress. Psychiatric Services 65(4), 483–489. [PubMed: 24382666]

Salazar de Pablo G, Catalan A, Fusar-Poli P, 2020. Clinical Validity of DSM-5 Attenuated Psychosis Syndrome: Advances in Diagnosis, Prognosis, and Treatment. JAMA Psychiatry 77(3), 311–320. [PubMed: 31746950]

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511(7510), 421–427. [PubMed: 25056061]

Schultze-Lutter F, Klosterkötter J, Gaebel W, Schmidt SJ, 2018a. Psychosis-risk criteria in the general population: frequent misinterpretations and current evidence. World Psychiatry 17(1), 107–108. [PubMed: 29352561]

Schultze-Lutter F, Klosterkötter J, Ruhrmann S, 2014a. Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. Schizophrenia Research 154(1–3), 100–106. [PubMed: 24613572]

Schultze-Lutter F, Michel C, Ruhrmann S, Schimmelmann BG, 2018b. Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. Psychological Medicine 48(7), 1167–1178. [PubMed: 28889802]

Schultze-Lutter F, Michel C, Schmidt SJ, Schimmelmann BG, Maric NP, Salokangas RKR, Riecher-Rössler A, van der Gaag M, Nordentoft M, Raballo A, Meneghelli A, Marshall M, Morrison A, Ruhrmann S, Klosterkötter J, 2015. EPA guidance on the early detection of clinical high risk states of psychoses. European Psychiatry 30(3), 405–416. [PubMed: 25735810]

Schultze-Lutter F, Renner F, Paruch J, Julkowski D, Klosterkötter J, Ruhrmann S, 2014b. Self-reported psychotic-like experiences are a poor estimate of clinician-rated attenuated and frank delusions and hallucinations. Psychopathology 47(3), 194–201. [PubMed: 24192655]

Schultze-Lutter F, Schimmelmann BG, Klosterkötter J, Ruhrmann S, 2012. Comparing the prodrome of schizophrenia-spectrum psychoses and affective disorders with and without psychotic features. Schizophrenia Research 138(2–3), 218–222. [PubMed: 22551680]

Schultze-Lutter F, Schimmelmann BG, Ruhrmann S, Michel C, 2013. 'A rose is a rose is a rose', but at-risk criteria differ. Psychopathology 46(2), 75–87. [PubMed: 22906805]

Schultze-Lutter F, Klosterkötter J, Gaebel W, Schmidt SJ, 2018. Psychosis risk criteria in the general population: frequent misinterpretations and current evidence. World Psychiatry 17(1), 107. [PubMed: 29352561]

Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K, Presumey J, Baum M, Van Doren V, 2016. Schizophrenia risk from complex variation of complement component 4. Nature 530(7589), 177–183. [PubMed: 26814963]

Seo M, Tamura K, Shijo H, Morioka E, Ikegame C, Hirasako K, 2000. Telling the diagnosis to cancer patients in Japan: attitude and perception of patients, physicians and nurses. Palliative medicine 14(2), 105–110. [PubMed: 10829144]

Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M, 2012. Prediabetes: a high-risk state for diabetes development. Lancet 379(9833), 2279–2290. [PubMed: 22683128]

Tang Y, Wang J, Zhang T, Xu L, Qian Z, Cui H, Tang X, Li H, Whitfield-Gabrieli S, Shenton ME, 2019. P300 as an index of transition to psychosis and of remission: Data from a clinical high risk for psychosis study and review of literature. Schizophrenia research https://www.sciencedirect.com/science/article/pii/S092099641930074X.

US NIMH, 2019a. Funding Opportunity Announcement: Clinical High Risk for Psychosis Research Network, https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-20-340.html

US NIMH, 2019b. Funding Opportunity Announcement: Clinical High Risk for Psychosis: Data Processing, Analysis, and Coordination Center, https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-20-341.html

Uttinger M, Koranyi S, Papmeyer M, Fend F, Ittig S, Studerus E, Ramyead A, Simon A, Riecher-Rossler A, 2018. Early detection of psychosis: helpful or stigmatizing experience? A qualitative study. Early Interv Psychiatry 12(1), 66–73. [PubMed: 26362478]

van Tricht MJ, Nieman DH, Koelman JHTM, van der Meer JN, Bour LJ, de Haan L, Linszen DH, 2010. Reduced parietal P300 amplitude is associated with an increased risk for a first psychotic episode. Biological Psychiatry 68(7), 642–648. [PubMed: 20627236]

Volkow ND, Koob GF, Croyle RT, Bianchi DW, Gordon JA, Koroshetz WJ, Perez-Stable EJ, Riley WT, Bloch MH, Conway K, Deeds BG, Dowling GJ, Grant S, Howlett KD, Matochik JA, Morgan GD, Murray MM, Noronha A, Spong CY, Wargo EM, Warren KR, Weiss SRB, 2018. The conception of the ABCD study: From substance use to a broad NIH collaboration. Developmental Cognitive Neuroscience 32, 4–7. [PubMed: 29051027]

Walker EF, Trotman HD, Pearce BD, Addington J, Cadenhead KS, Cornblatt BA, Heinssen R, Mathalon DH, Perkins DO, Seidman LJ, Tsuang MT, Cannon TD, McGlashan TH, Woods SW, 2013. Cortisol levels and risk for psychosis: Initial findings from the North American Prodrome Longitudinal Study. Biological Psychiatry 74(6), 410–417. [PubMed: 23562006]

Wang C, Ji F, Hong Z, Poh JS, Krishnan R, Lee J, Rekhi G, Keefe RSE, Adcock RA, Wood SJ, 2016. Disrupted salience network functional connectivity and white-matter microstructure in persons at risk for psychosis: findings from the LYRIKS study. Psychological medicine 46(13), 2771–2783. [PubMed: 27396386]

Warner R, 2002. Early intervention in schizophrenia: a critique. Epidemiologia e Psichiatria Sociale. 11(4), 248–255. [PubMed: 12585015]

Webb JR, Addington J, Perkins DO, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Seidman LJ, Tarbox SI, Tsuang MT, Walker EF, McGlashan TH, Woods SW, 2015. Specificity of incident diagnostic outcomes in patients at clinical high risk for psychosis. Schizophrenia Bulletin 41, 1066–1075. [PubMed: 26272875]

Welsh P, Tiffin PA, 2012. Observations of a small sample of adolescents experiencing an At-Risk Mental State (ARMS) for psychosis. Schizophrenia Bulletin 38(2), 215–218. [PubMed: 22021662]

WHO and IDF, 2006. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation., https://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

Woods S, Walsh B, McGlashan T, 2012. Diagnostic reliability and validity of the proposed DSM-5 attenuated psychosis syndrome, 6 March 2020 http://iepavcl.eppic.org.au/content/diagnostic-reliability-andvalidity-proposed-dsm-5-attenuated-psychosissyndrome.

Woods SW, Miller TJ, McGlashan TH, 2001. The “prodromal” patient: both symptomatic and at-risk. CNS Spectr 6(3), 223–232. [PubMed: 16951657]

Woods SW, Powers AR III, Taylor JH, Davidson CA, Johannesen JK, Addington J, Perkins DO, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH, 2018. Lack of diagnostic pluripotentiality in patients at clinical high risk for psychosis: Specificity of comorbidity persistence and search for pluripotential subgroups. Schizophrenia Bulletin 44(2), 254–263. [PubMed: 29036402]

Woods SW, Walsh BC, Powers III AR, McGlashan TH, 2019. Reliability, validity, epidemiology, and cultural variation of the Structured Interview for Psychosis-risk Syndromes (SIPS) and the Scale Of Psychosis-risk Symptoms (SOPS), in: Li H, Shapiro DI, Seidman LJ (Eds.), Handbook of Attenuated Psychosis Syndrome Across Cultures: International Perspectives on Early Identification and Intervention. Springer, New York, pp. 85–113.

Woods SW, Walsh BC, Saksa JR, McGlashan TH, 2010. The case for including Attenuated Psychotic Symptoms Syndrome in DSM-5 as a psychosis risk syndrome. Schizophrenia Research 123, 199–207. [PubMed: 20832249]

Yang LH, Link BG, Ben-David S, Gill KE, Girgis RR, Brucato G, Wonpat-Borja AJ, Corcoran CM, 2015. Stigma related to labels and symptoms in individuals at clinical high-risk for psychosis. Schizophrenia Research 168(1–2), 9–15. [PubMed: 26314731]

Yung AR, Buckby JA, Cotton SM, Cosgrave EM, Killackey EJ, Stanford C, Godfrey K, McGorry PD, 2006. Psychotic-like experiences in nonpsychotic help-seekers: Associations with distress, depression, and disability. Schizophrenia Bulletin 32(2), 352–359. [PubMed: 16254060]

Yung AR, Nelson B, Thompson AD, Wood SJ, 2010. Should a “Risk Syndrome for Psychosis” be included in the DSMV? Schizophr Res 120(1–3), 7–15. [PubMed: 20382506]

Zhang T, Li HJ, Tang Y, Niznikiewicz MA, Shenton ME, Keshavan MS, Stone WS, McCarley RW, Seidman LJ, Wang JJ, 2018. Validating the predictive accuracy of the NAPLS-2 psychosis risk calculator in a clinical high-risk sample from the SHARP (Shanghai at risk for psychosis) program. American Journal of Psychiatry 175(9), 906–908.

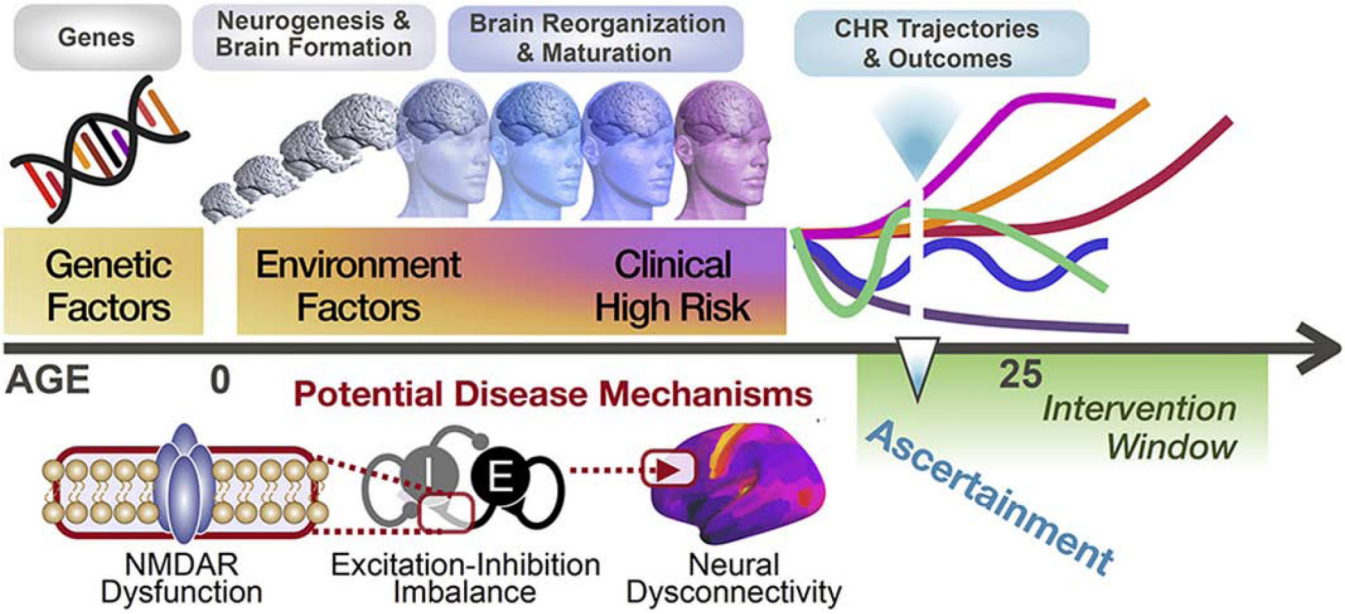

Figure. Hypothetical Model of Disease Mechanisms and Illness Trajectories Associated with Clinical High Risk.

The Figure illustrates a model wherein heterogeneous genetic, neurobiological, and environmental factors interact to affect neurogenesis, brain formation, and brain reorganization and maturation to produce the Clinical High Risk (CHR) syndrome via potential disease mechanisms such as NMDA receptor dysfunction, excitation/inhibition imbalance, and/or neural disconnectivity and yielding heterogeneity of CHR trajectories both before and after ascertainment.