What are the Implications of a Psychosis Risk Syndrome Label? 
A Diathesis-Stress Conceptualization

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Abstract

Research suggests that identifying youth at risk for developing psychosis early may help to improve the course of illness, but there is also concern that disclosure of a risk syndrome label may come with harm. Notably, the mechanism through which harm might be conferred has not been evaluated in a theoretical context. Without an informed discussion of this topic, it is difficult to approach the period following disclosure in a manner that balances beneficence and non-maleficence. In this topical review, we use a diathesis-stress model perspective to evaluate potential factors that identified youth may face following the disclosure of a psychosis risk syndrome label and how these factors could engage a vulnerable stress system that may drive the onset of a psychotic disorder.

We propose an exploratory model that is designed to integrate post-disclosure stressors with a diathesis-stress conception of psychosis and highlight how these factors may be sources of stress or resiliency depending on subjective appraisal. Our exploratory model is one potential way to organize information in this growing area and we use it to discuss related ethical considerations moving forward. Ultimately, a better understanding of the post-disclosure period may help direct a novel research agenda and inform best practices.

Key words: psychosis risk syndrome, stress
Despite advances in research, treatment, and technology, mental illness continues to be associated with high levels of personal and economic costs, often incurring millions of dollars in healthcare costs to society (Insel, 2010; Wu et al., 2005). As a result, there is a current drive towards early identification and preventive care (Greenberg, Domitrovich, & Bumbarger, 2001; Insel, 2007; Macdonald, Goines, Novacek, & Walker, 2017). This shift has focused on identifying and providing targeted preventative treatment to adolescents and young adults who are at risk for developing serious mental illness (Betts, Gullone, & Allen, 2009; Correll, Hauser, Auther, & Cornblatt, 2010; Miklowitz et al., 2014). Early identification and preventive care often focus on adolescence, as this is a time when many chronic and serious mental illnesses evolve (Greenberg et al., 2001). In this regard, there has been a specific focus on identification of psychosis risk, as psychotic disorders, such as schizophrenia, typically emerge in young adulthood and remain a chronic illness throughout life (Fusar-Poli et al., 2012).

In this context, a body of research suggests that individuals meeting criteria for a high-risk or prodromal syndrome have a likelihood of imminent transition to a psychotic disorder (Cannon et al., 2008). Identifying at-risk youth early may help to improve the course of illness (McGorry et al., 2013; Schmidt et al., 2015), but there is also concern that disclosing this state may come with harm (Macdonald et al., 2017). In this light, there is an accumulation of literature attending to the ethical principles of autonomy, beneficence, and non-maleficence that highlights the benefits and risks that need to be considered when disclosing and/or treating an adolescent with a psychosis risk syndrome label (Corcoran, 2016; Macdonald et al., 2017; McGorry, Yung, & Phillips, 2001; Mittal, Dean, Mittal, & Saks, 2015; Yang et al., 2013). Specifically, benefits of disclosure can help explain symptoms (Mittal et al., 2015), and individuals can make lifestyle changes aimed at prioritizing risk reduction (Corcoran, 2016; Macdonald et al., 2017; Miklowitz et al., 2014).

Yet disclosure of a psychosis risk label may be iatrogenic, causing additional and potentially unnecessary stress to the identified individual (Edo, Torrents-Rodas, Rovira, & Fernandez-Castro, 2012; Macdonald et al., 2017; Mittal et al., 2015). This is particularly concerning as stress has been linked to symptom development and diagnostic conversion (Hankin & Abramson, 2001; Holtzman et al., 2013; Pruessner, Cullen, Aas, & Walker, 2017). Specifically, the neural diathesis-stress model posits that an early biological vulnerability to the hypothalamic-pituitary-adrenal (HPA) axis, an integral biological stress system, later interacts in the adolescent period with both individual factors
and environmental stressors, which can trigger a cascade of events that culminates in expression of dysfunctional neural circuits that subserve psychotic symptoms (Pruessner et al., 2017; Howes & McCutcheon, 2017; Walker et al., 2008). This notion draws primarily on the extant evidence concerning the effects of HPA axis secretion of glucocorticoids (i.e. cortisol in humans) on brain and behavior. For example, activation of glucocorticoid receptors in the hypothalamus and pituitary trigger the negative feedback loop of the HPA axis. Impaired functioning of glucocorticoid receptors can keep cortisol levels high and cause difficulty in the resolution of the stress response, contributing to dysregulation of the system over time (Laruelle & Abi-Dargham, 1999; Yuii, Suzuki, & Kurachi, 2007). Therefore, persistent and acute stress can increase sensitivity while negatively affecting the negative feedback system that regulates the stress response.

It appears clear that the stress system is a critical intermediary factor between the external environment and pre-existing vulnerability factors in psychosis (Pruessner et al., 2017); thus, increased stress experienced during the post-disclosure period likely modulates any effects that receiving a risk syndrome label may have on the eventual course of illness. But the experience of stress itself is idiosyncratic (Phillips, Francey, Edwards, & McMurray, 2007), and there are many potential pathways between receiving a risk diagnosis and engaging the stress system. Further, this is a nuanced area, and there is not a linear relationship between receiving a psychosis risk syndrome label and putative course of illness. Indeed, a majority of youth who receive the label do not fare worse (anywhere between 70-90% do not develop a psychotic disorder; Cannon et al., 2008) and further, while the field has continued to grow, and more and more cases are being identified, the transition rates are in fact declining across the world (Yung et al., 2007). Clearly, some intermediary factors may be harmful, whereas other individual differences or modulating circumstances may be protective. In summary, while the field agrees there are benefits and potential risks accompanying disclosure, and there are recommended decision models to help balance ethical considerations when disclosing a risk label (Macdonald et al., 2017), the critical factors intervening between a psychosis risk syndrome label and eventual course have not been explored.

While excellent work has started to examine normative and pathological biological responses to stress, as well as how this may ultimately drive psychosis (Corcoran et al., 2003; M. Pruessner, Cullen, Aas, & Walker, 2017; Walker & Diforio, 1997; Howes & McCutcheon, 2017), currently our understanding of how receiving a risk syndrome label may ultimately come into play is limited.
Specifically, to date, there has been little discussion about what types of added factors may occur during the post-disclosure period and engage the vulnerable stress system highlighted in the neural diathesis stress model. However, information at this level will be most critical for weighing ethical decisions during the post-disclosure period, as well as for imparting psychoeducation, making treatment decisions (accounting for risk and resiliency considerations specific to each person), designing novel interventions, and setting new research agendas. As such, it is important to start to unpack potential mechanisms of change between receiving a psychosis risk syndrome label and engaging a vulnerable stress system that may ultimately drive onset of a psychotic disorder. The potential intervening factors explored in this paper include stigma, social isolation, family conflict, engagement in the healthcare system, and uncertainty about the future. Factors will be discussed and then integrated into a proposed exploratory model of vulnerability and psychosocial interactions that rest upon a diathesis-stress perspective. Therefore, connections to psychological and biological stress responses, specifically focusing on cortisol as the output of HPA-axis activation, will be highlighted in the context of our exploratory model.

**Potential intervening factors**

*Stigma*

One prominent factor that may drive the relationship between receiving a psychosis risk syndrome label and later course is stigma. Stigma is conceptualized as a common experience for people seeking or continuing treatment in mental health services (Corrigan, 2004) and people labeled as mentally ill are stigmatized more than those with other health conditions (Socall & Holtgraves, 1992). Notably, people with psychotic disorders are judged more harshly than people with depression or anxiety disorders (Pescosolido, Monahan, Link, Stueve, & Kikuzawa, 1999). It has been shown that a psychosis risk label also evokes stigmatizing attitudes among peers and self-stigma in the identified individual (Rüsch et al., 2014; Yang et al., 2013). In the context of the psychosis risk label, it has been hypothesized that stigmatization can negatively impact identified individuals and result in internalization of pejorative social stereotypes, negative emotional reactions, and harmful behavioral coping strategies (Yang, Wonpat-Borja, Opler, & Corcoran, 2010).

Stress-coping models conceptualize stigma as a stressor for people with mental illness (Link & Phelan, 2006; Miller, Levin, & van Laar, 2006; Rüsch et al., 2009). Indeed, stigma has been
associated with self-reported psychological stress in patients with psychosis (Rüsch et al., 2009) and in individuals given a psychosis risk label (Rüsch et al., 2014). Specifically, stigma related stress has been shown to be associated with impaired well-being among youth at risk for psychosis independent of other factors, such as age and comorbid disorders (Rüsch et al., 2014). Additionally, in a longitudinal study following youth at risk for psychosis, greater self-reported perceived harm due to stigma predicted transition to schizophrenia; therefore, it was conceptualized that stigma stress may increase the risk of transition to psychosis (Rüsch et al., 2015). This evidence supports the idea that the stigma can be conceptualized as a stressor that individuals in the post-disclosure period may face that could engage the vulnerable stress system and contributes to an increase in symptomatology.

**Social Isolation**

In general, social relationships (i.e. experiencing problems with school, parents, friends, and boy/girlfriends) are the top stressors reported by adolescents (Stark, Spirito, Williams, & Guvevremont, 1989) and social isolation is connected to poor well-being and mental health (Kawachi & Berkman, 2001; Andrew Steptoe, Shankar, Demakakos, & Wardle, 2013). Notably, youth with a psychosis risk label have pre-existing levels of social isolation; they report having fewer close friends, less diverse social networks, less perceived social support, poorer relationship quality with family and friends, and more loneliness (Robustelli, Newberry, Whisman, & Mittal, 2017). Given that this study showed that being lonely, having fewer, and worse quality relationships was associated with greater symptom severity and lower overall functioning, it is important to consider how receiving a psychosis risk label has the potential to increase social isolation and engage vulnerable stress systems.

First, social isolation may be induced by disclosing the psychosis risk label to peers. In a recent study that interviewed individuals with a psychosis risk diagnosis about their views on genetic testing for schizophrenia and related disorders, the authors discuss that a surprisingly high number of the youth reported they would tell close friends about genetic risk for schizophrenia (Lawrence et al., 2016). Given the impact of public stigma (see above for a detailed exploration), disclosing psychosis risk information to friends/peers could result in friends/peers withdrawing (Yang et al., 2013). Second, identified youth themselves may withdraw from peers after receiving a psychosis risk diagnosis, even if the individual does not disclose the label, due to the effects of self-stigma and
shame (Corrigan, 2004; Rüsch et al., 2014). Taken together, receiving a risk label has the potential to make peer interactions more stressful and increase social isolation for youth. While stigma may play a role, social isolation independently is highly relevant and under-discussed in youth who are at risk for developing psychosis. Markedly, there is a current drive to develop interventions to reduce loneliness in people with mental health problems and future research is needed to evaluate promising proposed approaches (Mann et al., 2017).

**Family conflict**

Research suggests that family conflict is another factor that may influence course after receiving a psychosis risk syndrome label. Family stress and conflict is common in people with mental illnesses (Martens & Addington, 2001; Walder, Faraone, Glatt, Tsuang, & Seidman, 2014), and empirical reviews theorize that stressful family social environments can lead to accumulating risk for mental health disorders, as well as major chronic diseases and early mortality (Repetti, Taylor, & Seeman, 2002). Accumulating research suggests that adolescents with a psychosis risk syndrome label have pre-existing levels of family conflict and family environment is related to changes in symptomatology (Dominguez-Martinez, Medina-Pradas, Kwapi, & Barrantes-Vidal, 2014; McFarlane & Cook, 2007; O'Brien et al., 2006; Schlosser et al., 2010). Notably, there is evidence to suggest that family criticism and hostility rates rise in the first few years after the onset of psychosis (Hooley & Richters, 1995) and high levels of criticism and hostility in the family environment are linked to increased risk of relapse in schizophrenia (Bachmann et al., 2002). As such, ethical guidelines for the identification and treatment of psychosis risk syndromes specify that family dynamics warrant specific attention as families may react differently to the label and reactions have the potential to increase family distress (Macdonald et al., 2017). While more prospective research with respect to family conflict before and after a psychosis risk label is needed, it is possible that pre-existing levels of family conflict could be exacerbated during the post-disclosure period of receiving a psychosis risk label and engage the vulnerable stress system.

**Engagement in the healthcare system**

The recommended treatment for individuals receiving a psychosis risk syndrome label varies from symptom monitoring to active treatment depending on symptom severity (Schmidt et al., 2015). At the very least, the individual will have to attend evaluation and feedback appointments to receive
a risk label; therefore, all individuals who receive a psychosis risk syndrome label will go through the process of making and attending a few appointments, and some will then engage in active treatment. Financial strain, logistical challenges, and treatment experience may be prominent stressful factors related to youth participating in the healthcare system during the post-disclosure period that could engage the vulnerable stress system. Financial strain is interpreted as a common measure of chronic life stress (Aneshensel, Rutter, & Lachenbruch, 1991). Notably, individuals diagnosed with schizophrenia report high levels of economic hardship (Bengtsson-Tops & Hansson, 1999) and difficulty navigating the cost of treatment (Mojtabai, 2009; Mojtabai et al., 2011). Furthermore, many families report financial strain as a result of caring for a family member with schizophrenia and the financial costs of the illness, including treatment costs, cause serious problems for families (Holden & Lewine, 1982). Given that financial strain is associated with outcome in patients with schizophrenia (Mattsson, Topor, Cullberg, & Forsell, 2008), there is the potential for financial stress to increase in the post-disclosure period and exacerbate symptoms.

In addition to financial strain, there are a number of logistical stressors associated with engaging in the healthcare system that youth who have received a psychosis risk diagnosis may face. Logistical challenges could include difficulty with transportation, inconvenient hours (Mojtabai, 2009), and lack of accessibility, such as not knowing where to go for resources (Fox, Blank, Rovnyak, & Barnett, 2001). Luckily, in most cases identified youth will be receiving the risk diagnosis from a provider who can offer individualized referrals that are easily accessible; however, this is not always the case and there is the potential for unexpected barriers to treatment. Additionally, the youth’s experience in engaging in treatment could be a source of added stress. Across mental health concerns, young people in particular report psychological stress and fear about the act of help-seeking (Gulliver, Griffiths, & Christensen, 2010). Additionally, characteristics of the potential providers, such as race, the ability of the provider to provide help, their credibility, and whether they understand youth, are reported sources of stress to youth seeking help (Gulliver et al., 2010). More thorough examination of the stressors that youth with a psychosis risk label face while engaging in the healthcare system is needed to better understand their specific experience. Taken together, there is preliminary evidence to suggest that youth engaging in the healthcare system during the post-disclosure period of a psychosis risk diagnosis could experience stress related to financial strain, logistical challenges, and treatment experience.
Uncertainty about the future

Lastly, uncertainty about the future after receiving a risk label may also influence course. Adolescence is a period that is characterized by identity formation, transition to independence, and decision-making. In particular, future decision-making and concerns regarding the future are commonly reported stressors for adolescents (Brown, O’Keeffe, Sanders, & Baker, 1986). Receiving a psychosis risk syndrome label has the potential to complicate decisions about the future. Young people who had been diagnosed with a psychotic disorder report that their personal goals changed when they became ill and expressed uncertainty about their ability to achieve future goals (Bassett, Lloyd, & Bassett, 2001). Due to concern and uncertainty about future functioning and stigma (Haroun, Dunn, Haroun, & Cadenhead, 2006; Yang et al., 2010), individuals given a risk label may encounter more stress when making decisions about the future. Specific topics of future decision making that have the potential to promote added stress to individuals given a psychosis risk syndrome label include college, treatment, medication, job/career goals, insurance, place of residence, and family planning (Corcoran, Malaspina, & Hercher, 2005; Corrigan, Markowitz, & Watson, 2004; Macdonald et al., 2017; McGorry et al., 2001; Mittal et al., 2015). These life decisions may lead to immediate or eventual financial strain. For example, after receiving a risk label, an adolescent may decide not to apply to college or certain jobs, which would result in earning less money in the future. Given that decisions are experienced as stressful, it is important to understand how future-decision making is related to the stress response and symptomatology in youth receiving a psychosis risk syndrome label.

Proposed exploratory model

As noted, the field agrees identifying youth at-risk for psychosis early may help to improve the course of illness and there is potential associated harm, yet the intervening factors between receiving a risk label and outcome are poorly understood. The current overview highlights factors that are associated with acute and chronic stress and can occur during the post-disclosure period. Notably, these variables may also engage the vulnerable HPA axis stress system, a biological stress system that undergoes significant changes during adolescence and has been implicated in research focusing on youth at risk for psychosis (Walker et al., 2008). Specifically, in regards to stigma, experiencing discrimination and unfair treatment is associated with increased cortisol response in the general population (Townsend, Major, Gangi, & Mendes, 2011). Negative peer interactions and
loneliness from social isolation have also been associated with deficits in HPA-axis functioning in youth. For example, bullied children show lower cortisol responses than comparison children in response to stress (Adam, Hawkley, Kudielka, & Cacioppo, 2006; Ouellet-Morin et al., 2011) and feelings of loneliness have been associated with a higher cortisol awakening response (Adam et al., 2006; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004). While more studies including youth at risk for psychosis are needed, it has been theorized that the impact of social evaluative stressors on HPA-axis functioning could mediate the effects of stress in triggering or worsening the symptoms of psychosis in those with a preexisting vulnerability (van Winkel, Stefanis, & Myin-Germeyns, 2008).

Family environment during adolescence has also been tied to endocrine function (Flinn & England, 1995; Luecken, Kraft, & Hagan, 2009). For example, individuals who had negative relationships with their family members exhibited significantly lower salivary cortisol across a challenging role-play task than those from positive families (Luecken et al., 2009), and conflict at home has been associated with children having lower cortisol at wake up and flatter diurnal cortisol slopes (Slatcher & Robles, 2012). In youth who were identified as being at risk for developing psychosis, elevated baseline cortisol levels were associated with fewer initial positive statements from caretakers (Carol & Mittal, 2015). Similarly, financial strain may also be related to HPA axis functioning as abnormal cortisol levels have been observed in children with low socioeconomic status (Dowd, Simanek, & Aiello, 2009; Lupien, King, Meaney, & McEwen, 2000). While there has been little work specifically examining the way in which engaging in the healthcare system impacts cortisol, daily stress has been tied to HPA-axis dysfunction, as individuals at above average genetic risk for psychotic disorder have higher diurnal cortisol levels and increased cortisol reactivity to daily stress compared to controls (Collip et al., 2011). Lastly, uncertainty about the future and future decision making also has the potential to engage the HPA axis as making decisions is stressful and elicits both a psychological and physiological stress response in people in general (Starcke & Brand, 2012).

Taken together, there is evidence to suggest that individuals who received a psychosis risk syndrome label may experience post-disclosure stressors, such as stigma, social isolation, family conflict, engaging in the healthcare system, and uncertainty about the future, and these added factors may engage the vulnerable stress system highlighted in the neural diathesis stress model. Based on this information, we have proposed an exploratory model of vulnerability and psychosocial
interactions that rest upon a diathesis-stress perspective. The model illustrates potential factors that can result during the post-disclosure period and engage the vulnerable stress system that may ultimately drive onset of a psychotic disorder (see Figure 1).

**Figure 1:** Exploratory model of vulnerability and psychosocial interactions after receiving a psychosis risk syndrome label

Note: The proposed exploratory model uses a diathesis stress model perspective and illustrates potential mechanisms of change between receiving a psychosis risk syndrome label and engaging a vulnerable stress system that may ultimately drive onset of a psychotic disorder. Potential factor identified may be sources of stress or resiliency depending on the subjective appraisal of acute and chronic stress.

The proposed model shows that presenting with current vulnerability factors (e.g. first degree relative with psychosis), expressed symptoms (e.g. attenuated positive symptoms), and characteristics (e.g. decline in functioning) can result in an individual learning about and receiving a psychosis risk syndrome label. Depending on subjective appraisal, there is the potential for the
identified youth to experience added acute and chronic stressors during the post-disclosure period. For example, many youth experience stigma and family conflict after they receive a psychosis risk syndrome label. Social isolation and uncertainty about the future are also reported in individuals who receive a psychosis risk label. Additionally, to receive a psychosis risk syndrome label, these individuals are tasked with engaging in the healthcare system, and some may continue to seek out additional care. It is important to note again that stress is idiosyncratic and these domains may also be sources of resiliency. The current model theorizes that an individual’s subjective appraisal of these factors as acute and chronic stress could activate the vulnerable HPA system and interact with normative and pathological neuroendocrine development and other environmental risk factors and stressors. These interactions could thus ultimately lead to symptom onset/exacerbation or help serve as protective factors/targets for intervention. Importantly, individual differences in the expression and subjective appraisal of these factors also emphasize potential areas of resiliency that could protect against symptomatology.

**Where do we go from here?**

This proposed model suggests that following a psychosis risk syndrome label, a number of factors have the potential to engage a vulnerable stress system. However, it is currently unclear what role these factors ultimately play in impacting the small, but clinically significant, proportion of youth who go on to develop psychosis. Further, a question remains about the larger proportion of youth who do not go on to develop psychosis but may still be negatively impacted by stress associated with disclosure. Currently, there is general consensus that the work of early identification is important and necessary to promote beneficence (Macdonald et al., 2017; Corcoran, 2016; McGorry et al., 2001; Yang et al., 2013). At the same time, it also seems likely that the act of disclosure, a necessary consequence of this work, may contribute to stress, and therefore play a pathogenic role (Edo et al., 2012; Macdonald et al., 2017; Mittal et al., 2015). So how should the field move forward in a way that approaches the post-disclosure period in a manner that promotes non-maleficence (e.g., limiting undue costs, medication side-effects, further stigma), while also balancing beneficence (promoting wellness by limiting stress)?

We argue that more research is needed to better understand HPA-axis vulnerability and interactions with social stressors in youth at-risk for psychosis. Until we have empirical evidence to support our assertions, it is not currently possible to provide a definitive course forward. In the face
of this uncertainty, the goal of any post-disclosure strategies should be to benefit all youth who receive the risk label, regardless of what outcome subgroup they represent (i.e., false positive, true positives who did not develop psychosis because of successful intervention, and true positives, who developed the disorder regardless of currently available treatments). Any recommended treatment must also be of low burden (affordable, widely available, without strong side-effects), include limited risk of further stigma, and notably, not solely engage the stress system. More research and guidelines are also needed to better understand the ways in which a provider gives a psychosis risk syndrome label to an individual and the individual's level of symptoms in the context of the current model. Until experimental research better informs our understanding of causality, we recommend several options following disclosure that address multiple aspects of risk and functioning, including stress management as well as other treatment targets.

Given the associated risks around stigma and social isolation (e.g. loneliness, lack of support system), ethically informed best practices might include providing referrals for social skills training, psychoeducation about stigma, and suggested resources to help these individuals feel less alone, such as peer/care-givers group therapy (Landa et al., 2016). Further, as it is clear that the family system may be impacted after a risk label, best practices might include directing families to promising efficacious interventions, such as Family Focused Treatment (Miklowitz et al., 2014; Miklowitz et al., 2013), and therapeutic social support groups conducted online (Zhang et al., 2017). It is also clear that engagement in the healthcare system and uncertainty about the future may play a role in engaging the stress system. While the noted therapeutic interventions may help to mitigate stress related to these factors, institutional change around our healthcare system, as well as the way we treat individuals with mental illness, is also sorely needed (Corrigan, 2004; Lawrence & Kisely, 2010). Following disclosure, providers moderating between clients and healthcare systems will also need to balance competing principles of rights based and legal justice.

As the field continues to work toward advances in early identification and preventive treatment, ethical standards posit that it is increasingly important to understand the added stressors associated with preventive care, especially after a psychosis risk syndrome label is given. The current topical review illustrates how stigma, social isolation, family conflict, engagement in the healthcare system, and uncertainty about the future are related to psychological and biological stress responses in individuals who are given a psychosis risk syndrome label. Future studies are
necessary to explore the hypothesized model, as understanding the mechanisms of change between receiving a risk label and symptom onset is valued information that can inform psychoeducation, treatment decisions (accounting for risk and resiliency considerations specific to each person), the design of novel interventions, and new research agendas. Additionally, the current review focuses on potential intervening factors that could increase stress during the post-disclosure period; however, this is not an exhaustive list of potential factors and future studies examining additional factors, such as factors related to functioning, are needed. Overall, understanding these mechanisms is vital for developing empirical evidence that supports ethically informed post-disclosure strategies to eliminate harm and allow individuals who are at risk for developing psychosis to have the most successful outcomes possible.

References:


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