Shortcomings of calculating risk for psychosis:**Critical remarks on predictive modeling in psychosis risk research**

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Abstract

Background: Recent developments in research on the clinical risk of psychosis have resulted in introducing 'risk-calculators' based on the principles of predictive modeling in order to improve the risk of transition to psychosis. Although 'risk-calculators' have the potential to be clinically useful, it is essential to consider important pitfalls of application of predictive modeling to 'at-risk states for psychosis'.

Methods: A critical narrative review of existing 'risk-calculators' for patients fulfilling at-risk for psychosis states criteria has been conducted.

Results: The predictive validity of 'risk-calculators' has limitations due to backward chaining problem and heterogeneity of etiology and psychopathology of at-risk states for psychosis. Moreover, the knowledge of risk factors and, in particular, their dynamic combinations is scarce at the recent stage which limits predictive modeling. 'Risk-calculators' and predictive modeling for long-term outcomes may be violated due to the dynamic characteristics of the development of psychosis and the fact of high sensitivity to violations in initial conditions of complex systems.

Conclusions: An introduction of 'risk-calculators' is an important step in the field, however, it has several important limitations. Further developments addressing existing limitations of predictive modeling and characteristics of at-risk states is warranted.

As a consequence of the ongoing development and progress in predictive modeling statistics, ‘risk calculators’¹⁻³ for predicting the clinical risk of psychosis have been introduced. Predictive modeling in clinical samples is a promising contribution to the field. However, a number of shortcomings of this approach have been addressed in and outside psychiatry that have bearing on the conclusions that can be derived from studies modeling the risk for adverse mental health outcomes. We argue that these shortcomings should be considered in order to facilitate further developments in predictive risk modeling.

Existing predictive models (e.g., risk calculators)¹⁻³ predict future risk of developing full-blown disorder (e.g., psychosis) in high-risk samples based on backward chaining. Some processes and life events that preceded the onset of psychosis are considered as risk factors. In other words, the outcome that is predicted must occur and it is modelled by preceded factors that best fit to the data. Yet, the problem of translating backward chaining into forward predictions has been recognized early in the philosophy of logic. It is unlikely, that mental states considered as a complex dynamic system⁴ can be characterized by Newtonian principles, in which, under ideal conditions, backward and forward inferences are reversible. Simply put, starting from output and moving backwards to the input may enable us to *approximate* why some event occurred. Yet, the given input is likely to provide a different output when considered in the framework of forward chaining. For instance, unfavorable neuropsychological functioning (or subclinical psychotic symptoms, etc.) at baseline (retrospective measure) is not changeable over time in the model. Hence, a static prediction model may explain some part of the variance in the outcomes that have been already known (e.g., transition to psychosis). It leads to the paradox that what we are able to predict is the event that already occurred based on the data that we observed prior to the event. However, as Soren Kirkegaard stated ‘life can only be understood backwards; but it must be lived forwards’. Backward chaining is likely inevitable in psychiatry which has an important implication for predictive modeling – it leads to the model uncertainty. Furthermore, the widely recognised non-ergodicity of psychopathology⁵ may also lead to uncertainty of predictive modeling. We argue that these aspects should be recognized and considered in the further development of predictive modeling of the risk for psychosis.

The situation is even more complicated when one considers that there are multiple and heterogeneous aetiological and phenotypic pathways to psychosis⁶. Without dynamic assessments⁴, the models face the problem of predicting dynamic, often long-term, changes based on limited and static measures. Some empirical and methodological progress has been made on this need for dynamic predictive modeling of psychosis risk in our recent work⁷.

Existing predictive modeling is also limited by the fact that to date there is no well-defined set of factors and their combination(s) that are known to contribute substantially to a risk of psychosis. Instead, there is a large list of different potential risk factors. Contrary to this, some existing risk calculators consider a maximum of eight factors⁸ and some of them build their predictive algorithm based only on age, sex and ethnicity¹. Resilience factors that likely may reduce the impact of the risk factors on progressing towards psychosis are not well understood

and often not considered at all. As the number and range of potential risk and resilience factors has been not been well established, the utility of their combination is simply unknown. Moreover, we do not know unknowns ('unknown unknowns'), i.e. factors not yet considered that may potentially be involved in the risk for psychosis and other psychiatric conditions. Hence, when dealing with systems as complex as mental states (especially unusual) at this stage we remain condemned to a high degree of *uncertainty*, which should be recognized and incorporated into predictive models.

Importantly, according to chaos theory, observed behavior in complex systems is often stochastic and its prediction is highly sensitive to changes in initial conditions. This is why even when the nature of the event (psychosis onset) is deterministic, this does not imply that the event is necessarily predictable. Considering the principles of chaos theory, predictive modeling should pay close attention to violations of initial conditions. It is likely that different processes that are considered as risk factors for psychosis vary in their temporal dynamics. Hence, predictive models that based on factors that are highly violated over time may have a limited timeframe in which prediction is accurate.

Furthermore, it should be recognized that contrary to physical phenomena, with which many predictive modeling techniques have been developed, mental states have no clear spatial and temporal dimensions that may be easily measured. Hence, qualitative and quantitative aspects of the relationship between different predictive variables may change over time. Without taking into consideration the qualitatively different and distinctive nature of mental phenomena predictive modeling in psychiatry may be unreliable. Uncertainty in predictive modeling in psychiatry is not simply a matter of imperfect statistical algorithms, but rather is a consequence of the principles of dynamic complex systems and the nature of mental phenomena themselves. Nevertheless, modeling the degree of uncertainty and limits of prediction in different psychiatric conditions, including risk states, may be beneficial for further developments in the field. For instance, it may be of clinical utility to model time frames over which predictions for different outcomes are reliable and valid. It is likely that different mental states may have variable time frames over which they can be accurately predicted.

The issues mentioned above lead to a cautious interpretation of the conclusions drawn from the existing approach to predictive modeling, currently formulated in 'risk calculators' for psychosis and in psychiatry generally. In practice, it is impossible to build models considering all known factors. However, at this stage of research the minimal complexity required in predictive models for risk states for psychosis or other conditions has not been established (i.e., which factors and their interactions should be considered in the model to accurately predict the desired outcome over a certain timeframe?). The discussion of the shortcomings of existing predictive models should also be coupled with the limitations of UHR criteria and psychiatric diagnosis in general. We argue that some of the shortcomings may be addresses statistically (e.g., time limits of predictions, modeling unknowns factors). Precise psychiatry hoping for better prediction may require consideration of dynamic processes that underlie often static

binary diagnostic categories. The recently suggested approach⁵ to combine macro-level (e.g., clinical interviews according to existing diagnostic criteria) and micro-level assessment (e.g., experience sample methodology, digital phenotyping with a dense assessment points in a patient's real-life environment) in a dynamic, prospective fashion may serve as theoretical guidelines. Contrary to what has been stated by Cannon et al.², there may be great value in emphasizing that showing and discussing with service users the degree of uncertainty in our predictions of the future is important when developing means of dealing with present discomfort associated with subclinical psychotic symptoms.

Finally, it is of note that none of the existing risk calculators considered the way that service users *interact* with external systems, including early detection services. Do we not expect any impact of early interventions on the risk estimate itself?

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