Need for evidence-based early intervention programmes: a public health perspective

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ABSTRACT
This paper attempts to discuss why the early intervention agenda based on the current convention of ‘ultra-high risk’ (UHR) or ‘clinical high risk’ (CHR) for ‘transition’ to psychosis framework has been destined to fall short of generating a measurable and economically feasible public health impact. To summarise: (1) the primary determinant of the ‘transition’ rate is not the predictive value of the UHR/CHR but the degree of the risk-enrichment; (2) even with a significant pre-test risk enrichment, the prognostic accuracy of the assessment tools in help-seeking population is mediocre, failing to meet the bare minimum thresholds; (3) therapeutic interventions arguably prolong the time-to-onset of psychotic symptoms instead of preventing ‘transition’, given that the UHR/CHR and ‘transition’ lie on the same unidimensional scale of positive psychotic symptoms; (4) meta-analytical evidence confirms that specific effective treatment for preventing ‘transition’ (the goal—primary outcome—of the UHR/CHR framework) is not available; (5) the UHR/CHR ‘transition’ is a precarious target for research given the unpredictability driven by the sampling strategies and the natural ebb and flow of psychotic symptoms within and between individuals, leading to false positives; (6) only a negligible portion of those who develop psychosis benefits from UHR/CHR services (see prevention paradox); (7) limited data on the cost-effectiveness of these services exist. Given the pitfalls of the narrow focus of the UHR/CHR framework, a broader prevention strategy embracing pluripotency of early psychopathology seems to serve as a better alternative. Nevertheless, there is a need for economic evaluation of these extended transdiagnostic early intervention programmes.

WHAT IS THE CLINICAL UTILITY AND PROGNOSTIC ACCURACY OF UHR/CHR ASSESSMENT TOOLS?
As discussed, the clinical utility of UHR/CHR assessment tools primarily depend on the degree of progressive risk enrichment ensured by selective sampling and filtering at each help seeking attempt. Meta-analytical evidence shows that even with a significant pretest risk enrichment, the prognostic accuracy of these assessment tools in help-seeking population is mediocre, failing to meet the bare minimum thresholds, with positive likelihood ratios (LR) of 1.82 and 1.9 and negative LRs of 0.09 and 0.25 for the Structured Interview for Psychosis-Risk Syndrome and the Comprehensive Assessment of At Risk Mental State.

WHAT IS THE COST-EFFECTIVENESS OF SPECIAL SERVICES FOR UHR/CHR?
Given the scarcity of UHR/CHR cases and low ‘transition’ rates, it is highly questionable whether the targeted UHR/CHR early intervention programmes may achieve any economically feasible public health success—see prevention paradox (figure 1). A recent retrospective investigation of electronic health records data from South East London showed that 16.3% of the patients presented to mental health services with a first-episode psychotic disorder (FEP) had a prior contact with local prodromal services, similar to recently disclosed data from Melbourne. However, only 4.1% met criteria for UHR/CHR and consequently ‘transitioned’, while the remaining 12.3% had already been diagnosed with FEP at initial contact with prodromal services. A similar trend, lending support to the prevention paradox, has also been shown in other cohorts across the world—only a negligible portion of those who develop FEP benefits from UHR/CHR services. Strikingly, two decades of UHR/CHR service research, although growing exponentially across the
IS THERE AN AVAILABLE THERAPEUTIC INTERVENTION THAT CAN PREVENT ‘TRANSITION’ TO PSYCHOSIS IN UHR/CHR POPULATION?

Over half a century, the classical Wilson and Jungner criteria for disease screening have set the standards for appraising the need for population screening programmes in healthcare (box 1 adapted from the WHO Bulletin). The UHR/CHR programme, although an indicated prevention strategy, arguably meets some of these principles to a degree; yet it fails to meet the most essential criterion: availability of effective treatment for disease prevention. The most recent network meta-analysis of all randomised controlled trials of pharmacological and non-pharmacological interventions for UHR/CHR showed no evidence for specific effect of any intervention, including needs-based treatment (also placebo), in preventing ‘transition’ to psychosis. The authors discussed that these recent findings, contradicting the early meta-analyses that reported a positive effect, are mainly driven by the non-significant findings from more recent trials. In this regard, it is also arguable that these therapeutic interventions are merely prolonging the time-to-onset of psychotic symptoms instead of preventing ‘transition’ to clinical psychosis spectrum disorder given that both binary categories of UHR/CHR and ‘transition’ are measured on the same unidimensional scale of positive symptoms (from mild to severe) rather than a multidimensional assessment of outcome and functioning as a more clinically relevant alternative.

IS THE UHR/CHR BINARY ‘TRANSITION’ OUTCOME A VALID PHENOTYPE FOR RESEARCH?

Research exploiting binary transition outcome appears like clockwork, with each study proposing a novel biological marker of transition, such as thalamic dysconnectivity or disorganised gyrification network properties as of lately and possibly many more in the future. Much of the appeal of the binary transition paradigm is in its capacity to simplify the interpretation of findings and provide a basis for transition to clinical practice. The rising trend of this research design is unusual considering that the psychiatry research is moving away from categorical diagnosis towards an all-encompassing psychosis-spectrum research framework.

The most concerning issue is the unpredictability embedded in the UHR/CHR concept. First, transition is not a binary shift but a dimensional shift in positive psychotic symptoms per definition and therefore influenced by the natural ebb and flow of psychotic symptoms within and between individuals, leading to false positives. Second, it is highly unlikely the same study design would conclude the same finding across different clinical settings or time periods where transition rates vary dramatically depending on multiple factors as described previously. Given this unpredictability of transition rates that are primarily driven by heterogeneity in study sampling methods, it is highly questionable whether a novel biological marker of transition can be independently replicated in another study in another setting.

CONCLUSION

It is all too easy to stand by the status quo and champion the UHR/CHR concept given the virtue of a commitment to early intervention for young people at-risk and the enticing simplification of the UHR/CHR framework in clinical and research practice, but our decision-making should be guided by evidence—evidence that can come from nowhere but epidemiology and public health.

To give an example from medicine, there is a hot debate over the clinical utility of screening programmes. Even the standard screening programmes that have been part of routine clinical and public health practice over decades, such as diabetes mellitus and breast and prostate cancers, are under fire for failing to generate a significant improvement in key outcome measures, such as disease-specific and all-cause mortality. In this regard, we believe that the field, after two decades of clinical research, should at least be open for discussion of concerns over the UHR/CHR programme in the light of data. In fact, it is encouraging to see that even the prime movers of the traditional UHR/CHR paradigm move beyond a narrow framework and adopt a broader prevention strategy acknowledging pluripotency.

Also, instead of the pragmatic surrogate outcome of ‘transition’, higher-level outcomes such as functioning and quality of life may serve as more clinically relevant and service-user-centred outcomes for measuring effectiveness of the early intervention programmes. Nevertheless, there remains a continuing need for rigorous economic evaluation of these extended trans-diagnostic programmes.

Overall, we reiterate the fact that we are required to adhere to evidence-based mental healthcare standards in early intervention practice to make a measurable public health impact.

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