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Contents

Predicting the development of schizophrenia

Chuma & Mahadun[1] report on a much needed and topical meta-analysis of prospective studies investigating the predictive validity of prodromal criteria in schizophrenia. The potential importance of early identification and treatment cannot be underestimated. The authors should be congratulated for helping clarify whether the identification component is currently worthwhile. I have no doubt that this paper is generally well conducted and for the 'ultra-high-risk strategy' sample size reasonable but I am afraid I cannot agree with their interpretation of results. In particular, they conclude that that both ultra-high-risk and basic-symptoms criteria are valid and useful tools in predicting the future development of schizophrenia among the 'at-risk population', and that ultra-high-risk criteria were able to 'correctly predict schizophrenia' (citing sensitivity of 81%), while being able to 'exclude this condition with some certainty' (citing specificity of 67%). Taken at face value, clinicians would conclude that these methods both rule in those who are going to develop schizophrenia and rule out those who will not develop schizophrenia with high certainty. A small point, but sensitivity relates more closely the ability to rule out a condition (and is linked with negative predictive value) and specificity to ruling in a condition; hence the Sacket acronym SP-in and SN-out. In black and white terms, a specificity of 67% immediately suggests there will be a problem with false positives. But neither sensitivity nor specificity is a substitute for positive predictive value and negative predictive value which are the actual accuracy rates for every person identified as at high risk (screen positive) or low risk (screen negative) by these tools after taking into account the conversion rate. I am uncertain why the authors have presented clinically obscure statistics like DOR but omit the informative ones, namely positive predictive value (PPV)/negative predictive value (NPV).

Using the pooled estimate of 81% sensitivity and 67% specificity and a conversion rate of 21% (402 of 1918 at baseline), the PPV of the ultra-high-risk method(s) would be 39.4%, meaning only four out of ten identified as 'will progress to schizophrenia' actually would do so, and six would not. Of course we do not know whether others would progress if we extend the follow-up period but this is currently speculation requiring re-examination of these tools over a longer period. Hypothetically, if 30% of people progressed, then the PPV of ultra-high-risk method(s) could rise to 50%, which is still disappointing in my opinion. More encouragingly perhaps, even at 21%, the NPV would be 93.0%; meaning almost 19 out of 20 thought to be at low risk would not progress. The numbers for those using basic symptom criteria are similar but with even better NPV (PPV = 38.6%; NPV = 98.7%). That said, it is not initially obvious that only 60–70% of people who will not convert are put in a low-risk category by the tool (i.e. it is redundant in a third) and basic symptom data come from only one study with 160 participants.

I appreciate that many might find these statistical terms confusing. Previously, I have proposed a simple adjustment of false positives and false negatives per every 100 patients seen, which I called real-world interpretation/yield. So, for every 100 individuals thought to be at risk and subject to ultra-high-risk criteria, 17 would be correctly classified as converters to schizophrenia and 4 would be missed; and 53 would be correctly classified as non-converters but 26 would be falsely identified. In effect, there would be six times as many false positives as false negatives. If each 'positive' were treated, then (by ratio of false positives to true positives) 50% more patients without any prospect of psychosis would be treated than those actually at risk of psychosis. I wonder whether these error rates are really acceptable when mental health resources are stretched and long-term adverse effects of antipsychotics are more than ever before seen as problematic. I therefore ask the authors to reconsider whether these approaches are entirely valid for both rule-in and rule-out purposes when the data suggest mainly the latter. I also suggest a novel future study in which clinicians working with high-risk patients are randomised to predicting risk with and without the tools, a method that would elucidate the 'added value' in clinical practice.

1 Chuma J, Mahadun P. Predicting the development of schizophrenia in high-risk populations: systematic review of the predictive validity of prodromal criteria. *Br J Psychiatry* 2011; **199**: 361–6.

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The aim of Chuna & Mahadun's study[1] is compelling and of great clinical interest for preventive interventions in psychosis. Unluckily, the results presented by the authors are not reliable as they are undermined by severe methodological caveats.

First, the systematic research of the literature failed to uncover the majority of studies reporting follow-up transition rates in a sample of individuals at high risk (HR) for psychosis. The authors included only 12 studies but many more were available in the electronic databases (references supplied). Second, the authors did not check for potential overlapping between samples including studies enrolling the same individuals. For example, Yung *et al* (2003)[2] and Yung *et al* (2004)[3] were both retrieved despite the authors of these studies clearly stating in their manuscript that the 'current paper [2004] continues that research [2003; $n = 49$] by expanding the sample size to 104'. The same applies to Yung *et al* (2005)[4] and Yung *et al* (2008),[5] while Woods *et al* (2009)[6] is a revised analysis of Cannon *et al* (2008).[7] Third, the authors stated in the inclusion criteria that the included studies 'had a clearly specified population, from which a prodromal criterion was administered to identify clearly those with prodromal symptoms [HR +] from those without [HR −]'. There is no such a 'clearly specified population' from which the high-risk individuals are sampled. The sampling is based on help-seeking behaviours and does not epidemiologically represent the local population; in fact, the prevalence of high-risk symptoms in the general population is unknown. The second requirement to be included in the Chuma & Mahadun's meta-analysis was that 'the two groups [HR+ and HR −] were then followed up for a number of months and assessed again with a diagnostic instrument to determine those who had converted to schizophrenia'. This is really surprising as the vast majority of the longitudinal studies

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did not follow-up the help-seeking individuals who underwent the clinical assessment at the prodromal services but were not considered at risk for psychosis (HR–). Consequently, it is completely obscure how the authors may have estimated the correct prevalence of false negatives (HR–, who developed psychosis over time) in their analysis. Given all the above concerns, I feel the results of this meta-analysis should be considered carefully as pilot data strongly undermined by significant methodological biases.

1 Chuma J, Mahadun P. Predicting the development of schizophrenia in high-risk populations: systematic review of the predictive validity of prodromal criteria. *Br J Psychiatry* 2011; **199**: 361–6.

2 Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, et al. Psychosis prediction: 12 months follow up of at risk (prodromal) group. *Schizophr Res* 2003; **60**: 21–32.

3 Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychological and clinical features. *Schizophr Res* 2004; **67**: 131–42.

4 Yung AR, Phillips LJ, Yuen HP, McGorry PD, Kelly D, Dell'olio M, et al. Mapping the onset of psychosis: the comprehensive assessment of at risk mental states. *Aust NZ J Psychiatry* 2005; **39**: 964–71.

5 Yung AR, Nelson B, Stanford C, Simmons MB, Cosgrave EM, Killackey E, et al. Validation of 'prodromal' criteria to detect individuals at ultra high risk of psychosis: 2 year follow up. *Schizophr Res* 2008; **105**: 10–7.

6 Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, et al. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. *Schizophr Bull* 2009; **35**: 894–908.

7 Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry* 2008; **65**: 28–37.

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Authors' reply: Dr Fusar-Poli identified a number of studies reporting follow-up transition rates, which is not the same as predictive the validity of the tests or criteria. Most, if not all, of the studies he identified did not have information on predictive attributes of the tests or criteria, such as sensitivity and specificity. However, they had useful information on transition rates. From these it is impossible to know how good the tests/criteria were in ruling in or out the risk of developing schizophrenia from prodromal symptoms, since these studies were not systematically following up those who tested negative to the test.

Dr Fusar-Poli raised another important issue regarding overlapping of samples. We checked for double publication, but not necessarily overlapping of samples. We were interested in knowing how good the test is in predicting schizophrenia in high-risk populations. We therefore were interested in diagnostic attributes of a test in each study/subsample. The values for sensitivity and specificity for Yung *et al* (2003)[1] and Yung *et al* (2004)[2] were not identical. For the purposes of predictive validity of a test, these are two different studies. Yung *et al* (2005)[3] had a follow-up of 6 months ($n = 105$) and Yung *et al* (2008)[4] had a follow-up of 24 months ($n = 292$). Again, these are different studies, we are not sure whether there was overlapping of samples in these two but we don't see how this would affect how good the test is at ruling in or out the risk of developing schizophrenia. The same can be said with studies by Cannon *et al*[5] and Woods *et al*,[6] the diagnostic attributes of the Cannon study were not identical to Woods' study.

Dr Mitchell raises important points regarding the predictive validity of prodromal criteria. In particular, Dr Mitchell is right to suggest that the positive predictive value and negative predictive value statistics are more intuitively informative than sensitivity and specificity, and so their reporting would have been beneficial. We also agree that assessing the clinical usefulness of prodromal criteria requires further consideration. We plan to further examine this important question in a subsequent paper. We welcome Dr Mitchell's proposal for a randomised study where high-risk patients are randomised to predicting psychosis with or without formal tests for prodromal criteria.

1 Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, et al. Psychosis prediction: 12 months follow up of at risk (prodromal) group. *Schizophr Res* 2003; **60**: 21–32.

2 Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychological and clinical features. *Schizophr Res* 2004; **67**: 131–42.

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Abortion, mental health and charges of guilt by association

Coleman's meta-analysis of abortion and mental health studies[1] was harshly criticised in three letters by five authors (Robinson, Stotland, Nadelson, Coyne, and Littell) who all cited an *Ethics & Medicine* article[2] I wrote (not Coleman) as evidence that Coleman's study cannot be trusted. My full response[3] is summarised as follows.

First, Robinson's[4] assertion that I am Coleman's 'leader' is nonsense. We have no institutional, financial or personal entanglements. Second, I gathered data that required the analysis of research psychologists. I am thankful that Coleman agreed to analyse it and help present it in a scientifically accurate and impartial manner. As a biomedical ethicist, I explore the intersections of medicine, science, philosophy, theology, ethics and the law. When writing papers intended for each of these fields, I seek to use the language and tools appropriate to each field.

Third, the cited article was a response to a pro-life philosopher who argued that any evidence of emotional suffering of women following abortion is essentially irrelevant to the moral argument against abortion and counterproductive to pro-life efforts.[5] The core of my response was that Christians have an obligation to 'consistently demonstrate as much concern for women as for their unborn children', and that 'our advocacy for women must be consistent and unconditional both for those who are facing crisis pregnancies and for those who have had abortions'. I further argued that 'the harm abortion does to women is just as real as that done to the human fetus'.[2]

Fourth, it also reflected my sincere belief that abortion involves substantial dangers to specific subgroups of women. Unfortunately, critics have distorted this into the charge that I seek to scare women with exaggerated risks.[6] That is untrue. There are real risks, especially for certain higher-risk groups.[7] Women