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## **NEGATIVE TRIALS IN PSYCHOSIS PREVENTION: THE NEGLECTED IMPORTANCE OF PRETEST RISK ENRICHMENT**

Dear Editor

In the wake of the recently published  $\omega$ -3 polyunsaturated fatty acids multisite trial (NEURAPRO) in the journal (McGorry et al, n=304<sup>1</sup>), the three largest studies of preventative interventions in individuals at ultra high risk (UHR) for psychosis have turned out to be negative (Morrison et al, n=288<sup>2</sup>, McFarlane et al, n=292<sup>3</sup>), suggesting that it may not currently be possible to prevent psychosis. However, the actual risk of psychosis in these interventional studies was found to be extremely low, even in the control group (11.2% in McGorry et al at 1y<sup>1</sup>, 9% at 2y in Morrison et al and 2.3% at 2y in McFarlane et al <sup>3</sup>, implying that these negative findings are likely to be secondary to small statistical power.

On a conceptual level, these studies challenge the underlying assumption that it is acceptable to meet specific psychometric criteria at intake to be slotted into the UHR category. Actually, the predictive power of the UHR criteria is not fixed priority, but is strongly dependent on the risk enrichment of the samples to which they are applied (i.e. “pretest” risk)<sup>4</sup>. This is due to the psychometric characteristics of these UHR instruments: they are good to rule out psychosis, but only moderately useful to rule in psychosis<sup>4</sup>. Therefore, majority of the observed risk to psychosis is not gained through UHR assessment per se, but is obtained before the assessment (pretest phase) during the recruitment of these individuals. Pretest risk enrichment in samples undergoing an UHR assessment remains substantial (15% at 38 months) and highly heterogeneous (9%-24% at 38 months)<sup>4</sup>. Pretest risk enrichment is modulated by the type of recruitment strategies adopted to select individuals for UHR assessment<sup>4</sup>. For example, recruiting individuals who were already filtered by adult mental health services is associated with higher pretest risk enrichment, as compared to recruiting individuals through intensive community outreach<sup>5</sup>. Not surprisingly, the lowest transition risk was reported in McFarlane et al, that has adopted a strong “community outreach and education program aimed at teachers, school, and college counsellors”<sup>3</sup>. Due to the heightened pressure to recruit participants into interventional studies, it is possible that a substantial proportion of these samples had been recruited through community outreach, diluting the transition risks.

It therefore seems expedient to control the pretest risk enrichment of samples recruited into future interventional studies for psychosis prevention by using pretest risk stratification models that have been recently validated in this journal<sup>5</sup>.

## References:

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