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Dear editors,

We have read with great interest the systematic review and meta-analysis by Dr Lang and colleagues[1] in the Journal of the American Academy of Child and Adolescent Psychiatry. The authors evaluated the transition rates of individuals <18 years old at clinical high risk for psychosis (CHR-P) after 1 year, 2 years and ≥5 years of follow-up, finding remarkably lower transition rates than those reported by previously published meta-analyses[2, 3]. They further assessed the proportion of psychosis cases preceded by pre-identified CHR-P diagnoses.

The authors included only individual studies in which the whole sample was <18 years. Only nine studies (with 436 individuals) were included in at least one of the time points evaluated. Furthermore, four studies were included at 2 years follow-up and ≥5 years follow-up. We have concerns about the strict cut-off of 18 years employed. The mean age of onset for schizophrenia-spectrum disorders and primary psychotic states is 20.5 years: only 12% appear before 18 years, while 50% appear by 25 years[4]. Thus, the exclusion of studies with participants diagnosed with CHR-P at 18 or older is concerning as it conflicts with the neurodevelopmental biology of psychosis and with the transitional nature of the CHR-P paradigm, which typically cuts across adolescents and young adults aged 12 to 35 years old. The associated problem is that because of the reduced number of studies retrieved, the associated statistical power is low.

We believe that a better meta-analytic approach to overcome the limited statistical power while at the same time testing the prognostic validity of the age cut-off at 18 years would have been to include all CHR-P samples with a mean age <18 years and conduct sensitivity or meta-regression analyses. The probability of transition to psychosis in previously published systematic reviews and meta-analyses in CHR-P adolescents can be found in the Table 1. In our recent meta-analysis we observed a probability of developing psychosis of 19% (95% CI: 17%-22%) at 2 years increasing to 28% (95% CI 20%-37%) at >4 years[3]. We found no impact of age in metaregression analyses (Beta=0.0165, 95%CI from -0.0362 to 0.0692)[3, 5]. In another meta-analysis, we included CHR-P samples with a mean age <18 years and then run sensitivity analyses comparing the subset of studies enrolling only samples of individuals all younger than 18 years vs those which included some individuals over 18 years. We found a probability of developing psychosis of 23% (95% CI: 18%–29%) at 2 years and 23.3% (95% CI: 17.3%–30.7%) at ≥3 years and again no differences with respect to the age 18 threshold[2]. An associated problem of small powered meta-analysis may be that the findings are highly unstable as one single study can change drastically the results. For instance, the current

review included in the 2-year meta-analysis a study including individuals with schizotypal personality disorder[6]. This group does not automatically equate to CHR-P individuals if functional deterioration criteria are not ascertained and met. In line with this, in a previous meta-analysis, authors observed that studies with lower quality were associated with a lower transition to psychosis (11%, 95% CI: 2% to 24%) compared to those with a higher quality (19%, 95% CI: 11% to 28%)[7]. Furthermore, we have recently demonstrated that age is not a significant modulator of clinical outcomes other than psychosis in CHR-P individuals, such as attenuated positive symptoms, negative psychotic symptoms, depressive symptoms or remission[8].

We agree with the authors that the capacity for psychosis prevention associated with the CHR-P paradigm in children and adolescents is limited and that most of the actual risk of developing psychosis is accounted for by the way CHR-P individuals are recruited, well before their assessment for a potential CHR-P state. This limitation is intrinsically inherited by the indicated nature of the CHR-P paradigm, which can only benefit a small portion of the population[9]. Several strategies are under testing, including large scale automatic screening methods for healthcare and community risk enrichment with pre-screening questionnaires[10, 11]. We also agree with the authors when they highlight the need for developmentally sensitive approaches when considering psychosis risk[1], since childhood and adolescence are highly crucial for the development and maturation of brain structures. This also has important therapeutic implications. Among others, previous research has shown that among the recommended needs-based and psychological interventions[12], younger individuals may benefit more from family interventions or cognitive remediation, which may improve cognition, symptoms and functioning[2].

In conclusion, we argue that there is no evidence that age impacts the probability of developing psychosis in CHR-P individuals, and that adolescents CHR-P people remain a vulnerable patient group which needs ongoing collaborative research and preventive efforts.

Table 1: Transition to psychosis in previously published systematic reviews and meta-analyses

Study	Transition at 1 year follow-up	Transition at 2 years follow-up	Long-term transition
Lang 2021[1]	9.5% (5.5%-14.2%) K=7	12.1% (6.7%-18.6%) K=4	16.1% (5.6-30%) K=4 *≥5 years follow-up*
Catalan 2020[2]	19.8% (14.6-26.3%) K=7	23.0% (18.0-29.0%) K=7	23.3% (17.3-30.7%) K=5 *≥3 years follow-up*
Raballo 2020[7]	17.5% (9.9-26.5%) K=11 *0.5-6 years follow-up*		
Tor 2018[13] (systematic review)	16.9–20% K=3	7–21% K=3	22.7–23.3% K=2 *6-year follow-up*

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