Name of Journal: World Journal of Psychiatry
Manuscript NO: 67085
Manuscript Type: ORIGINAL ARTICLE

Dear Lian-Sheng Ma

Please, find attached the revised version of our manuscript “Clinical high-risk criteria of psychosis in 8- to 17-year-old community subjects and inpatients not suspected to develop psychosis” for submission to the World Journal of Psychiatry.

In our revision, we paid close attention to the reviewer’s and editors’ comments. Our responses to them are detailed below.

We hope that our manuscript now meets the high standards of your journal and, again, confirm that it contains original work not submitted for publication elsewhere.

With best regards, also in the name of my coauthors
Frauke Schultze-Lutter

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Reviewer #1:
**Scientific Quality:** Grade B (Very good)
**Language Quality:** Grade C (A great deal of language polishing)
**Conclusion:** Minor revision
**Specific Comments to Authors:** This is a very well designed and well conducted study that is of great interest and significance.
**RESPONSE 1:**
We thank the reviewer for this positive perception of our paper.

I think it could be made more readable if the premise and aims were stated more simply. Instead of the very unwieldy "if....then....." I would recommend stating something like "We set out to.....because.....:
**RESPONSE 2:**
In our scientific arguments, we followed the structure of simple inference within the framework of propositional logic (one of the basics of scientific reasoning). Simple interference is commonly following the structure of a premise (if A is x then B is y or: $A_x \rightarrow B_y$) to reach the conclusion $B_y$ when A is x.
In our case, the premise A could take on 3 possible expressions from which 3 different conclusions result. Thus, our aim was to detect which expression A is showing in order to decide on the correct conclusion. This, proposition logical approach cannot be expressed other than in “if...then” conditions, in order to follow the appropriate style of propositional logic. This framework, however, is now more clearly stated as follows:
“Following a propositional logic approach, the aim of this paper was to examine, which of these alternative explanatory models of CHR criteria and symptoms – pluripotential syndrome, transdiagnostic risk factor / dimension, and severity marker – ~~might fit~~ best fits ~~to~~ the data of an age group, in which CHR criteria and symptoms are likely the least psychosis-specific[21,23]. To that end~~this aim~~, we cross-sectionally studied the frequency of CHR criteria and symptoms in an 8- to 17-year-old randomly recruited sample of the Swiss community and in an 8- to 17-year-old inpatients whose main diagnosis was a disorder that, earlier, had been longitudinally associated with an elevated risk to develop psychosis in adulthood[41,42] (Suppl. Table 1). ~~Further, an 8- to 17-year-old randomly recruited sample of the Swiss community was assessed for the same criteria and symptoms, also cross-sectionally.~~ The three alternative explanatory models were associated with in the following differential ~~a priori hypotheses~~premises:
(i) In the case of the CHR criteria and symptoms acting as a pluripotential syndrome, these should not be detectable after the onset of severe mental disorder, this is after their

transformation in a diagnostically specific disorder in the inpatient group. Rather CHR criteria and symptoms should still be detectable as a potential precursor state in the community subjects of that roughly a third must be expected to develop a mental disorder in their lifetime[43]. Consequently, if CHR criteria and symptoms would be more frequent in community subjects compared to inpatients, then they are likely ~~in case of CHR states being~~ pluripotential~~, CHR criteria and symptoms should be more frequent in community subjects compared to inpatients~~.

(ii) In the case of CHR criteria and symptoms representing a transdiagnostic risk factor or dimension, they would be expected to accumulate in the extreme range of persons with mental disorders. Thus, if CHR criteria and symptoms would ~~and, thus, to~~ be more frequent in the inpatients compared to community subjects, then they likely represent a transdiagnostic risk factor or dimension.

(iii) Lastly, in the case of CHR criteria and symptoms being a severity marker of psychopathology, they should be associated with the illness severity and, relatedly, with the degree of functional impairment. Consequently, if CHR criteria and symptoms would show a significant negative correlation with functioning, then they likely represent a severity marker of psychopathology."

Also, readers would prefer if everything were in the active rather than the passive voice.

**RESPONSE 3:**

We have converted the text where reasonable, thereby closely following the advice given by the APA (https://apastyle.apa.org/style-grammar-guidelines/grammar/active-passive-voice). This states that

"Both the active and the passive voice are permitted in APA Style. However, writers often overuse the passive voice.

- Use the active voice as much as possible to create direct, clear, and concise sentences, especially when you are writing about the actions of people.
- Use the passive voice when it is more important to focus on the recipient of an action than on who performed the action, such as when describing an experimental setup."

I have no quarrel with the study but it would have a much greater impact if it could be much more simply and clearly written.

**RESPONSE 4:**

We carefully revised the text towards being simpler to read, in doing so, we mainly shortened or split up long sentences with more than one subclause.

## 6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

**(1)** ***Science editor:*** 1 Scientific quality: The manuscript describes an observational study of the clinical high-risk criteria of psychosis in 8- to 17-year-old community subjects and inpatients not suspected to develop psychosis. The topic is within the scope of the WJP. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This is a very well designed and well conducted study that is of great interest and significance. The questions raised by the reviewers should be answered;

**RESPONSE 5:**

We again thank the reviewer and editor for their positive comments about our study.

(3) Format: There are 8 tables; (4) References: A total of 102 references are cited, including 34 references published in the last 3 years; (5) Self-cited references: There are 16 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and

remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

**RESPONSE 6:**

We have now cut-down the 16 self-references to 8 (of newly 93 references) by omitting the following 9 references (numbers of the first submission):


**16** Schultze-Lutter F, Ruhrmann S, Fusar-Poli P, Bechdolf A, Schimmelmann BG, Klosterkötter J. Basic symptoms and the prediction of first-episode psychosis. Curr Pharm Des 2012;18(4): 351-357 [PMID: 22239566 DOI: 10.2174/138161212799316064]

**18** Schultze-Lutter F, Schimmelmann BG, Ruhrmann S, Michel C. 'A rose is a rose is a rose', but at-risk criteria differ. Psychopathology 2013;46(2): 75-87 [PMID: 22906805 DOI: 10.1159/000339208]

**25** Schultze-Lutter F, Ruhrmann S, Michel C, Kindler J, Schimmelmann BG, Schmidt SJ. Age effects on basic symptoms in the community: A route to gain new insight into the neurodevelopment of psychosis? Eur Arch Psychiatry Clin Neurosci 2020;270(3): 311–324 [PMID: 30361925 DOI: 10.1007/s00406-018-0949-4]

**27** Schultze-Lutter F, Schmidt SJ. Not Just Small Adults - The Need for Developmental Considerations in Psychopathology. Austin Child Adolesc Psychiatry 2016;1(1): 1001 [URL: https://austinpublishinggroup.com/child-adolescent-psychiatry/fulltext/aca p-v1-id1001.php]

**50** Schultze-Lutter F. [The Basic-Symptom Concept and its Influence on Current International Research on the Prediction of Psychoses]. Fortschr Neurol Psychiatr 2016;84(12): 748–755 [PMID: 27951606 DOI: 10.1055/s-0042-119025]

**64** Schultze-Lutter F, Schimmelmann BG, Ruhrmann S. The near Babylonian speech confusion in early detection of psychosis. Schizophr Bull 2011;37(4): 653–655 [PMID: 21558142 DOI: 10.1093/schbul/sbr039]

**77** Schultze-Lutter F, Klosterkötter J, Michel C, Winkler K, Ruhrmann S. Personality disorders and accentuations in at-risk persons with and without conversion to first-episode psychosis. Early Interv Psychiatry 2012;6(4): 389–398 [PMID: 22260339 DOI: 10.1111/j.1751-7893.2011.00324.x]

**79** Schultze-Lutter F. Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. Schizophr Bull 2009;35(1): 5-8 [PMID: 19074497 DOI: 10.1093/schbul/sbn139]

**80** Schultze-Lutter F, Nenadic I, Grant P. Psychosis and Schizophrenia-Spectrum Personality Disorders Require Early Detection on Different Symptom Dimensions. Front Psychiatry 2019;10: 476 [PMID: 31354543 DOI: 10.3389/fpsyt.2019.00476]


2 Language evaluation: Classification: Grade C. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form, and the written informed consent. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by German Research Foundation, Swiss National Science Foundation. The topic has not previously been published in the WJP. 5 Issues raised: (1) The language classification is Grade C. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240;

**RESPONSE 7:**

The reviewer commented solely on the style but not at all on the correctness of the English, in doing so mainly criticizing the passive voice – a critique that is debatable in itself (*see for example: Ferreira, F. (2021). In defense of the passive voice. American Psychologist, 76(1), 145–153. https://doi.org/10.1037/amp0000620*). Thus, we revised the English without the

help of a language editing company that would mainly correct language errors but not style. Next to the first author who has passed the Cambridge Certificate of Proficiency, a colleague who is a native English speaker, M. Thomson, again carefully proof-read the paper.
This decision was further backed up by the fact that none of the 4 language editing companies recommended at https://www.wjgnet.com/bpg/gerinfo/240 is cooperating with the Heinrich-Heine University or the University of Bern; and applying for payment for a language editing by the respective economic department would have taken considerably more time than the 14 days granted for revision.

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);
**RESPONSE 8:**
We are sorry for this omission. We possibly confused this point as asking for the approved grant application submitted to the funding agency rather than for the letter of approval send by the funding agency. We have now provided both.

and (3) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.
**RESPONSE 9:**
The Article Highlights” section is now added at the end of the main text prior to the Acknowledgements. It reads as follows:
“***Research background***
Many patients with clinical high-risk of psychosis (CHR) criteria do not develop psychosis, in particular if they are still in their childhood and adolescence. Therefore, CHR criteria were suggested to be not a risk indicator of psychosis development but (1) a pluripotential syndrome that will transform itself into all kinds of mental disorder, (2) a transdiagnostic risk factor from that all kind of different disorders develop, or (3) simply a severity marker of mental disorders.
***Research motivation***
The simple non-conversion to psychosis and the persistence or new-occurrence rate of non-psychotic mental disorders in CHR samples, however, do not allow for the conclusion of any of the three alternative explanatory models, which might explain why they are often proposed interchangeably. Thus, to gain more insight into the nature of CHR symptoms and criteria, we examined the differential implications that each of these models has on the occurrence of CHR criteria and symptoms and their association with a proxy measure of illness severity in patients with severe mental disorders, i.e., inpatients, and in community subjects. We expected that any pattern of group differences indicative of one of the alternative explanatory models should become particularly apparent in a child and adolescent sample as CHR symptoms and criteria were reported to be more frequent but less clinically relevant and less associated with psychosis in children and adolescents compared to adults.
***Research objectives***
Following a propositional logic approach, we examined which of the three alternative explanatory models of CHR criteria and symptoms would best fit our data. The three alternative explanatory models were associated with in the following differential premises with respect to the data:

1. If CHR criteria and symptoms are more frequent in community subjects compared to inpatients, then they are likely pluripotential. This was assumed because a pluripotent syndrome would have transformed into a mental disorder and, thus, not present in inpatients, but in a community sample wherein a proportion can be expected to develop a mental disorder in future.
2. If CHR criteria and symptoms are more frequent in inpatients compared to community subjects, then they likely represent a transdiagnostic risk factor or dimension. This was assumed because they would aggregate in persons with mental illness.

3. If CHR criteria and symptoms show a clinically relevant, significant negative correlation with functioning as a proxy measure of illness severity, then they likely represent a severity marker of psychopathology.

***Research methods***

As part of the Bi-national Evaluation of At-Risk Symptoms in children and adolescents (BEARS-Kid) study, we cross-sectionally examined the frequency and severity of CHR criteria and symptoms in an 8- to 17-year-old randomly recruited sample of the Swiss community (n=233) and in an 8- to 17-year-old inpatients (n=306) whose main diagnosis was a disorder that, earlier, had been associated with an elevated risk for psychosis in adulthood (obsessive compulsive and anxiety, attention deficit, eating, and autism-spectrum disorder) using chi-square and non-parametric analyses. Furthermore, the associations between psychosocial functioning, and CHR criteria and symptoms were analysed with bivariate and partial correlation analyses, the latter controlling for group membership. CHR criteria and symptoms according to the ultra-high risk and the basic symptom approach were assessed in clinical interviews by trained psychologists using the Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY). Furthermore, we followed up 78.5% of the participants after one-year, and 61.4% after two years past baseline for a conversion to psychosis.

***Research results***

The 7.3%-prevalence rate of CHR criteria in community subjects did not differ significantly from the 9.5%-rate in inpatients. Frequency and severity of CHR criteria never differed between the community and the four inpatient groups. The frequency and severity of CHR symptoms differed between the community and the four inpatient groups only in four CHR symptoms: *suspiciousness/persecutory ideas* of the SIPS as well as tho*ught pressur*e, *derealization* and *visual perception disturbances* of the SPI-CY. The persistent pattern of these differences was consistent with a transdiagnostic risk factor or dimension, i.e., these symptoms were more frequent and severe in inpatients, in particular in those with eating, anxiety/obsessive-compulsive and autism-spectrum disorders. Furthermore, low functioning was – if at all – at most weakly related to the severity of CHR criteria and symptoms; the highest, yet weak correlation was for *suspiciousness/persecutory ideas*. Four participants had developed a psychotic disorder within two years past baseline. In doing so, the two-year conversion rate in participants with CHR criteria was 11.5% and, the comparison of the conversion rate in participants with and without CHR criteria at baseline exhibited the highest, near moderate effect size of all comparisons.

***Research conclusions***

This study was the first to systematically study alternative explanatory models for current CHR states, which propose that CHR criteria and symptoms would represent a pluripotent syndrome, a transdiagnostic risk factor or dimension, or even merely a marker for the severity of any mental disorder. The general lack of systematic differences in the frequency and severity of CHR criteria and symptoms between inpatients and community subjects, and the lack of a sufficiently strong association between functioning, and CHR criteria and symptoms did not support any of these alternative explanatory models. Rather, the strongest, though still only moderate effect was found for the association of CHR criteria and the subsequent development of a psychotic disorder within two years. This association, however, appears not strong enough to conclusively explain the role of CHR criteria and symptoms in children and adolescents by their psychosis-predictive potential. Thus, overall, our results more clearly indicate what CHR symptoms and criteria are *not* rather than indicating *what* they are.

Only four CHR symptoms – *suspiciousness/persecutory ideas* of the SIPS, and *thought pressure*, *derealization* and *visual perception disturbances* of the SPI-CY - exhibited a pattern of group differences indicative of a transdiagnostic risk factor, in particular with respect to eating, autism-spectrum, and anxiety and obsessive-compulsive disorders. Thus, their inclusion and definition in current CHR criteria should be critically examined in future studies.

***Research perspectives***

Our results add to the growing support of the view that CHR criteria should be regarded as a self-contained disorder or syndrome. To more fully test this assumption, future community studies should evaluate the effect of CHR criteria on help-seeking and mental wellbeing. If persons meeting CHR criteria generally suffer from their CHR symptoms, seek help for them, and/or experience disturbances in psychosocial functioning irrespective of, or in addition to, the effects of any other potential comorbid mental disorder, CHR criteria would fulfil general criteria for mental disorders in terms of a CHR Syndrome. Thus, further research on CHR symptoms and criteria, and their cause and meaning in children and adolescents is needed to better understand their significance in this age group, and to detect factors that convey their higher clinical relevance in adulthood."

6 Re-Review: Not required. 7 Recommendation: Conditional acceptance.

**RESPONSE 10:**

Thank you for conditionally accepting our paper. Please, note that we had difficulties with the links for signing the Copyright Agreement License that did not reach 4 of our authors – likely for firewall reasons. Within the 5-day deadline for signing, on Monday the 15th of July, we contacted both the helpdesk and the editorial office about it and provided alternative email addresses for these authors. Yet, these problems prevented us from signing the license within 5 days.

**(2)** ***Company editor-in-chief:*** I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Psychiatry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. However, the quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

**RESPONSE 11:**

We thank the reviewer and editors for their positive perception of our paper. Please see RESPONSE 7 to the scientific editor for our comments on the language editing.