DOI:
10.1017/S0033291723003203

Letter to the Editor on "Baseline benzodiazepine exposure is associated with greater risk of transition in clinical high-risk for psychosis (CHR-P): a meta-analysis"

Nicholas R. Livingston, MSc[1], Paolo Fusar-Poli, MD PhD[2,3,4], and Gemma Modinos, PhD[1,5]

[1] Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK
[2] Department of Psychosis Studies, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK
[3] OASIS service, South London and Maudsley NHS Foundation Trust, London, UK
[4] Department of Brain and Behavioural Science, University of Pavia, Pavia, Italy
[5] MRC Centre for Neurodevelopmental Disorders, King's College London, London, UK

Corresponding author:
Name: Nicholas R. Livingston
Address: Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, 16 De Crespigny Park, SE5 8AF, London, UK
Email address: nicholas.livingston@kcl.ac.uk
Telephone: +44207 848 0002

Word Count: 927
Number of references: 9

To the Editors,

Raballo, Poletti, and Preti (2023) recently published in this journal results of a meta-analysis investigating the association of baseline benzodiazepine (BDZ) exposure and risk of subsequent psychosis development in individuals at clinical high-risk for psychosis (CHR-P). As the authors state, this is an important, yet under-researched area given that prescription of BDZ to CHR-P individuals when joining a CHR-P service is relatively common (~16-17%; Raballo et al., 2023; Livingston et al., 2023). With a small sample of only five studies included in the meta-analysis, the authors report that CHR-P individuals exposed to BDZs at baseline had an almost x2.5 increased risk of developing psychosis during the follow-up period (range 12-36 months) compared to those who were BDZ-unexposed. The authors conclude that, as reflected in the manuscript title, "*Baseline benzodiazepine exposure is associated with greater risk of transition in clinical high-risk for psychosis…*". We raise several concerns about this manuscript.

Firstly, the meta-analysis is based on a very small number of studies and therefore the findings should be considered cautiously, in particular given the high clinical and neurobiological heterogeneity of this patient population.

Secondly, the study overlooked confounding-by-indication. The data do not come from randomised controlled trials of BDZ treatment, and therefore BDZ prescription is done so by a clinician which is influenced by clinical and demographic factors (e.g., baseline symptom severity, age, etc.) that are also associated with increased risk of transition to psychosis (Fusar-Poli et al., 2020). Therefore, the true association of BDZ exposure and subsequent psychosis transition is confounded. Our recent study (Livingston et al., 2023) was designed to examine the effects of baseline BDZ exposure (total number of days of BDZ exposure within $\pm$3 months after accessing a CHR-P clinical service) on real-world clinical outcomes (occurring from 3 months after baseline until date of last observation) in 567 CHR-P individuals. In line with our observations above, we found that compared to individuals who were BDZ-unexposed (n=462), those who were BDZ-exposed (n=105) were more likely to be older, of black ethnicity, have higher attenuated psychotic symptom (APS) severity, shorter duration of untreated APS, and to have experienced a transient psychotic episode (BLIPS). As mentioned above, all of these factors are known to be associated with an increased risk of developing psychosis (Fusar-Poli et al., 2020). Without controlling for these confounds, we found similar results to Raballo and colleagues (BDZ-exposed vs BDZ-unexposed individuals had an increased risk of transition to psychosis [HR = 1.61, p = 0.04]), but this effect disappeared after controlling for confounding-by-indication through propensity score matching (HR = 0.86, p = 0.58). Our findings suggest that the increased risk ratio observed in Raballo and colleagues' study is

driven by confounding-by-indication, precluding their study from being able to disentangle the confounds influence on transition from that of BDZ exposure specifically.

Thirdly, the authors conclusions are not substantiated by the data and contain inflammatory language. The authors only briefly acknowledge confounding-by-indication in the limitations, but this is not reflected in the title, abstract or conclusion, the latter of which misleadingly states: "*baseline exposure to BDZ in newly enrolled CHR-P is associated with an enhanced risk of imminent transition to psychosis*". Such strong claims that may impact clinical practice should be avoided in the presence of substantial confounding-by-indication as they may harm patients and clinicians. For example, we have recently demonstrated in 4,483 individuals of ages 14-35 with a first episode of psychosis that early BDZ treatment can be safely considered alongside antipsychotic treatment (Arribas, Solmi, Thompson, Oliver, & Fusar-Poli, 2022). There are further unjustified claims, such as referring to antipsychotic treatment in CHR-P individuals as having a "pro-transition effect". This claim of causation, based on a previous meta-analysis by the same authors which did also not account for confounding-by-indication (Raballo, Poletti, & Preti, 2020), is unwarranted, and in overt contrast with a recent Cochrane review showing no high quality evidence that available treatments are impacting transition to psychosis in CHR-P populations (Bosnjak Kuharic, Kekin, Hew, Rojnic Kuzman, & Puljak, 2019).

Finally, there are some further concerns regarding the studies they included. One was a brain imaging study (Kristensen et al., 2021), despite this being explicitly stated as an exclusion criteria: "*articles that were unrelated to the main topic (i.e. studies on brain imaging…)*". Additionally, there are discrepancies between the data reported in Francesconi et al. (2017) and those in Table 1 of this manuscript. Raballo and colleagues report 14 BDZ-exposed individuals transitioned, but in Table 2 of the original study this number is 10 (although this number also includes individuals who did not meet CHR-P criteria at baseline, so the number of BDZ-exposed CHR-P individuals is likely <10). Finally, the heterogeneity is quite large, as the included studies varied substantially in terms of age, proportion of BDZ exposure, antipsychotic/antidepressant exposure, gender ratio, geographical location, sample size, and year of publication. Whilst the authors report no relevant heterogeneity with an I^2 statistic of 0% and non-significant Cochran's Q of 1.49, research (von Hippel, 2015) suggests that meta-analyses with n<7 should interpret these statistics with caution, and that for I^2 statistic confidence intervals should be relied on heavily for interpretation, which are extremely broad in this study (0-79%).

Due to the above concerns and substantial methodological limitations, the conclusions of this meta-analysis are flawed and not evidence based, and therefore should be urgently rectified to avoid any detrimental impact on clinical practice.

Competing interests: PFP has received research funds or personal fees from Lundbeck, Angelini, Menarini in the past 36 months. GM has received consultancy fees from Boehringer Ingelheim. NRL has no competing interests to declare.

References

Arribas, M., Solmi, M., Thompson, T., Oliver, D., & Fusar-Poli, P. (2022). Timing of antipsychotics and benzodiazepine initiation during a first episode of psychosis impacts clinical outcomes: Electronic health record cohort study. *Frontiers in Psychiatry*, *13*, 976035. doi: 10.3389/fpsyt.2022.976035

Bosnjak Kuharic, D., Kekin, I., Hew, J., Rojnic Kuzman, M., & Puljak, L. (2019). Interventions for prodromal stage of psychosis. *Cochrane Database of Systematic Reviews*. doi: 10.1002/14651858.CD012236.pub2

Francesconi, M., Minichino, A., Carrión, R. E., Chiaie, R. D., Bevilacqua, A., Parisi, M., … Cadenhead, K. (2017). Psychosis prediction in Secondary Mental Health Services. A Broad, Comprehensive Approach to the "at Risk Mental State" Syndrome. *European Psychiatry*, *40*, 96–104. doi: 10.1016/j.eurpsy.2016.09.002

Fusar-Poli, P., De Micheli, A., Signorini, L., Baldwin, H., de Pablo, G. S., & McGuire, P. (2020). Real-world long-term outcomes in individuals at clinical risk for psychosis: The case for extending duration of care. *EClinicalMedicine*. doi: 10.1016/j.eclinm.2020.100578

Kristensen, T. D., Glenthøj, L. B., Ambrosen, K., Syeda, W., Raghava, J. M., Krakauer, K., … Ebdrup, B. H. (2021). Global fractional anisotropy predicts transition to psychosis after 12 months in individuals at ultra-high risk for psychosis. *Acta Psychiatrica Scandinavica*, *144*(5), 448–463. doi: 10.1111/acps.13355

Livingston, N. R., Micheli, A. D., McCutcheon, R., Butler, E., Hamdan, M., Grace, A. A., … Modinos, G. (2023). Effects of Benzodiazepine Exposure on Real-World Clinical Outcomes in Individuals at Clinical High-Risk for Psychosis. *medRxiv*. doi: 10.1101/2023.08.15.23294108

Raballo, A., Poletti, M., & Preti, A. (2020). Meta-analyzing the prevalence and prognostic effect of antipsychotic exposure in clinical high-risk (CHR): When things are not what they seem. *Psychological Medicine*, *50*(16), 2673–2681. doi: 10.1017/S0033291720004237

Raballo, A., Poletti, M., & Preti, A. (2023). Baseline benzodiazepine exposure is associated with greater risk of transition in clinical high-risk for psychosis (CHR-P): A meta-analysis. *Psychological Medicine*, 1–7. doi: 10.1017/S0033291723002180

von Hippel, P. T. (2015). The heterogeneity statistic I2 can be biased in small meta-analyses. *BMC Medical Research Methodology*, *15*(1), 35. doi: 10.1186/s12874-015-0024-z