Psychological Medicine

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Cite this article: Livingston NR, Fusar-Poli P, Modinos G (2024). 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'. *Psychological Medicine* **54**, 215–216. https://doi.org/10.1017/S0033291723003203

Received: 26 September 2023
Revised: 3 October 2023
Accepted: 4 October 2023
First published online: 3 November 2023

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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'

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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%; Livingston et al. 2023; Raballo 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 2.5× 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.

First, 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.

Second, 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 ±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, have shorter duration of untreated APS, and to have experienced a transient psychotic episode (brief limited intermittent psychotic symptoms, 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 *v.* BDZ-unexposed individuals had an increased risk of transition to psychosis [hazard ratio (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.

Third, 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 4483 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 'protransition 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. While 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. P. F.-P. has received research funds or personal fees from Lundbeck, Angelini, and Menarini in the past 36 months. G. M. has received consultancy fees from Boehringer Ingelheim. N. R. L. has no competing interests to declare.

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https://doi.org/10.1017/S0033291723003203 Published online by Cambridge University Press