Reply to Seon et al.'s 'To prevent arrest and convictions, prescribe antipsychotics'

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In our recent study (Sariaslan, Leucht, Zetterqvist, Lichtenstein, & Fazel, 2021), we examined associations between 10 individual antipsychotics and multiple crime outcomes among 74 925 individuals who had been prescribed antipsychotics at least once between 2006 and 2013 in Sweden. To account for time-stable individual-level unmeasured confounding (e.g. genetic risks and childhood environmental factors), we adopted the within-individual design, where we compared risks of the outcomes within the same persons across time (e.g. during periods when they were either on or off their antipsychotic medications). We found that the patients had considerably lower crime risks during periods when they were on antipsychotic medications as compared to periods when they were off the same medications. We further found that these associations were stronger for patients who were clozapine, olanzapine, and risperidone compared to other antipsychotics, such as quetiapine and haloperidol.

Seon et al. (2021) have raised five points of criticism against our paper. First, they initially argued that we had not sufficiently taken 'race and immigration' into account, although this criticism is restricted to our crude between-individual estimates, which were not the primary outcomes. The rationale for presenting such estimates is to offer a baseline evaluation of the population-wide associations that can be explained by different sets of confounders in subsequent models. To this end, we used the within-individual design that accounted for an aggregate of all time-invariant factors, which included 'race' and all pre-baseline environmental influences, such as immigration.

The second point raised in their letter refers to time-varying confounders that may explain some of the observed associations, which we discussed. Seon et al. propose that measures of 'vulnerability' and delays in medical treatment may constitute candidate confounders that we had not accounted for. First, although it remains unclear what specific type of 'vulnerability' the authors are referring to, previous research has shown that socioeconomic vulnerability does not explain much of the associations between antipsychotic prescriptions and crime outcomes in Sweden (Bhavsar et al., 2019). Second, we do not think that treatment delays are an important factor because we observed a consistent pattern of associations in patients receiving long-term injectables, who would have received their medications on time. In the current paper, we also discussed the importance of triangulating our findings with randomised controlled trials (RCTs), which we argued were broadly consistent. In fact, a recent meta-analysis examining the effectiveness of antipsychotics on many different outcomes found that findings derived from real-world studies were congruent with those from RCTs (Katona, Bitter, & Czobor, 2021). Clearly, we were not able to control for all time-varying confounders, but such factors need to be examined in large-scale studies with rigorous controls for unmeasured confounding before drawing strong conclusions about their role in the aetiological pathways between antipsychotic prescription use and subsequent crime outcomes.

We disagree with Seon et al. that the analyses of clozapine as a class of drugs were underpowered. Previous work from an earlier cohort was underpowered for violent conviction (Fazel, Zetterqvist, Larsson, Långström, & Lichtenstein, 2014), but the current study reported a clear protective effect with confidence intervals (CIs) that did not cross 1 (adjusted rate ratio: 0.28; 95% CI 0.18–0.44).

Third, it remains unclear how Seon et al. suggest that crime rates should be measured. Compared to many related studies in the field, we adopted a much broader approach by examining six outcomes covering three crime types (e.g. violent crime, drug-related crime, and any crime) using both arrest and conviction data. We were, therefore, able to capture a broad range of registered criminal acts. This means, as Seon et al. imply, that we have missed criminal acts that have not come to the attention of the authorities. Alternative approaches of measuring unregistered criminality, such as self-reports, typically suffer from a wide range of other limitations, including selection bias, attrition over time, and inflated measurement error. The latter is exacerbated in patients with psychiatric disorders and when using within-individual designs, which ultimately leads to artificial reductions of the associations to the null (Sariaslan, Arseneault, Larsson, Lichtenstein, & Fazel, 2020).

Fourth, we agree with Seon et al. that there will be unobserved heterogeneity in our sample that could potentially be measured using more detailed diagnostic information. This does,

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however, not change the validity of our main finding that antipsychotic prescriptions are *on average* associated with considerably lower risks of the crime outcomes even when one uses the individuals as their own controls across time, and that these associations also vary across individual antipsychotics. Whether specific diagnostic categories moderate these associations could be investigated in future studies by using even larger samples to obtain sufficient statistical power. Rate reduction referred to percentage change and the categories men and women to the biological sex of participants.

Fifth, we do not agree about the stigma point, which appears to repeat a common misunderstanding. We think that stigma is best addressed by preventing crime in people with psychosis, and not by denying the links of a small but significant association between psychosis, related disorders and violent outcomes (Sariaslan et al., 2020; Whiting, Lichtenstein, & Fazel, 2021). Furthermore, we agree with Seon et al. that it is important to identify environmental factors that could potentially cause violence risk in psychotic disorders to inform the development of effective interventions. We have previously identified a number of such candidate causes in stressful life events (Sariaslan, Lichtenstein, Larsson, & Fazel, 2016) but not in measures of socioeconomic status (Sariaslan, Larsson, Lichtenstein, & Fazel, 2017).

In conclusion, using a very large sample of nearly 75 000 people prescribed antipsychotics, we found that their risk of being either arrested or convicted of violent, drug-related, or other crimes was clearly reduced during periods when the patients were on *v.* off antipsychotics. Mechanisms may include medications reducing psychotic symptoms linked to violence (e.g. persecutory delusions), other associated symptoms (e.g. hostility) or by reducing comorbid substance misuse. We are not suggesting that this should be the only approach to reducing crime risks in patients with psychiatric disorders, but the evidence from trials and high-quality observational studies indicates that it is an important approach.

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