Citation for published version (APA):
How common is secondary psychosis? Estimates from a systematic review and meta-analysis

The estimated lifetime risk of developing a psychotic disorder is approximately 3%\(^1\). In most cases, psychosis arises in the context of a primary (“non-organic”) psychiatric disorder, such as schizophrenia. However, in a subset of cases, psychotic symptoms are secondary to the effects of an underlying disease state\(^2\) or an exogenous agent (e.g., a recreational drug)\(^3\). Identifying secondary psychosis is critical to providing patients with appropriate care, which may include treatment for the underlying cause\(^4\). Whilst it is recognized that psychosis can have a secondary basis, the proportion of patients with a secondary cause is unknown.

We searched electronic databases (Medline, PsycINFO and Global Health) up to August 2022, alongside references of included articles and reviews. We selected studies that: a) included patients presenting with psychosis; b) assessed for a secondary cause; and c) assigned a primary or secondary diagnosis for each patient. We did not select studies that: a) excluded patients with a suspected or confirmed secondary psychosis, or b) provided insufficient data to calculate the proportion of patients with a secondary cause. We also excluded studies in which psychotic symptoms were not the main presenting problem (e.g., studies reporting the prevalence of psychotic symptoms in patients presenting with memory impairment). Where two or more studies shared the same sample, the larger was included. There were no age or language restrictions.

Using meta-analytic methods, we estimated the proportion of patients with psychosis due to a secondary cause, defined as psychosis “probably” or “definitely” arising as the result of an underlying (not primary psychiatric) condition, or an exogenous agent (e.g., illicit substance, prescribed medication). MOOSE guidelines were followed, and the protocol was prospectively registered (CRD42023427237) (see also supplementary information).

Based on 33 independent studies (N=26,534), 11% (95% CI: 7-16) of patients with psychosis had a secondary cause, after exclusion of a statistical outlier, with marked between-study heterogeneity (I\(^2\)=98%). The estimated proportion of 11% corresponds to an average number needed to assess in order to detect one case of secondary psychosis of approximately 10.

The most common psychosis with a secondary cause was drug-induced psychosis (12%; 95% CI: 6-19). The proportion of psychosis due to any underlying medical cause was 5% (95% CI: 3-9), with the most common medical causes being infection (1%; 95% CI: 0-4) and autoimmune disease (1%; 95% CI: 0-2) (see also supplementary information).

Subgroup analysis found a significant effect of clinical context (p=0.04), with patients in a general hospital setting more likely to have a secondary cause (38%; 95% CI: 35-41; n=5) than patients seen in a psychiatric setting (7%; 95% CI: 6-8; n=20). There was also an effect of geographical area (p=0.003), with patients in Africa most likely to have a secondary cause. Meta-regression found no association with publication year, sample size or mean age.

Restricting studies to those which included patients presenting with a first-episode psychosis resulted in a slightly increased estimate of 14% (95% CI: 8-22; n=18), whilst restricting studies to those with a mean sample age under 35 years resulted in an increased estimate of 23% (95% CI: 10-39; n=13). Studies that assessed for multiple causes of secondary psychosis resulted in an almost unchanged estimate of 13% (95% CI: 7-21; n=20). When urine analysis was routinely performed, estimates for secondary psychosis increased to 23% (95% CI: 11-37; n=8). More modest changes were observed when electroencephalogram (8%; 95% CI: 0-27, n=3), cerebrospinal fluid analysis (5%; 95% CI: 2-9; n=5), blood tests (5%; 95% CI: 0.1-13; n=11), and magnetic resonance imaging (MRI) (4%; 95% CI: 1-7; n=2) were routinely performed. Funnel plot inspection and Egger’s test (p=0.15) did not indicate publication bias (see also supplementary information).
There are several important limitations to acknowledge in interpreting these estimates. The attribution of causality in secondary psychosis is challenging. For example, traumatic head injury\textsuperscript{5} and psychoactive substances\textsuperscript{6} are recognized causes of secondary psychosis, but are also risk factors for the onset of a primary psychotic disorder, such as schizophrenia. Additionally, most studies did not employ a standardized approach to assessment, possibly leading to under-detection of secondary causes. On the other hand, some studies might be enriched for certain secondary causes, leading to ascertainment bias. Furthermore, some causes of secondary psychosis have been discovered only relatively recently, such as anti-NMDA receptor encephalitis\textsuperscript{2}, and therefore would not have been detected in earlier studies.

Our finding that a substantial minority of patients with psychosis have a secondary cause has important implications for clinical practice. Clinicians should be mindful of the need to exclude a secondary cause, particularly in patients presenting with psychosis for the first time. In particular, our findings suggest that clinicians working in a general hospital setting should have a particularly high index of suspicion that a patient with psychosis has a secondary cause.

In clinical practice, it is often infeasible to undertake extensive investigations in all patients with psychosis to exclude every potential secondary cause. However, our findings seem to suggest that it may be advisable to carry out investigations for common secondary causes (such as a urine screen for illicit substances and blood tests for physical health disorders) in all patients presenting with a first episode of psychosis. A caveat to this is the need to consider other contextual factors, such as the net clinical benefit and economic constraints. For example, a urine drug screen can assist with the diagnosis of drug-induced psychosis, and has the benefit of being cheap, widely available, easy to interpret and presenting minimal risk to a patient, thus favoring its routine use.

There are no well-established “red flags” to indicate which individuals are at the highest risk of secondary psychosis. However, previous studies suggest that certain phenomenological characteristics, such as visual hallucinations, are more likely to be associated with secondary causes\textsuperscript{8}. Prospective clinical studies, using standardized investigations and psychiatric assessments, are indicated to determine the demographic and clinical characteristics associated with secondary psychosis.

Graham Blackman\textsuperscript{1-4}, Ronan Byrne\textsuperscript{3}, Neha Gill\textsuperscript{5}, Jack B. Fanshawe\textsuperscript{1,2}, Vaughan Bell\textsuperscript{5,6}, Cameron Watson\textsuperscript{1,5,9,10}, Nikolaos Koutsouleris\textsuperscript{3,7,8}, Paolo Fusar-Poli\textsuperscript{3,5,7}, Thomas A. Pollak\textsuperscript{3,5}, Philip McGuire\textsuperscript{1-4}

\textsuperscript{1}Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK; \textsuperscript{2}Oxford Health NHS Foundation Trust, Oxford, UK; \textsuperscript{3}Department of Psychology Studies, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK; \textsuperscript{4}NIHR Oxford Health Biomedical Research Centre, Oxford, UK; \textsuperscript{5}South London and Maudsley NHS Foundation Trust, London, UK; \textsuperscript{6}Research Department of Clinical, Educational and Health Psychology, University College London, London, UK; \textsuperscript{7}Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich, Germany; \textsuperscript{8}Max-Planck Institute of Psychiatry, Munich, Germany; \textsuperscript{9}Neuropsychiatry Research and Education Group Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK; \textsuperscript{10}Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK

P. Fusar-Poli, T.A. Pollak and P. McGuire are joint last authors. This work was supported by the NIHR Oxford Health Biomedical Research Centre. Supplementary information on the study is available at ...