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Revisiting the incidence of schizophrenia: learning about the other half

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General Introduction

Vignette

In 2005, mr. Jansen from The Hague, then 35 years old, was treated for posttraumatic stress disorder (PTSD). A few years later, in 2009 when he was 39 years old, he was treated for alcohol abuse, and subsequently diagnosed with schizophrenia.

As subject for epidemiological research, he would be included in studies of PTSD and perhaps alcohol abuse, but not in studies of schizophrenia. Why?

The standard for measuring the treated incidence of schizophrenia is the so-called First Contact (FC) method. By the rules of that method, mr. Jansen was not counted because he did not present psychotic symptoms when he first contacted mental health services in 2005.

Because he was not identified at first contact, he was never counted as a case; and because he was never counted as a case, his characteristics were not studies. As a result, his personal clinical history and treatment never got much attention in scientific studies, clinical textbooks and treatment programmes.

So, If the standard description of schizophrenia systematically overlooks subjects like mr. Jansen, how reliable can it be? The answer hinges on the question *whether cases like his are rare or common*. And that question, in a nutshell, is what this thesis is all about.

The incidence of schizophrenia

Schizophrenia spectrum disorders disable large numbers of people (Whiteford et al., 2013). Globally, roughly 21 million people are living with schizophrenia. Demographic changes are expected to push this number higher. Schizophrenia symptoms can appear early in life and can seriously impair functioning even into old age. In 2016, schizophrenia contributed 13.4 (95% CI: 9.9–16.7) million years lived with disability (YLD) to the global burden of disease, or 1.7% of total YLDs (Charlson et al., 2018). The health state with the highest disability weight is acute schizophrenia (0.76) (Salomon et al., 2012). Schizophrenia is a low prevalence disorder, but it is so disabling that it ranked 12th as most disabling among 310 diseases and injuries in that same year (Vos et al., 2017). Of all mental disorders, schizophrenia has the highest societal cost [1] per patient (Christensen et al., 2020). Full recovery from schizophrenia is unlikely (Jaaskelainen et al., 2012), somatic comorbidity is frequent (Buckley et al., 2008; Upthegrove et al., 2016), and life expectancy is much reduced (Laursen et al., 2014).

Valid estimates of the incidence of schizophrenia are a basic requirement to calculate schizophrenia's societal burden (Whiteford et al., 2013) and coordinate the delivery of services to the afflicted (Cohen et al., 2015). Comparing incidence rates between various risk groups can highlight the causes of schizophrenia and uncover opportunities for prevention and treatment (van der Werf et al., 2012).

What makes an incidence estimate *valid*? Formally, the incidence rate is the count of all first onsets of a clearly defined disorder, in a clearly defined population, at the first moment the subject meets the criteria for the disorder (Rothman, 2021). But for schizophrenia diagnosing the disorder at the moment of first onset is difficult. The symptoms of schizophrenia occur on a continuum from subclinical to very severe (Guloksuz & Os, 2017; Kaymaz & Os, 2010; Linscott & Os, 2010; Unterrassner et al., 2017), and they do not always, or not immediately, lead to dysfunction or medical treatment. Patients typically start with aspecific prodromal symptoms (Häfner et al., 2013). Co-morbidity is common (Buckley et al., 2008; Upthegrove et al., 2016), both sequentially and in parallel. There is a large variation in clinical presentation (Andreasen, 1995; Os & Kapur, 2009). Not every patient will develop the full clinical syndrome. The truth is that doctors are well aware that the first signs of schizophrenia are often difficult to detect—contrary to the textbook

1 I.e. all costs, both direct and indirect, regardless of who pays them.

stereotype [2]. Because onset is often gradual or insidious, diagnosis can be delayed or not occur at all. This produces imprecise figures.

Currently, we have no reliable way to detect the onset of psychosis in the population, and so to estimate anything like a true *population incidence* of the disorder. We are limited to a second best solution: detecting the subset of cases which come into contact with health services and are formally diagnosed with the schizophrenia syndrome, i.e. the *treated incidence*. The treated incidence of schizophrenia is generally considered a reasonable proxy for the population incidence. Two arguments support this interpretation: most cases of schizophrenia will ultimately come into contact with psychiatric services (Weiser et al., 2012), and those who never do are probably not sufficiently impaired to meet the disability criterium for a formal diagnosis.

The first contact approach

The standard method for estimating the treated incidence of schizophrenia is known as the *First Contact (FC)* design. The FC design involves screening subjects for signs of psychosis when they present for psychiatric treatment. Subjects who are screened positive undergo standardized diagnostic procedures to establish whether they meet the criteria for schizophrenia.

Earlier methods used in the 1960s and 1970s had serious limitations, and the FC design was originally developed to solve them. The prototypical FC design was developed in the course of an effort spanning 1974–1992 (Cooper, 1972; Feighner, 1972; Jablensky et al., 1992; Kendell et al., 1968; Sartorius et al., 1974; R. J. Simon, 1971; Spitzer, 1978; Wing, 1974). It allowed for better comparisons between disparate populations because it standardized which services were monitored, how this monitoring had to take place, and how the schizophrenia diagnosis should be made. It was population-based, covering all health services. It used standardized diagnoses. It applied rigorous exclusion criteria to safeguard against overcounting. It provided uniform samples of treatment naive cases of incident schizophrenia. It accomplished this standardization by focusing on a *subset of the total case population*, namely those subjects which not only had schizophrenia but which also presented their symptoms at the first time in their life they sought mental health care. In this way, it provided higher specificity at the cost of lower sensitivity. This was not a problem for its intended use at the time, which was to identify a subset of

2 The textbooks seem to suggest otherwise (Addington et al., 2007; American Psychiatric Association, 2013; Murray, 1997), describing schizophrenia as a 'devastating disorder, with acute onset in the second or third decade of life' (National Institute of Mental Health, 2020).

schizophrenic patients with similar clinical characteristics in different countries. But it became a problem later, when this *narrow use case* was expanded. This happened during the 1990s, as a research practice emerged that used the FC design not only for identifying a subset of cases, but also for estimating the treated incidence itself, i.e. an *expanded use case*.

Meta-analyses of incidence studies may have played in a crucial role in this respect, because they tend to treat *FC based incidence estimates* as equal to *treated incidence estimates*. We summarize the meta-analyses of the last decades in the box below. Because the quality criteria used in the leading meta-analyses assigned higher scores to FC based studies over alternative approaches, the effect sizes included in the meta-analyses were almost entirely based on FC studies.

We note (see also chapters 2 and 8) *three unspoken assumptions* underlying this practice: (a) subjects with an ultimate diagnosis of schizophrenia do not seek treatment for other mental symptoms before the onset of psychosis; (b) the onset of schizophrenia is nearly always in early adulthood; and (c) cases identified by the FC method are representative of the population with schizophrenia.

Box: findings from meta-analyses

Several meta-analyses of studies reporting on the incidence of psychosis and schizophrenia have been published over the past decades (Jongsma et al., 2019; Kirkbride, Errazuriz, et al., 2012; McGrath et al., 2004; van der Werf et al., 2012).

McGrath et al. (2004) surveyed the worldwide literature 1965–2001 and reported a median treated schizophrenia incidence rate of 15.2 (interquartile rate 7.7 to 43) per 100 000 person years for all ages, based on 170 effect sizes from 55 studies. Van der Werf et al. (2012) surveyed the worldwide literature 1950–2009 and reported a median treated schizophrenia incidence rate of 18.3 (interquartile rate 10.9 to 28.9) for all ages, based on 1021 effect sizes in 90 studies. Kirkbride, Errazuriz, et al. (2012) surveyed studies performed in England, published 1950–2009 and reported a pooled treated schizophrenia incidence rate of 15.2 (95% confidence interval 11.9 to 19.5), based on 50+ effect sizes from 83 studies. Jongsma et al. (2019) surveyed the worldwide literature published 2002–2017 and reported a median treated incidence schizophrenia incidence rate of 21.7 (interquartile rate 5.6 to 52) and a pooled rate of 13.1 (95% confidence interval 9.0 to 15.0). Her meta-analysis included the study (Hogerzeil et al., 2014) presented in chapter 2.

Pooled estimates derived from meta-analyses are typically considered the best available estimate of the treated incidence rate. As such, they are cited everywhere in textbooks and introductory paragraphs of manuscripts. Therefore, the currently accepted numbers for the incidence of schizophrenia are based on the FC design. Also, the incidence estimates used for the first calculations of the global burden of schizophrenia (World Health Organization, 2001) were all based on FC studies (Ayuso-Mateos, 2002).

The register based approach

Before the FC design became the standard, incidence estimates were based on data from *traditional case registers*. For several reasons, traditional case registers were deemed relatively unreliable from the 1970s onward: they tended to cover psychiatric hospitals only, they had trouble differentiating new patients from previously diagnosed patients, and trouble tracing exactly in which (other) catchment area they had first been diagnosed. Data collection from multiple sources, quality control and data integration were mainly manual and only partly computerized at the time. Researchers typically worked with highly aggregated, quarterly data sets and could not easily reconstruct individual pathways through mental health services. Furthermore, both clinical practice and health administrations were much less standardized than they are now.

These constraints were resolved by two widely adopted reforms: (1) the DSM or ICD classifications applied by uniformly trained psychiatrists, and (2) the advent of electronic health administrative records, rigorously standardized and under active quality control for administrative and health insurance purposes. As developing countries' mental health facilities increasingly adopted *electronic Health Administrative Datasets (eHADs)*, new types of case registers that correct the shortcomings of traditional (analog) registers could be developed.

Under specific conditions, an eHAD can be used as an *electronic Psychiatric Care Register (ePCR)* [3]. ePCRs are suited for identifying onsets of schizophrenia because all cases need treatment at some point in time, and treatment is organized locally. Treatment for schizophrenia usually requires collaboration of many local services. For the treatment

3 Not all eHADs are ePCRs. For that, an eHAD must accurately list all first onsets of a condition for a given population catchment area over a specified time span. Ideally, at every health facility, at every point of treatment, stratified by traditional confounders like age and gender, and if possible, by other risk factors like migrant status, socioeconomic status (SES), and so on. When high-quality municipal data (population numbers and covariate distribution), personal identifiers (birth date, sex, zip code, civic status, SES, etc.) and clinical data (services used, diagnoses, etc.) are combined in a data warehouse, these conditions are met.

of psychotic disorders, such collaboration often results in a regional monopoly. Subjects diagnosed in primary mental health care with symptoms indicative of schizophrenia are immediately referred to these facilities. Visitors presenting to local services with psychosis are referred back to services in their own catchment area.

The ePCR of The Hague, The Netherlands

For the purpose of this thesis, we set up an ePCR for schizophrenia for the city of The Hague, The Netherlands over the period 1997–2012. The Hague is an ethnically diverse city of roughly 500 000 inhabitants, representative of many medium sized cities in Northern Europe. The main provider of mental health services in the catchment area is the Parnassia Psychiatric Institute (PPI). For all practical purposes, the PPI has a monopoly for the treatment of psychotic disorders. The catchment area, the local organization of mental health services and the quality of the eHAD together meet the requirements to form an ePCR for schizophrenia spectrum disorders. The PPI provided an IT-infrastructure, with eHAD records stored in a data warehouse. The data allowed for a longitudinal reconstruction of diagnostic and treatment pathways of subjects ultimately diagnosed with schizophrenia between 1980–2013. The data from 1997 onwards were deemed sufficiently reliable for epidemiologic research. Further details about the data warehouse and the ePCR are given in chapter 2.

The opportunity for a direct comparison between the FC standard and ePCRs

Two members of our research group (Hans W. Hoek and Wim Veling) had previously used the FC method (the standard at that time) to estimate the incidence of schizophrenia in the city of The Hague between 1997–2005, for the population in general as well as for the five largest migrant groups (Veling et al., 2007). The ePCR created for this thesis provided a unique opportunity to compare the FC standard directly with the new ePCR approach, in the same population.

Research questions

So, two ways to estimate the incidence of schizophrenia were at our disposal: the standard First Contact (FC) design and a new electronic Psychiatric Case Register (ePCR) design. In this thesis, we investigated the following question:

Which method (ePCR or FC) should be used to estimate the treated incidence of schizophrenia?

More specifically, the following subquestions:
1. *Do the ePCR and FC methods agree?*
2. *If they disagree, why?*
3. *How do our findings fit into the existing evidence?*

Structure of the thesis

Set between this general introduction (chapter 1) and a general discussion (chapter 9) are seven chapters.

We begin by explaining how it became apparent that different methods lead to different estimates of the incidence of schizophrenia (i.e. subquestion 1). In chapter 2, we describe how we sought to validate our new ePCR-based method by replicating a prior FC study performed in the same catchment area. We compare data from the psychiatric case register of The Hague over 1980–2009 with data previously collected in a FC study, and apply both methods to calculate the incidence (IR) of schizophrenia for subjects aged 20–54 years in the same catchment area and over the same period (October 2000 to September 2005).

In chapters 3–5 we explore the discrepancies between the FC approach and the ePCR approach (i.e. subquestion 2) in terms of the three assumptions listed above. In chapter 3, we examine whether (a) psychosis is the first presentation of schizophrenia in the large majority of cases. We use the psychiatric case register of the Hague to study a cohort of 1753 subjects aged 18–35 years at first contact who were diagnosed with a psychotic disorder between 2005–2009, and explore their history of help-seeking behavior in secondary psychiatric services prior to the first onset of psychosis. In chapter 4, we examine whether (b) the onset of schizophrenia is predominantly before the age of 40, using the psychiatric case register of The Hague to estimate the incidence and lifetime morbid risk of schizophrenia by age and sex, over ages 20–79 between 1997 and 2012. In chapter 5, we examine whether (c) cases identified by the FC method are representative of the population with schizophrenia. We use the data from the direct comparison in chapter 2 to compare both methods' estimates of the age and sex adjusted incidence rate ratios (IRR) for the three largest migrant groups, relative to the Native Dutch population.

In chapters 6–8, we explore the impact of differences in study design on incidence estimates (i.e. subquestion 3). In chapter 6, we introduce a framework to classify various

study designs that have been used in different studies, consisting of three dimensions (coverage of mental health services, time frame of the diagnosis, and accuracy of the diagnosis). In chapter 7, we review the recent literature on the treated incidence of schizophrenia published 2005–2019, using the taxonomy from chapter 6 to organize the various findings in groups of studies using comparable methods, and to examine to what extent this taxonomy can explain the observed heterogeneity of results, and how our ePCR findings fit in the existing literature. In chapter 8, we argue for a hybrid of ePCR and FC methods as the way forward.

Chapter 9 is a summary and general discussion of the findings in the thesis. We conclude the thesis with a general summary in Dutch.