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Revisiting the incidence of schizophrenia: learning about the other half

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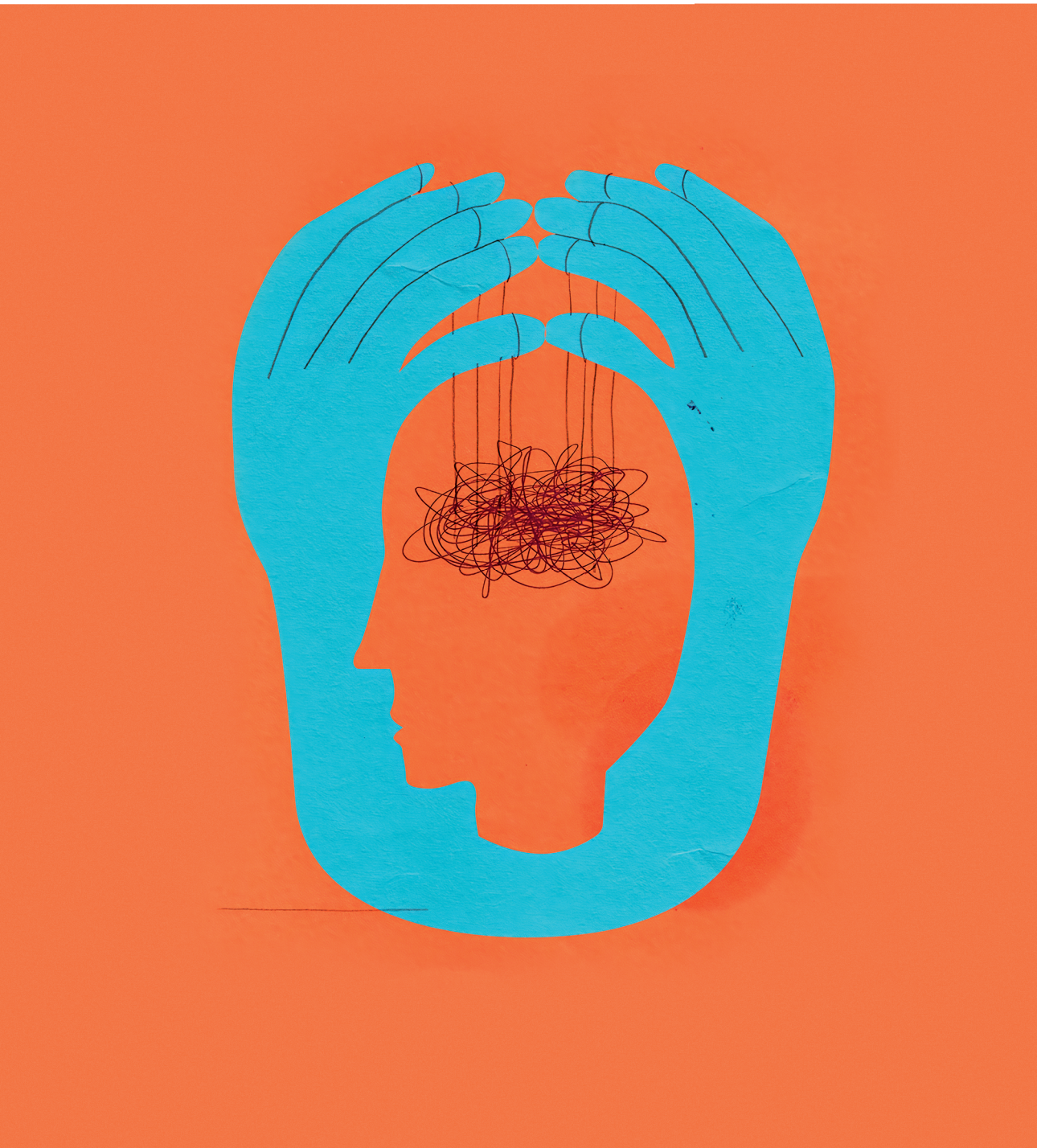
REVISITING THE INCIDENCE OF SCHIZOPHRENIA

Learning about the *other* half

Simon Jan Hogerzeil



Learning about the *other* half

Simon Jan Hogerzeil

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REVISITING THE INCIDENCE OF SCHIZOPHRENIA

Learning about the *other* half

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"Quod differtur non aufertur (What is deferred is not avoided)"

—Sir Thomas More (1478–1535)

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1

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.

2

Direct comparison of First Contact vs. ePCR-based case finding

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Abstract

BACKGROUND — The incidence of schizophrenia is commonly estimated by screening for psychosis among subjects presenting to psychiatric services. This approach (using a first contact sampling frame) cannot account for cases that did not meet criteria for schizophrenia at first contact. We compared the usual approach directly with a register-based approach (using a longitudinal sampling frame) that also includes subjects initially diagnosed with other non-schizophrenic disorders.

METHOD — We compared data from the electronic Psychiatric Case Register (ePCR) of The Hague over 1980–2009 with data previously collected in a first contact study, and applied both methods to calculate the incidence of schizophrenia for subjects aged 20–54 years in the same catchment area and over the same period (October 2000 to September 2005). We reconstructed treatments pathways and diagnostic histories up to the end of 2009 and performed sensitivity analyses.

RESULTS — The ePCR identified 843 first onsets of schizophrenia, corresponding to a treated incidence rate (IR) of 69 per 100 000 person years [95% confidence interval (CI) 64–74]. The first contact study identified 254 first onsets, corresponding to a treated IR of 21 per 100 000 person years (95% CI 18–23). Two-thirds of the difference was accounted for by subjects treated for other disorders before the onset of psychosis, and by patients in older age groups.

CONCLUSION — The incidence of schizophrenia was three times higher in a longitudinal register study than in a high-quality first contact study conducted in the same population. Risk estimates based only on first contact studies may have been affected by selection bias.

Introduction

Valid incidence rates (IRs) are necessary to study the causes of schizophrenia and estimate the burden of disease in the population. It is difficult to identify all first onsets of schizophrenia in a population because the disorder commonly starts with non-specific symptoms. By definition, clinicians can only diagnose schizophrenia after the onset of psychosis.

The incidence of schizophrenia is commonly estimated by screening for psychosis among subjects seeking treatment, using a 'first contact sampling frame'. Incidence studies using this sampling frame (i.e. first contact studies) are typified by the World Health Organization (WHO) landmark Ten-Country study (Jablensky et al., 1992). In that study, residents of a specified catchment area seeking first-in-lifetime mental health treatment for any mental disorder at any helping agency were screened for schizophrenia-like symptoms or gross behavioural abnormalities, followed by a standardized assessment for screen positives. Later high-quality first contact studies have also included subjects returning to mental health services after a prior treatment episode for non-psychotic mental disorder, or subjects developing a first psychosis during the first stages of treatment (Anderson, 2012; Bourque et al., 2010; Cheng et al., 2010; Kirkbride, Errazuriz, et al., 2012). Other variants include 'first admission' studies (i.e. subjects presenting to in-patient services) and 'early intervention' studies (i.e. subjects presenting to services for early intervention for psychosis). A feature common to all first contact studies is that subjects screened negative at first contact are censored for the remainder of that treatment episode. Case ascertainment for screen positives includes consulting case-notes or administrative records (e.g. older registers) and applying standardized diagnostic protocols (van der Werf et al., 2012).

Studies using a first contact sampling frame have no systematic procedure to account for onsets of psychosis among ongoing patients (i.e. subjects in the population who were already under treatment for other non-schizophrenic mental disorders at the start of the study) or for onsets of psychosis that occur after the initial phase of inclusion (i.e. screened negative at first onset and during initial follow-up, but manifesting at later stages of a continuous treatment episode). Some studies have accepted such cases if they presented themselves by chance. The proportion of cases missed as a result of this limitation was considered negligible (Cooper et al., 1987; Kirkbride et al., 2006; McGrath et al., 2004). However, several studies have suggested that, in high-income countries, schizophrenia is frequently diagnosed only at later stages of treatment, when subjects have first received treatment for another mental disorder. These patients do not manifest as 'first contacts' but as ongoing patients (Anderson et al., 2010; Bromet et al., 2011; Brugha et al., 2004; Cadenhead et al., 2010; Kessler et al., 2005; Murray et al., 2009; Rietdijk

et al., 2011; Veen et al., 2004). Thus, studies using a first contact sampling frame (even when they allow for prior contacts for non-psychotic mental disorders) may considerably underestimate the total treated IR of schizophrenia.

Two worldwide meta-analyses of the incidence of schizophrenia have been published over the past decade (McGrath et al., 2004; van der Werf et al., 2012). McGrath et al. (2004) reported a median IR for schizophrenia of 20 per 100 000 person years among subjects aged 15–54 years [interquartile range (IQR) 10.2–22] and van der Werf et al. (2012) reported a median IR for schizophrenia of 18 per 100 000 person years for subjects aged ≥15 years (IQR 10.9–28.9). Core estimates in both studies were almost entirely based on first contact studies. For example, in the (very large) meta-analysis by van der Werf et al. (2012), 97.8% of the total number of person years pooled in the meta-analysis were based on first contact studies of the first admission type (i.e. subjects identified in large in-patient registers on the basis of the discharge diagnosis after the first admission), with prototype first contact studies such as the WHO Ten-Country study contributing the rest (Galdos et al., 1993; Os et al., 1995; Thorup et al., 2007; van der Werf et al., 2012). Stratified analyses in the meta-analyses showed that incidence estimates did not differ systematically between subtypes of first contact studies. Commonly reported schizophrenia IRs are thus restricted to onsets of schizophrenia during the first stage of treatment.

To account for onsets of schizophrenia at any stage of treatment, a longitudinal sampling frame is necessary, collecting data on service utilization and diagnostic histories over many years for all subjects in a specified population. This approach has been used in several register and birth cohort studies (Bray et al., 2006; Bresnahan et al., 2000; Isohanni et al., 2001; Jörgensen et al., 2010; Kodesh et al., 2012; Salokangas et al., 2010; Sørensen et al., 2010; Sutterland et al., 2013; Thorup et al., 2007; Vanasse et al., 2011; Wahlbeck et al., 2001). Although nearly all of these studies reported higher IRs for schizophrenia than first contact studies, their findings have not been included in the core estimates of the meta-analyses, and neither have they been interpreted as evidence that a longitudinal sampling frame results in higher incidence estimates (Anderson, 2012). Furthermore, this hypothesis has not been tested formally, by comparing the longitudinal approach with conventional first contact screening in a single population.

In the current study we used the population-based electronic Psychiatric Case Register (ePCR) of The Hague from 1980 to 2009 to identify onsets of schizophrenia at any stage of treatment, and whatever the prior diagnosis. The ePCR is an electronic data warehouse of all psychiatric services in The Hague (population 472 087 in 2005) that is synchronized daily with all service utilization records.

Using the ePCR, we calculated a more inclusive estimate of the treated incidence of schizophrenia. For comparison, we used individual-level data from a prior 'prototype' first contact study (Veling et al., 2007) as an estimate of the treated incidence of schizophrenia based on a first contact sampling frame. We compared the two estimates by applying both methods to the same population over the same period, linking both data sets at the level of individual patients.

Method

We compared the IR estimates of schizophrenia based on the first contact approach and the ePCR approach. We standardized the comparison as much as possible by using the same measure (the treated IR) for the same disorder (DSM-IV schizophrenia codes 295.x), for the same age group (age 20–54 years) and in the same population (all citizens of The Hague, from October 2000 to September 2005).

ePCR-based IR

The ePCR of The Hague is a data warehouse uploaded from the patient registration systems of the Parnassia Psychiatric Institute. Through successive mergers of all mental health, forensic and drug addiction services, Parnassia has become almost the sole institutional provider of psychiatric services for adults in The Hague, including in-patient, out-patient, day and psychiatric residential care, emergency services, and collaborative services for all municipal police stations and most general practitioners (GPs). Not included are around 20 small private psychiatric practices, together serving less than 5% of all subjects treated for mental disorders, and a minority of GPs. Private psychiatrists and GPs, however, nearly always refer subjects with psychotic disorders to Parnassia's more integrated services. As a result, almost all subjects with psychotic disorders are treated at Parnassia and are listed in the ePCR of The Hague. The areas surrounding the catchment area are similar in terms of urbanization and availability of services for psychotic disorders. Dutch services for psychotic disorders have clear geographical boundaries. Subjects presenting with psychosis outside their home area are typically identified by their home address (postcode) and referred back to their own area as soon as possible.

The ePCR contains information on date of birth, country of birth of patients and their parents, successive zip codes, DSM-IV diagnoses and all service contacts for each patient treated at Parnassia from 1997 onwards. Historical (but less complete) records are searchable back to 1980 to identify patients treated before 1997. Diagnoses are recorded at intake and are audited on a regular basis at case conferences, upon internal referrals

and when treatment is ended. They are classified according to DSM-IV under supervision of either a psychiatrist or a clinical psychologist. Parnassia's administrative procedures include checking and updating diagnoses and service utilization records. All changes are automatically updated in the ePCR.

To calculate IRs based on the ePCR, we examined diagnostic histories of all subjects who had had any service contact with Parnassia during 1980–2009 (n = 249 409). We defined onset of schizophrenia (numerator) as subjects who received a first ePCR diagnosis of schizophrenia (DSM-IV 295.x) during the 5-year study period from 2000 to 2005, and who resided in The Hague and were aged 20–54 years at the time of the index diagnosis. We used the detailed municipal data available in The Hague to calculate the number of person years (denominator of the IR).

Annual census data were available for the population of The Hague aged 20–54 years over the 5-year study period (n = 233 803 in 2000, increasing to n = 250 671 in 2005); the total number of person years of observation in the study was 1 221 486. We computed the IR for schizophrenia, defined as the number of treated incident cases per 100 000 person years in the study population (i.e. citizens of the catchment area). Cases contributed person time until the onset of schizophrenia (the actuarial method).

First contact IR

To calculate the first contact IR, we used individual-level data from a first contact study previously conducted in the same catchment area (Veling et al., 2007). In brief, the study used a first contact sampling frame to estimate the incidence of all psychoses, excluding psychoses related to somatic disorders or substance abuse. The criteria for inclusion and exclusion were similar to those used in the WHO Ten Country study (Bourque et al., 2010; Cooper et al., 1987; Jablensky et al., 1992). The authors collaborated with local GPs and (resident) psychiatrists to identify every citizen of the catchment area aged 15–54 years who made first contact with a physician for a (suspected) psychotic disorder. Residents in psychiatry interviewed screen-positive cases using the Comprehensive Assessment of Symptoms and History (CASH; (Andreasen, 1992)). Trained nurses interviewed their families using the Instrument for the Retrospective Assessment of the Onset of Schizophrenia [IRAOS; (Häfner et al., 1992)]. The residents integrated all available clinical information into a narrative of the patient's illness. Two psychiatrists used the narrative to make a consensus DSM-IV diagnosis. Subjects with substance-induced psychotic disorder, a psychotic disorder due to a somatic condition or a non-psychotic disorder were excluded. Subjects with schizophreniform or schizo-affective disorder were classified as having schizophrenia. First episodes of psychosis diagnosed as schizophrenia by the

researchers received further treatment at a service for Early Psychosis and were followed for the duration of the study. Screen-negatives and first episodes diagnosed with other types of psychosis were treated elsewhere and not actively followed beyond the initial phase of treatment. There was no systematic provision to identify subjects who met criteria for schizophrenia at later stages of treatment.

In the original study, 364 residents of the catchment area had been identified with a first psychosis in the age range 20–54 during the 5-year period 2000–2005; psychoses related to somatic causes or substance abuse were excluded. For our comparison, we included only the subset of 254 subjects diagnosed with schizophrenia (i.e. DSM-IV codes 295.x). We used the same denominator for the first contact estimate as we did for the ePCR estimate and the same formula for the IR.

Comparison of the onsets identified with the two methods

We cross-tabulated onsets identified with the two methods to examine whether these subjects were different in terms of gender, initial clinical diagnosis in the first year of treatment, age at first diagnosis of schizophrenia and duration of prior treatment.

Sensitivity analysis

We considered two potential sources of bias in the ePCR estimate. First, the ePCR may overestimate the number of onsets of schizophrenia if it lists subjects moving into the catchment area who have already been diagnosed with schizophrenia elsewhere; these subjects should not count as onsets. Mental health contacts outside the catchment area cannot be ruled out with register data alone. To estimate the bias introduced by this 'in-migration' phenomenon, we queried the records from the municipality to identify the exact date of settlement in the catchment area. Municipal data were available for citizens who remained in the area until 2010 or later, and only subjects with very complete identifying data could be matched. We obtained the exact date of settlement in the catchment area for 80% (170/213) of the cases identified by both methods and for 71% (475/665) of the additional cases identified by the register. When no municipal data were available, we used register data as a conservative proxy (i.e. the first date that a subject was listed as a citizen in the register). We defined as 'suspect for in-migration' any instance where the index diagnosis of schizophrenia was made within 6 months after the subject settled in the catchment area, that is the same cut-off as used in the WHO Ten-Country study (Jablensky et al., 1992).

Second, the ePCR may overestimate the number of onsets of schizophrenia if clinicians overdiagnosed schizophrenia. We conducted three analyses to examine the diagnostic va-

lidity and stability of onsets of schizophrenia identified by the ePCR. First, to examine the diagnostic stability, we compared the two methods in terms of how long subjects kept their schizophrenia diagnosis, by estimating survival functions over the first 5 years after the index diagnosis. A schizophrenia diagnosis was considered 'unstable' if it was withdrawn permanently for any reason (either because it was audited and rediagnosed or because the disorder had remitted). Second, to estimate bias from spurious diagnoses (short-lived diagnoses resulting from administrative error, etc.), we listed subjects for whom the index diagnosis was withdrawn during the first year, or who were lost to follow-up during the first year. In this analysis, subjects in the first contact study for whom stability data were missing (33/254 or 13%) were assumed to have perfect diagnoses. Third, to evaluate the diagnostic validity, we examined the diagnostic history and referral pathways after the index diagnosis up to 2009 and graded the validity of the index ePCR diagnosis as 'standard', 'high' or 'very high'. We defined diagnostic validity as 'standard' when the schizophrenia diagnosis was made (or continued) by one or more qualified psychiatrists according to DSM-IV procedures and criteria. We defined validity as 'high' when diagnoses had been audited and reconfirmed by a service specializing in psychotic disorders (i.e. implying a thorough diagnostic procedure followed by a consensus diagnosis by a team of psychosis specialists). We defined validity as 'very high' when a research diagnosis had been made or the diagnosis had been made by one of Parnassia's senior experts in schizophrenia. To identify subjects with a research diagnosis, we contacted all colleagues involved in the original first contact study, other schizophrenia-related studies or working at Parnassia's schizophrenia early detection services and obtained access to their study data. We then listed as having a 'research diagnosis', subjects for whom schizophrenia was at some point diagnosed using either the CASH or the Schedule for Clinical Assessment in Neuropsychiatry (Wing, 1990). 'Senior experts in schizophrenia' were defined as psychiatrists with senior functions in research on schizophrenia, residency training in psychotic disorders or clinical management of the schizophrenia early intervention programme. Nine of the Parnassia Psychiatric Institute's psychiatrists met these criteria. Not all subjects with an index diagnosis of schizophrenia were audited by a service specializing in psychosis, or seen by a senior expert in schizophrenia. The 'standard validity' category may therefore also contain patients with diagnoses that would have withstood any more specialized audit.

Under the Dutch 'Medical Research Involving Human Subjects' Act (WMO), analysis of ePCR data did not require approval by the local medical ethics committee.

Statistical analyses

All statistical analyses were conducted with SPSS version 19.0 (SPSS Inc., USA). Confidence limits for the IRs were based on the Poisson distribution (mid-p exact test)

(Rothman et al., 2008). Kaplan–Meier statistics were used to compare the cumulative proportions of stable diagnoses between the two methods.

Results

Primary results

Table 2.1 shows the treated incidence of schizophrenia by gender and age as estimated with the two methods. The ePCR identified 843 onsets of schizophrenia, corresponding to a treated IR of 69 per 100 000 person years [95% confidence interval (CI) 64–74]. The first contact study reported 254 onsets of schizophrenia, corresponding to a treated IR of 21 per 100 000 person years (95% CI 18–23).

Comparison of the onsets identified with the two methods

Of the 254 subjects reported in the first contact study, 213 were also listed as incident cases of schizophrenia in the register at some point in time. Of the remaining 41 cases, two could not be matched in the ePCR at all, 24 were matched but had no diagnostic records, and 17 had diagnostic records but schizophrenia had never been recorded. In our analyses we conservatively assumed that all 41 cases not listed in the register as incident cases were nevertheless true incident cases of schizophrenia that had been missed by the register.

Of the 213 cases listed in both systems, 55 cases were excluded from the register's count because of differences in timing of the registration (they had aged into an older age group by the time they were registered or were registered after the study period). The direct overlap between the two systems was therefore 158 cases.

The register identified another 685 cases that were not listed in the first contact study's count. Of these, 20 had in fact been included in the original first contact study at a younger age than included in our comparison (i.e. 15–19 years) and were later identified by the register when they had reached the 20–24-year age group and met the inclusion criteria. It is therefore not correct to classify them as 'cases identified exclusively by the register'. Excluding these 20 subjects resulted in a final number of 665 additional cases identified exclusively by the register during the study period.

Table 2.2 shows the characteristics of onsets identified by the two methods. Of the 665 cases not included in the first contact study but listed in the register, 78.8% did not meet criteria for schizophrenia during the first year of treatment; 66.1% had a treatment

history of ≥5 years, were aged 40–54 years, or both. Finally, 65.0% were found among patients already under psychiatric treatment before the start of the study period.

Table 2.1 Treated IR of schizophrenia in The Hague (NL), from October 2000 to September 2005

		First Contact[a]		ePCR	
Age (years)	Person years	n	IR (95% CI)	n	IR (95% CI)
Men					
20–24	73 384	61	83 (64–106)	98	133 (109–162)
25–29	94 433	56	59 (45–76)	95	100 (82–122)
30–34	109 474	33	30 (21–42)	100	91 (75–111)
35–39	101 256	25	25 (16–36)	99	98 (80–119)
40–44	89 950	8	9 (4–17)	80	89 (71–110)
45–49	78 390	1	1 (0–6)	63	80 (62–102)
50–54	74 541	2	3 (0–9)	43	58 (42–77)
Total	621 427	186	30 (26–35)	576	93 (85–101)
Women					
20–24	80 067	20	25 (16–38)	36	45 (32–62)
25–29	97 194	23	24 (15–35)	33	34 (24–47)
30–34	101 544	10	10 (5–18)	30	30 (20–42)
35–39	91 072	10	11 (6–20)	48	53 (39–70)
40–44	82 826	3	4 (1–10)	32	39 (27–54)
45–49	75 256	1	1 (0–7)	48	64 (48–84)
50–54	72 101	1	1 (0–7)	38	53 (38–72)
Total	600 059	68	1 (9–14)	262	44 (39–49)
Persons					
20–24	153 451	81	53 (42–65)	134	87 (73–103)
25–29	191 626	79	41 (33–51)	128	67 (56–79)
30–34	211 018	43	20 (15–27)	130	62 (52–73)
35–39	192 328	35	18 (13–25)	147	76 (65–90)
40–44	172 777	11	6 (3–11)	112	65 (54–78)
45–49	153 646	2	1 (0–4)	111	72 (60–87)
50–54	146 642	3	2 (1–6)	81	55 (44–68)
Total	1 221 486	254	21 (18–23)	843	69 (64–74)

ePCR electronic Psychiatric Case Register
n number of first onsets of schizophrenia
IR treated incidence rate of schizophrenia per 100 000 person years
CI confidence interval
.[a] First Contact study (Veling et al., 2007)

Table 2.2 Characteristics of first onsets of schizophrenia

	First contact only[a]	First contact and ePCR	ePCR only
Gender			
Men	28 (68.3)	158 (74.2)	446 (67.1)
Women	13 (31.7)	55 (25.8)	219 (32.9)
Total	41 (100.0)	213 (100.0)	665 (100.0)
Initial clinical diagnosis			
Schizophrenia		63 (29.6)	141 (21.2)
Other non-affective psychosis	14 (34.1)	39 (18.3)	105 (15.8)
Substance abuse	1 (2.4)	5 (2.3)	37 (5.6)
Major depressive disorder		7 (3.3)	20 (3.0)
Bipolar disorder			11 (1.7)
Other disorders	1 (2.4)	32 (15.0)	80 (12.0)
No diagnosis during first year	1 (2.4)	67 (31.5)	271 (40.8)
No records in register	24 (58.5)		
Age at first diagnosis of schizophrenia (years)			
20-24	14 (34.1)	67 (31.5)	60 (9.0)
25-29	11 (26.8)	68 (31.9)	83 (12.5)
30-34	6 (14.6)	37 (17.4)	102 (15.3)
35-39	5 (12.2)	30 (14.1)	125 (18.8)
40-44	3 (7.3)	8 (3.8)	105 (15.8)
44-49	1 (2.4)	1 (0.5)	110 (16.5)
50-54	1 (2.4)	2 (0.9)	80 (12.0)
Median (IQR)		27.0 (23.7-32.2)	35.9 (28.6-43.3)
Initiated treatment			
Before the study period		43 (20.2)	432 (65.0)
During the study period		170 (79.8)	233 (35.0)
Duration of prior treatment			
1 day		37 (17.4)	62 (9.3)
1 day to 1 year		50 (23.5)	95 (14.3)
1-5 years		95 (44.6)	179 (26.9)
>5 years		31 (14.6)	329 (49.5)
Median (IQR)		1.3 (0.4-3.4)	4.9 (1.1-8.8)

ePCR electronic Psychiatric Case Register
IQR interquartile range
.[a] First Contact study (Veling et al., 2007)

All values are given as n (%) or median (IQR)

Sensitivity analyses

Diagnostic stability data were available for 213/254 (84%) persons identified in the first contact study and 843/843 (100%) persons identified by the register. From the index diagnosis up to 2009, cases identified by both methods went through a median of four additional diagnostic audits (IQR 3–6) by two independent psychiatric services (IQR 1–3), with a median interval between audits of 1.0 years (IQR 0.7–1.2). For additional cases identified only by the register, median numbers and ranges of audits and services were identical, and the interval between audits nearly equal (median 1.1 years, IQR 0.7–1.5). The share of subjects who were not audited within the first 3 years after the index diagnosis was 9% for subjects identified by both methods and 10% for additional cases identified by the register. For the first contact study, the 5-year diagnostic stability was 92.8% (95% CI 88.4–97.1; mean follow-up 4.51 years). For the register, the 5-year diagnostic stability was 90.8% (95% CI 88.5–93.0; mean follow-up 4.85 years). During the first year after the index diagnosis, 10/843 register diagnoses were withdrawn and 116 were lost to follow-up; and 0/254 first contact diagnoses were withdrawn and 16 were lost to follow-up. Excluding these short-lived (i.e. possibly spurious) diagnoses did not affect the 3.3 ratio between the IR estimates by both methods. Subjects identified by both methods had lived in the catchment area for a median of 6.7 years (IQR 2.2–21.7) and additional cases identified by the register for a median 9.15 years (IQR 2.3–22.1). Of 843 onsets identified by the ePCR, we listed 42 (5%) subjects residing in the catchment area for less than 6 months before the index diagnosis (i.e. 'suspect for in-migration').

Discussion

Of the 843 cases listed in the register, 79 (9.4%) were diagnosed by a psychiatrist but were never audited by a service specializing in psychotic services (i.e. 'standard validity'), 277 (32.9%) were audited and confirmed by a service specializing in psychotic disorders (i.e. 'high validity'), 292 (34.6%) were audited and confirmed by a senior expert in schizophrenia, and 195 (23.1%) received a research diagnosis of schizophrenia in the course of an epidemiological study (i.e. together classified as 'very high validity'). Table 2.3 shows incidence estimates (excluding possible in-migration) based on incremental levels of available evidence supporting the validity of the clinical diagnoses used in the register.

Using the ePCR, we estimated the treated IR of schizophrenia at 69 per 100 000 person years for subjects aged 20–54 years in the city of The Hague from October 2000 to September 2005. This estimate is three times higher than a previous estimate from a high-quality first contact study that was conducted in the same population over the same

period. At least two-thirds of the difference was accounted for by subjects treated for more than 5 years before the onset of psychosis, and by subjects who were aged > 40 years before a clinician diagnosed them as meeting criteria for schizophrenia.

Table 2.3 Adjusting for in-migration and levels of evidence supporting the diagnosis
Incidence estimates (excluding possible in-migration) at incremental levels of evidence available to support the validity of the clinical schizophrenia diagnoses used in the register.

		In-migration		Excluding in-migration	
		Yes	No	Cumulative	
	n	n	n	n	IR (95% CI)
Very high validity					
Included in a study (i.e. research diagnosis)	195	0	195	195	16 (14-18)
Audited and confirmed by a senior expert in schizophrenia	292	18	274	469	38 (35-42)
High validity					
Audited and confirmed by a service specializing in psychotic disorders	277	7	270	739	61 (56-65)
Standard validity					
Diagnosed by one or more psychiatrists but not audited by a service specializing in psychotic disorders	79	17	62	801	66 (61-70)
All onsets of schizophrenia identified by the LPR		42	801	843	69 (64-74)

ePCR electronic Psychiatric Case Register
n number of first onsets of schizophrenia
IR treated incidence rate of schizophrenia per 100 000 person years
CI confidence interval

Limitations

It is reassuring that the diagnostic stability of schizophrenia diagnoses was similar for the subjects identified in the ePCR and in the first contact study. Our sensitivity analyses show that in an extreme scenario (i.e. counting only a selection of subjects audited and confirmed by senior schizophrenia experts or researchers), the estimate would be 38 per 100 000 person years. More realistically (i.e. excluding subjects suspected of in-migration and considering diagnoses made by specialized teams as valid cases), we consider an IR of 61 per 100 000 person years as the most likely minimum estimate. This conservative estimate is nearly three times higher than the first contact estimate of 21 per 100 000 person years. The sources of bias we considered can only partly explain the threefold difference between the estimates. It is unlikely that the difference between the ePCR and first contact study estimates is due to some unusual characteristic of the first contact study used for the comparison, the catchment area or the study period. As noted earlier, the study emulated the WHO Ten-Country study and met the highest quality standards (Bourque et al., 2010; Kirkbride, Errazuriz, et al., 2012; McGrath et al., 2004).

Its findings were similar to the median values reported in two worldwide meta-analyses (McGrath et al., 2004; van der Werf et al., 2012). Our catchment area is similar to many other cities where first contact studies have been conducted. An exploratory analysis of annual schizophrenia IRs did not provide evidence of a notable period effect (data not shown).

We do not know whether such a large difference between the two methods would also have been found in the past in high-income countries or would currently be found in low resource settings. Subjects may be less likely to seek treatment before the onset of psychosis when mental health services are less available, resulting in a smaller difference. In high-income countries, the use of mental health services has increased greatly since the Ten-Country study (Anderson et al., 2010; Brugha et al., 2004; Cadenhead et al., 2010; Kessler et al., 2005; Murray et al., 2009; Rietdijk et al., 2011). In low resource settings, access to formal mental health services is limited and subjects may contact traditional healers at first, which might rule them out in a strict first contact design (Jablensky et al., 1992; Kale, 1995).

Interpretation

We suggest that fundamental differences in design are the most plausible explanation for the nearly threefold difference observed between the estimates from the first contact study and the ePCR. Although both methods seek to identify onsets of schizophrenia among treated patients, in the first contact design subjects are observed only at the beginning of mental health treatment whereas the ePCR can identify onsets at any stage of treatment. In addition, in practice, first contact studies tend to focus on ascertaining cases under age 40, perhaps due to a longstanding belief that few cases have their onset at older ages, and more recently due also to the interest in early intervention. Our data show that the majority of subjects with an ultimate diagnosis of schizophrenia sought mental health treatment several years before they met the full criteria for the disorder. At that stage, they were no longer 'first contact' and were not actively followed by the first contact design. The insidious onsets observed in our study are consistent with retrospective studies in first contact samples, reporting that depressive and negative symptoms manifest from 6 years before the diagnosis of schizophrenia, and are followed by social disability 2 to 4 years later (Murray et al., 2009).

As noted earlier, other studies have used a longitudinal approach to estimate the incidence of schizophrenia. Birth cohort studies (generally restricted to hospitalized subjects) have reported cumulative findings consistent with IRs ranging from 25 to 50 per 100 000 person years for subjects aged 15–45 (Bresnahan et al., 2000; Isohanni et al.,

2001; McGrath et al., 2004; Sørensen et al., 2010; Wahlbeck et al., 2001). Findings from eight register-based studies in Mannheim, California, Denmark, Stockholm, Finland, Israel and two provinces in Canada, along with one study in Melbourne combining an intensive early detection program with longitudinal in-and out-patient data, indicated IRs in the range 30–90 per 100 000 person years in the age range 15–65 years. These high estimates were not commented upon at the time (Bray et al., 2006; Häfner & Heiden, 1986; Kodesh et al., 2012; Thorup et al., 2007), or attributed to chance (Bresnahan et al., 2000), to the sensitivity of the early detection method (Amminger et al., 2006), to period and cohort effects (Bresnahan et al., 2000; Vanasse et al., 2011), or to risk factors such as urbanization (Jörgensen et al., 2010), latitude or immigration (Dealberto, 2013). Considered together, these studies are consistent with our hypothesis that accounting for cases identified at later stages of treatment results in higher IRs.

Implications

One implication of our finding is that current public health estimates of the societal impact of schizophrenia may need to be revised. A tripling of the estimate of the IR implies that schizophrenia's current 14th position in the WHO's ranking of most burdensome diseases in high-income countries would shift to a substantially higher position (Ayuso-Mateos, 2002).

Another implication is that the methods to detect risk factors for schizophrenia may need to be revised. Many well-known risk factors have been detected with first contact studies. If such studies have overlooked up to two-thirds of the schizophrenia cases, reported results may have been affected by selection bias.

3

Pathways to psychosis

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Abstract

BACKGROUND — Knowledge of pathways to care by help-seeking patients prior to the onset of psychosis may help to improve the identification of at-risk patients. This study explored the history of help-seeking behavior in secondary mental health care services prior to the onset of the first episode of psychosis.

METHOD — The psychiatric case register in The Hague was used to identify a cohort of 1753 people in the age range of 18–35 at first contact who developed a psychotic disorder in the period from 1 January 2005 to 31 December 2009. We retrospectively examined the diagnoses made at first contact with psychiatric services.

RESULTS — 985 patients (56.2%) had been treated in secondary mental health services prior to the onset of psychosis. The most common disorders were mood and anxiety disorders [n = 385 (39.1%) and substance use disorders [n = 211 (21.4%)]. Affective psychoses were more often preceded by mood/anxiety disorders, while psychotic disorder NOS was more often preceded by personality disorder or substance abuse. The interval between first contact and first diagnosis of psychosis was approximately 69 months in cases presenting with mood and anxiety disorders and 127 months in cases presenting with personality disorders.

CONCLUSION — This study confirms the hypothesis that the majority of patients with psychotic disorders had been help-seeking for other mental disorders in secondary mental health care prior to the onset of psychosis.

Introduction

Many risk factors contribute to the development of psychotic disorders. Some are distant, such as genetic and other pre- and perinatal risk factors (Harrison & Weinberger, 2004; Keshavan et al., 2005). Others are more proximal, such as cannabis abuse in adolescence (Moore et al., 2007). The development of psychopathology has in many cases been found to be a prodromal sign for the development of psychotic disorders. Social decline, depression and anxiety problems, sleeping problems, cognitive disturbances and psychotic-like experiences (PLEs) often precede the onset of psychosis (Häfner et al., 2005; Häfner, 2000; Klosterkötter et al., 2001; Krabbendam & Os, 2005; Velthorst et al., 2010; Yung, Yung, et al., 2005).

Retrospectively, PLEs almost always precede frank psychosis, but prospectively only 8% of new cases with PLEs in the general population develop a psychosis within 24 months (Hanssen et al., 2005).

PLEs do not differ in intensity in patients compared with non-patients, but both groups do differ in their need for care (Stip & Letourneau, 2009) and in the distress associated with the symptoms (Yung, Buckby, et al., 2005). Need for care and distress are important determinants of help-seeking behavior, and seeking help for disorders other than psychosis might be an important mode of presentation of psychosis. It is also shown that people who report sub-clinical psychosis are more help-seeking than those subjects who do not report sub-clinical symptoms (Murphy et al., 2010). The combination of risk factors does raise the odds of developing a psychotic disorder. For instance, in a population-based study (NEMESIS) two or more sub-clinical psychotic symptoms with depressed mood result in a forty percent chance of developing a psychosis within 24 months (Hanssen et al., 2005).

A review by Anderson et al. (2010) found help-seeking behavior in 33–98% of patients who experienced a first psychotic episode. Some of the studies included in the review found that patients contacted their GPs before the onset of schizophrenia psychosis (Norman et al., 2004). Only two studies have explored help-seeking behavior during the prodromal stage in more detail. In a retrospective study in a cohort of 24 schizophrenia patients, 19 patients (75%) sought help prior to the onset of psychosis (Bota et al., 2005). Of these patients, 14 were diagnosed with an Axis I diagnosis and 15 were prescribed medication or had a psychological intervention. Another retrospective study found evidence for prodromal disorders in 80% of 86 first-episode (schizophrenia) patients of whom 40% showed prodromal help-seeking behavior for these disorders (Addington et al., 2002). These proportions of help-seeking behavior (40 and 75%) are based on small

sample sizes, and a more accurate estimate of the prevalence of help seeking behavior in larger populations entering the secondary mental health services before the onset of the disorder would be helpful.

Does help-seeking in secondary mental health services result in the detection of frank psychosis at a much earlier stage? Apparently it does not. Researchers found that the delay in secondary mental health care services was associated with a duration of untreated psychosis that was seven times longer than a direct referral to a first-episode psychosis department. They concluded that intervention is required in secondary as well as primary care services to reduce the duration of untreated psychosis (Boonstra, Wunderink, Sytema, et al., 2008; Brunet et al., 2007). Health care professionals do not seem to detect the development of psychosis when treating other disorders, or perhaps they are convinced that the psychotic symptoms are secondary to other problems. If a substantial proportion of patients who are likely to develop psychosis in the future do seek help in secondary mental health services, then screening for sub-clinical psychotic symptoms might be a strategy to prevent a lengthy period of untreated psychosis. Targeted intervention might even postpone or prevent a first psychotic episode. An important question remains: *what proportion of people with a first psychotic episode has been help-seeking in health services at the prodromal stage?*

In this study prodromal help-seeking behavior and diagnoses over time were retrospectively explored in all consecutive cases with a psychotic disorder recorded in a psychiatric case register during five years in a well-defined urban catchment area. Additionally, we examined the time between first contact and first diagnosis of psychotic disorder.

Method

Subjects

The cohort of subjects was identified in the psychiatric case register of the Parnassia Psychiatric Institute (n = 1753). This institute has been the single provider of adult mental health care (18 years and over) in The Hague for over four decades. The Hague is one of the five largest cities of the Netherlands and the catchment area covers approximately 450 000 inhabitants. The psychiatric case register contains data about inpatient and outpatient service utilization as well as patient characteristics such as all the diagnosis and demographic information from the earlier contact on. This afforded the opportunity to examine the clinical history of patients who experienced a first episode of any psychotic disorder between 2005 and 2009. The current study explored the clinical help-seeking pathways of

patients aged between 18 and 35. The 14–35 year age group is considered to have the highest risk of developing psychosis (DeLisi, 1992). However, Parnassia only provides adult care (18 years and over) and therefore we had to use the age criterion of 18–35 years.

The inclusion criteria for this study were:

1. The development of a first registered DSM IV-diagnosis of affective (schizoaffective disorder, bipolar disorder or mood disorder with psychotic features) or non-affective psychosis (schizophrenia and other psychotic disorders) between January 2005 and December 2009;
2. Age between 18 and 35 years at first contact with Parnassia;
3. Residence in The Hague.

Excluded were patients with substance-induced psychotic disorders.

Statistical analyses

The distribution assumptions of the data were tested and did not meet the criteria for parametric tests. Non-parametric Mann-Whitney-tests, Kruskal-Wallis tests and two-tailed multinomial logistic regression were applied for differences in time between first contact and transition into psychosis for the different psychotic diagnoses and the different first contact diagnoses. Mann-Whitney-U tests were used to follow up significant findings of the Kruskal-Wallis tests. We used Bonferroni correction to ensure the Type I errors did not build up to more than a .05 level of significance (critical value of .05 divided by the number of Mann-Whitney-U tests we have conducted). Kaplan-Meier analysis was performed for survival analyses: this study uses backward recurrence times. The Kaplan-Meier analysis is therefore only used to explore the time from first contact until diagnosis in the psychosis spectrum (Allison, 1985). Chi-square analyses were used to test the association between type of psychotic onset and clinical history. Adjusted standardized residuals of chi-square cross-tabulation analyses were conducted between first contact diagnosis and psychotic disorders in which negative adjusted residuals in a cell correspond to a smaller number of cases than expected by chance and positive residuals correspond to more cases (corrected for small N in the groups).

Results

Subjects

In the years 2005 to 2009, 1753 people aged between 18 and 35 years at first contact with Parnassia were diagnosed with a psychotic disorder: 1015 men and 738 women. The mean age of first contact with services was 26.0 years (*sd* = 5.1, median = 26.0) and the mean age when diagnosed with psychosis was 32.1 (*sd* = 7.9, median = 32.0) years.

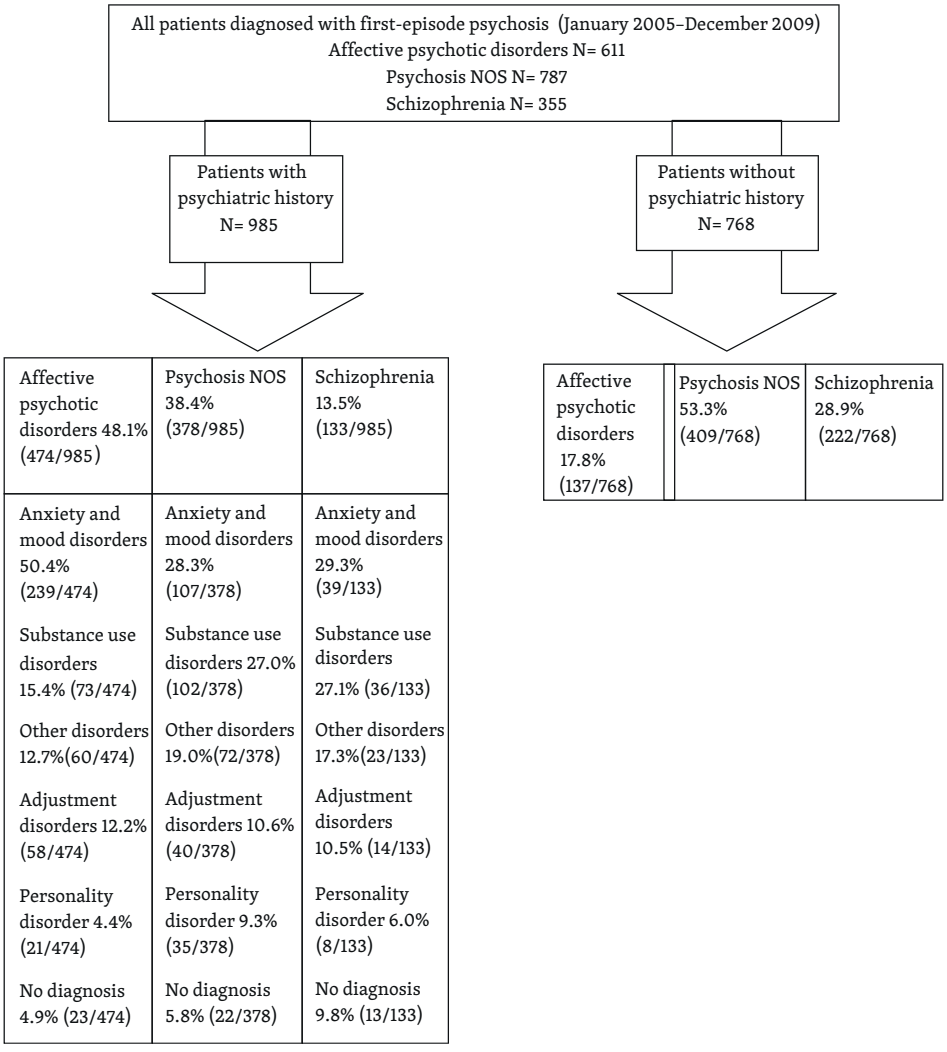

Figure 3.1 Patients with and without a psychiatric history and their initial diagnoses

First contact diagnoses

Figure 3.1 displays the help-seeking pathways to psychosis: 768 (43.8%) patients were diagnosed with schizophrenia spectrum (schizophrenia, schizophreniform disorder, schizoaffective disorder and delusional disorder) (DSM 295.xx and 297.1), psychotic disorder NOS including brief psychotic disorder (DSM 298.xx) or affective psychotic disorder (bipolar disorder and depression with psychotic features, DSM 296.xx) at first contact. Women were overrepresented in the group with affective psychosis (*n* = 137; 62.8%), and men were more often diagnosed in the schizophrenia spectrum (*n* = 222; 72.1%) and with psychotic disorder NOS (*n* = 409; 67.7%) at first contact.

Table 3.1 The likelihood of psychiatric treatment in the prodromal stage of a psychotic disorder

	Psychotic disorder at first contact	No psychotic disorder at first contact	χ^2
	(n = 768)	(n = 985)	
Affective psychotic disorder[a] (n = 611)	↓↓ (n = 137)	↑↑ (n = 474)	χ^2 (2, 1753) = 174.3, p < .001
Psychotic disorder NOS (n = 787)	↑ (n = 409)	↓ (n = 378)	χ^2 (2, 1753) = 38.6, p < .001
Schizophrenia (n = 355)	↑ (n = 222)	↓ (n = 133)	χ^2 (2, 1753) = 63.4, p < .001
Male (n = 1015)	↑ (n = 488)	↓ (n = 527)	χ^2 (1, 1753) = 25.1, p < .001

↑↑ or ↓↓ adjusted standardized residuals > |10| or < |-10|
↑ or ↓ adjusted standardized residuals > |5| or < |-5|
[a] Bipolar disorder and mood disorders with psychotic features.

Chi-square cross-tabulation analysis between the initial disorder and transition diagnosis in which adjusted standardized residuals reflect a higher or lower number of cases than expected, corrected for small numbers. Negative adjusted residuals in a cell correspond to a smaller number of cases than expected by chance, positive residuals correspond to more cases. Adjusted standardized residuals outside the range -2.5 and +2.5 indicate significant differences between observed and expected numbers.

Of those patients who were diagnosed with affective psychotic disorders, fewer than expected were psychotic at first contact (see Table 3.1). Conversely, patients diagnosed with non-affective psychosis were more often psychotic at first contact. Men were more often diagnosed with a psychotic disorder at first contact.

A total of 985 patients (56.2%) had a history of treatment for non-psychotic Axis I or II disorders before the onset of the first psychotic episode (see figure 3.1). The largest groups of these patients had been referred for treatment for anxiety and mood disorders, substance use disorders and adjustment disorders. Whereas women had more anxiety,

Table 3.2 The characteristics of people with a non-psychotic diagnosis preceding psychotic disorder

Initial diagnosis (clustered)	n	Female	Mean age at first contact in years (*se*)	Mean age at first psychosis in years (*se*)	Mean time from first contact to diagnosis of psychotic disorder in months (*se*)	Median time in months to diagnosis of psychotic disorder
Anxiety and mood disorders	385	215 (55.8%)	27.5 (.23)	33.4 (.32)	70.0 (2.92)	56
Substance use	211	37 (17.5%)	26.2 (.33)	35.8 (.50)	115.1 (3.98)	127
Other disorders[a]	155	88 (56.8%)	26.2 (.40)	32.7 (.65)	78.2 (6.23)	67
Adjustment disorders	112	59 (52.7%)	27.8 (.43)	34.3 (.65)	77.5 (5.71)	62
Personality disorder	64	26 (40.6%)	26.1 (.60)	36.6 (.90)	125.3 (8.22)	129
Not diagnosed	58	33 (56.9%)	25.9 (.64)	33.5 (.85)	91.2 (6.6)	88
Total	985	458 (46.5%)	26.9 (.15)	34.2 (.22)	86.6 (2.04)	78

[a] Other disorders are disorders that are not very common in this data set, e.g. sexual disturbances, relationship problems or eating disorders.

mood and adjustment disorders in the help-seeking history, men had been treated more often for substance use and personality disorders.

The diagnoses at first contact and estimated time to diagnosis of psychotic disorder are presented in Table 3.2.

Time between first contact and psychosis

To measure the mean time from first contact to first diagnosis of psychosis among patients who entered the secondary mental health care services for other mental problems, we excluded those patients who were diagnosed with psychosis at first contact from the analysis. It took 86.6 months (*se* = 2.04) to be diagnosed in the psychosis spectrum from first contact for non-psychotic disorders; the median was 78.0 months (Table 3.2). About 23% made the transition to psychosis in the first two years.

No differences were found in mean time between first contact and first psychotic diagnosis for the various clusters of psychosis (Kruskal-Wallis: H (2) = 3.03, p=.219). The Mann-Whitney-U test was used to measure the effect of gender on mean time to transition. The difference between mean time from first contact to psychosis in men (mean = 94.8, *sd* = 67.8, median = 99.0 months) compared with women (mean = 78.5, *sd* = 71.2, median = 66.0 months) was statistically significant (U = 100 054, z = 4.6, p < 0.001).

The mean time between first contact and first-episode psychosis differed for first contact diagnosis (Kruskal-Wallis: H (5) = 82.6, p < 0.001). Mann-Whitney-U tests were used to

follow-up this finding. A Bonferroni correction was applied. All effects were reported at a .0016 level of significance (.05/30). People first diagnosed with anxiety and mood disorders, adjustment disorders and other disorders developed psychosis sooner than

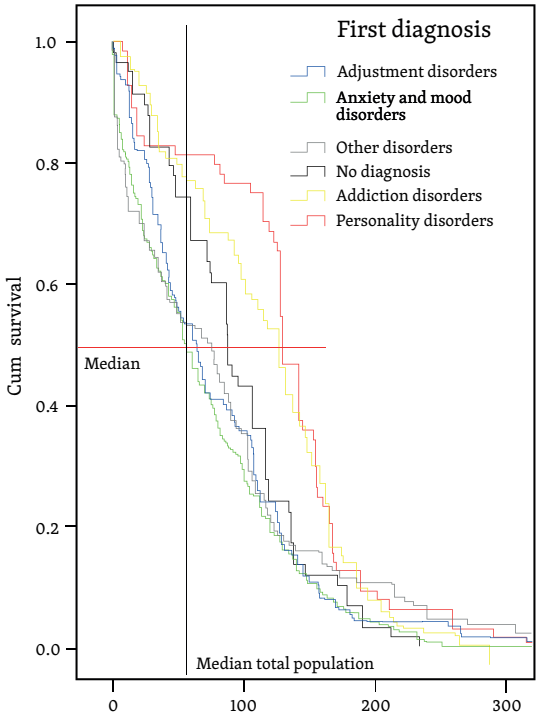

Figure 3.2 Survival curve for transition to psychosis after accessing secondary mental health service for each initial diagnosis separately. Months between first contact and psychosis

people with no diagnosis, substance use problems or personality disorders at first contact. Regression analysis was used to correct for age at first contact, gender and type of psychotic onset, and the differences in mean time to psychosis diagnoses for the first contact diagnosis remained significant ($F(4980) = 21.8$, $p < 0.001$). Figure 3.2 shows the survival curves for the various first contact diagnoses and shows the same differences in time to transition for the various first contact disorders.

Onset of psychosis

The clinical history is shown in Table 3.3 and varies between the psychosis subtypes. Whereas patients diagnosed with bipolar disorders were more likely to have had anxiety and mood disorders in the prodromal phase, patients with psychosis NOS were more

often diagnosed with premorbid substance use disorders, other disorders and personality disorders.

Table 3.3 The association between initial diagnosis and psychotic disorder subgroup

		Affective psychotic disorders[a]	Psychotic disorder NOS	Schizophrenia
Anxiety and mood disorders	n observed	277	134	46
	n expected	220	177	61
	st. adj. residuals	6.9	-5.3	-2.6
Substance use	n observed	93	120	41
	n expected	122	98	34
	st. adj. residuals	-4.1	3.2	1.5
Other disorders[b]	n observed	65	87	25
	n expected	85	68	24
	st. adj. residuals	-3.3	3.1	0.4
Adjustment disorders	n observed	74	45	17
	n expected	65	53	18
	st. adj. residuals	1.6	-1.4	-.03
Personality disorder	n observed	24	39	10
	n expected	35	28	10
	st. adj. residuals	-2.7	2.7	0
No diagnosis	n observed	25	24	15
	n expected	31	25	9
	st. adj. residuals	-1.5	-0.2	2.5
	χ^2	χ^2 (5, 985) = 59.3, p < .001	χ^2 (5, 985) = 38.9, p < .001	χ^2 (5, 985) = 59.3, p < .001

[a] Bipolar disorder and mood disorders with psychotic features
[b] Other disorders are disorders that are not very common in this data set, e.g. sexual disturbances, relationship problems or eating disorders

Chi-square cross-tabulation analysis between the initial disorder and psychotic disorder subgroup diagnosis in which adjusted standardized residuals reflect a higher or lower number of cases than expected, corrected for small numbers. Negative adjusted residuals in a cell correspond to a smaller number of cases than expected by chance, positive residuals correspond to more cases. Adjusted standardized residuals outside the range –2.5 and +2.5 indicate significant differences between observed and expected numbers.

Discussion

Pathways to psychosis

This study explored the clinical help-seeking pathway to psychosis. Of the patients (n = 985) who had been diagnosed within the psychosis spectrum, 56.2% had received treatment in the secondary mental health services for various non-psychotic disorders prior to the onset of psychosis. The most common prodromal disorders were anxiety and mood disorders. High rates were also found for substance use disorders and adjustment disorders. The average time from first contact to transition into psychosis was 87 months. Patients with anxiety and mood disorders (69 months) developed a first-episode psychosis significantly sooner than those who sought help for personality disorders (127 months).

The various types of psychotic disorders were associated with different pathways to care. The patients who were psychotic at first contact were mostly diagnosed with schizophrenia and psychosis NOS, whereas the help-seeking group were dominated by affective psychosis. Several Axis I and II disorders precede the onset of psychosis, but patients who had been diagnosed with affective psychosis had been seeking help more often for mood and anxiety disorders, whereas patients with psychotic disorder NOS reported more premorbid substance use disorders and personality disorders. Furthermore, the analyses found gender differences. Women sought help in secondary mental health care services more often prior to the onset of psychosis than men, and women were more likely to develop affective psychosis, whereas men were more often diagnosed with schizophrenia after onset of psychosis.

The results of the present study are in line with the findings reported in previous small studies of schizophrenia patients (Addington et al., 2002; Bota et al., 2005), which found a prodromal help-seeking pathway in 40–75% of the patients with schizophrenia. They reported mainly symptoms of depression. Häfner et al. showed that eight out of ten most frequent initial symptoms were shared by the group with severe depression and the group with prodromal symptoms of schizophrenia. In patients with schizophrenia, these symptoms precede and overlap with negative symptoms (Häfner et al., 2005). Studies of high-risk patients also reported a help-seeking pathway in approximately 50% of the patients (Platz et al., 2006; Preda et al., 2002). Although we also found mood and anxiety disorders to be the most prevalent disorders in the help-seeking history (39% of the population), the results show that patients who were diagnosed with psychotic syndromes were help-seeking in the prodromal phase for all kinds of Axis I and Axis II disorders. The high rate of anxiety and mood disorders in the prodromal stage is probably due to the fact that mood and anxiety disorders are quite common in the general

population (Bijl et al., 1998). It might be that there are no distinct help-seeking pathways to psychosis; psychotic symptoms are prevalent in several Axis I and II disorders (Eaton et al., 2007) and interact with non-psychotic symptoms until they cross the threshold of frank psychosis. Schizophrenia in particular was not associated with specific prodromal disorders. So, not only mood and anxiety disorders are risk factors for developing psychosis, but psychopathology in general is a risk factor as well.

After the transition into psychosis, diagnoses fluctuate over time as well. In a sample of first-episode patients, only 30–40% meet the criteria for a disorder in the schizophrenia spectrum (McGorry et al., 2008). The other patients are diagnosed with other psychotic disorders and can be seen as having a risk for developing schizophrenia in the future as the percentage that will progress to schizophrenia will increase over time. Furthermore, patients once diagnosed with schizophrenia could be diagnosed with affective psychosis later on. This might be the result of a lack of specificity of symptoms of schizophrenia and related psychotic disorders (Eaton et al., 2007); symptoms can be seen in patients suffering from other disorders (e.g. negative symptoms versus depressive symptoms) and even in the general population (Os et al., 2000). It makes sense to examine psychotic disorders from a dimensional perspective, i.e. with psychotic symptoms on a continuum of severity, in contrast to the previous categorical or dichotomous perspective (Os et al., 2000).

The results show that many psychotic people were treated for substance use problems prior to the onset of psychosis. This is in line with findings that substance use—cannabis use in particular—is a risk factor for developing psychotic symptoms (Moore et al., 2007; Murray et al., 2007). Cannabis use contributes to a complex set of risk factors and vulnerability (Arseneault et al., 2004).

The mean time from first contact to the diagnosis of psychotic disorder was 87 months and therefore much higher than the mean time of 32 months found in the study by Bota et al., (2005). This is perhaps due to the fact that we measured time to transition into psychosis plus time to diagnosis. As mentioned, patients who were in treatment with secondary services for non-psychotic disorders in the prodromal stage had seven times longer duration of untreated psychosis after onset of psychosis than patients who were psychotic at first contact (Boonstra, Wunderink, Sytema, et al., 2008; Brunet et al., 2007; Norman et al., 2004). In addition, psychological treatments targeting non-psychotic mental disorders, but also anti-psychotic and anti-depressive medications, may have decreased the distress with sub-clinical psychotic symptoms as well. The final common pathway from prodromal stage to psychosis is characterized by catastrophizing interpretations of psychosis-like symptoms and end in highly emotional secondary delusion on such things

as the origin and purpose of voices. Cognitive behavior therapy, anti-psychotic medication or anti-depressive medication reduce emotional arousal (French, 2004). As a result, treatment in secondary mental health care may have delayed the onset of psychosis.

First-episode population

We have found a different population than populations reported in other first-episode studies (Addington et al., 2002; Bota et al., 2005). The mean age of psychotic onset in studies is mainly the result of the selected age range of the recruitment population. Research populations are restricted by age criteria (e.g. inclusion till the age of 35), ignoring the fact that—although the risk of developing psychosis decreases with age—older people can suffer from a first episode of psychosis as well. For instance, recruitment in adolescent populations found a mean onset age of 19 or 20 (Morrison et al., 2011; Yung et al., 2010). Häfner et al. found a mean age at first admission in hospital of 29 years for psychosis and even of 31 for schizophrenia in an adult population (Häfner et al., 1993). As Parnassia only provides adult care (18 years and over), the mean age is higher than the mean age in adolescent populations, but comparable to the mean age found by Häfner et al. In addition, this study used an age range of 18–35 years at intake for non-psychotic disorders, but had no restricted age criteria for the onset of psychosis. This means that late onsets are also present in the current study. Women in particular are associated with late onset of psychosis. In contrast to other studies reporting on first-episode cohorts, we included almost 50% women. This suggests that these (older) women might be overlooked in studies of young first-episode cohorts (DeLisi, 1992; Häfner et al., 1993).

We found that women were inclined to seek help prior to the onset of psychosis more often than men. This is in accordance with the findings that women tend to seek mental help more often and at an earlier stage of the illness than men (Lane & Addis, 2005). Women were more likely to be diagnosed with anxiety and mood disorders, and men with non-affective psychosis and substance use disorders at first contact. Affective symptoms, social conflict and help-seeking are more often associated with psychotic disorder in females, while negative symptoms and cognitive limitations characterize the developmental impairment in male psychotic disorder (Os et al., 2010).

Clinical implications

The results of this study could contribute to the improvement of early detection strategies. Both the low incidence of psychotic disorders and high prevalence of psychotic symptoms in the population create a compelling need to find samples with a heightened psychosis proneness in order to be able to identify people at risk for developing psycho-

sis. Most early detection services use referral by primary care givers as an enrichment strategy. However, recognizing those patients that go on to develop psychosis may be particularly challenging as the early symptoms resemble the early symptoms of depression or anxiety (Häfner et al., 2005). The results of this study show that the majority of people who developed a psychotic disorder had been help-seeking in the prodromal stage. This opens the opportunity for the implementation of a closing-in strategy in secondary mental health care services that combines several risk factors; this is required in order to filter out a sample with a high base rate of at-risk people to reduce the number of false positives (McGorry et al., 2003; Os & Delespaul, 2005). Although the current results give no information about the prevalence of cases compared with non-cases and therefore no information about the psychosis proneness of the general help-seeking population, we can safely assume that the prevalence of psychosis proneness is higher in the help-seeking population than in the general population. The estimated lifetime prevalence of mental disorders is 25% in the population at large (Vollebergh, 2003); 60% of the psychotic people who seek help in the prodromal phase are part of this small group. This is in line with the expectation of van Os & Delespaul (2005), who estimated the prevalence of schizophrenia in secondary mental health care services at 7%, compared with a prevalence of 0.6% in the general population.

Strengths and limitations

The major strength of the current study is that the sample is based on data of all consecutive cases of psychotic disorder in the catchment area within a five-year time frame. The sample has no selection bias. It is an epidemiologically representative sample with strong external validity.

Another strength of this study is that in using the psychiatric case register it has access to all the diagnostic information about the patients from the first contact with the mental health provider to date, reducing the likelihood of recall bias when data are collected retrospectively by interviewing. The diagnoses were made in accordance with the guidelines of the DSM IV.

A limitation of our study is the fact that the duration of untreated psychosis is included in the time leading up to a diagnosis of psychotic disorder. The longer mean time before psychotic disorder diagnosis could be the result of a considerably longer delay in diagnosing psychotic disorder (Brunet et al., 2007) A second limitation is that we have no knowledge about the treatment history of patients who previously had contact with child and adolescent psychiatric services. Parnassia only provides adult care (18 and over). The relatively high age of onset could be caused by failure to include some of the youngest

first contacts with a psychotic disorder. In addition, it is unknown whether patients received treatment by primary services (e.g. GPs, psychiatric nurses or psychologists). In 2001 almost 5.5% of the Dutch population was prescribed anti-depressants —in 80% of cases by their GPs (Baan et al., 2003). Being unaware of treatment by GPs and primary care services, we have some false negatives in the sample. These patients were regarded as having no history of help-seeking behavior. The number of help-seeking patients in the prodromal stage has been slightly underestimated. On the other hand, we explored whether there is a possibility of detecting high-risk patients in secondary mental health care services and we were therefore looking for evidence that the majority of psychotic people had been using these services for other mental problems preceding the first episode of psychosis.

A third limitation is that our data set did not include information on treatments. Non-psychotic patients were perhaps prescribed antipsychotic medication off-label. Although antipsychotic medication prescription to patients with sub-clinical psychotic symptoms is not recommended in clinical practice guidelines, research showed that 21% of high-risk patients used antipsychotic medication without being full-blown psychotic (Nieman et al., 2009).

Conclusion

The majority of people who have developed a psychotic disorder had been help-seeking for other mental disorders in the prodromal period. Not all those with mental problems will develop a psychosis, but a selection of people with, for example, depression and PLEs probably have an elevated risk of developing a psychosis in the near future. The findings of this study encourage the identification of patients at risk of developing a psychotic disorder in a help-seeking population in secondary mental health care.

4

Schizophrenia across the lifespan

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Abstract

BACKGROUND — The idea that schizophrenia manifests before age 40 has shaped research and clinical practice. The customary method to study incidence and age of onset (first contact sampling frame) was not designed to study onset after age 40. Here, we used a cumulative sampling frame to estimate the incidence rate (IR) and lifetime morbidity risk (LMR) and age of onset of schizophrenia.

METHOD — We estimated age- and sex-stratified incidence rates, and lifetime morbidity risk for schizophrenia over ages 20–79 years in the city of The Hague in The Netherlands during a 15-year study period. We used a register covering all psychiatric services, applied a cumulative time frame, and used clinical diagnoses.

RESULTS — The pooled incidence of schizophrenia was 47 (95% confidence interval (CI) 45 to 49) per 100 0000 person years over the age range 20–79 year. The incidence decreased from 67 (95% CI 63 to 71) in the age range 20–39 years, 45 (95% ci 42–49) in the age range 40–59 years, and 19 (95% ci 16 to 22) in the age range 60–79 years. The lifetime morbidity risk (LMR) up to age 79 was 3.7% for males and 2.3% for females. At least 5 out of 6 (84%) of schizophrenia cases were diagnosed at age ≥ 30 years, and nearly half (46%) at age ≥ 40 years.

CONCLUSION — Schizophrenia can manifest at any age and at any stage of treatment. Onset after age 30 is the norm, not the exception. Case finding should extend across the lifespan.

Introduction

Schizophrenia's age of onset has been debated for a long time. From Kraepelin's initial dementia praecox construct (Kraepelin, 1919) onwards, schizophrenia has been conceptualized as 'striking in late adolescence and early adulthood' (Harris & Jeste, 1988; Howard et al., 2000; Vahia et al., 2010)), with female onset typically delayed by 5 to 10 years compared to males. Up to 1987, DSM-III diagnostic criteria even stipulated that schizophrenia should start before the age 45 (American Psychiatric Association, 1980). Although age limits were removed in later versions of the DSM (American Psychiatric Association, 1994), research and clinical care have focused first on diagnosing and treating adolescents and young adults with psychosis. Indeed, schizophrenia can be very disabling for younger people who are at the beginning of their adult life (Castle et al., 1997; Häfner et al., 1998; Jeste et al., 1995; Ochoa et al., 2006), but this does not justify a neglect of subjects with onset at older ages. If clinical textbooks and authoritative sources (Marshall & Rathbone, 2011; National Institute of Mental Health, 2020) describe schizophrenia as typically manifesting before age 30, then psychiatrists may remain unsure how to diagnose psychosis manifesting at a later age.

Despite strong a priori assumptions, onset of schizophrenia after age 40 is common. From 2000 onwards, the categories 'late onset schizophrenia' (LOS) and 'very late onset schizophrenia-like psychosis'(VLOSLP or, more commonly, VLOS) were adopted to describe chronic psychosis first manifesting after age 40 and age 60 respectively (Howard et al., 2000). In Howard et al. (2000)'s consensus, onset before age 40 is defined as 'early onset schizophrenia (EOS). Harris & Jeste (1988) reviewed the incidence literature published from 1913 to 1986 and estimated the proportion of cases with onset of schizophrenia after the age of 40 at roughly 25%. More recently, an international first contact study in six countries of subjects aged between 18–65 at first psychosis estimated the proportion of cases with onset between ages 35–65 years at 35–50% (Jongsma et al., 2019). In England, early intervention services (EIP) have started accepting referrals aged 35–65 years since 2016. Clay et al. (2018) have reported that adults aged 35 and over represented 25.7% of all new referrals to early intervention for psychosis (EIP) services in the Cambridgeshire and Peterborough catchment areas in the UK. The Early Intervention research community is starting to focus on onset of psychosis after age 35 (Greenfield et al., 2016; Lappin et al., 2016). This raises the question: how is the onset of schizophrenia distributed over the lifespan?

Studies of schizophrenia's age of onset are hampered by the prevailing practice of first contact studies (Jongsma et al., 2019; Kirkbride, Jones, et al., 2012; van der Werf et al., 2012). In the first contact approach, there is no systematic procedure to account for

onsets of psychosis among *ongoing* patients (i.e. subjects who were already under treatment for other non-schizophrenic mental disorders at the start of the study) or, among *new* patients, onsets of psychosis at later stages of treatment for other mental disorders (Hogerzeil & Hemert, 2019; Hogerzeil & Susser, 2017).

In a previous study we compared a first contact incidence estimate directly with a more inclusive, longitudinal register based method among subjects aged 20–54 years (Hogerzeil et al., 2014). The register estimated the incidence rate at 69 per 100 000 person years [95% confidence interval (CI) 64–74] and the first contact study estimated it at 21 per 100 000 person years (95% CI 18–23). Two-thirds of the difference was accounted for by subjects treated for other disorders before the onset of psychosis (Rietdijk et al., 2011), and by patients in older age groups. As noted above, DSM criteria allow for onset after age 45 since at least 1987 (American Psychiatric Association, 1987). But first contact studies are often limited to monitoring specialized services for early detection of first-psychosis, which in practice tend to exclude onsets presenting after (roughly) age 35 years because they are not the target population for these services (Clay et al., 2018).

In the present study we used the electronic Psychiatric Case Register of The Hague to estimate the incidence rate (IR) of schizophrenia in the age range from 20 to 79 years and the lifetime morbidity risk (LMR) up to age 79 years.

Methods

Psychiatric Register

Our study was conducted in The Hague, The Netherlands, over the period from 1997 to 2012. Data on incident cases of schizophrenia were identified in the cumulative Psychiatric Register of Parnassia Psychiatric Institute (PPI). The cumulative register-based method to estimate the incidence of schizophrenia has been described in detail elsewhere (Hogerzeil et al., 2014). In short, the register is a data warehouse uploaded from the patient registration systems of PPI, which is a merger organization of virtually all providers in the city of The Hague and a few providers in surrounding areas. The register includes virtually all inpatient-, outpatient-, day- and psychiatric residential care, emergency services, and collaborative services with municipal police stations and a large number of general practitioners. We estimate that more than 95% of citizens of the The Hague with non-affective psychosis during the study period were treated at PPI and were listed in the register. The register contains information on date of birth, successive home addresses (zip codes), DSM-IV diagnoses and all service contacts for each patient

treated at PPI from 1997 onwards. Historical (but less complete) records are searchable back to 1980 to identify patients treated before 1997. Register diagnoses were recorded at intake and were audited on a regular basis at case conferences, upon internal referrals, and when treatment was completed. They were classified according to the DSM-IV under supervision of either a psychiatrist or a clinical psychologist.

Case ascertainment

To identify incident cases, we examined diagnostic and zip code histories of all subjects who had had any service contact with PPI during 1980–2012. We defined onset of schizophrenia (numerator) as subjects who received a register diagnosis of schizophrenia (DSM-IV 295.x) for the first time, at any stage of treatment, whatever the prior diagnosis, during the 15-year study period from 1997–2012, who resided in the city of The Hague and were aged 20–79 years at the time of the index diagnosis.

We excluded subjects first diagnosed with dementia and later with schizophrenia, but included subjects first diagnosed with schizophrenia and later with dementia (if this occurred years later). To further reduce the odds of confusing psychotic disorder due to a medical condition and schizophrenia, we excluded onsets ≥ 80 years entirely. As a result, in this study the VLOS category (normally defined as onsets aged 60–100+ years) is restricted to 60–79 years.

For an accurate count, new onsets should not be confused with known cases returning to psychiatric services after an interruption. That is easy if the date of the index diagnosis is known for every case. But for our study this required data going back to 1918, to cover the period at risk between ages 20–79 years for any subject diagnosed with schizophrenia during the 1997–2012 study period.

The data in the register go back to 1980 and our study ended in 2012. This meant that we could distinguish new cases from returning patients only for subjects born from 1960 onwards. For that subset we could calculate the incidence up to age 52 years—after which they would be censored.

We chose a two-pronged approach: (1) to estimate the incidence for ages 20–49 years we restricted our data to subjects born after 1960; and (2) to estimate the incidence for ages 50–79 years, we first quantified the bias caused by incomplete follow-up by collecting additional information for a random sample of cases, and then used that information to apply a correction to our crude results.

To quantify the bias caused by incomplete follow-up, we inspected the digital case notes of a random sample of cases listed in the register. We used only cases with at least one follow-up diagnostic record after 2010 (subjects lost to follow-up before that date typically had no digital case notes), and took a 30% sample of those. For each sampled case, a resident psychiatrist (under supervision of an old age psychiatrist) used the case notes to reconstruct the history of mental health treatment and diagnoses, both inside and outside the catchment area, between date of birth and september 2016. When discrepancies with the register-based classification were found, subjects were either reclassified to another age category (e.g. in cases of administrative delay) or excluded from the study (e.g. prevalent cases migrating into the area, returning to services after many years, or cases of dementia misdiagnosed as schizophrenia). We used the percentage of cases reclassified in the random sample to adjust our estimate of the number of cases, for each 10-year age band between 50–79 years of age and for males and females separately.

Incidence rates

We calculated the incidence rate (IR) per 100 000 person years by sex and age-category. We used the detailed municipal data available in The Hague to calculate the number of person years (denominator of the IR). Annual census data were available for the population of The Hague aged 20–79 years over the 15-year study period (n = 346 328 in 1997, increasing to n=387 443 in 2012); the total observation time in the study was 4 071 893 person years.

Lifetime morbidity risk

We calculated the lifetime morbidity risk (LMR) for schizophrenia as the cumulative sum of year by year age- and sex-specific incidence rates using the adjusted numbers from age ≥ 20 years, expressed as a percentage of the population (Jablensky et al., 1992; Saha et al., 2005).

We incorporated an offset into our LMR calculation to account for first onsets of schizophrenia occurring between 0–19 years of age, because that interval is not included in our data set. The offset (0.4% for males, 0.3% for female) was chosen as the cumulative incidence of schizophrenia between 0–19 years reported by Pedersen et al. (2014), a register based study with the same design as our study (general psychiatric services, cumulative time frame, clinical diagnoses) in arguably a very similar country (Denmark), albeit in a mixed urban and rural population as compared to our fully urban study population.

Ethical considerations

Under the Dutch 'Medical Research Involving Human Subjects' Act (WMO), analysis of register data does not require approval from a medical ethics committee.

Results

In 1997–2012, the register listed 3169 incident cases of schizophrenia in the age range 20–79 years. Of these, we audited 244 cases aged 40–79 years. Of these, 84 (34%) were known cases migrating into the study area or returning to mental health care. Of these false-positive cases, more than half had been diagnosed with schizophrenia more than 20 years before the index date recorded in the register (interquartile rate 14 to 27 years, maximum 55 years). The remaining 157 (64%) were confirmed as incident cases of schizophrenia.

The adjustments applied the numbers listed in the register for each age and sex category are described in Supplement 1. The net effect of the adjustments was a 20% (167/819) reduction in the total number of cases aged 50–79 years, resulting in an estimation that 2754 citizens aged 20–79 years were first diagnosed with schizophrenia in the period 1997–2012.

The incidence of schizophrenia by age and gender is listed in Table 4.1 and graphically presented in Figure 4.1. The male IR peaked at 113 (95% confidence interval 99 to 128) per 100 0000 person years at ages 20–29 and decreased linearly to 21 (15 to 29) at ages 70–79 years. The female IR peaked at 43 (37 to 48) per 100 0000 person years at age 30–39 years, with a plateau of 40 (36 to 45) between ages 40–59 years, and decreasing thereafter to 22 (17 to 28) at ages 70–79 years. Around 50–59 years of age the female incidence overtook male incidence.

Table 4.1 Schizophrenia incidence rates by sex and age of onset

Age of onset	Person years	*n*	IR	95% CI
Men				
EOS	789 943	738	93	(87 to 100)
20–29	206 439	233	113	(99 to 128)
30–39	583 504	505	87	(79 to 94)
LOS	760 952	385	51	(46 to 56)
40–49	325 740	207	64	(55 to 73)
50–59	435 212	178	41	(35 to 47)
VLOS	468 638	69	15	(12 to 19)
60–69	287 633	31	11	(7 to 15)
70–79	181 005	38	21	(15 to 29)
Total	2 019 533	1192	59	(56 to 62)
Women				
EOS	747 811	295	39	(35 to 44)
20–29	208 046	65	31	(24 to 40)
30–39	539 765	230	43	(37 to 48)
LOS	723 815	290	40	(36 to 45)
40–49	298 924	114	38	(31 to 46)
50–59	424 891	176	42	(36 to 48)
VLOS	580 736	130	22	(19 to 27)
60–69	310 550	71	23	(18 to 29)
70–79	270 186	59	22	(17 to 28)
Total	2 052 362	715	35	(32 to 37)
Persons				
EOS	1 537 754	1033	67	(63 to 71)
20–29	414 485	298	72	(64 to 81)
30–39	1 123 269	735	65	(61 to 70)
LOS	1 484 767	675	45	(42 to 49)
40–49	624 664	321	51	(46 to 57)
50–59	860 103	354	41	(37 to 46)
VLOS	1 049 372	199	19	(16 to 22)
60–69	598 182	102	17	(14 to 21)
70–79	451 190	97	21	(17 to 26)
Total	4 071 893	1907	47	(45 to 49)

Source *Psychiatric Register of The Hague (1997–2012)*
EOS Early Onset Schizophrenia
LOS Late Onset Schizophrenia
VLOS Very Late Onset Schizophrenia-like Psychosis
IR incidence rate per 100 0000 person years
CI confidence interval

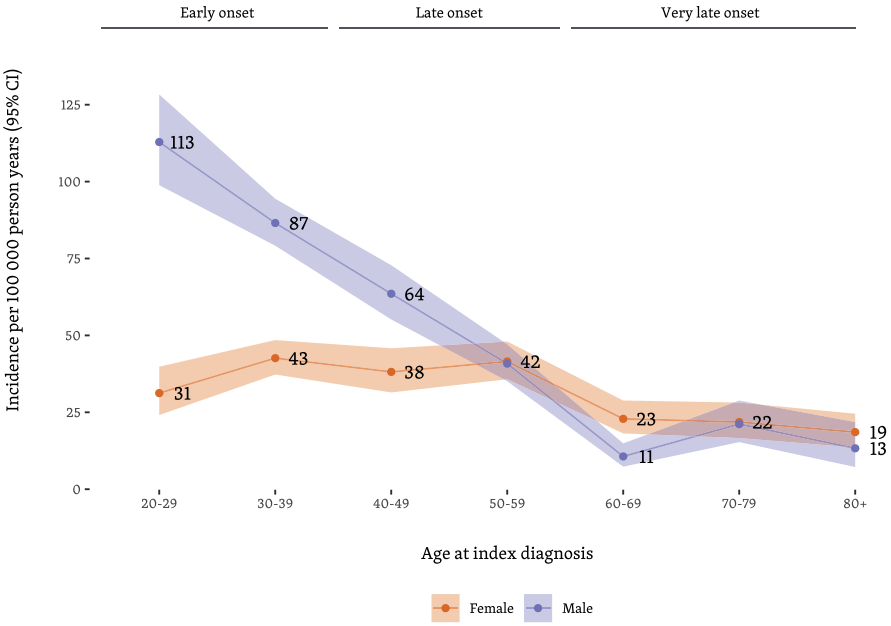

Figure 4.1 Schizophrenia IR by gender and age of onset in 10-year categories from 20–79 years

Source: Psychiatric Register of The Hague (1997–2012); CI: 95% confidence interval

The incidence of schizophrenia for ages 20–79 years was 47 per 100 000 person years (95% confidence interval 45 to 49). It was 67 (63 to 71) for EOS, 45 (42 to 49) for LOS, and 19 (16 to 22) for VLOS (Table 4.1).

Of onsets between 20–79 years, 84.4% (1609/1907) were diagnosed ≥ age 30 and 45.8 % (874/1907) ≥ age 40 years. This distribution was more extreme for females (90.2% ≥ 30 years and 55.7% ≥ 40 years) than for males (80.4% ≥ 30 years and 38.1% ≥ 40 years).

The lifetime morbidity risk (LMR) is shown in Figure 4.2. For males up to 79 years, the LMR over the life course showed an initially steep slope flattening over time. For females, the line was linear, increasing at a nearly constant rate. The lifetime morbidity rate up to age 79 years was 3.7% for males and 2.3 % for females. Our study did not examine onsets ≥ 80 years, but the steady accumulation of case showed no sign of stopping for either sex.

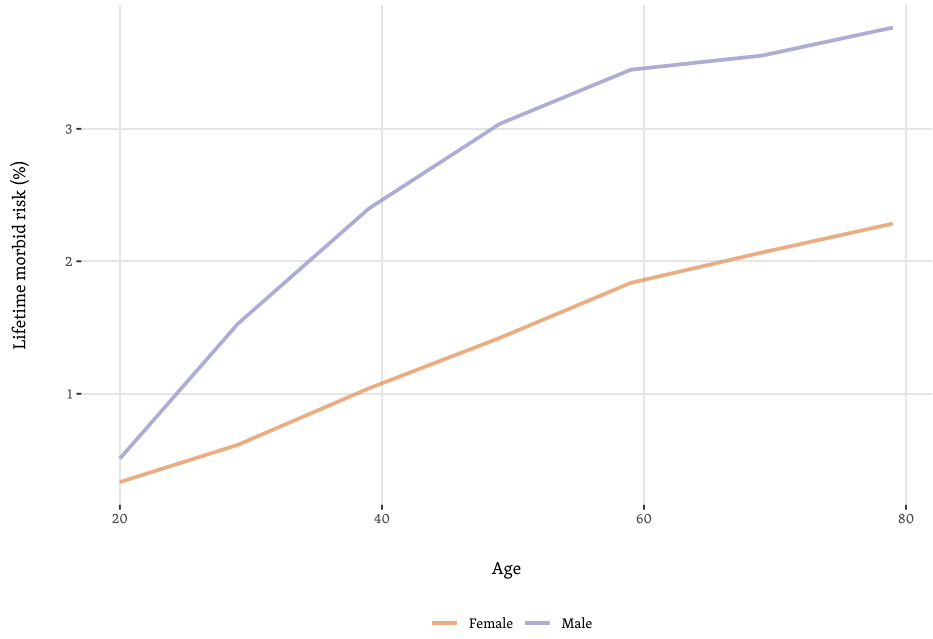

Figure 4.2 Lifetime morbidity risk (LMR) of schizophrenia
Source: Psychiatric Register of The Hague (1997–2012). LMR: lifetime morbidity risk of schizophrenia, calculated as the cumulative sum of year by year age and sex specific incidence rates per 100 0000 person years from age ≥ 20 years, expressed as a percentage. We applied an offset (0.4% for males, 0.3% for females) to account for the LMR up to age 19 years.

Discussion

We used a cumulative psychiatric case register to estimate the age and sex-specific incidence rates and cumulative incidence of schizophrenia over the lifespan, in a large city in The Netherlands. We estimated that 2754 citizens aged 20–79 years were first diagnosed with schizophrenia in the period 1997–2012. The incidence rate decreased from 73 for EOS, to 43 for LOS, and to 19 per 100 0000 person years for VLOS. At least 5 out of 6 (84.4%) of schizophrenia cases were diagnosed ≥ age 30 years, and nearly half (45.8%) ≥ age 40 years. The lifetime morbidity rate up to age 79 years was 3.7% for males and 2.3% for females.

Here, we compare our register based estimates with (a) the standard first contact approach, and with (b) another study using the same, cumulative register, approach as we did.

Van der Werf et al. (2012) reviewed all studies published 1950–2009 reporting the incidence of schizophrenia, and included mainly studies applying a first contact sampling

frame. In their study, the median incidence rate was 24.7 (interquartile range 15.4 to 36.1) per 100 0000 person years for EOS, 12.2 (7.0 to 21.7) for LOS and 5.9 (3.0 to 12.7) for VLOS. Their first contact based estimates are roughly three to four times lower than our register-based estimates (67, 45 and 19 per 100 0000 person years respectively). This is consistent with recent reports that studies applying a first contact sampling frame underestimate the IR of schizophrenia by a factor of 3 or more, because they cannot account for subjects who first seek psychiatric care for another mental disorder or subjects presenting to services after age 40 (Hogerzeil et al., 2014; Hogerzeil et al., 2021).

Pedersen et al. (2014) used a national psychiatric register with a cumulative time frame to estimate the incidence of schizophrenia in the entire population of Denmark. They did not provide exact numbers by age, but data extracted from a figure using the online tool 'WebPlotDigitizer' (Rohatgi, 2019) provide a rough approximation: they estimated the incidence of schizophrenia at roughly 50 per 100 0000 person years for EOS, 15 for LOS and 10 for VLOS. These estimates use the same approach as we did, but in a mixed urban and rural population, are roughly 1.5 to 3 times lower than our estimates in an urban population. This is consistent with multiple reports that the schizophrenia incidence estimates are roughly 1.6 to 2.4 times higher in urban populations than in mixed or rural populations (Castillejos et al., 2018; Hogerzeil et al., 2021; Vassos et al., 2016, 2012).

Likewise, our estimate of the LMR (3.7% for males and 2.3% for females) is three to five times higher than the median estimate of 0.7% (interquartile range 0.3 to 2.7%) reported in a worldwide meta-analysis of schizophrenia prevalence studies by Saha et al. (2005). That meta-analysis included mostly population surveys (which severely underestimate the LMR). A cumulative register-based estimate from Denmark (Pedersen et al., 2014) estimated the LMR at 2.2% for males and 1.9% for females in a mixed urban and rural population. That difference can again be explained by the fact that our estimate is exclusively urban.

So, the difference between our findings and those in two other studies turn on two points: differences in study design (first contact vs cumulative time frame), and differences in study population (mixed urban and rural vs. strictly urban). Our findings also agree with the results of a systematic review of Northern European studies 2008–2019, in which we explored the impact of study design on schizophrenia incidence estimates (Hogerzeil et al., 2021). The relevant factor here is study design: in practice, the first contact approach does not adequately capture the large number of onsets occurring after roughly age 40 years.

Strengths of this study include: (a) a large (over 500 000) urban, multi-ethnic study population in Northern Europe; (b) a case register based on >30 years of electronic health administrative records, (c) covering all general, specialized (tertiary, emergency or outreaching) psychiatric services in the catchment area over (d) a long time frame from which service pathways and diagnostic histories can be reconstructed, and onsets of schizophrenia diagnosed at any stage of treatment anywhere in the mental health system can be detected; and (e) carefully audited (Hogerzeil et al., 2014) clinical schizophrenia diagnoses, widely considered to be reliable, (Fusar-Poli et al., 2016; Uggerby et al., 2013) and possibly more conservative than standardized research diagnoses (Hogerzeil et al., 2021).

Our study has several limitations.

There are three sources of false positive cases: (a) misdiagnosis, and known cases incorrectly counted as new cases when presenting to psychiatric services, either after (b) migrating into the catchment area, or (c) when returning after an interruption.

About (a) misdiagnosis, extensive sensitivity analyses performed in a prior study demonstrated that the clinical diagnoses of schizophrenia in our register are valid (Hogerzeil et al., 2014).

About (b) migration of known cases into the catchment area, we previously estimated by cross-matching with municipal data that less than 5% of citizens diagnosed with schizophrenia aged between 20–54 years had migrated into the catchment area during our study period. For citizens aged 55–79 years the number is probably lower.

About (c) returning patients, two points:.

Firstly, because the register did not include diagnoses made in psychiatric services for the youth (which stop around age 20), it is likely that many cases diagnosed before age 20 (which should have been excluded) were incorrectly counted as new when they presented to adult psychiatric services. This must have inflated our estimates, especially in the 20–29 years age bracket. Data from a cumulative register based study by Pedersen et al. (2014) provide an upper limit for the extent of this problem. In that study, 25% of the number of males diagnosed with schizophrenia before age 29 had been diagnosed before age 20 (i.e. LMR by age 29 divided by LMR by age 20). For females this number was 34%. This suggests that if all known cases diagnosed with schizophrenia before age 20 presented to adult psychiatric services between ages 20–29 years and were incorrectly

included as incident cases, they may account for 25% and 34% of the age 20–29 incidence estimate for males and females, respectively.

Secondly, although follow-up was complete for the younger group (ages 20–49 years), it was incomplete for subjects born before 1960 (i.e. the 50–79 years age bracket). Our case-note based audit in the older group uncovered large numbers of subjects returning into psychiatric treatment after interruptions of several decades. We corrected aggressively for this bias, but this may not have been enough.

As noted in the introduction, the focus of clinical care and research is currently expanding to include the over 35 year olds with first onset psychosis (Clay et al., 2018; Greenfield et al., 2016; Lappin et al., 2016). Our register-based approach is more inclusive than the standard FC-approach and offers further evidence that late and very late onsets are not an exception, but the norm.

To date, the WHO's calculations of the burden of disease attributed to schizophrenia (Charlson et al., 2018) have used first contact based IR estimates and population survey based LMR estimates as input (Ayuso-Mateos, 2002). Our findings provide further evidence that these numbers are far too low. If more inclusive estimates (such as those provided by cumulative registers, which are roughly three times higher than those used currently) were used as input instead, schizophrenia's rank in the list of most burdensome disorders would shift substantially.

Conclusion

Schizophrenia can manifest at any age and at any stage of treatment. Onset after age 30 is the norm, not the exception. Case finding should extend across the lifespan.

5

Incidence of schizophrenia among migrants

Published as:

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Abstract

BACKGROUND — To estimate the effect of selective sampling on First Contact (FC) studies of the relation between migration and schizophrenia.

METHOD — We compared the FC method directly with a more inclusive electronic Psychiatric Case Register (ePCR) method, by letting both methods estimate age and sex adjusted incidence rate ratios (IRR) in the population of The Hague aged 20–54 years, for the three largest migrant groups (first and second generation Caribbean, Turkish, and Moroccan) relative to the native Dutch population.

RESULTS — Both methods found that the adjusted IRR was higher for migrants than for native Dutch [all migrants IRR = 1.70 (95% CI 1.30–2.21) for the ePCR method and 1.91 (95% CI 1.15–3.25) for the FC]. The IRR for Moroccans was significantly lower in the ePCR [IRR 2.69 (95% 2.10–3.41)] than in the FC study [4.81 (3.41–6.68)]. The FC method was relatively more inclusive for migrants presenting at earlier ages, or with shorter durations of prior treatment (DPT) than the native Dutch. This resulted in differential sampling and artificially higher IRRs for Moroccan and, to a lesser extent, Turkish migrants.

CONCLUSION — We confirm that the incidence of schizophrenia is raised twofold for migrants compared to nonmigrants. Using the ePCR method, however, IRR estimates were less pronounced for most migrant groups than in a high quality FC study conducted in the same population. The FC method may overestimate the risk of schizophrenia for migrant groups who seek first mental health at a relatively younger age, or who present directly with schizophrenia.

Introduction

Background

Researchers have traditionally used the First Contact (FC) method (Hogerzeil et al., 2014) to examine the relation between migration and first episodes of schizophrenia (FES) or first episodes of psychosis (FEP); they used either the WHO's original FC design (Jablensky et al., 1992), later variants that allowed for prior contacts with mental health services (Fearon et al., 2006; Kirkbride, Errazuriz, et al., 2012; Veling et al., 2007), or psychiatric registers restricted fully (Weiser et al., 2007) or mainly (Cantor-Graae et al., 2003; Cantor-Graae & Pedersen, 2007) to first admissions.

A worldwide meta-analysis of studies using the FC method and published between 1977 and 2008 estimated the overall incidence rate ratio (IRR) of schizophrenia at 2.1 (95% 1.8–2.4) for first generation migrants and at 2.4 (95% 2.0–2.9) for second generation migrants, compared to nonmigrants (Bourque et al., 2010). Very high IRRs were reported in the UK for Black Caribbean [first generation IRR 3.9 (3.4–4.6); second generation 5.8 (3.5–2.4)] and Black Africans [first generation IRR 4.3 (2.8–6.8); second generation 3.7 (2.2–6.3)], and in the Netherlands for Moroccans [first generation IRR 4.0 (2.5–6.3); second generation 5.8 (2.9–11.4)] (Veling et al., 2006).

We have reported before that the FC method can seriously underestimate the incidence of schizophrenia. Using an electronic Psychiatric Case Register (ePCR) to estimate the incidence of schizophrenia, we found that up to two thirds of incident cases had not been included in a FC study conducted in the same population and time frame (Hogerzeil et al., 2014). Subjects had been missed in the FC study because they were no longer prototypical 'first contact' by the time they met criteria for schizophrenia, and at that point were not actively monitored within the FC design anymore (e.g. two thirds had been treated for more than five years before the onset of psychosis, or were aged 40 or older at the time of diagnosis).

Objective

If the FC method misses two thirds of the schizophrenia onsets, it is logical to ask whether prior findings in FC samples are true for all onsets of schizophrenia, or only true for the subset detected by the FC method.

For example, selective sampling could distort FC studies if one population has systematically shorter or longer pathways to the index diagnosis than the other.

In the present study we compared the FC and ePCR methods directly in the same study population over the same period *to estimate the effect of selective sampling on First Contact (FC) studies of the relation between migration and schizophrenia*.

We restricted our study to schizophrenia to allow for a direct comparison with a FC study (Veling et al., 2007), which reported schizophrenia IRs, and as a logical next step from an earlier incidence study by our group (Hogerzeil et al., 2014), which used exactly the same population and comparison.

Methods

Case finding with the ePCR method

The ePCR method to estimate the incidence of schizophrenia has been described elsewhere (Hogerzeil et al., 2014). In short, the ePCR of The Hague is a data warehouse uploaded from the patient registration systems of the Parnassia Psychiatric Institute. It includes virtually all inpatient-, outpatient-, day- and psychiatric residential care, emergency services, and collaborative services for all municipal police stations and a large number of general practitioners. Almost all subjects with psychotic disorders in the city of The Hague are treated at Parnassia and are listed in the ePCR. The ePCR contains information on date of birth, countries of birth of patients and their parents, successive postal codes, DSM-IV diagnoses and all service contacts for each patient treated at Parnassia from 1997 onwards. Historical (but less complete) records are searchable back to 1980 to identify patients treated before 1997. Diagnoses are recorded at intake and are audited on a regular basis at case conferences, upon internal referrals and when treatment is completed. They are classified according to the DSM-IV under supervision of either a psychiatrist or clinical psychologist.

To calculate the IR and IRR with the ePCR, we examined diagnostic histories of all subjects with any service contact with Parnassia in 1980–2009 (n = 249 409). We defined the onset of schizophrenia (numerator) as subjects who received a first ePCR diagnosis of schizophrenia (DSM-IV 295.x) during the five-year study period 2000–2005, and who resided in The Hague and were aged 20–54 (the age range covered by both methods) at the time of the index diagnosis.

Case finding with the FC method

The FC method has been described elsewhere (Hogerzeil et al., 2014; Veling et al., 2007). We used individual level data from a first contact study previously conducted in the same catchment area to calculate incidence rates (IR) and ratios (IRR). The original study used a FC sampling frame to estimate the incidence of all psychoses, excluding psychoses related to somatic disorders or substance abuse. Patients with schizophreniform or schizoaffective disorder were merged into the schizophrenia category. In the original study, 364 residents of the catchment area had been identified with a first psychosis in the age bracket 20–54 during the five-year period 2000–2005. For the comparison in our study, we used only the subset of 254 subjects diagnosed with schizophrenia (i.e. DSM-IV codes 295.x).

Calculation of the incidence rates and ratios

The same denominators and the same formula of IR and IRR were used for the FC estimate and the ePCR estimates.

We used detailed data from the municipality to calculate the number of person years (denominator of the incidence rate). Annual registration data were available for the population of The Hague aged 20–54 years over the five year study period (n = 233 803 in 2000, increasing to n = 250 671 in 2005); the total number of person years of observation in the study was 1 221 486.

We used the classification of ethnicity of The Netherlands' Bureau of Statistics, i.e. Dutch ethnicity is assigned to citizens who are Dutch-born and whose parents were also born in The Netherlands (hereafter referred to as Dutch). If a citizen, or (one of) his or her parents, was born abroad, he or she is assigned to the group of people born in that country. If the parents were born in different foreign countries, the country of birth of the mother determines the assignment to a particular group. In the Netherlands foreign countries of birth are condensed into six categories: (1) Morocco, (2) Surinam, (3) Netherlands Antiles, (4) Turkey, (5) Western or westernized countries (northern, southern or western Europe, the former Yugoslavia, the USA, Canada, Australia, New Zealand, Japan or former Netherlands East Indies) and (6) all other (non-western) countries. For this study we merged categories (2) and (3) into the group 'Caribbean' and categories (5) and (6) into the group 'Other'. Information about first versus second generation status and socioeconomic status (e.g. income level, employment, or level of education) was not reliably available in the ePCR data, and was therefore not included in the analysis. We defined the IR for schizophrenia as the number of treated incident cases per 100 000

person years in the study population. We calculated unadjusted IRs and IRRs for each method, and for the three migrant groups relative to the native Dutch. We adjusted the estimates for age and sex by applying the same Poisson regression model to both data sets.

Comparison of treatment pathways of onsets identified by each method, for each migrant group separately

We compared treatment pathways of onsets identified by each method, for each migrant subpopulation separately. To compare both methods accurately, we excluded onsets listed in the FC who were never listed in the ePCR, and corrected for spurious effects from delays in registration. Among citizens aged 15–54, the ePCR found 843 onsets of schizophrenia. The FC study found 254 onsets; the subset used for the comparison consisted of 213 subjects 'identified by both methods' and 665 additional subjects 'identified only by the ePCR during the study period'; for a detailed account, see the results section in Hogerzeil et al. (2014).

We defined the duration of prior treatment (DPT) as the interval between first contact with mental health services for any mental disorder and the index diagnosis of schizophrenia, in years.

Sensitivity analyses

We reported previously that inmigration of identified patients and problems with validity of the clinical diagnoses used in the ePCR were likely to be small (Hogerzeil et al., 2014). Briefly, 95% of ePCR cases had resided in the catchment area for six months or longer before being diagnosed with schizophrenia, with a median duration of residence of at least 6.7 years (IQR 2.2–21.7). More than 90% of incident diagnoses listed in the ePCR had been audited and confirmed by schizophrenia specialists, or were in fact research diagnoses. Index diagnoses were audited yearly (IQR 0.7–1.2 years), and the 5-year diagnostic stability was 90% or higher.

For this study, we performed additional sensitivity analyses for each migrant group separately to examine differentials in inmigration or diagnostic validity between the subpopulations.

Statistical analyses

All statistical analyses were conducted in R version 3.2.4 with the packages 'epitools', 'qcc' and 'ggplot2'. Confidence limits for the IR and IRR were based on the Poisson distribution,

using a mid-P exact test (Rothman et al., 2008). We used Fisher's exact test for count data to compare proportions. We modelled the incidence rates of schizophrenia with a generalized linear model using a log link and a quasi-poisson family (i.e. estimating the dispersion parameter from the data to adjust for over-dispersion).

Results

Comparison of the two methods' estimates of incidence rates and -ratios

Table 6.1 shows adjusted and unadjusted IR and IRR of schizophrenia for each migrant group, for the ePCR and FC methods separately. The unadjusted IRR for all migrants relative to the native Dutch was 2.10 (1.63–2.73) in the FC study and 1.69 (1.47–1.94) in the ePCR. With the exception of the Caribbean group, all IRR estimates for migrants groups were lower in the ePCR than in the FC. This difference was statistically significant for Moroccans only, with an age and sex adjusted IRR estimate of 4.81 (95% 3.41–6.68) in the FC study compared to 2.69 (95% CI 2.10–3.41) in the ePCR.

When compared with the FC method, the ePCR added relatively more cases to the native Dutch category (346 cases in the ePCR vs. 91 cases in the FC; 280% more) and relatively fewer cases to the Moroccan category (77 vs 46; 67% more). The resulting larger size of the native Dutch reference category in the ePCR estimates reduced the age and sex adjusted IRR slightly for migrants in general (from 2.1 in the FC to 1.9 in the ePCR). As the Moroccan group increased much less than the Dutch using the ePCR method, their IRR decreased significantly (from 4.81 to 2.69). A similar but less pronounced shift was found for Turkish migrants.

Table 6.1 Schizophrenia incidence rates and incidence rate ratios for migrants relative to the native Dutch, for two methods

		Complete data (ePCR of The Hague)				First contact sample (Veling et al., 2007)			
	person years	n	IR (95% CI)	unadj. IRR (95% CI)	adj. IRR (95% CI)	n	IR (95% CI)	unadj. IRR (95% CI)	adj. IRR (95% CI)
All	1 221 486	843	69 (64 to 74)			254	21 (18 to 24)		
Native Dutch	659 589	346	52 (47 to 58)			91	14 (11 to 17)		
Migrants	561 897	497	88 (81 to 97)	1.69 (1.47 to 1.94)	1.70 (1.30 to 2.21)	163	29 (25 to 34)	2.1 (1.63 to 2.73)	1.91 (1.15 to 3.25)
Caribbean	159 426	180	113 (97 to 131)	2.15 (1.79 to 2.57)	2.18 (1.83 to 2.6)	40	25 (18 to 34)	1.82 (1.24 to 2.62)	1.70 (1.19 to 2.4)
Turkish	77 198	57	74 (56 to 96)	1.41 (1.06 to 1.85)	1.40 (1.06 to 1.83)	26	34 (22 to 49)	2.45 (1.55 to 3.74)	1.94 (1.26 to 2.88)
Moroccan	54 430	77	141 (112 to 177)	2.70 (2.10 to 3.44)	2.69 (2.1 to 3.41)	46	85 (62 to 113)	6.14 (4.27 to 8.7)	4.81 (3.41 to 6.68)
Other	270 843	183	68 (58 to 78)	1.29 (1.07 to 1.54)	1.30 (1.09 to 1.54)	51	19 (14 to 25)	1.37 (0.96 to 1.92)	1.32 (0.95 to 1.82)

'ePCR' electronic Psychiatric Case Register of The Hague, 'PY' person years, 'IR' incidence rate per 100 000 person-years, 'IRR' incidence rate ratio, relative to the native Dutch, 'CI' confidence interval, all either 'unadj' unadjusted or 'adj' adjusted for age and sex

Comparison of the treatment pathways of onsets included by the two methods

Age at first contact and duration of prior treatment are shown in Figure 5.1, stratified by migrant group, and by method (cases identified by both methods versus additional cases identified by the ePCR). Sociodemographic characteristics and pathway characteristics are given in Supplement 2.

Subjects identified by both methods (n = 213) were aged 30 or less at first contact (median 26.2 years; interquartile rate (IQR) 25.3–27.0 years for all subjects), and had been treated for less than five years before the index diagnosis of schizophrenia (DPT = median 2.3 years; IQR 1.9–2.7). In this subset, all migrant subgroups had similar ages at first contact, and duration of treatment.

Among 665 additional cases identified by the ePCR the majority had a relatively late onset. Most were aged 30 or older at first contact (median 32.1 years; IQR 31.4–32.8 for all subjects), and had been treated for more than five years before the index diagnosis of schizophrenia (DPT = median 5.7 years; IQR 5.3–6.1). They were mainly Caribbean and native Dutch diagnosed at relatively older ages, and native Dutch with relatively longer durations of prior treatment.

Sensitivity analysis

Sensitivity analyses indicated that for the Caribbean, Turkish and Moroccan cases, measures of potential inmigration, diagnostic stability and diagnostic validity in the ePCR were equivalent to those of the native Dutch (Supplement 3). Nonparametric tests indicated that clinicians were not slower to diagnose psychotic symptoms as schizophrenia (e.g. indefinitely diagnosing 'psychosis NOS') with native Dutch than with migrant subpopulations (i.e. no migrant differentials in the interval between initial diagnosis of psychosis (any type other than schizophrenia) and ultimate diagnosis of schizophrenia: Kruskal–Wallis v2 = 6.8164, df = 4, p = 0.1459).

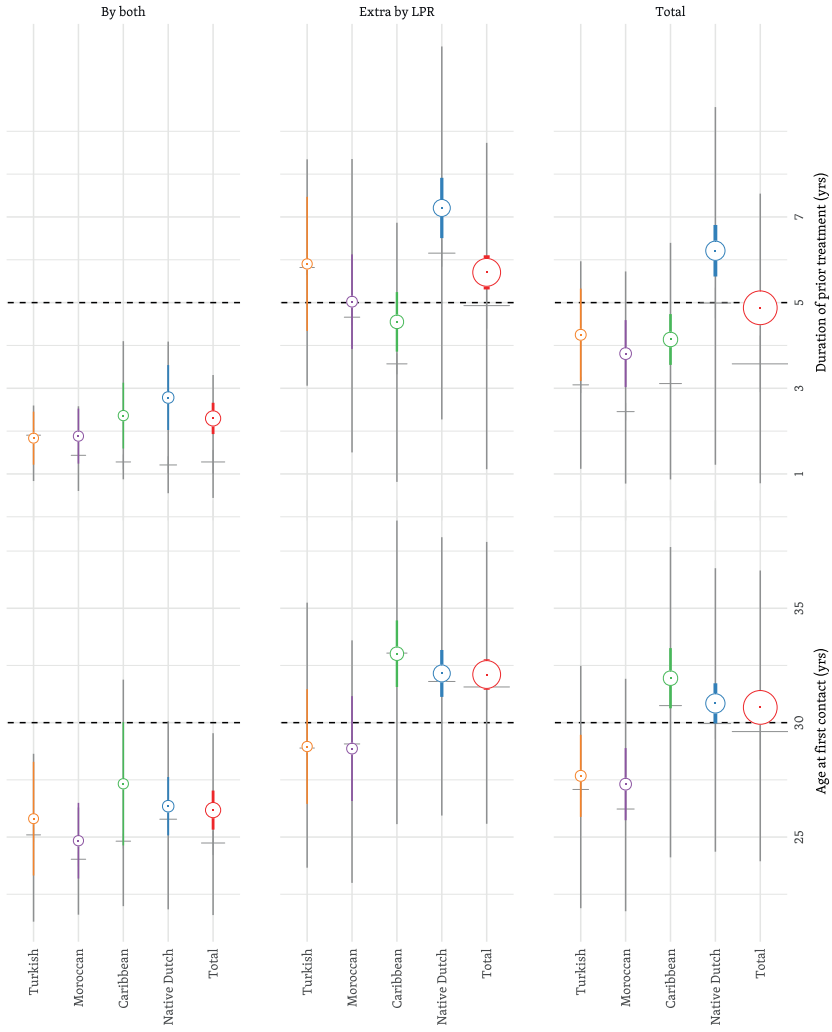

Figure 5.1 Migrant differentials in pathways to index diagnosis

Grey horizontal bars represent the interquartile rate, the gray crosshair represents the median; colored horizontal bars represent the 95% confidence interval of the mean, colored bullets represent the mean; the size of the colored bullets and the thickness of the colored bars is proportional to the number of cases

Discussion

Both the FC and the ePCR methods found that the age and sex adjusted IRR is significantly higher for all migrant groups compared to the native Dutch [for all migrants IRR 1.70 (95% CI 1.30–2.21) for the ePCR method and 1.91 (95% CI 1.15–3.25) for the FC].

The IRR for Moroccans was significantly lower in the ePCR [IRR 2.69 (95% 2.10–3.41)] than in the FC study [4.81 (3.41–6.68)]. The IRR estimates in the ePCR were also lower for the Turkish and higher for the Caribbean than in the FC study, but these shifts were not statistically significant.

Interpretation

In one population, the FC identified 254 onsets schizophrenia, and the ePCR 843 onsets. The onsets identified only by the ePCR had a different mix of migrants than the onsets identified by both methods. The ePCR method identified a relatively large number of native Dutch and Turkish onsets with a long DPT, and Caribbeans engaging with mental health services at older ages. The FC method identified mostly migrants with earlier onsets (presenting at earlier ages and with shorter DPT than the native Dutch), which in practice resulted in overinclusion of Moroccans and, to a lesser extent, Turkish migrants.

The evidence on the relation between migration and the incidence of schizophrenia is nearly exclusively based on the FC sampling frame (Hogerzeil et al., 2014; van der Werf et al., 2012). Danish register studies (Cantor-Graae et al., 2003; Cantor-Graae & Pedersen, 2007) have used the ePCR method, but in their region had no corresponding FC estimates available for direct comparison. Indirect comparisons of their findings with FC data in other countries (Coid et al., 2008; Veling et al., 2006) are complicated by methodological differences (e.g. other clinical populations, other migrant groupings).

The evidence on migrant differentials in pathways to diagnosis is difficult to interpret because the social, cultural and health service context varies widely between countries (Anderson et al., 2014), and because there is no standardized definition of pathways to- and through mental health services. Prior studies have used overlapping concepts such as 'access to mental health services' (Bermejo et al., 2012; Fassaert et al., 2009), 'duration of untreated psychosis' (DUP) (Anderson et al., 2013), 'negative pathways' (Morgan et al., 2004) and (in our study) 'age at first contact with mental health services' or 'duration of prior treatment'.

There is some evidence on migrant differentials in pathways through mental health services. Studies from the UK have reported that people from African descent with a first episode of psychosis (FEP) are more likely than other migrant groups to come into contact with mental health services through negative and adversarial routes (Anderson et al., 2014; Mann et al., 2014). Similar findings were later reported for Moroccans and Caribbean in Rotterdam (Mulder et al., 2006) and Amsterdam (Wit et al., 2010).

Migrant differentials in pathways through services (sometimes resulting in overinclusion in FC samples) may help explain why FC studies report that certain migrant groups have a very high risk of schizophrenia (Anderson et al., 2014; Ghali et al., 2013; Mann et al., 2014; Morgan et al., 2005). This might be the case for Moroccans in the Netherlands (Veling et al., 2007) and Black Africans and Black Caribbean in the UK (Kirkbride, Errazuriz, et al., 2012), because these groups are also known to have more negative (and in our study, shorter/earlier) pathways through services, compared to migrants with a lower risk of schizophrenia, and compared to non migrants.

Various mechanisms may explain how migration is related both to a higher risk of schizophrenia and to earlier or shorter pathways through services. Higher levels of stress (Walker & Diforio, 1997; Zubin & Spring, 1977), related to factors such as social defeat (Selten et al., 2013), discrimination (Veling, 2013; Veling et al., 2007) or ethnic density (Veling et al., 2008) may not only increase the lifetime risk of schizophrenia, but also lead to earlier onsets and negative pathways. Such 'precipitated onsets' could be mediated by social processes related to culture, stigmatization, or (lack of) social support (Morgan et al., 2004), by causing more dysfunction or modifying the clinical presentation.

Migrant differentials in pathways through care do not necessarily distort schizophrenia IRR estimates, as long as all possible pathways to the index diagnosis are accounted for. This is not a problem for the ePCR method. But for some groups in FC studies it may lead to inflated IRR estimates because the FC method over includes groups with early onsets and short DPTs.

Strengths and limitations

The main strengths of our study are that it was conducted in a well defined urban catchment area with a 45% share of migrants, that the FC study used in the comparison meets the highest quality standards (Bourque et al., 2010; Kirkbride, Errazuriz, et al., 2012; McGrath et al., 2004; Veling et al., 2007), and that the ePCR was based on a data warehouse, synchronized every day with data from virtually all mental health services in the

catchment area. The longitudinal sampling frame covered all treatment pathways from 1980 to 2009.

Both methods were restricted to treated subjects, and typical limitations of treated incidence studies apply, such as the risk of overinclusion of cases (e.g. due to inmigration of prevalent cases into the catchment area, or diagnostic errors), and the risk of underinclusion (e.g. due to cases avoiding mental health treatment entirely). Sensitivity analyses showed that potential distortions by these factors were likely to be small: very few cases moved into the catchment area shortly before the index diagnosis was made, and the diagnostic process was robust (Hogerzeil et al., 2014).

Migrant differentials in access to mental health care would affect both methods equally, and therefore, cannot account for the differences observed between them; furthermore, surveys of access to care from different countries (Bermejo et al., 2012; Fassaert et al., 2009) and meta-analyses of DUP-studies (Anderson et al., 2013) reported no systematic differentials.

There is evidence that migrants drop out of mental health treatment more frequently than nonmigrants (Anderson et al., 2012; O'Brien et al., 2008). Some migrants may have dropped out before the onset of schizophrenia and then been missed by one or both methods. This would deflate the migrant IRR estimate. In the 20–54 working age bracket, access to welfare benefits would be an additional incentive for undiagnosed but disabled schizophrenia patients to reengage with mental health services. These and other cases who reengaged would be listed in the register and ultimately detected as incident cases. They may then have been classified in an older age group.

Cross-cultural diagnostic bias could also have confounded our IRR estimates (Adeponle et al., 2012; Gara et al., 2012; Selten et al., 2012; Zandi et al., 2010). We did not estimate cross-cultural diagnostic bias directly in the present study. Indirectly, however, we found no migrant differentials in diagnostic validity or stability in either FC or ePCR study samples. As noted above, clinicians were not more conservative in diagnosing schizophrenia with native Dutch than with migrant subpopulations.

Unfortunately, we had no reliable data to examine potential confounding from socioeconomic status (SES) at time of onset. In our study (Table 1), the incidence of psychotic disorders for Turkish immigrants was only modestly increased, while they have much lower income, educational and employment levels than Surinamese migrants, whose relative risk was high (Veling & Susser, 2011). In the literature, the strength and nature of the relation between SES and schizophrenia remains unclear (Dohrenwend et al., 1992; Kwok,

2014; O'Donoghue et al., 2016; Veling & Susser, 2011). In line with two comparable studies (Hjern et al., 2004; Kirkbride et al., 2008), we expect that adjusting for individual SES in our data would attenuate the migrants' IRR estimates but not explain them.

Our findings of overinclusion of subjects presenting at younger ages and/or with shorter duration of prior treatment probably apply to all FC studies of schizophrenia (i.e. first episode of schizophrenia or FES), but we have not shown that it applies to studies of all psychoses (i.e. first episode of psychosis, or FEP).

It seems prudent to assume that selective sampling also occurs in FEP studies. To assume otherwise, for migration as a risk factor, would imply that there are no migrant groups with FEP who present at systematically younger ages, or who have systematically shorter DPT, compared to other migrant groups or to nonmigrants. To our knowledge, this hypothesis has not yet been tested directly.

The indirect evidence is mixed. As noted above, Anderson et al. (2014) found that specific migrant groups such as Blacks with FEP had more negative pathways than nonmigrants. High quality FC studies in the UK (Coid et al., 2008; Fearon et al., 2006) and in The Hague have reported migrant IRRs for both FES and FEP, and the patterns were similar. Finally, we speculate that overdiagnosis of psychosis among migrants (diagnostic bias) could translate into earlier diagnosis of psychosis among migrants. There is some evidence that diagnostic bias distorts FEP and FES differently (Veling, 2013), but the direction and extent of this difference is unclear.

Conclusion

Compared to the FC method, the ePCR method also found that the incidence of schizophrenia is raised roughly twofold for migrants compared to nonmigrants, but its IRR estimates are less extreme. To the extent that additional cases identified by the ePCR method are true incident cases of schizophrenia, ePCR estimates are more precise (larger sample, smaller confidence intervals) and possibly more valid (less differential sampling) than FC estimates. Migration is related both to a higher risk of schizophrenia and to specific pathways through services. The FC method may overestimate the risk of schizophrenia for migrant groups who tend to seek first mental health care at young age, or who present directly with schizophrenia.

Our results suggest a new explanation for the very high risk of schizophrenia measured among some migrant groups in FC studies: some migrant populations are found in higher

numbers in FC samples not only because they develop schizophrenia more frequently, but also because they follow other pathways through treatment than nonmigrants do.

Other risk factors associated with the pathway to the index diagnosis such as age, gender or socioeconomic factors may also result in differential sampling in FC studies and should also be re-examined.

6

Design choices

Published as:

Hogerzeil, S. J., & Hemert, A. M. van. (2019). Design choices when estimating the treated incidence of schizophrenia. *Psychological Medicine*, *49*(15), 2635–2636. https://doi.org/10.1017/s0033291719001338

Letter to the editor

Anderson et al. (2018) estimate the gap between the number of incident cases of schizophrenia aged 16–50 in Ontario, Canada in 1997–2015, and the number who were enrolled into Early Psychosis Intervention (EPI) services. Their analysis is a direct comparison between administrative records and the standard method for estimating the treated incidence.

The standard method (known as the 'first contact design') involves screening subjects for signs of psychosis when they present for psychiatric treatment. Subjects screened positive then undergo standardized diagnostic procedures to establish the criteria for schizophrenia. But studies based on administrative records have suggested that two out of three cases may be missed this way (Hogerzeil et al., 2014; Jongsma et al., 2019; Pedersen et al., 2014).

Anderson et al. (2018) also found that two out of three cases of schizophrenia had remained unknown to EPI services. Not all cases met EPI-services' inclusion criteria, but still a substantial number of true cases of schizophrenia had been missed. In their discussion, Anderson et al. (2018) focused on the issue of incomplete coverage of services, but this is only one of several design aspects that matter.

We propose to distinguish three design aspects where complete case finding can go wrong: coverage of services, time frame of the diagnosis, and accuracy of the diagnosis. We believe that these distinctions can help to understand the five- to ten-fold variation in incidence between populations, which is commonly reported but only partially explained (Jongsma et al., 2019, 2018; McGrath et al., 2004).

Coverage of services where cases can be detected. These may range from (1) very specialized services such as EPI services, emergency or inpatient services, extending to (2) general psychiatric or addiction services, and further to (3) primary care or somatic medical care or ultimately to (4) the general population.

Time frame of the diagnosis, the interval allowed between the first contact with a service and the moment a diagnosis can be made. It may range from (1) case ascertainment at first contact only, extending to (2) later stages of treatment, e.g. subjects presenting initially with another diagnosis, ultimately extending to a (3) life-time follow-up.

Accuracy of the diagnosis, ranging from diagnosis based on (1) research diagnostic procedures, extending to (2) clinical criteria diagnoses (e.g. DSM-5 or ICD-10) and (3) non standardized diagnostic procedures.

This can be illustrated in 3D, where design choices along the x y z axes determine a box, the volume of which represents the incidence estimate. Figure 6.1 illustrates how the first

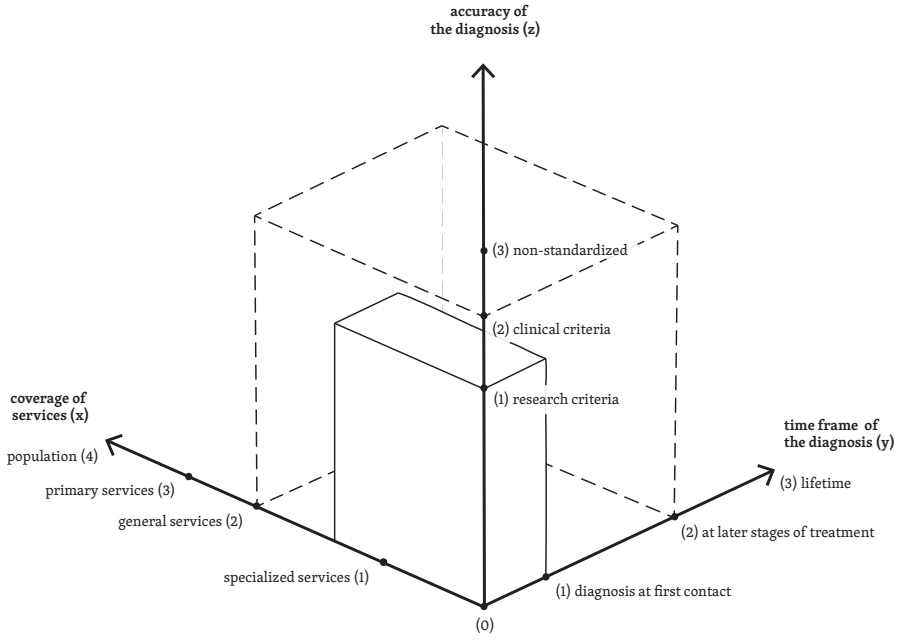

Figure 6.1 Graphical illustration of three design aspects for studies measuring the incidence of schizophrenia
The volume of the solid box represents the incidence as estimated in a typical first- contact design and that of the dotted box the incidence as estimated in electronic administrative records.

contact design (solid box; i.e. typically measured as first contacts at specialized services, using research diagnoses) results in a lower incidence compared to cumulative records (dotted box; i.e. typically measured at all psychiatric services, using clinical diagnoses over much longer time spans).

Case-register studies from the 1950s to the 1970s typically focused on inpatient hospital services, with long time frames and non-standardized diagnoses. The first contact studies of the 1990s and later focused on a wider coverage of services and better diagnostic accuracy, while restricting the time frame (Jablensky et al., 1992). That approach has high specificity but low sensitivity: many subjects with an ultimate diagnosis of schizophre-

nia will be missed because they do not meet criteria for the disorder when they first seek treatment (Hogerzeil et al., 2014; Rietdijk et al., 2011).

Longer time frames became possible with (a) the wide adoption DSM or ICD based clinical diagnoses and (b) well maintained administrative records in (c) institutions serving all psychiatric needs of well-defined populations. Such databases can now be used to reconstruct diagnostic histories or treatment pathways through services, up to the first diagnosis of schizophrenia, capturing new onsets along pathways that cannot be covered with the standard approach. This new approach is more sensitive, although it might come at the expense of some diagnostic specificity.

The study by Anderson et al. (2018) is the second to compare first contact and cumulative methods directly. Their study can be understood as a replication of our finding (Hogerzeil et al., 2014) that in administrative data the incidence of treated schizophrenia is two to threefold higher than detected using the first contact design. Now replicated, this finding has obvious implications for estimates of the number of cases affected, and for the organization of services. Furthermore, considering subjects with psychosis at first contact as 'prototype cases' may have distorted our understanding of schizophrenia by spuriously highlighting a younger age of onset and a more acute clinical presentation than seen in actual administrative records (Hogerzeil et al., 2016).

Study design matters a lot when estimating the incidence of schizophrenia. To interpret incidence studies or to make meaningful comparisons between them, we need a more elaborate classification of study designs, as suggested here.

7

Impact of differences in study design

Published as:

Hogerzeil, S. J., Hoek, H. W., & Hemert, A. M. van. (2021). The impact of study design on schizophrenia incidence estimates: A systematic review of Northern European studies 2008–2019. *Schizophrenia Research, 231*, 134–141. https://doi.org/10.1016/j.schres.2021.03.017

Abstract

BACKGROUND — The best estimates of the incidence of schizophrenia range more than 25-fold from 3 to 80 per 100 000 person years. To what extent do differences in study design explain this wide variation?

METHOD — We selected all studies published between 2008–2019 reporting the incidence of schizophrenia in general populations of Northern Europe. We identified 17 estimates covering 85 million person years and more than 15 000 individual cases. The estimates ranged from 4–72 per 100 000 person years (median 30; interquartile range 13–41). We classified the estimates in terms of three study design factors (coverage of services, time frame, and diagnostic quality) and two population factors (urbanicity and age).

RESULTS — A meta-regression model of the three design factors, using the two population factors as covariates, explained 91% of between-study variation. studies performed in general psychiatric services reported similar estimates [incidence rate ratio 1.12 (95% confidence interval 0.88 to 1.43)] to those performed in specialized services. But studies applying a cumulative time frame to diagnosis reported fourfold higher estimates [4.04 (3.14 to 5.2)] than those applying a first contact time frame. And studies based on clinical diagnoses reported lower estimates [0.55 (0.43 to 0.72)] than those based on standardized research diagnoses. The three study design factors by themselves explained 67% of between-study variation.

CONCLUSION — When comparing incidence rates from different populations, distortions arising from differences in study design can eclipse differences caused by schizophrenia risk factors, such as gender, age or migrant status.

Introduction

Rationale

Systematic reviews report a wide variation between estimates of the incidence of schizophrenia. Two international reviews together cover the period 1950–2017: one review of schizophrenia incidence studies published between 1950–2000 reported estimates ranging from 4–52 per 100 000 person years (van der Werf et al., 2012), while the other review of psychosis incidence studies published between 2002–2017 reported schizophrenia incidence estimates ranging from 3–76 per 100 000 person years (Jongsma et al., 2019). Variation between countries with different cultures and health care systems can be expected, but reviews of incidence from similar countries also show wide variations: a review of UK studies published in 1950–2009 reported estimates ranging from 4–32 per 100 000 person years (Kirkbride, Jones, et al., 2012); while another review of studies published between 1992–2012 with estimates from the Netherlands, Sweden and Denmark ranged from 9–80 per 100 000 person years (Vassos et al., 2012).

One explanation for the wide variation is that different rates result from different population characteristics, i.e. with different distributions of risk factors for schizophrenia. Populations with higher numbers of young adults or higher numbers of males, for example, are likely to report higher incidences than studies focusing on the population at large (Jongsma & Jones, 2019; Thorup et al., 2007). Similarly, studies in larger cities commonly report higher incidences than studies from rural areas (Vassos et al., 2016), and rates tend to be higher among immigrants than native inhabitants in an area (Bourque et al., 2010; Selten et al., 2019).

Another explanation for the variation could be that different rates result from different study designs. In a previous study, we used two different study designs to estimate the incidence of schizophrenia in the city of The Hague in the Netherlands (Hogerzeil et al., 2014). The first approach we used was a standard first contact design, which is generally considered the standard for incidence studies of schizophrenia. The second approach was based on a longitudinal case-register extracted from electronic hospital records. In the database, we could follow patients beyond their first contact to detect diagnostic changes over the course of treatment. This longitudinal case-register approach resulted in an estimate that was more than three times higher than the estimate based on the first contact approach [69 (95% confidence interval (CI) 64 to 74) vs. versus 21 (18 to 23) per 100 000 person years]. The impact of single aspects of study design was explored in several world-wide meta-analyses that included studies from heterogeneous populations (Bourque et al., 2010; McGrath et al., 2004; van der Werf et al., 2012). These analyses

uncovered no clear patterns. Two recent meta-analyses (Castillejos et al., 2019; Jongsma et al., 2019) examined this issue using meta-regression. Castillejos et al. (2019) reviewed only the literature based on first contact sampling and reported that methodological differences helped to explain between-study heterogeneity. Jongsma et al. (2019) compared case registers with first contact studies and reported that register-based estimates are systematically higher [with a multivariable model relative risk of 2.51 (95% CI 1.24 to 5.21)]. However, neither review was set up to quantify the relative importance of different factors in study design.

Objectives

We have previously proposed to categorize the design of incidence studies on three factors: *coverage of services*, *time frame of the diagnosis*, and *reliability of the diagnosis* (Hogerzeil & Hemert, 2019).

Our aim in this review was to examine to what extent reported incidence estimates are related to these three design factors, and so to distinguish artifacts from 'true' variation due to population characteristics. We hypothesized that estimates would be higher in studies with a wider service cover, longer time frames, and clinically oriented diagnoses.

To test this, we systematically identified all studies on the incidence of schizophrenia published from 2008–2019. We used meta-regression analysis to examine the impact of design features on the incidence estimates, adjusting for the impact of population characteristics.

Methods

This meta-analysis and meta-regression followed PRISMA guidelines (Liberati et al., 2009).

We based our study on the recent meta-analysis by Jongsma et al. (2019), which covered all the original research on the incidence of non-organic, adult-onset psychotic disorder published in 2002–2017. Her method in turn was based on a previous systematic review by Kirkbride, Errazuriz, et al. (2012), which covered the research conducted in England on the incidence of non-organic adult-onset psychosis, published in 1950–2009. Jongsma et al. (2019)'s search was very thorough, and had no restrictions on language of publication, study design, or publication status. It also searched for gray literature via published conference proceedings, author correspondence, and bibliographical searches.

Information sources

We included all studies included in Jongsma et al. (2019)'s meta-analysis and all citations listed in the supplemental data provided with Jongsma's study. To cover studies published after Jongsma et al. (2019)'s review, we performed a systematic search for additional studies published up to December 31st 2019.

Search

We used the same search string used by Jongsma et al. (2019), which she adapted from Kirkbride, Errazuriz, et al. (2012), to query PubMed for studies published between January 1st 2018 and December 31st 2019 (see Supplement 4). We performed bibliographic searches whenever possible. We had no language restrictions. We did not query other databases. We did not search the gray literature.

Eligibility criteria

We did not examine studies published before 2008 because one category of interest (applying a cumulative time frame) relies on types of clinical diagnostic practice and electronic data warehouses that only started to emerge at that time. We limited our selection to Northern European studies to reduce potential heterogeneity in health care systems. We considered only incidence estimates for schizophrenia to reduce potential heterogeneity in diagnostic practices.

Therefore, citations were eligible if they contained incidence data, or data from which incidence could be derived (numerator and denominator); included patients (aged 18–64 years) diagnosed with a first episode of schizophrenia; covered populations in Northern Europe; were published between 2008 and 2019, and were listed either in Jongsma et al. (2019)'s meta-analysis (if published 2008–2017) or in PubMed (if published 2018–2019).

Study selection and data collection process

We (AH and SH) first selected on title. We included studies if their title mentioned: (a) 'incidence', 'rate' or 'risk', and (b) one of the words 'schizophrenia', 'psychosis' or 'mental disorders'. We excluded studies with titles referring to specific subgroups as indicated by one of the diagnostic specifiers 'affective', 'postpartum', 'drugs or substance induced psychosis', or subpopulation specifiers 'in or among' 'migrants', 'youth', 'veterans', 'military', 'type 1 diabetes', 'adoptees', 'epilepsy' or 'immune-mediated inflammatory disease'.

We (SH) then selected on the full text. We included studies if they reported estimates of the incidence of 'narrow schizophrenia', defined as 'DSM-IV 295.x' or 'ICD-10 code F20 (including F21 and F25 if possible)' in the general population. We excluded non-European and South European studies to reduce heterogeneity from different healthcare systems and cultural effects on seeking healthcare.

If two or more studies reported on the incidence of schizophrenia in the same population, we included only one. To decide which one, we (SH and AH) assigned priority according to study period (more recent, larger) and quality (more detailed information, state-of-the-art procedures) to arrive at consensus. If two or more methods had been used in the same population, we included one estimate for each method.

Data items

For each study and (if necessary) for each type of study design applied in that study, we collected data related to publication, study period, study population (i.e. country, area, urbanicity, sex and age), study design (i.e. coverage of services, time frame of diagnosis, reliability of diagnosis), and the incidence estimate (i.e. cases and person years at risk).

Coverage of services could range from: (1) 'specialized services' such as Early Psychosis Intervention (EPI) services, and emergency or in-patient services, to the broader set of (2) 'general'psychiatric or addiction services, and further to (3) primary or somatic medical care, and ultimately to (4) the general population. The time frame of diagnosis is the interval between the first contact with a service and the moment a diagnosis is made. It could range from: (1) case ascertainment at first contact, to (2) later stages of treatment, e.g. subjects presenting initially with another diagnosis, ultimately extending to (3) life-time follow-up. Finally, the reliability of diagnosis could range from diagnosis based on: (1) research diagnostic procedures, to (2) clinical criteria diagnoses (e.g. DSM-5 or ICD-10) and (3) non-standardized diagnostic procedures.

Age was categorized according to Howard et al. (2000) in 'early onset' (age < 40 years), 'late onset (age 40–59 years) and 'late onset' (age > 60 years). Urbanicity was classified in three categories: urban, rural, and mixed (i.e. for entire population estimates, such as studies from Denmark). We used the level of urbanicity that each study had assigned to itself.

Assessment of study quality

Kirkbride, Errazuriz, et al. (2012) and Jongsma et al. (2019) used a 7-point quality score. That score was not applicable to our review on 3 out of the 7 points because they relate to the first contact design in particular ('standardized research diagnosis' and 'leakage study') or to studies of risk factors such as ethnicity ('blinding to demographic variables'). For inclusion in our meta-analyses, we required that all studies meet at least all four remaining criteria ('defined catchment area', 'accurate denominator', 'population based case-finding', and 'inclusion criteria'). We nevertheless scored studies on all 7-points for consistency with Kirkbride, Errazuriz, et al. (2012) and Jongsma et al. (2019). For our purposes we considered any study meeting the four core criteria listed above as 'high quality'.

Summary measures

The principal summary measure was the treated incidence rate of schizophrenia per 100 000 person years in the general population.

Synthesis of results

All incidence rates are expressed as number of cases per 100 000 person years. We calculated exact confidence intervals for Poisson rates using the pois.exact() function from the 'epitools' package (Aragon et al., 2017) in R version 3.6.1 (R Core Team, 2020).

We calculated pooled incidence rates for each category of study population (i.e. age, urbanicity) and study design (i.e. coverage, time frame, reliability).

We calculated the proportion of between-study variance explained by the covariates by comparing the estimated between-study variance τ^2, with its value when no covariates are fit τ_0^2. Adjusted R^2 is the relative reduction in the between study variance $R^2 = \tau_0^2 - \tau^2$ (Harbord & Higgins, 2008).

Additional analyses + meta-regression + sensitivity analysis

To examine how our three design factors related to the incidence, adjusting for differences in population characteristics, we first calculated unadjusted pooled incidence ratios for each of the three variables of interest (coverage, time frame and reliability), and the two covariates (urbanicity and age). Next, to adjust for interdependencies between variables, we conducted a multivariable meta-regression analysis to estimate incidence ratios for

each factor in a single model. To allow for variation both within and between studies, we used a mixed-effects model with restricted maximum likelihood (REML) estimators. We used the Knapp-Hartung adjustment to obtain more reliable confidence intervals (Knapp & Hartung, 2003) and permutation tests to assess the robustness of our model (Higgins & Thompson, 2004). The regression was performed using the 'meta' (Balduzzi et al., 2019) and 'metaphor' packages (Viechtbauer, 2010) in R.

To rule out bias from including estimates from our own research group (i.e. tilting the scale towards results that confirm our prior findings) we repeated the meta-regression analyses without our own data.

Results

Study selection

The results of the study selection are summarized in a flowchart (Figure 7.1).

Jongsma et al. (2019) identified a total of 125 unique publications between 2008–2017, listed in her review or in the supplement. The search in the PubMed database yielded 527 publications between 2018–2019.

Based on title, we included 70/527 publications from our Pubmed search (left-hand column in the flowchart) and 68/125 publications from Jongsma et al. (2019)'s study (right-hand column) that explicitly mentioned: (a) 'incidence', 'rate' or 'risk', and (b) one of the words 'schizophrenia', 'psychosis' or 'mental disorders'. We then excluded 50/70 and 5/68 studies because the titles included the words 'review' or 'meta-analysis', resulting in respectively 20 and 63 studies. We then excluded 14/20 and 14/63 studies, with titles referring to specific subgroups as indicated by one of the diagnostic specifiers or subpopulation specifiers, resulting in respectively 6 and 49 remaining studies.

Based on the full text, we excluded 4/6 and 9/49 studies from non-European or South-European populations resulting in respectively 2 and 40 remaining studies. We then excluded 1/2 and 18/40 studies because they did not report estimates of the incidence of 'narrow schizophrenia'. Finally, we excluded 1/1 and 10/22 studies for miscellaneous reasons: two studies that did not describe a general population, one study where coverage and time frame could not be assessed, one study that was a conference abstract, one study with a small population sample ($n < 4000$), and 6 studies that reported duplicate or overlapping findings.

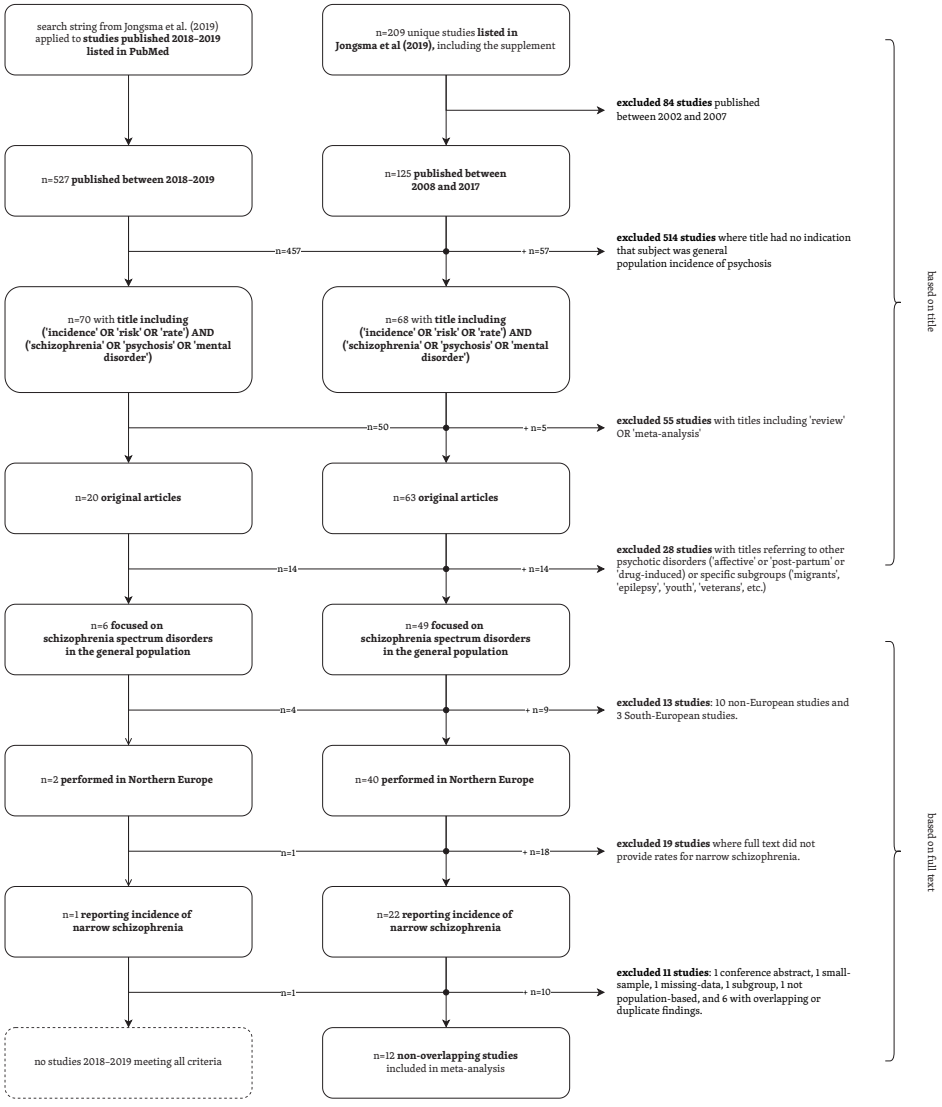

Figure 7.1 PRISMA flowchart

To identify these six duplicates, we determined that the remaining 18 publications described estimates in 15 study populations in four countries, i.e. six from Denmark (Castagnini & Foldager, 2013; Kühl et al., 2016; Nielsen et al., 2017; Paksarian et al., 2015; Sørensen et al., 2015; Vassos et al., 2016), two from Sweden (Jörgensen et al., 2010; Söderlund et al., 2015), two from the Netherlands (Boonstra, Wunderink, Wit, et al., 2008; Hogerzeil et al., 2014) and five from the United Kingdom (Bhavsar et al., 2014; Kirkbride et al., 2017; Kirkbride et al., 2008; Kirkbride, Jones, et al., 2012; Reay et al., 2010). Although some publications described the same population, the study designs were different and

were therefore included separately in our analysis. All others were treated as duplicates and excluded.

Our selection procedure resulted in a set of 12 publications (Bhavsar et al., 2014; Boonstra, Wunderink, Wit, et al., 2008; Castagnini & Foldager, 2013; Hogerzeil et al., 2014; Jörgensen et al., 2010; Kirkbride et al., 2017; Kirkbride, Jones, et al., 2012; Paksarian et al., 2015; Reay et al., 2010; Salokangas et al., 2010; Sørensen et al., 2015; Szoke et al., 2016). All studies had previously been included in Jongsma et al. (2019)'s meta-analysis. The search for new studies published 2018–2019 identified no new publications meeting all criteria for inclusion in this meta-analysis.

Study characteristics

Table 7.1 shows the incidence estimates with the associated design and population factors. Between 2008 and 2019, 12 European studies together reported 17 estimates of the incidence of schizophrenia in the general population. These studies were from the Netherlands (n = 2) (Boonstra, Wunderink, Wit, et al., 2008; Hogerzeil et al., 2014), UK (n = 4) (Bhavsar et al., 2014; Kirkbride et al., 2017; Kirkbride, Jones, et al., 2012; Reay et al., 2010), Sweden (n = 1) (Jörgensen et al., 2010), Denmark (n = 3) (Castagnini & Foldager, 2013; Paksarian et al., 2015; Sørensen et al., 2015), Finland (n = 1) (Salokangas et al., 2010) and France (n = 1) (Szoke et al., 2016).

All 12 studies were population-based, had specific inclusion criteria, and had an accurate denominator for a defined catchment area, i.e. had a quality score of 4 or higher in terms of Kirkbride, Jones, et al. (2012) 7-point score and were considered 'high quality' for our purposes. Our scores diverged from those by Jongsma et al. (2019) for three studies (Bhavsar et al., 2014; Boonstra, Wunderink, Wit, et al., 2008; Reay et al., 2010) because we classified them as population-based, and as having an accurate denominator. In our sample, seven studies scored 4/7 points, four scored 5/7 points (Bhavsar et al., 2014; Kirkbride et al., 2017; Reay et al., 2010; Szoke et al., 2016), and one (Kirkbride, Jones, et al., 2012) scored 6/7 points. The quality factor 'research diagnosis'—by definition—was always present in our category 'using research diagnosis' and vice-versa. Otherwise, there was no association between study quality and study design, or between study quality and estimate size.

Table 7.1 Characteristics of 12 Northern European studies reporting 17 incidence rates (IR) of schizophrenia, published between 2008 and 2017

		Study quality	Country	Obs	Person years	IR	95% CI	Design factors			Population factors	
								Coverage	Time frame	Diagnosis	Age of onset (yrs)	Density
1	Reay et al. (2010)	5	UK	60	1 363 485	4.4	3.4 to 5.7	Specialized	First contact	Clinical	< 60	Rural
2	Boonstra et al. (2008)	4	NL	24	348 222	7.0	4.4 to 103	General	First contact	Clinical	< 40	Rural
3	Castagnini and Foldager (2013)	4	DK	4576	49 921 662	92	8.9 to 9.4	General	First contact	Clinical	< 60	Mixed
4	Szoke et al. (2016)	5	FR	66	536 168	12.3	9.5 to 15.7	General	First contact	Clinical	< 60	Urban
5a	Jorgensen et al. (2010)	4	SE	46	348 351	132	9.7 to 17.6	Specialized	First contact	Clinical	< 40	Urban
6	Kirkbride et al. (2017)	5	UK	350	2 021 663	17.3	15.5 to 192	General	First contact	Research	< 40	Mixed
7a	Hogerzeil et al. (2014)	4	NL	254	1 221 486	20.8	18.3 to 23.5	General	First contact	Research	< 60	Urban
5b	Jorgensen et al. (2010)	4	SE	96	348 351	27.6	22.3 to 33.7	General	First contact	Clinical	< 40	Urban
8	Sorensen et al. (2015)	4	DK	15 074	49 898 592	302	29.7 to 30.7	General	Cumulative	Clinical	< 60	Mixed
7b	Hogerzeil et al. (2014)	4	NL	238	748 423	31.8	27.9 to 36.1	General	First contact	Research	< 40	Urban
9	Kirkbride et al. (2014)	6	UK	268	828 546	32.3	28.6 to 36.5	General	First contact	Research	< 60	Urban
10a	Salokangas et al. (2011)	4	Ft	9442	27 661 925	34.1	33.4 to 34.8	Specialized	Cumulative	Clinical	< 60	Mixed
11	Paksarian et al. (2015)	4	DK	6469	15 800 000	40.9	39.9 to 41.9	General	Cumulative	Clinical	< 40	Mixed
10b	Salokangas et al. (2011)	4	FI	6988	16 638 863	42.0	41 to 43	Specialized	Cumulative	Clinical	< 40	Mixed
12	Bhaysar et al. (2014)	5	UK	405	741 758	54.6	49.4 to 60.2	General	First contact	Research	< 40	Urban
7c	Hogerzeil et al. (2014)	4	NL	843	1 221 486	69.0	64.4 to 73.8	General	Cumulative	Clinical	< 60	Urban
7d	Hogerzeil et al. (2014)	4	NL	539	748 423	72.0	66.1 to 78.4	General	Cumulative	Clinical	< 40	Urban

Rates were classified according to study design (coverage, time-frame and diagnosis) and population factors (age of onset and urbanicity), and are presented in ascending order of incidence. 'Obs' number of cases, 'IR' incidence rate of narrow schizophrenia.

Estimate characteristics

In total, study selection and data extraction resulted in 17 estimates of the treated incidence of 'narrow schizophrenia' in the general population, for a variety of study designs (i.e. coverage in two levels, time frame in two levels, and reliability in two levels) applies to a variety of study populations (i.e. age in two levels, urbanicity in three levels), adding up to 85 million person years at risk.

This sample contained no estimates in primary care, somatic care, or in the general population. We dropped gender as category for analysis because this information was typically not provided. Information on population characteristics was available for two categories only: age range and urbanicity. There was insufficient information to separate 'early onset' from 'late onset' (40–59 years) and no data were available for 'very late onset' (> 60 years). We therefore merged the age categories into 'early onset' (age < 40 years) and 'early to late onset' (< 60 years). Urbanicity could be assessed for all studies. Three studies (Hogerzeil et al., 2014; Jörgensen et al., 2010; Salokangas et al., 2010) reported estimates based on more than one design or subpopulation and therefore contributed more than one estimate to our data set.

Meta-analysis

Incidence estimates ranged from 4.4 (Reay et al., 2010) to 72.0 (Hogerzeil et al., 2014) per 100 000 person years (median 30; interquartile range 13–41 per 100 000 person years).

The pooled estimate was 40.2 per 100 000 person years (95% confidence interval 39.5 to 40.8) for early onsets (< 40 years) and 23.1 per 100 000 person years (95% confidence interval 22.8 to 23.3) for early-to-late onsets (< 60 years).

Between study heterogeneity (I^2) in the study sample was 98.7% and 99.9% for early and early-to-late onsets, respectively.

Meta-regression

Unadjusted pooled incidences and incidence ratios for individual factors in study design or study population are shown in Table 7.2. In this single variable comparison, no significant differences were found for coverage of services, quality of diagnosis, or age of onset. For 'time frame for diagnosis', the incidence estimates were more than threefold higher for cumulative time frames versus first contact studies (incidence ratio 3.21; 95% CI 3.13 to 3.30). In addition, estimates from rural populations were roughly six-fold lower than in urban populations (0.12; 95% CI 0.10–0.15).

Table 7.2 Unadjusted pooled incidence rates and incidence rate ratios for individual aspects of study design or type of study population

		N	Obs	Person years	IR	95% CI	unadj IRR	95% CI
Coverage of services	Specialized services	4	16 536	4 601 2624	35.9	35.4 to 36.5	ref	
	General psychiatric services	13	29 202	12 4384 780	23.5	23.2 to 23.7	0.65	0.64 to 0.67
Time frame to diagnosis	First contact	11	6 383	58 428 115	10.9	10.7 to 11.2	ref	
	Cumulative	6	39 355	111 969 289	35.1	34.8 to 35.5	3.21	3.13 to 3.30
Quality of diagnosis	Research diagnosis	5	1 515	5 561 876	27.2	25.9 to 28.6	ref	
	Clinical diagnosis	12	44 223	164 835 528	26.8	26.6 to 27.1	0.98	0.94 to 1.04
Age of onset	Early-to-late onset	8	30 583	132 653 350	23.1	22.8 to 23.3	ref	
	Early onset	9	15 155	37 744 054	40.2	39.5 to 40.8	1.74	1.71 to 1.78
Urbanicity	Urban	9	2 755	6 742 992	40.9	39.3 to 42.4	ref	
	Mixed	6	42 899	161 942 705	26.5	26.2 to 26.7	0.65	0.62 to 0.67
	Rural	2	84	1 711 707	4.9	3.9 to 6.1	0.12	0.10 to 0.15

'N' number of estimates, 'Obs' number of observed cases, 'IR' incidence rate per 100 000 person years, 'IRR' incidence exact Poisson confidence interval

Results of our multivariable meta-regression analysis are presented in Table 7.3. The meta-regression indicated that among adults aged 15–59 years in a general urban population, a study using research diagnoses made in specialized services and applying a first contact time frame would estimate the incidence of schizophrenia at 25 per 100 000 person years (Knapp-Hartung adjusted 95% CI 15 to 40). But in the same population—a study using clinical diagnoses would report a 0.55 (0.38 to 0.81) times lower estimate, and one applying a cumulative time frame would report a 4.04 (2.78 to 5.87) times higher estimate. If the same design were used in mixed and rural settings, estimates would be 0.54 (0.39 to 0.75) and 0.33 (0.18 to 0.6) times lower, respectively. If age of onset were to be restricted to early age of onset, the estimate would be 1.34 (1.02 to 1.75) times higher. Extending coverage to general psychiatric services would not increase estimates significantly (1.12 times; 95% CI 0.88 to 1.43).

The three study design factors together explained 67% of between study variance (adjusted R^2). A complete model, including the two differences in study population explained 91% of between-study variance.

Permutation tests confirmed that the estimators were robust. Running the meta-regression on subsets (i.e. the set of estimates reporting 'early onset' and the set of estimates for 'early-to-late onset' separately) did not change the outcome. Likewise, removing our own data (Hogerzeil et al., 2014) did not change the outcome.

Table 7.3 Multivariate meta-regression analysis, modeling incidence rate ratios' estimates in terms of coverage of service, time frame for diagnosis, and quality of diagnosis, with urbanicity and age as covariates

		IRR	95% CI (unadjusted)	p.crude	95% CI adj1	p.adj1	p.adj2
Coverage of services	Specialized services	1.00	ref		ref		
	General psychiatric services	1.12	(0.88 to 1.43)	0.354	(0.78 to 1.61)	0.495	0.501
Time frame to diagnosis	First contact	1.00	ref		ref		
	Cumulative	4.04	(3.14 to 5.2)	0.000	(2.78 to 5.87)	0.000	0.001
Quality of diagnosis	Research diagnosis	1.00	ref		ref		
	Clinical diagnosis	0.55	(0.43 to 0.72)	0.000	(0.38 to 0.81)	0.007	0.008
Age of onset	Early-to-late onset	1.00	ref		ref		
	Early onset	1.34	(1.12 to 1.6)	0.002	(1.02 to 1.75)	0.036	0.036
Urbanicity	Urban	1.00	ref		ref		
	Mixed	0.54	(0.44 to 0.67)	0.000	(0.39 to 0.74)	0.001	0.001
	Rural	0.33	(0.22 to 0.49)	0.000	(0.18 to 0.6)	0.002	0.003

The intercept for the meta-regression model was 25 per 100 000 person years (95% CI 15 to 40). 'IR' incidence rate per 100 000 person years, 'IRR' incidence rate ratio, 'ref' reference category, '95% CI adj1' 95% confidence interval after Knapp-Hartung adjustment, 'p.adj1' p value after Knapp-Hartung adjustment, 'p.adj2' p value after permutation test.

Discussion

We conducted a review of 12 selected studies on the incidence of narrow schizophrenia in the general adult population published between January 1st 2008 and December 31st 2019. We examined the impact of differences in study design on the variation of reported incidences. We found 17 estimates in six countries, covering more than 15 000 individual cases and 85 million person years.

We examined the impact of three study design characteristics (coverage, time frame, reliability of diagnosis), adjusting for population characteristics with two covariates (age, urbanicity). Differences in study design together explained 67% of between-study variation, while a more complete model, including age and urbanicity as covariates, explained 91%. In our model, a longer 'time frame' resulted in four-fold higher estimates, and clinical diagnoses, compared to standardized research diagnoses, reduced estimates by half.

The four-fold difference between estimates based on cumulative vs. first contact time frames is in line with our previous study, where we compared a cumulative case-register design to a first contact design in a single population (in the Netherlands), which demonstrated a 3.3-fold higher estimate for the cumulative time frame (Hogerzeil et al., 2014). Similarly, other case-register studies have tended to report higher incidence estimates than first contact studies (Anderson et al., 2018; Jongsma et al., 2018; Kirkbride, Errazuriz, et al., 2012; McGrath et al., 2004; Pedersen et al., 2014; Thorup et al., 2007). The findings in this study agree with our previous findings (Hogerzeil et al., 2014) and confirm them independently since our conclusions did not change when we removed our own data from the analysis. They confirm the threefold difference between register studies and first contact studies reported in Jongsma et al. (2019)'s meta-analysis. They expand on her finding by untangling the relative contributions of separate design aspects.

One limitation of the first contact approach as commonly practiced is that it cannot account for long delays in reaching an ultimate diagnosis of schizophrenia. Most patients with schizophrenia first report to services with other symptoms, such as depression, anxiety or substance abuse (Hogerzeil et al., 2014; Rietdijk et al., 2011; Simon et al., 2017). They may also present with psychotic symptoms, but not per se schizophrenia. In our prior study (Hogerzeil et al., 2014), the median interval between first contact and the index diagnosis of schizophrenia was 4.9 years (interquartile range 1.1 to 8.8), but the interval sometimes extended beyond 25 years. In theory, Jablensky et al. (1992)'s original first contact inclusion criteria do not exclude patients who first contacted services for other reasons. But in practice, most first contact studies have not actively screened for

onsets of schizophrenia among patients contacting services for other reasons, or patients currently under treatment for other reasons than psychosis.

A criticism on our approach could be that we focus our review on narrowly-defined schizophrenia. Many first contact studies nowadays are performed in Early Intervention services, as close as possible to the emergence of psychotic symptoms. Such services tend to work with provisional clinical diagnoses such as 'psychosis NOS' (not reviewed here), of which many are perhaps ultimately diagnosed with schizophrenia at later stages of treatment. So they treat more (future) cases of schizophrenia than is reflected in their provisional numbers. Our focus on narrow-schizophrenia therefore favors case registers compared to first contact studies because registers work with ultimate rather than provisional diagnoses. Although the criticism can be a valid explanation for lower incidence estimates in first contact studies, it also underscores the potential under detection of true cases of narrow-schizophrenia in such designs.

Prior work suggests that both the primary care system and general psychiatric services play an important role in first diagnosis of psychotic disorder, and these physicians may be involved in ongoing psychiatric care, especially in settings where specialized services are unavailable (Anderson et al., 2018; Rietdijk et al., 2011; Simon et al., 2017). We had no data on the incidence of schizophrenia in primary care, somatic medical care or the general population. But contrary to our expectation, we found no differences between specialized vs general psychiatric services as channels for case-detection. This has implications for healthcare: in that increasing service coverage (beyond services typically used by psychotic patients) to detect more cases of incident schizophrenia will not result in better estimates, if the time frame remains limited to diagnosis at first contact. One explanation could be that every subject with clinically relevant schizophrenia is eventually referred to specialized services (Weiser et al., 2012), and can be counted at that later point in time if the study design allows for such a pathway to care.

The two-fold difference between estimates based on research diagnoses vs. clinical diagnoses was also unexpected. It runs counter to common intuition that clinicians diagnose schizophrenia too easily and that relying on (presumably) conservative, standardized research procedures would result in lower (but more valid) incidence estimates (Castillejos et al., 2019; Jongsma et al., 2019). The idea that research diagnoses are to be preferred over clinical diagnoses is contradicted by reports that clinical diagnoses can be valid (Dalman et al., 2002; Ekholm et al., 2005; Ludvigsson et al., 2011; Uggerby et al., 2013) and stable over time (Fusar-Poli et al., 2016). Because our sample contained no ePCR studies with research diagnoses, comparisons between studies based on clinical vs. research diagnoses were restricted to first contact studies. The counter-intuitive

finding therefore bears primarily on first contact studies. It offers a new perspective, by suggesting that clinicians may in fact be more conservative than researchers in diagnosing schizophrenia. We speculate that clinicians are reluctant to diagnose schizophrenia formally to avoid the stigma associated with the label.

Limitations

The large attrition of eligible studies was a consequence of the quality criteria adopted to answer our research question. We restricted our search to studies published from 2008 onwards because clinical practices have become more standardized and electronic patients records better available in recent years. The further restriction to studies from Northern Europe resulted in a high-quality study sample that was comparable in terms of culture and health systems. Despite the small number of studies, the sample still covered 85 million person years and more than 15 000 cases of schizophrenia.

The risk of bias is lower for incidence studies than for RCTs. They are not blinded or randomized. There are no financial or ideological incentives to distort the incidence estimate, or the association between study method and incidence. The quality scores of the studies included in our review were high and not related to estimate size. Our update for the years 2018–2019 did not include the gray literature, however, and we did not query databases other than Pubmed. But arguably studies not listed on Pubmed are no different with respect to our main finding.

Another limitation is that our information on population characteristics was only for age and urbanicity. We had limited information on relevant age bands and no information on gender, ethnicity or other socio-economic or biological risk factors. Despite this limitation, including age and urbanicity as covariates in our final regression model explained 91% of between-study variation. This may be due to the homogenous selection of studies (all from Northern Europe), which was helpful to demonstrate the specific contribution of design factors. But our findings underestimate the contribution of other population characteristics as a source of variation.

Finally, in our statistical model, we did not account for interactions between study design characteristics and population characteristics. Such interactions are plausible, e.g. older, non-migrant females with mild symptoms are less likely to be included in first contact studies than young migrant males with acute onset of psychosis (Hogerzeil et al., 2016). In our analyses, the net effect would be conservative, e.g. selection bias in first contact studies in favor of including subjects with higher incidence of schizophrenia would shrink the contrast with ePCRs observed in this study.

Conclusions

In conclusion, our selective review demonstrates that differences in study design explain most of the wide variation in reported estimates of the incidence of schizophrenia. This artefact can eclipse true but smaller variations in population risk factors such as gender, age and migrant status. To distinguish cause from noise, future systematic reviews should apply standardized categorizations by type of design (Edwards et al., 2019; Hogerzeil & Hemert, 2019).

8

Learning about the *other* half

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Mr. J. from The Hague was treated for posttraumatic stress disorder as a young man, later treated for alcohol abuse, and then, at age 39, diagnosed as having schizophrenia. He would probably not be counted in a *First Contact (FC)* study, the gold standard for measuring incidence of (treated) schizophrenia and other psychoses. In fact, many people who develop psychoses are missed by first contact studies. Precise estimates are premature, but recent studies indicate that about half can be missed. How could this happen, and what are the implications?

The first contact design was introduced in the 1970s by the World Health Organization . The crucial innovation was the attempt to identify and then assess all people in a defined population over a specified period who initially contacted a helping agency and reported symptoms suggestive of psychosis. The range of helping agencies was wide and context specific, including, for example, traditional healers in India. The first contact design has since been the gold standard for measuring incidence of schizophrenia and other psychoses.

The first contact design requires all care providers to identify and refer to the research team any suspected case of psychosis. This is difficult to achieve. Accumulating evidence ranging from studies of traditional healers to studies using *electronic Psychiatric Case Registers (ePCR)* suggests that first contact studies struggle to monitor all people at all agency entry points and to ascertain first onsets of psychosis among people who previously sought help for a nonpsychotic mental disorder. Here we focus on what we have learned from high-quality ePCRs.

What is the impact of incomplete monitoring of entry points? In this issue, Simon et al. (2017) report that when using an ePCR constructed from health insurance records, they found that the incidence of psychosis and the proportion with a late onset were higher than reported previously from first contact studies. Other ePCRs, such as in Denmark and The Hague, have reported similar findings. Because ePCR studies have included methods to validate the first onsets detected, misclassification does not explain a discrepancy of this magnitude. We concur with Simon et al. (2017) that *the discrepancy is partly due to more complete monitoring of entry points*, resulting in detection of first onsets that would be missed in first contact studies, especially in older age groups.

What is the impact of incomplete detection of cases previously treated for a nonpsychotic disorder? In The Hague, Hogerzeil et al. (2014) directly compared the results from an ePCR with those from an excellent first contact study done in the same population over the same period. The ePCR identified large numbers of people like Mr J, who had been missed in the first contact study. We suggest that the *more complete detection of first*

onsets among people already treated for other mental disorders explains another part of the discrepancy.

What are the implications for researchers? In the evolution of psychiatric epidemiology, initially first-admission studies and later first contact studies replaced previous methods for incidence studies of (treated) psychosis. We propose that in contexts where ePCRs can be constructed, a new gold standard could now be considered: a *hybrid design that combines the strengths of ePCRs with those of first contact studies*. ePCRs offer the best approach to detect suspected first onsets seen by the health system. First contact studies offer the best approach to evaluate these potential first onsets, using well trained clinical interviewers and standardized instruments for both initial and follow-up assessments. First contact studies also encompass people seen by helping agencies outside the formal health system. Although a hybrid design will present new practical problems, such as ethical issues pertaining to use of registry data for referral to a research study, we think that in many contexts these problems can be solved. The next step is to test the hybrid design in the field.

What are the implications for clinicians? We need to revise prevailing views about the syndrome of schizophrenia as currently defined. The incidence is higher, the age of onset is often much later, and many (perhaps most) people with an ultimate diagnosis of schizophrenia have been treated for other mental disorders. We need not curb the enthusiasm generated by early intervention studies focusing on early-onset psychoses. Nor should we dismiss the wide range of important results from first contact studies, many of which will remain valid. But *it is time to get to know the other half*—the people with schizophrenia or other psychotic illnesses who tend to be undercounted and overlooked. We do not know whether their illnesses have different causes or whether they would respond to early interventions, but we need to find out.

9

Summary and general discussion

Summary of findings

We started our thesis (chapter 1) by highlighting the burden of disease caused by schizophrenia and stressing the importance of valid incidence estimates for researchers and health policy makers. We explained that detecting all incident cases of schizophrenia in a population is difficult since the onset is often gradual. Then, we described the current standard method to estimate the treated incidence of schizophrenia: the *First Contact (FC) design*. We pointed out that the FC design was not originally intended to determine the treated incidence, but that in the 1990s, a research practice arose which used the design for that purpose. We identified three unspoken assumptions underlying that practice. We then introduced another approach based on data from The Hague's electronic Psychiatric Case Register. A unique opportunity presented itself to compare both approaches in one population. This provided the basis for our main research question:

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

We broke that question down into three subquestions:

First, we asked: *do the ePCR and FC methods agree?* In chapter 2, we compared the results from both methods in exactly the same study population and study period. The ePCR estimate was about three times higher than the FC estimate (69 vs 21 per 100 000 person years, respectively).

Second, we asked: if they disagree, why? To answer that question, we tested three assumptions that underly the use of the FC method to estimate the treated incidence of schizophrenia, with the following results:

Assumption (a) was tested in chapter 3. There, we examined retrospectively which initial diagnoses were made at first contact with psychiatric services, for 1753 subjects aged 18–35 years diagnosed with any psychotic disorder between 2005–2009. For all types of psychoses, 56% (985/1753) had been treated in secondary mental health services prior to the onset of psychosis. For the subset of 355 subjects diagnosed specifically with schizophrenia, 62% (222/355) were diagnosed at first contact, but 38% (133/355)[4] first got another diagnosis of non-psychotic mental disorder. This finding contradicts assumption (a).

4 Subjects first diagnosed with another type of psychosis but ultimately diagnosed with schizophrenia were not included in that figure, so 38% is a lower bound.

Assumption (b) was tested in chapter 4. There, we used the ePCR to estimate the incidence and lifetime morbid risk of schizophrenia by age and sex, among citizens of The Hague aged 20–79 years between 1997–2012. Nearly half (46%) of onsets were diagnosed after age 40 years. This finding contradicts assumption (b).

Assumption (c) was tested in chapter 5. There, we used the data from chapter 2 to calculate age and sex adjusted incidence rate ratios (IRR) for the three largest migrant groups, relative to the Native Dutch population. The FC method was relatively more inclusive for migrants presenting at earlier ages or with shorter durations of prior treatment (DPT) than the native Dutch. Finding differential sampling in the FC method contradicts assumption (c).

Third, we asked: *how do our findings fit into the existing evidence?* In chapter 6, we first introduced a framework to classify the various study designs that have been used in different studies, along three dimensions (i.e. *coverage* of mental health services, *time frame* of the diagnosis, and *accuracy* of the diagnosis). In chapter 7, we then reviewed all studies published between 2008–2019 that reported the treated incidence of schizophrenia in general populations in Northern Europe (like ours). In a meta-regression, our framework of study design (chapter 6) explained 67% of between-study variation. A *full* model—i.e. also accounting for differences between study populations in age and urbanicity—explained 91% of between study variation. According to that model, studies conducted in general psychiatric services reported similar estimates to those conducted in specialized services (incidence rate ratio 1.12 with 95% confidence interval 0.88 to 1.43). But studies applying a cumulative time frame to diagnosis reported fourfold higher estimates (4.04; 3.14 to 5.2) than those applying a first contact time frame. And studies based on clinical diagnoses reported lower estimates (0.55; 0.43 to 0.72) than those based on standardized research diagnoses. In chapter 8, we summarized the vulnerabilities of the FC method. We then proposed a hybrid design that incorporates the ePCR method's benefit of inclusive case finding with the FC method's diagnostic standardization.

Interpretation

The findings from chapters 2, 5 and 7 allow us to explain why the FC and ePCR methods' estimates diverged by a factor three (chapters 2 and 5). The approaches were different in three ways: First, in contrast to the FC-design, the ePCR applies a cumulative time frame—which, according to our meta-analysis, may have increased the estimate fourfold on average. Second, it was based on clinical diagnoses—which may have reduced it by half. And finally, its coverage of services was slightly better—which again may have increased the estimate somewhat.

Our meta-analysis (chapter 7) explains why previous studies (Jongsma et al., 2019; Kirkbride, Errazuriz, et al., 2012; Stafford et al., 2018; van der Werf et al., 2012; Vassos et al., 2012) measured vastly different incidence rates in otherwise similar populations: different designs yield different results.

We are not the first to investigate the effect of study design on incidence estimates [5]. In their meta-analyses of incidence studies, McGrath et al. (2004) and van der Werf et al. (2012) included only studies with a first contact sampling frame and *within that category* observed no other differences by design. Jongsma et al. (2019) later did include several studies with a cumulative time frame (including our study from chapter 2, and *pooling two types of register studies (with both FC and cumulative time frames)* observed that register-based studies reported higher rates than FC-studies. Our studies add to the literature by explicitly separating and quantifying the different factors.

Revision of the framework introduced in chapter 6

The framework formulated in chapter 6 (Figure 9.1a) sought to untangle the opposite effects of three dimensions of study design. But the findings in the meta-analysis (chapter 7) require us to update it somewhat.

In our initial version of the framework (chapter 6), we expected that researchers would be more conservative in diagnosing schizophrenia than clinicians.

Edwards et al. (2019) followed our framework but noted that not every case meeting diagnostic criteria is recognized as such by clinicians and/or receives care. As a result, they anticipated that studies reporting clinical diagnoses (in their words,) would produce lower estimates than studies reporting study diagnoses (in their terms).

We quantified the relative effect of each of these dimensions on the incidence estimate in our meta-analysis (chapter 7). Our meta-analysis results generally confirmed our initial framework (chapter 6), but—as Edwards et al. (2019) predicted—studies based

5 The question drew a lot of attention when the need for standardized diagnosis became clear (Cooper, 1972; Kendell et al., 1968), and it was centered on the seminal WHO first contact studies (Jablensky et al., 1992; Sartorius et al., 1974). Kendell et al. (1993) outlined in detail the difficulties of estimating the incidence of schizophrenia. It has been consistently been shown that covering more types of facilities results in higher incidence rates (Amminger et al., 2006; Anderson et al., 2018; Jörgensen et al., 2010). Similarly, the notion that a longer time frame for diagnosis results in higher incidence rates (Amminger et al., 2006; Bresnahan et al., 2000; Kleinhaus et al., 2011), as well as the idea that the first contact design can result in selection bias, were discussed several times (Aleman et al., 2003; Kleinhaus et al., 2011).

on clinical diagnoses appear to yield lower estimates than studies based on standardized research diagnoses.

Figure 9.1b shows a *new illustration of our revised framework*. In response to a reviewer's suggestion, we changed the name of the axis from 'accuracy' to 'reliability' of the diagnosis. We reordered the values on that axis to (1) clinical, (2) science, and (3) non-standardized diagnosis. As a consequence, the relative sizes of the boxes representing the two approaches in the diagram have changed.

Systematic comparison of both methods

Before answering the main research question, we will compare the pros and cons of each method in terms of the updated framework (i.e. *coverage*, *time frame*, *reliability*), and in terms of *generalisability* and *feasability*.

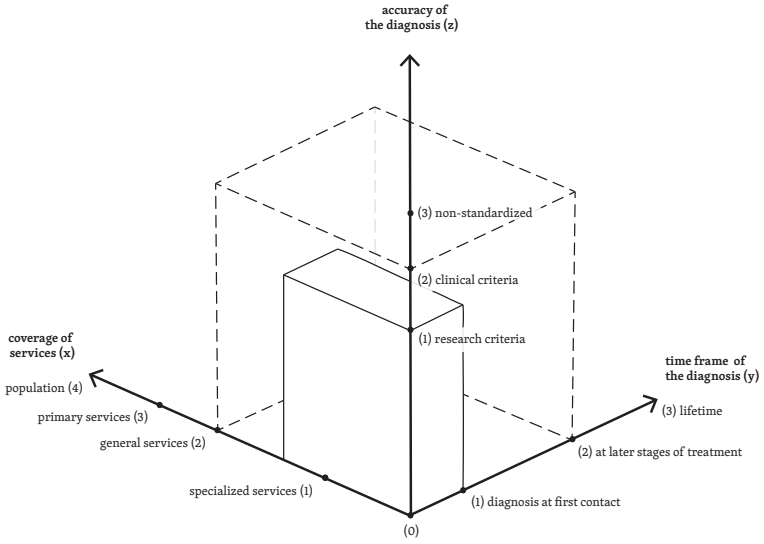
In terms of *service coverage*, the FC method is typically restricted to a (specialized) subset of the psychiatric services, whereas the ePCR method covers all services.

Also, the FC method is typically restricted to younger cases, usually aged <40 years (i.e. early onsets), whereas the ePCR method potentially covers the entire lifespan (i.e. also late and very-late onsets).

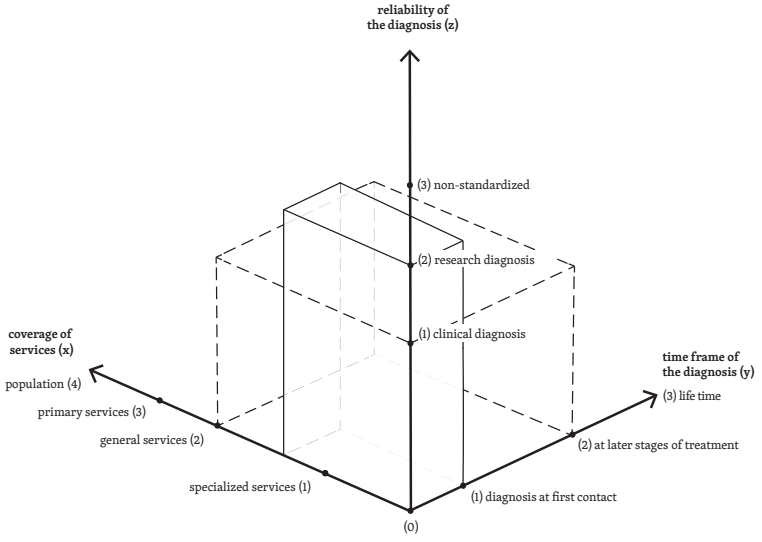
In terms of *time frame to diagnosis*, the FC method (i.e. using a first contact time frame) is restricted to initial diagnoses, whereas the ePCR method (i.e. using a cumulative time frame) covers the entire diagnostic history over the lifespan, and so can work with ultimate diagnoses.

Together, these characteristics imply that the ePCR method should be able to capture most incident cases of treated schizophrenia, whereas *by design* the FC method will capture only a special *subset*, i.e. younger patients who manifest schizophrenia-like symptoms at first contact with (specialized) services.

Service coverage appears to be less important than time frame or reliability among these factors (chapter 7). This means that if the time frame for diagnosis is long enough, full coverage of all psychiatric services might not be required. Most patients will likely be referred to specialized services when they are diagnosed with schizophrenia, and can then be counted.



(a) Initial illustration



(b) Revised illustration

Figure 9.1 Revision of the framework's illustration

The volume of the solid box represents the incidence as estimated in a FC study and the volume of the dotted box the incidence as estimated in an ePCR study.

In terms of *reliability of the diagnosis*, the prototype FC approach (Jablensky et al., 1992; Veling et al., 2007) is based on standardized study diagnoses. But in reality, many FC studies have used clinical diagnoses made in services for Early Detection of Psychosis (chapter 7). The ePCR approach is fully based on clinical (administrative) diagnoses.

So, are standardized research diagnoses better than clinical diagnoses? *If* a clinician decides to formally diagnose schizophrenia, that diagnosis is probably accurate (Dalman et al., 2002; Ekholm et al., 2005; Fusar-Poli et al., 2016; Ludvigsson et al., 2011; Uggerby et al., 2013) and stable [chapter 2, and Fusar-Poli et al. (2016)]. It seems the problem is rather that clinicians often *don't* diagnose schizophrenia when standardized procedures (and DSM criteria) suggest they should (chapter 7). We speculated (chapter 7) that they may be reluctant to formally diagnose schizophrenia due to the stigma associated with the diagnosis. This implies that underestimation (missing true cases) is more likely than overestimation (incorrectly including non-cases) when using clinical diagnoses in either FC or ePCR methods.

The degree to which each approach's study samples represent the overall schizophrenia population is referred to as *generalisability*. Can the FC approach be used to determine risk factors for schizophrenia even though it underestimates the incidence? The issue is that the FC design requires subjects to present to facilities *in a particular way* in order to be counted [6]. The problem is that many risk factors for schizophrenia also affect how people present to facilities. Men and women, migrants and natives, the elderly and the young, for example, have vastly different coping mechanisms, social support, attitudes toward medical care, help-seeking actions, clinical presentation, and so on. They may not be subjected to the same degree of stress or stigma, and they do not break down in the same way or at the same rate. As a result, they do not take the same routes to and from psychiatric care [7]. To put it another way, selection bias is built into the design. The results in chapters 2 and 5 showed that the FC approach does indeed produce a biased sample. We may conclude that risk factors identified in FC studies inform us about a subset of schizophrenia cases that present to services in a particular way, while risk factors identified in ePCR studies can inform us about cases with a broader range of clinical presentations.

6 This way, the FC has requirements stricter than the DSM. Whereas the DSM doesn't require a minimum age of onset, the FC approach does. Also, whereas the DSM does not stipulate which route to and through care a subject should take, the FC approach demands that subjects have psychotic symptoms precisely when they seek help for the first time in their life. Subjects meeting these additional conditions above and beyond the DSM criteria are exceptions: they correspond to subjects with an acute onset, who are often genetically (strongly) predisposed to psychosis and so on.

7 In technical jargon: the FC approach creates a causal structure known as *conditioning on a common effect of two variables* (Hernán et al., 2004).

With *feasability*, we mean the preconditions and costs associated with each method. We will review separately two types of efforts: those to (a) identify all cases, and those to (b) exclude all non-cases.

To (a) identify all cases, an FC study requires a massive effort to include all entry points in the system in the study, and a lot of manpower to monitor and interview subjects with schizophrenia-like symptoms who present at relevant entry points. But it requires no electronic Health Administrative Dataset (eHAD). Creating an eHAD-based ePCR from scratch would be prohibitively expensive. Arguably, eHADs have arisen in advanced economies over the past decade, among other reasons because health insurers have forced a culture of detailed and secure registration for financing purposes. Some of these eHADs can be repurposed as an ePCR. In practice, FC studies are typically short-term initiatives, whereas ePCR studies may be ongoing.

With respect to (b) the efforts to exclude all non-cases, the issue is that known (prevalent) cases can migrate into the catchment area, or return to psychiatric services after dropping out for many years or receiving care outside of the catchment area. In population based studies, such cases have to be identified and excluded from the counts.

In the FC method, researchers can simply ask participants about their diagnostic history and date of settlement during the face-to-face interviews. It is then straightforward to exclude known cases who settled into the area less than six months ago (Jablensky et al., 1992) and known cases from the area who return to psychiatric services. Here, the FC strategy is simple and effective.

In contrast, in the ePCR method, the algorithm queried the history of zipcodes and diagnoses to identify instances of in-migration or returning cases. But because the period at risk extends from childhood to old age, the algorithm requires records reaching back for up to 60 years to be complete. So a key problem with *young* ePCRs [8] is that they cannot distinguish new cases from known cases of schizophrenia unless they have accumulated many decades of data [9].

8 i.e. running on a few decades of data only.

9 To the best of our knowledge, no ePCR currently provides full coverage for the entire period at risk (ages 10 to 100). However, Scandinavian ePCRs, especially those from Denmark, may be very close to that point (Ludvigsson et al., 2011; Mors et al., 2011). Since they are typically national registers, internal migration is not an issue. In addition, they use social security numbers to link municipal databases to the ePCR. That way, they can identify people who have recently arrived in the country. Their ePCRs may also recognise identified cases returning to treatment from as far back as the 1970s, which is ten years earlier than our ePCR.

The good news is that the problem of data scarcity is self-limiting. Within 10 to 20 years several ePCRs will have accumulated data covering service use and diagnostic histories over the entire at risk period. From that point onwards, in-migration and known patients returning to services can be identified with high accuracy. Meanwhile, there are several work-arounds for young ePCRs waiting for data to accumulate. First, it is possible to estimate (and adjust for) the bias introduced by this problem by obtaining data from outside the eHAD, e.g. by consulting municipal data on (re)settlement histories (as we did in chapter 2), or by examining case-notes (as we did in chapter 4). Second, it can be solved completely by contacting cases identified by the ePCR to ask them directly (as done in the FC method, and in the hybrid method proposed in chapter 8).

Answer to the main research question

So *which method (ePCR or FC) should be used to estimate the treated incidence of schizophrenia?* The treated incidence should account for every first onset of schizophrenia. The difficulty is that subjects who are originally diagnosed with another medical condition can later be diagnosed with schizophrenia. That can happen anywhere in the mental health system, while under treatment for another disorder, and after any history of previous diagnoses. Such cases should be counted too, but the FC approach was not designed to detect them. Our answer is nevertheless, that *as long as their respective strengths and limitations are taken into account, both methods can be used*.

We have summarized the pro's and con's of each method in Table 9.1. In short, the FC method does not require an eHAD infrastructure but relies on intensive collaboration between clinicians on a project-like basis. First contact diagnoses at their best are based on standardized research procedures, in practice they are often based on clinical diagnoses. The FC methods has a simple and effective solution for identifying false positives. Inclusion typically stops if the onset is before 40 years of age. Because case finding is restricted to initial diagnoses (i.e. first contact time frame) *the FC approach provides the incidence rate and risk factors of a special subset consisting of roughly one third of the schizophrenia case population*: young subjects presenting schizophrenia-like symptoms at first contact.

The ePCR method requires a data warehouse containing accurate and complete health administrative records from all relevant psychiatric services within a defined catchment area. The database should have accumulated enough data to trace back the entire diagnostic history. If these preconditions are met, ongoing registration of incident cases of schizophrenia is straightforward, and vastly cheaper than any analog FC study. The ePCR can then identify onsets of schizophrenia anywhere in the mental health system, at any stage of treatment and after any history of prior diagnoses. It can still underestimate

Table 9.1 Pro's and con's of each method

		FC	ePCR	hybrid
coverage	services	specialized	general	general
time	diagnosis	initial	ultimate	ultimate
reliability	procedure using	research diagnosis interview	clinical diagnosis decades of data	both interview
generalizability	sample age	subset early onset	all treated entire lifespan	all treated entire lifespan
feasability	requires duration	manpower project	eHAD ongoing	both project

the treated incidence, however, because it relies on clinicians' diagnoses, who tend to be more conservative than researchers (chapter 7). It can provide reliable estimates of the treated incidence over the entire lifespan but—especially for late (LOS) and very-late onset (VLOS) cases—that use requires multiple decades of data to identify and exclude all instances of known cases migrating into the area or returning to psychiatric services after dropping out.

General strengths and limitations of this thesis

The strengths and limitations specific to each primary study (chapters 2, 5) and the meta-analysis (chapter 7) are discussed in each respective chapter.

Our general strategy was to compare both methods directly in a medium sized city in Northern Europe (The Hague, Netherlands 1997–2012) along three dimensions of study design (i.e. service coverage, time frame for diagnosis, and accuracy of diagnosis). We also confirmed our observations by reviewing all incidence studies conducted in Northern Europe and published between 2008 and 2019, applying a regression model that differentiated the impact of variations along the same three dimensions of study design, while also accounting for true differences between study populations (i.e. age and urbanicity).

In our primary studies, both methods were performed according to the highest standards. The data for the FC method were extracted from a first contact study that emulated the

WHO Ten-Country study, and that was classified by others in several meta-analyses (Bourque et al., 2010; Jongsma et al., 2019) as meeting high quality standards. The data for the ePCR method were based on a case register with just over 30 years of electronic health administrative records, covering all general, specialized (i.e. tertiary, emergency or outreaching) psychiatric services in the catchment area. From these data, service pathways and diagnostic histories could be reconstructed, and onsets of schizophrenia could be detected at any stage of treatment anywhere in the mental health system. The clinical diagnoses used in the ePCR were made by well trained clinicians. Once made, they were carefully audited and stable over time (chapter 2) [10].

Our catchment area for the ePCR was population based (city of The Hague) and strictly defined (by zip code). The municipality provided accurate census numbers by year, age (in 5-year brackets), sex and ethnicity. It was representative of medium sized cities in Northern Europe. The studies included in the meta-analysis were also performed in Northern Europe (i.e. United Kingdom, France, Netherlands, Denmark, Sweden, and Finland). We have assumed that these populations were similar enough to our own study population—in terms of organization of psychiatric services, health insurance coverage and help-seeking behavior—to be used for a replication of our findings.

We note three limitations that afflict *all* currently available methods to estimate the incidence of schizophrenia. First, the schizophrenia construct itself is problematic (Blom, 2004; Boyle, 1990; Guloksuz & Os, 2017). Second, only subjects treated for schizophrenia are counted [11]. Third, we do not know if our findings apply outside Northern Europe. Health services are different in the United States, Canada and Australia, but attitudes towards help-seeking seem the same as in Europe. Findings from ePCR studies from these countries also point in the same direction as our studies (Anderson et al., 2018). Our study did not cover schizophrenia incidence estimates from Low and Middle Income countries (LMIC) and we can therefore not make any judgment on replicability in these countries.

10 One could argue that diagnostic criteria have changed over time. This is not a problem here, because the criteria (DSM-IV at the time) did not change during our entire study period. Cases classified under DSM-III criteria during the 1980s were treated as 'known cases' and not counted.

11 According to Guloksuz & Os (2017), the true natural history of schizophrenia cannot be determined from a treated population because that sample only contains people with the most extreme manifestations of the condition and ignores those with milder forms who do not need treatment. This phenomenon is known as 'Berkson's bias' or 'outcome bias.' It arises when a disorder and the need for treatment (for example, arising from co-morbidity and other complicating) *concur*, i.e. together increase the likelihood of being included in the study sample. It can create spurious correlations and confound true risk factors. This bias is arguably greater in the FC approach since it detects only a subset of treated subjects. However, despite covering all paths of care, the ePCR approach is limited to subjects receiving treatment and thus also suffers from "outcome bias".

The degree to which our conclusions can be applies to other types of psychosis, the general population, or LMICs is restricted by these three general limitations. However, within this context (schizophrenia, treated incidence, Northern Europe), they do not invalidate our comparison of two approaches or our observations about the impact of differences in study design.

One limitation is specific for this thesis. The ePCR we used was relatively *young*, in the sense that it had not yet accumulated enough data to cover the entire period at risk for schizophrenia of each subject it monitored. How much could this have affected our findings? The ePCR used in this study had accumulated just over 30 years of data at the time of this thesis. According to sensitivity tests (chapters 2 and 4), up to the age of 40, distortions from in-migration or returning cases were minor (roughly 5 percent). However, beyond that age, the reliability of our ePCR decayed: the number of false positives increased to approximately 15% between the ages of 40–59 years, and even 40% between the ages of 60–79 years (chapter 7). We have adjusted for the bias resulting from this problem with several methods (discussed on page), but some remaining cases may either have been counted that should have been excluded (i.e. misclassification by confusing incident and prevalent cases), or counted correctly, but under the wrong age of onset group (i.e. misclassification by age). Any remaining distortions are arguably minor and inadequate to explain the major (2–5 fold) design-related effects found in this thesis.

Implications

The differences uncovered in this thesis between the FC and ePCR approaches have practical implications for researchers, clinicians, and policymakers.

Implications for policy makers

For policy makers, our findings imply that two to four times more persons develop schizophrenia every year than current incidence models assume. These subjects are already under treatment, so there is no need to expand general psychiatric services. But the provision of care for schizophrenia should be adjusted for the fact that the majority of new cases of schizophrenia are found among patients *already under treatment* for another mental disorder. This other half (chapter 8) may have other needs than subjects with an early/acute psychosis type of onset.

At a national and global scale, the calculations of the *global burden of disease* from schizophrenia need to be adjusted. Currently, they largely seem to be based on FC studies, which

implies a serious underestimation by a factor two or more (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators & Murray, 2018).

Implications for researchers

Whereas the FC design can be considered as the first solution to the limitations of traditional case registers for epidemiological research, psychiatric case registers based on modern electronic health administrative data sets now offer a second—much easier, much cheaper—solution to the same problem. ePCRs solve several limitations of the first contact method, adding the possibility to reconstruct individual pathways (both treatment and diagnostic) over time, across all psychiatric services within a catchment area. This way, they can provide a longitudinal perspective on the dynamics of psychosis over time.

We are aware that for many areas, especially in Low and Middle Income countries (LMIC) the ePCR method is not yet an option as it requires electronic health administrative data. These need to be complete, extensive and of high quality. It will take considerable time before such data will become more widely available. Until that time, the lack of ePCRs will restrict the value of international comparisons. In LMIC countries, the FC method may remain the only option for now, with the risk of systematically underestimating the incidence of schizophrenia.

If researchers have no other option than to use a FC method, they should be aware of its limitations, as the FC method seriously underestimates the incidence, and its selection bias distorts its risk factor estimates. They may want to make additional efforts, deviating from the original FC design, to identify cases at older ages, and at later stages of treatment.

We should also untangle the *relationship between risk factors and time*. The FC method covers only a short section of the at risk period for schizophrenia. As such, it cannot distinguish between factors that *cause* the onset of schizophrenia (i.e. among subjects which would have otherwise never developed the disorder), and factors that *accelerate* its onset (i.e. among subjects who would have otherwise developed the disorder later). The former factors raise the lifetime morbid risk (LMR), whereas the latter don't [12].

12 In general, a finer-grained study of the natural history of schizophrenia is needed (Os & Kapur, 2009). Such an analysis should take into account the complex dynamics that occur as single psychotic symptoms (Guloksuz & Os, 2017) progress (for some) into severe psychosis and chronic disability: as individuals first seek help, and some then percolate through successive filters and layers (Goldberg, 1992), ever deeper into the mental health system, sometimes in a straight line, but often with false starts and other diagnoses along the way.

We have argued in chapter 8 that a *hybrid* approach is possible, which combines the best of each method. In this hybrid, any subject with a first administrative diagnosis of psychosis (any type) would undergo standardized diagnostic protocols to arrive at a research diagnosis. This solution would be optimal in terms of coverage (complete), time frame to diagnosis (cumulative) and reliability (research diagnosis). It would require a high quality eHAD covering all services, but would not require multiple decades of data, because false-positives could be identified easily during the interviews.

Implications for clinical practice

Finally, our findings challenge the *textbook stereotype* of schizophrenia as a "devastating disorder with acute onset in the second or third decade of life" (National Institute of Mental Health, 2020). It has become clear that there is wide variation in how schizophrenia emerges. The onset is usually insidious, and in western societies most cases seek care for other disorders long before the onset of psychosis. Most new cases of schizophrenia can be found among subjects who are already under treatment. Onset after age 40 is common. Well-known risk factors for schizophrenia (gender, migrants, socio-economic status) are probably correct for cases with early (acute) onset, but their applicability to schizophrenia in general is unclear.

So we should *get to know the other half* of the schizophrenia population. What kind of care do they require? The older patient with late-onset schizophrenia, in particular, has received little attention (Cohen et al., 2000). In comparison to subjects with early onset schizophrenia (EOS), subjects with late onset schizophrenia (LOS) may have had more time to complete their education, find a career, and/or settle with partners and children before becoming ill. They would most likely need assistance to preserve what has been accomplished. Several scholars (Clay et al., 2018; Greenfield et al., 2016; Lappin et al., 2016) have recently suggested expanding Early Psychosis programs to include cases with LOS. Our findings support this development.

10

Samenvatting (Dutch summary)

Achtergrond

Voor dit proefschrift was onze hoofdvraag: Wat is de beste methode om de behandelde incidentie van schizofrenie te bepalen?

Tot voor kort werd de behandelde incidentie wereldwijd geschat op 20 per 100 000 persoonsjaren en de levenslange prevalentie ('lifetime morbidity rate' of LMR) op 700 per 100 000 personen. Op de WHO ranglijst van ziektes die het meeste leed veroorzaken (in 'disability adjusted life years' ofwel DALYs) staat schizofrenie in het Westen in de top 10.

Het is ingewikkeld om de incidentie van schizofrenie te bepalen want het ziektebeeld ontstaat geleidelijk, lijkt in het begin ook op depressie, angst of verslaving, en niet iedereen met schizofrenie zoekt hulp, of durft over al zijn klachten te praten. Het gebeurt daarom regelmatig dat de juiste diagnose pas na jaren behandeling wordt gesteld.

Tot voor kort was de First Contact (FC) methode de standaard manier om de incidentie te bepalen. Onderzoekers spraken af met alle hulpverleners in een omschreven gebied om bij nieuwe patiënten uit te kijken naar symptomen van schizofrenie vooral onder mensen jonger dan 40 jaar. Wie schizofrenie achtig gedrag vertoont werd doorverwezen naar de onderzoekers voor een zorgvuldige diagnose. Deze methode is ontwikkeld in de jaren 1970–1990 toen computers nog niet wijd gebruikt werden. Het was in die tijd een grote verbetering omdat het mogelijk werd om in uiteenlopende groepen steeds op precies dezelfde manier mensen te tellen. De betrouwbaarheid van deze methode was gebaseerd op drie aannames:

1. Mensen met schizofrenie krijgen geen psychiatrische zorg voordat ze psychotisch worden.
2. Na je 40ste kun je geen schizofrenie meer krijgen.
3. Mensen met schizofrenie die gevonden worden met de FC methode, hebben dezelfde eigenschappen als mensen met schizofrenie die niet geteld worden.

Het is ook mogelijk om de incidentie te bepalen met een casus register, maar registers waren in de 20ste eeuw nog onbetrouwbaar omdat er geen eenstemmigheid was over diagnosen, en registratie vaak summier was. Registers voor regio's moesten vaak handmatig worden bijgehouden. In de laatste decennia hebben twee ontwikkelingen verbetering gebracht in deze situatie. Ten eerste wordt de DSM nu overal gebruikt. Ten tweede hebben grote GGZ instellingen betrouwbare, elektronische administratiesystemen ('eHADs'), opgebouwd. Hierdoor is het nu mogelijk om een elektronisch psychiatrisch casus register (ePCR) op te zetten, dat in opzet veel betrouwbaarder is.

Voor dit proefschrift is een ePCR opgezet voor alle inwoners van de gemeente Den Haag die in de periode 1997–2012 tussen de 20–79 jaar oud waren. Dat was mogelijk omdat een grote GGZ instelling, Parnassia, een vrijwel monopolie heeft op alle psychiatrische zorg in de stad en alle gegevens digitaal waren opgeslagen. Van iedereen bij wie in die periode een psychose is vastgesteld, is in de digitale archieven de volledige histories van alle gestelde diagnosen sinds 1980 in kaart gebracht.

Veling en Hoek hadden al eerder in Den Haag de FC methode gebruikt om het incidentieijfer te berekenen over 1997–2005. Hierdoor was het mogelijk om de FC methode en de nieuwe ePCR methode direct te vergelijken in dezelfde bevolking en over dezelfde periode.

Bevindingen

In hoofdstuk 2 hebben we met beide methodes in dezelfde bevolking (inwoners van Den Haag tussen 20–54 jaar oud) op hetzelfde moment (jaren 1997–2005) het incidentiecijfer geschat. De schatting van de ePCR was ongeveer drie keer hoger dan van de FC methode: 69 tegen 21 gevallen per 100 000 persoonsjaren. De FC methode telt dus maar een klein deel van het totaal aantal gevallen.

In hoofdstuk 3 hebben wij de eerste aanname getest. We hebben 1735 mensen tussen 18–35 jaar onderzocht die tussen 2005–2009 volgens de ePCR voor het eerst formeel een psychose hadden gekregen. Wij vonden dat van alle mensen met de diagnose schizofrenie tenminste 38% al eerder een andere diagnose had gehad die geen psychose was.

In hoofdstuk 4 hebben wij de tweede aanname getest. We hebben de ePCR methode gebruikt om de incidentie van schizofrenie te bepalen voor alle inwoners van Den Haag tussen de 20–79 jaar, tussen 1997–2012, naar leeftijdsgroep, en naar geslacht. Bijna de helft (46%) van de gevonden gevallen kregen hun diagnose pas na hun 40ste. Mensen kunnen dus zeker na hun 40ste nog schizofrenie krijgen.

In hoofdstuk 5 hebben wij de derde aanname getest. Wij hebben weer de twee methoden vergeleken, maar ditmaal hebben we de relatieve incidentie bepaald voor autochtone Nederlanders en voor de drie grootste groepen allochtonen in Den Haag. Het was al bekend dat allochtone Nederlanders vaker schizofrenie krijgen dan autochtone Nederlanders; en wij vonden ook dat de incidentie onder allochtonen ongeveer 2x hoger was dan onder autochtonen. Maar het werd duidelijk dat de FC methode dit effect ten onrechte overschat, en zeker bij bepaalde groepen, zoals jonge Marokkaanse mannen. Het deel

van de mensen met schizofrenie die gevonden worden met de FC methode zijn dus niet representatief voor het geheel.

In hoofdstuk 6 introduceerden wij een model om alle gebruikte methoden te beoordelen op drie verschillende dimensies, om zinvolle vergelijkingen van de uitkomsten mogelijk te maken.

Die drie assen waren:
1. *Dekking*: De mate waarin in diverse niveaus van psychiatrische zorg gebruikt zijn om nieuwe gevallen te registreren (i.e. gespecialiseerde zorgprogramma's, de hele GGZ, of het hele zorgsysteem).
2. *Duur van de diagnostiek*: i.e. alleen eerste werkdiagnose, alle volgende diagnosen in de GGZ, of alle diagnosen gedurende de hele levensloop.
3. *Betrouwbaarheid van de diagnose*: De wijze waarop de diagnose is gesteld (i.e. volledig gestandaardiseerd voor wetenschappelijk onderzoek, klinische diagnose door een medisch specialist, of informele diagnose door leken en niet-medici).

In hoofdstuk 7 hebben wij relevante studies uit Noord-Europa tussen 2008–2019 vergeleken. Wij hebben uiteindelijk 17 metingen uit 12 studies volgens ons drie-assen model ingedeeld. In een meta-regressie blek dat ons drie-assen model 67% van de variatie tussen studies verklaarde. Als we leeftijd en verschillen tussen stad en platteland ook meewogen, verklaarde ons model 91% van de variatie. Metingen in gespecialiseerde zorgprogramma's bleken niet wezenlijk anders te zijn dan in de hele GGZ (IRR 1.12; 95% CI 0.88–1.43). Studies die rekening hielden met alle opeenvolgende diagnosen in de GGZ vinden 4.04 keer (95% CI 3.14–5.2) meer gevallen dan studies die alleen de eerste werkdiagnose gebruikt hadden. Tot onze eigen verrassing kwamen studies met gewone klinische diagnosen de helft lager uit dan studies met gestandaardiseerde research diagnosen (0.55; 95% CI 0.43–0.72).

In hoofdstuk 8 hebben we een 'hybride' methode voorgesteld die het beste van beide methodes verenigt.

Beschouwing

We waren aanvankelijk verrast toen uit de vergelijking in hoofdstuk 2 bleek dat de ePCR methode 3x meer gevallen vindt dan de FC methode. Door het werk in hoofdstukken 3–5 is nu duidelijk geworden waarom. De twee methodes verschillen op drie manieren. Ten eerste, de ePCR methode houdt rekening met alle opeenvolgende diagnosen, waardoor 4x

meer gevallen gevonden worden. Ten tweede is de ePCR gebaseerd op klinische diagnosen, wat de telling halveert ten opzichte van de FC methode, die gebaseerd is op gestandaardiseerde diagnostiek. Tenslotte is de dekking van de ePCR methode breder, wat de schatting weer iets verhoogt. Alles bij elkaar verklaart dit het verschil van ongeveer 3x. Verschillende uitkomsten uit vergelijkbare populatie kunnen volgens deze redenering worden verklaard door verschillende methodes die de onderzoekers gebruiken.

Welke methode is beter?

Bij de FC methode is de dekking meestal beperkt tot specialistische programmas voor mensen met psychose; die is dus kleiner dan bij de ePCR methode die alle psychiatrische zorg dekt. In de praktijk maakt dit weinig uit: uiteindelijk komen bijna alle gevallen van schizofrenie wel een keer in beeld bij de gespecialiseerde programmas waar ze alsnog geteld worden.

Met betrekking tot de duur van de diagnostiek gebruikt de FC methode meestal de eerste werkdiagnose onder de 40 jaar, terwijl de ePCR methode de ontwikkeling van het ziektebeeld over het hele leven bestrijkt. De ePCR methode is dus in staat om vrijwel alle nieuwe gevallen van schizofrenie te tellen die zich onder behandeling stellen, terwijl de FC methode slechts psychotische jong-volwassenen telt die zich melden bij gespecialiseerde zorgprogramma's.

Met betrekking tot betrouwbaarheid van de diagnose zijn de FC en ePCR methoden zowel verschillend als gelijk. De FC methode zou formeel moeten werken met gestandaardiseerde onderzoeksdiagnosen, maar in de praktijk worden vaak klinische diagnosen gebruikt. De ePCR gebruikt altijd klinische diagnosen.

Maar welke is beter, een onderzoeksdiagnose of een klinische diagnose? Klinische diagnosen worden doorgaans zorgvuldig gesteld, en houden vervolgens lang stand. Het lijkt erop dat psychiaters de diagnose vaak *niet* stellen terwijl dit volgens de DSM wel zou mogen—wellicht uit angst voor het stigma. Studies gebaseerd op klinische diagnosen lijken dus de incidentie van schizofrenie te onderschatten ten opzichte van studies gebaseerd op onderzoeksdiagnosen. Wij hebben ons drie-assen model later aangepast aan deze bevinding.

Als de FC methode het incidentieijfer onderschat, kan ze dan nog wel gebruikt worden om relatieve incidentiecijfers en risicofactoren te bepalen? De FC methode stelt *extra* eisen voordat een geval geteld mag worden: de patiënt moet niet alleen schizofrenie hebben volgens de DSM, maar moet ook herkenbaar psychotisch zijn op het moment dat hij

voor het eerst hulp zoekt. Deze extra eis maakt de meting onbetrouwbaar ('selectie bias') omdat mannen vs. vrouwen, autochtonen vs. allochtonen, ouderen vs. jongeren enz. niet op dezelfde manier ontregelen, of even snel om hulp vragen. De ene groep zal vaker 'aan de voordeur' psychotisch zijn dan de andere. Maar *eerder* in beeld komen is niet hetzelfde als *vaker* de diagnose krijgen. Wij kunnen dus niet zomaar aannemen dat risicofactoren die gelden voor mensen met een acuut beloop en vroeg ontstaan ook gelden voor mensen met een milder, geleidelijker beloop.

Beide methoden zijn dus bruikbaar mits men bewust is van de sterke en zwakke kanten.

De FC methode is niet geschikt om de incidentie voorbij het 40ste jaar te meten, en leert ons niets over de 'mildere' groep die zich anders of later presenteert. De ePCR methode identificeert veel meer mensen, maar mist er een aantal omdat psychiaters de diagnose relatief te weinig stellen. Als er tientallen jaren data van hoge kwaliteit beschikbaar zijn, biedt de ePCR veel mogelijkheden, met name voor de studies van zorgpaden door de GGZ, of over de incidentie van schizofrenie bij ouderen.

Beperkingen

Dit proefschrift heeft twee belangrijke beperkingen. Onze studies is alleen gebaseerd op resultaten uit Noord Europa. Ook had ons ePCR nog niet genoeg data verzameld om de volledige risico periode (het hele leven) te omvatten. Onze ePCR had 30 jaar verzameld, waar idealiter 50–60 gewenst zijn, met als gevolg dat de incidentie voor mensen van middelbare of oudere leeftijd overschat zou worden. We hebben deze verstoring grotendeels opgevangen met handmatige correcties.

Implicaties

Voor beleidsmakers betekenen onze bevindingen dat elk jaar twee tot vier keer zoveel mensen voor het eerst de diagnose schizofrenie krijgen dan eerder werd aangenomen. Deze mensen waren al onder behandeling, dus de zorg hoeft niet te worden uitgebreid. Maar er moet rekening worden gehouden met het feit dat de meeste nieuwe gevallen gevonden worden bij patiënten die al in behandeling zijn voor iets anders, en niet bij diegenen die met acute psychose voor het eerst in beeld komen. Ook moet opnieuw berekend worden waar schizofrenie moet staan op de wereldranglijst van belangrijkste ziektes, want die berekening is gebaseerd op FC cijfers. Met deze correctie zal schizofrenie veel hoger op de lijst komen te staan.

Voor onderzoekers betekent het dat er nu een goed alternatief voor de FC methode beschikbaar is gekomen. Met name is het nu mogelijk om longitudinale trajecten van diagnosen en zorggebruik in detail te bestuderen.

Daardoor kan de relatie tussen risicofactoren en tijd worden ontrafeld; bijvoorbeeld kan onderscheid maken tussen factoren die zorgen dat schizofrenie *vaker* ontstaat vs. factoren die zorgen dat (onvermijdelijke) schizofrenie *vroeger* ontstaat.

In de vele landen waar de zorg registratie systemen nog niet betrouwbaar genoeg zijn om een ePCR op te zetten, blijft de FC methode de beste optie. In dat geval moeten onderzoekers wel rekening houden met het feit dat de FC methode de incidentie fors onderschat, vooral bij ouderen en bij diegenen die al in zorg zijn, en dat dit probleem de schatting van risico-factoren vervormt (selectie bias). In de hybride methode die wij in hoofdstuk 8 bepleiten worden nieuwe gevallen van psychose opgespoord met een ePCR, en vervolgens onderworpen aan gestandardiseerde diagnostiek zoals bij de FC methode. Deze benadering, alhoewel kostbaar, zou optimaal zijn in alle drie dimensies van ons model (dekking, duur van de diagnostiek, betrouwbaarheid) zonder dat er tientallen jaren van data nodig zijn.

Tenslotte spreken onze bevindingen het cliché beeld uit tekstboeken tegen — dat schizofrenie vooral ontstaat voor het 40ste jaar, en dat mensen pas met een acute psychose in beeld komen bij de GGZ. Uit dit proefschrift blijkt dat er grote variaties bestaat in hoe, en hoe laat, schizofrenie ontstaat. In Noord Europa ontstaat de ziekte meestal geleidelijk; de meeste gevallen zijn al jaren in beeld bij de GGZ voordat psychose zichtbaar wordt. Het komt vaak voor dat de diagnose schizofrenie pas na het 40ste levensjaar wordt gesteld.

Schizofrenie is meer dan een “verwoestende stoornis, met acuut begin in de tienerjaren of studentenleeftijd”. Dat is de subgroep die gevangen wordt door de FC methode. Zij hebben vooral hulp nodig om hun leven op de rails te krijgen. We weten nog maar weinig over ouderen bij wie schizofrenie voor het eerst aan het licht komt. Deze mensen hebben meer tijd gehad om een opleiding af te ronden, een gezin te stichten, carrière te maken voordat ze ziek werden. Zij hebben vooral hulp nodig om dat wat bereikt is zo goed mogelijk te behouden.

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Addendum

Supplement 1: Details of the error rates (chapter 4)

	in random sample					in full dataset			
	before		after		fraction	before	fraction	after	computed
sex	age	n	age	n	%	obs	%	age	n
Male	20–29					678			
Male	30–39					557			
Male	40–49	53	10–19	2	0.038	405			
Male	40–49	53	_inmigration	4	0.075	405			
Male	40–49	53	20–29	8	0.151	405	0.151	20–29	61.1
Male	40–49	53	30–39	5	0.094	405	0.094	30–39	38.2
Male	40–49	53	40–49	34	0.642	405	0.642	40–49	259.8
Male	50–59	33	_inmigration	4	0.121	215			
Male	50–59	33	20–29	1	0.030	215	0.030	20–29	6.5
Male	50–59	33	30–39	3	0.091	215	0.091	30–39	19.5
Male	50–59	33	40–49	4	0.121	215	0.121	40–49	26.1
Male	50–59	33	50–59	21	0.636	215	0.636	50–59	136.8
Male	60–69	19	_inmigration	2	0.105	97			
Male	60–69	19	30–39	2	0.105	97	0.105	30–39	10.2
Male	60–69	19	40–49	1	0.053	97	0.053	40–49	5.1
Male	60–69	19	50–59	8	0.421	97	0.421	50–59	40.8
Male	60–69	19	60–69	6	0.316	97	0.316	60–69	30.6
Male	70–79	6	_inmigration	1	0.167	46			
Male	70–79	6	70–79	5	0.833	46	0.833	70–79	38.3
Male	80+	4	_inmigration	1	0.250	17			
Male	80+	4	80+	3	0.750	17			
Female	20–29					202			
Female	30–39					258			
Female	40–49	41	10–19	2	0.049	250			
Female	40–49	41	_inmigration	7	0.171	250			
Female	40–49	41	20–29	1	0.024	250	0.024	20–29	6.1
Female	40–49	41	30–39	6	0.146	250	0.146	30–39	36.6
Female	40–49	41	40–49	25	0.610	250	0.610	40–49	152.4
Female	50–59	29	20–29	2	0.069	188	0.069	20–29	13.0
Female	50–59	29	30–39	4	0.138	188	0.138	30–39	25.9
Female	50–59	29	50–59	23	0.793	188	0.793	50–59	149.1
Female	60–69	34	_inmigration	6	0.176	155			
Female	60–69	34	20–29	1	0.029	155	0.029	20–29	4.6
Female	60–69	34	30–39	6	0.176	155	0.176	30–39	27.4
Female	60–69	34	40–49	2	0.059	155	0.059	40–49	9.1

	in random sample					in full dataset			
	before		after		fraction	before	fraction	after	computed
sex	age	n	age	n	%	obs	%	age	n
Female	60–69	34	50–59	6	0.176	155	0.176	50–59	27.4
Female	60–69	34	60–69	13	0.382	155	0.382	60–69	59.3
Female	70–79	20	10–19	1	0.050	118	0.050	10–19	5.9
Female	70–79	20	_inmigration	2	0.100	118			
Female	70–79	20	30–39	3	0.150	118	0.150	30–39	17.7
Female	70–79	20	40–49	2	0.100	118	0.100	40–49	11.8
Female	70–79	20	60–69	2	0.100	118	0.100	60–69	11.8
Female	70–79	20	70–79	10	0.500	118	0.500	70–79	59.0
Female	80+	5	30–39	1	0.200	73	0.200	30–39	14.6
Female	80+	5	40–49	1	0.200	73	0.200	40–49	14.6
Female	80+	5	80+	3	0.600	73			

Supplement 2: Case characteristics (chapter 5)

	By both				Extra by ePCR				Total			
Migrant group	N	% male (n)	AFC (sd)	DPT (sd)	N	% male (n)	AFC (sd)	DPT (sd)	N	% male (n)	AFC (sd)	DPT (sd)
Native Dutch	81	74.1 (60)	26.3 (5.8)	2.8 (3.4)	278	65.1 (181)	32.2 (8.7)	7.2 (6)	359	67.1 (241)	30.8 (8.5)	6.2 (5.8)
Caribbean	35	74.3 (26)	27.3 (7.8)	2.4 (2.2)	151	68.9 (104)	33.0 (9.0)	4.6 (4.3)	186	69.9 (130)	31.9 (9.1)	4.1 (4.1)
Turkish	24	70.8 (17)	25.8 (5.9)	1.8 (1.5)	35	74.3 (26)	29.0 (7.3)	5.9 (4.6)	59	72.9 (43)	27.7 (6.9)	4.2 (4.1)
Moroccan	34	76.5 (26)	24.8 (4.7)	1.9 (1.8)	54	79.6 (43)	28.9 (8.4)	5 (4)	88	78.4 (69)	27.3 (7.4)	3.8 (3.7)
Other	39	74.4 (29)	26.2 (7.4)	1.9 (2.5)	147	62.6 (92)	33.0 (8.7)	4.3 (4.4)	186	65.1 (121)	31.6 (8.9)	3.8 (4.2)
Total	213	74.2 (158)	26.2 (6.3)	2.3 (2.7)	665	67.1 (446)	32.1 (8.8)	5.7 (5.2)	878	68.8 (604)	30.7 (8.6)	4.9 (5.0)

By both: incident cases identified by both methods; Extra by ePCR: additional cases identified by the electronic Psychiatric Case Register; AFC (sd): age at first contact with mental health services (standard deviation); DPT (sd): duration of prior treatment before the index diagnosis of schizophrenia (standard deviation)

Supplement 3: Sensitivity analyses (chapter 5)

	Caribbean		Turkish	
Number of cases	180		57	
Indicators of diagnostic validity				
Years in catchment area before index (95% CI)	9.4	(2.6 to 22.4)	14.1	(4.7 to 22.5)
Share LTF or retracted during first year after index (n)	10.6	(19)	3.5	(2)
Mean no of audits (95% CI)	4.5	(3 to 6)	5	(3 to 7)
Mean no of teams who did audits (95% CI)	2	(1 to 3)	2	(1 to 4)
Mean interval between audits, in years (95% CI)	1.1	(0.7 to 1.5)	1.1	(0.8 to 1.4)
5-year stability (95% CI)	89.5	(84.5 to 94.7)	92.7	(85.0 to 1)
Levels of available evidence to support clinical diagnosis of schizophrenia				
Research diagnosis (%)	34	(20.0)	23	(41.1)
Very high (%)	52	(30.6)	17	(30.4)
High (%)	69	(40.6)	13	(23.2)
Standard (%)	15	(8.8)	3	(5.4)
Suspect for in-migration (excluded)	10		1	
Incidence rates at incremental levels of available evidence				
Including only research diagnosis (95% CI)	21	(15 to 30)	30	(19 to 45)
Including also very high quality (95% CI)	54	(43 to 67)	52	(37 to 71)
Including also high quality (95% CI)	97	(83 to 114)	69	(51 to 90)
Including also standard quality (95% CI)	107	(91 to 124)	73	(55 to 94)
Including all cases — even suspect cases (95% CI)	113	(97 to 131)	74	(56 to 96)
Incidence ratios at incremental levels of available evidence				
Including only research diagnosis (95% CI)	2.0	(1.3 to 3)	2.8	(1.7 to 4.5)
Including also very high quality (95% CI)	1.8	(1.4 to 2.4)	1.8	(1.2 to 2.5)
Including also high quality (95% CI)	2.1	(1.7 to 2.5)	1.5	(1.1 to 1.9)
Including also standard quality (95% CI)	2.1	(1.7 to 2.5)	1.4	(1.1 to 1.9)
Including all cases — even suspect cases (95% CI)	2.2	(1.8 to 2.6)	1.4	(1.1 to 1.9)

Morrocan	Other	Native Dutch	All migrants	Total
77	183	346	497	843
7.4 (2.9 to 13.8)	4.8 (0.8 to 10.2)	11.1 (3.3 to 27.4)	7.4 (1.5 to 17.1)	8.5 (2.2 to 21.7)
7.8 (6)	24 (44)	15.9 (55)	14.3 (72)	14.9 (126)
4 (3 to 6)	4 (1 to 6)	5 (2 to 7)	4 (3 to 6)	4 (2 to 7)
2 (1 to 3)	2 (1 to 3)	2 (1 to 4)	2 (1 to 3)	2 (1 to 3)
1.2 (0.9 to 1.7)	1.1 (0.6 to 1.5)	1 (0.7 to 1.4)	1.1 (0.7 to 1.5)	1.1 (0.7 to 1.5)
88.1 (80.6 to 96.2)	92.8 (88.3 to 97.5)	90.6 (87.1 to 94.2)	90.7 (87.8 to 93.7)	90.6 (88.4 to 92.9)
26 (35.6)	42 (25.1)	70 (20.9)	125 (26.8)	195 (24.3)
26 (35.6)	55 (32.9)	124 (37)	150 (32.2)	274 (34.2)
20 (27.4)	53 (31.7)	115 (34.3)	155 (33.3)	270 (33.7)
1 (1.5)	17 (10.2)	26 (7.8)	36 (7.7)	62 (7.7)
4	16	11	31	42
48 (31 to 70)	16 (11 to 21)	11 (8 to 13)		
96 (71 to 125)	36 (29 to 44)	29 (25 to 34)		
132 (104 to 167)	55 (47 to 65)	47 (42 to 52)		
134 (105 to 169)	62 (53 to 72)	51 (45 to 57)		
141 (112 to 177)	68 (58 to 78)	52 (47 to 58)		
4.5 (2.8 to 7)	1.5 (1 to 2.1)	ref		
3.3 (2.4 to 4.4)	1.2 (1 to 1.6)	ref		
2.8 (2.2 to 3.6)	1.2 (1 to 1.4)	ref		
2.6 (2 to 3.4)	1.2 (1 to 1.5)	ref		
2.7 (2.1 to 3.4)	1.3 (1.1 to 1.5)	ref		

Supplement 4: Search strategy for PubMed (chapter 8)

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(((((((((inciden*[Title/Abstract]) OR epidemiolog*[Title/Ab-
stract])) OR ((((((episod*[Title/Abstract]) OR contact*[Title/
Abstract]) OR admission*[Title/Abstract]) OR admit*[Title/Ab-
stract])) AND (((first*[Title/Abstract]) OR 1st[Title/Abstract])
OR hospital*[Title/Abstract]))) OR ((case[Title/Abstract]) AND
register*[Title/Abstract])) OR case control*[Title/Abstract]) OR
((((prospectiv*[Title/Abstract]) OR population*[Title/Abstract])
OR communit*[Title/Abstract]) OR survey*[Title/Abstract]))) AND
(((((((((schizo*[Title/Abstract]) OR (((psychotic[Title/Abstract])
OR psychosis[Title/Abstract]) OR psychoses[Title/Abstract])) OR
bipolar disorder*[Title/Abstract]) OR delusion* disorder[Title/
Abstract]) OR (((((illness*[Title/Abstract]) OR disorder*[Title/Ab-
stract])) AND mental[Title/Abstract]) AND (((severe[Title/Abstract])
OR serious[Title/Abstract]) OR chronic[Title/Abstract]))) OR
SMI[Title/Abstract]) OR mani* depressi*[Title/Abstract]) OR chronic
psychosis) OR schizoaffective disorder) AND ( "2018/01/01"[PDat] :
"2019/12/31"[PDat] )
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Abbreviations

CASH	Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology (doi:10.1001/archpsyc.1992.01820080023004)
CI	Confidence Interval
DALY	Disability Adjusted Life Years
DPT	Duration of Prior Treatment
DSM	Diagnostic Statistical Manual
DUP	Duration of Untreated Psychosis
EIP	Early Intervention in Psychosis (a.k.a. EPI)
EOS	Early Onset Schizophrenia, i.e. < 40 years
EPI	Early Psychosis Interventions (a.k.a. EIP)
FC	First Contact design
FEP	First Episode of Psychosis
FES	First Episode of Schizophrenia
GGZ	Mental Health Services [Dutch 'Geestelijke Gezondheids Zorg']
GP	General Practitioner
HAD	Health Administrative Database
ICD	International Classification of Diseases
IQR	Inter Quartile Range
IR	Incidence Rate per 100 000 person years
IRAOS	Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses (doi:10.1001/archpsyc.1992.01820080023004)
IRR	Incidence Rate Ratio
LMIC	Low and Middle Income Countries
LMR	Lifetime Morbidity Rate
LOS	Late Onset Schizophrenia, i.e. ≥ 40 and < 60 years
LPR	Longitudinal Psychiatric Register [deprecated], a.k.a. ePCR
NOS	Not Otherwise Specified
PCR	Psychiatric Case Register
PLE	Psychosis Like Experiences
PPI	Parnassia Psychiatric Institute
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Post Traumatic Stress Disorder
PY	Person Years
RCT	Randomized Controled Trial
REML	REstricted Maximum Likelihood

SES	Socio-Economic Status
VLOS	Very Late Onset Schizophrenia, i.e. ≥ 60 years
VLOSLP	Very Late Onset Schizophrenia Like Psychosis, a.k.a. VLOS
WHO	World Health Organization
YLD	Years Lived with Disability

Curriculum Vitae

Simon Jan Hogerzeil werd op 30 augustus 1978 geboren in Den Haag. Hij groeide op in Ghana, Egypte en Zwitserland. In 1997 behaalde hij zijn *certificat de Maturité fédérale* bij het Gymnase de Bellerive in Lausanne (CH) en begon met de studie Geneeskunde aan de Universiteit Leiden.

Voor zijn doctoraal liep hij in 2001 een wetenschappelijke stage in het Academisch Ziekenhuis van de Universiteit van Nagasaki, Japan. In 2002 verrichte hij epidemiologisch onderzoek naar sterfte aan boord van slavenschepen van de Middelburgsche Commercie Compagnie in de 17e eeuw. Als keuze co-schap Sociale Geneeskunde bezocht hij in 2004 een dertigtal plattelands zorgposten in vier provincies van Iran, evenals de pyschiatrische noodhulp na de aardbeving van 2003 in de stad Bam (provincie Kerman). In 2004 ontving hij zijn artsenbul van de Universiteit Leiden, en begon als arts-assistent op voor het Eerste Psychose programma van de Parnassia Groep. In 2005 werd hij toegelaten tot een 'Agiko' traject, waarin dit promotieonderzoek gecombineerd werd met de opleiding tot medisch specialist, en de opleiding tot Epidemioloog B. Voor het onderzoek gebruikte hij de administratieve gegevens van de Parnassia groep als een psychiatrisch casusregister.

Na het afronden van zijn opleiding tot psychiater (2011) werkte hij van 2011–2017 op een polikliniek voor Transculturele Psychiatrie. In 2013 deed hij de opleiding tot rapporteur Pro Justitia. Van 2013–2019 hield hij een kleine privé praktijk voor Psychiatrie en Psychotherapie. Van 2017–heden werkte hij als psychiater ad interim opeenvolgend in de Acute Psychiatrie, derdelijns zorg voor volwassenen met Autisme, verschillende FACT teams, de gereformeerde christelijke GGZ, en op dit moment in de Kind- en Jeugdpsychiatrie.

Van 2011–2017 gaf hij als supervisor en tutor onderwijs aan psychiaters in opleiding bij de Parnassia Groep. Van 2015–2018 was hij gastdocent aan de faculteit Social Work van de Hogeschool Utrecht, en verzorgde hij post-hbo onderwijs over Gecompliceerde Rouw. In 2016 richtte hij samen met zijn vrouw een postbachelor opleidingsinstituut op (www.socialeacademieutrecht.nl), dat meerjarige deeltijdopleidingen tot psychosociaal therapeut verzorgt. Op de academie geeft hij zelf ook les. De komende jaren wil hij nieuwe (digitale) vormen van klinisch onderwijs en medisch specialistische bijscholing ontwikkelen.

Simon is getrouwd (2009) met Josje Geerse. Samen hebben zij twee zoons: Joris (2011) en Lieven (2015). Zij wonen in Oud Zuilen, bij Utrecht.

List of Publications

See the author's ORCID: 0000-0001-6269-179X page for an up-to-date list of publications

Baudelaire, C. P. Hogerzeil, S. J. (vertaler). (1998). *La Fanfarlo*. Hoorn: Hoogland & van Klaveren. isbn: 90 76347 02 6

van Hemert, A. M., Hogerzeil, S. J., Kwakkelstein, R., de Zoete, K., Geestelijke gezondheidszorg in Den Haag. (2006) *Gezondheidsmonitor Gemeente Den Haag*. Den Haag: Dienst OC&W; blz. 25-32.

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Hogerzeil, S. J., Richardson, D. (2007). Slave Purchasing Strategies and Shipboard Mortality: Day-to-Day Evidence from the Dutch African Trade, 1751–1797. *Journal of Economic History67* (1), 160-190. https://doi.org/10.1017/S002205070700006x, reprinted in Haycock, D. B. & Archer, S. (Editors) (2009) *Health and Medicine at Sea, 1700-1900*. Woodbridge: Boydell Press

Rietdijk, J., Hogerzeil, S. J., Hemert, A. M. van, Cuijpers, P., Linszen, D. H., & Gaag, M. van der. (2011). Pathways to psychosis: Help-seeking behavior in the prodromal phase. *Schizophrenia Research*, *132*(2-3), 213–219. https://doi.org/10.1016/j.schres.2011.08.009 [dit proefschrift]

Hogerzeil, S. J., Hemert, A. M. van, Rosendaal, F. R., Susser, E., & Hoek, H. W. (2014). Direct comparison of first-contact versus longitudinal register-based case finding in the same population: Early evidence that the incidence of schizophrenia may be three times higher than commonly reported. *Psychological Medicine*, *44*(16), 3481–3490. https://doi.org/10.1017/s003329171400083x [dit proefschrift]

Hogerzeil, S. J., Hemert, A. M. van, Veling, W., & Hoek, H. W. (2016). Incidence of schizophrenia among migrants in the Netherlands: A direct comparison of first contact longitudinal register approaches. *Social Psychiatry and Psychiatric Epidemiology*, *52*(2), 147–154. https://doi.org/10.1007/s00127-016-1310-8 [dit proefschrift]

Schrier, A. C., Hogerzeil S. J., de Wit, M. A. S., Beekman, A. T. F. (2017). Depressie en angst bij Turkse en Marokkaanse minderheidsgroepen in Nederland: prevalentie, symptomen, risico- en beschermende factoren in de algemene bevolking: een systematische review. *Tijdschrift voor Psychiatrie*; *59* 1, 30–39.

Hogerzeil, S. J., & Susser, E. (2017). Schizophrenia: Learning about the other half. *Psychiatric Services*, *68*(5), 425–425. [dit proefschrift]

Hogerzeil, S. J., & Hemert, A. M. van. (2019). Design choices when estimating the treated incidence of schizophrenia. *Psychological Medicine*, *49*(15), 2635–2636. https://doi.org/10.1017/s0033291719001338 [dit proefschrift]

Hogerzeil, S. J., Hoek, H. W., & Hemert, A. M. van. (2021). The impact of study design on schizophrenia incidence estimates: A systematic review of Northern European studies 2008–2019. *Schizophrenia Research*, *231*, 134–141. https://doi.org/10.1016/j.schres.2021.03.017 [dit proefschrift]

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Visual-Meta

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