Revisiting the incidence of schizophrenia: learning about the other half

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

Published as:

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

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.