Revisiting the incidence of schizophrenia: learning about the other half

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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

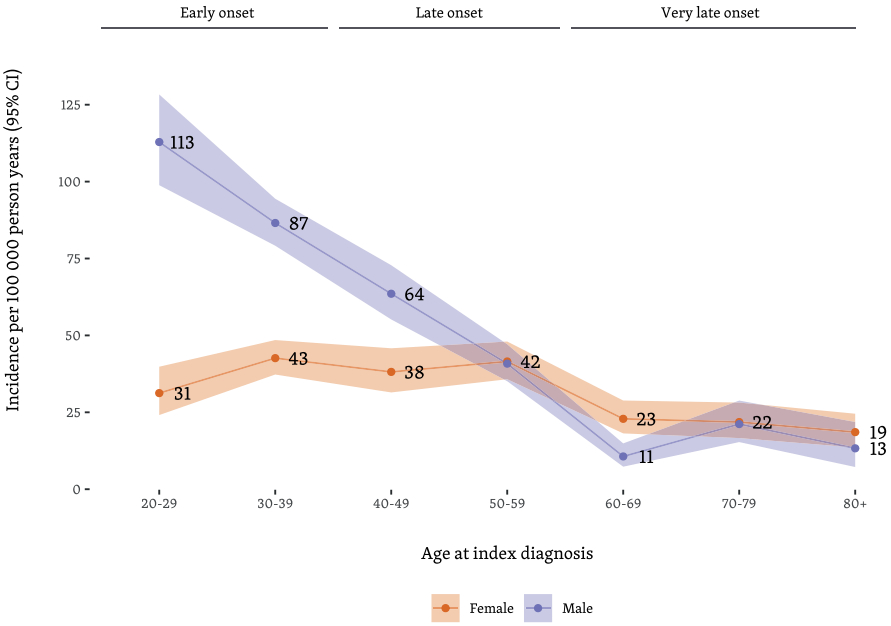

Figure 4.1 Schizophrenia IR by gender and age of onset in 10-year categories from 20–79 years

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.

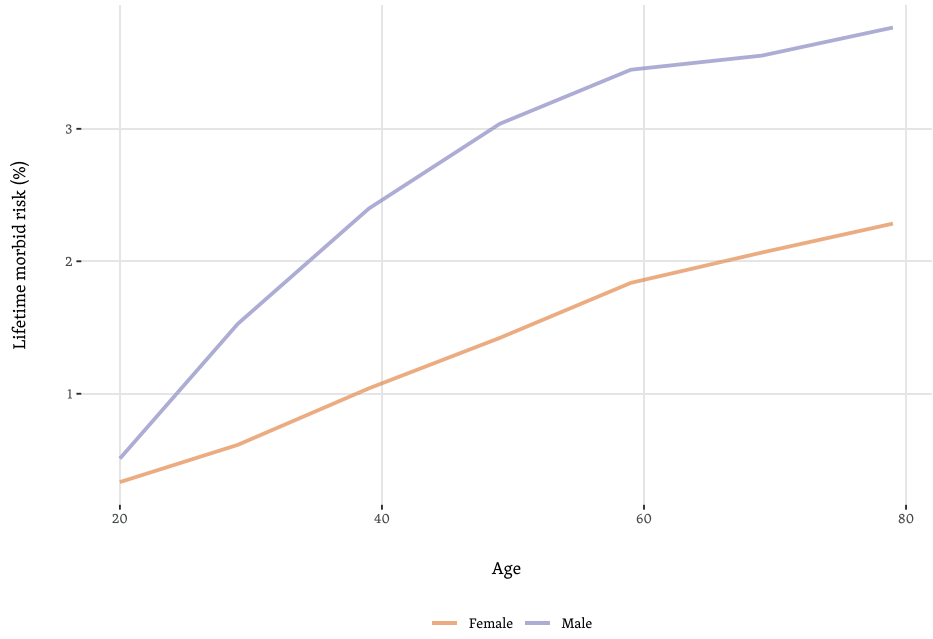

Figure 4.2 Lifetime morbidity risk (LMR) of schizophrenia
Source: Psychiatric Register of The Hague (1997–2012). LMR: lifetime morbidity risk of schizophrenia, calculated as the cumulative sum of year by year age and sex specific incidence rates per 100 0000 person years from age ≥ 20 years, expressed 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.