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REVIEW ARTICLE

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The burden of disease in early schizophrenia – a systematic literature review

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ABSTRACT

Background: Schizophrenia is a heterogeneous disorder with a burden that can vary greatly depending on the severity and the duration. Previous research has suggested that patients in the earlier stages of schizophrenia (typically first-episode schizophrenia) benefit from effective early treatment, however, a comprehensive review of the burden specifically in this population has not been undertaken. A systematic literature review was therefore conducted to characterize the clinical, economic, and humanistic burden, as reported in naturalistic studies of schizophrenia populations specifically at an early stage of disease in comparison with healthy controls, patients with chronic schizophrenia, and patients with other psychiatric disorders.

Methods and materials: Searches were conducted in MEDLINE, MEDLINE In-Process, Embase, PsycINFO, and EconLit databases for records published between January 2005 and April 2019, and of relevant conference abstracts published between January 2014 and May 2019. Data were extracted from relevant publications and subjected to qualitative evaluation.

Results: Fifty-two publications were identified for inclusion and revealed a considerable burden for early schizophrenia with regards to mortality, psychiatric comorbidities such as substance abuse and depression, poor social functioning, and unemployment. Comparisons with chronic schizophrenia suggested a greater burden with longer disease duration, while comparisons with other psychiatric disorders were inconclusive. This review uncovered various gaps in the available literature, including limited or no data on incarcerations, caregiver burden, and costs associated with early schizophrenia.

Conclusions: Overall, the burden of schizophrenia is apparent even in the early stages of the disease, although further research is required to quantify the burden with chronic schizophrenia and other psychiatric disorders.

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Introduction

Schizophrenia is a heterogeneous disease, which varies greatly in its manifestation across patient groups, disease course, and incidence in different parts of the world[1,2]. Globally it was estimated that there were approximately 20 million people with schizophrenia in 2017, amounting to around 12,500 years lived with disability[2]. It is a severe psychiatric disorder with patients experiencing disability throughout their illness, manifesting through alteration of thought, hallucinations, and delusions, amongst other negative and cognitive symptoms[3]. The illness may have consequences on social interaction and functioning which can impact day-to-day activities such as gaining or maintaining employment and relationships with family and friends[4]. The economic burden of schizophrenia is large, with a recent study suggesting most of this burden arises from indirect costs[5].

Despite advances in the understanding of the disease and the introduction of novel therapies, only a minority of people with schizophrenia fully recover[6]. Research has suggested that treating patients during the earlier stages of schizophrenia, typically within the first psychotic episode, increases the chance of recovery, reduces the risk of relapse, and could provide patients with more favorable long-term outcomes[7–10]. A meta-analysis of 10 randomized controlled trials (RCTs) concluded that early intervention in first-episode psychosis or early schizophrenia spectrum disorders was superior to usual care across all outcomes, including treatment discontinuation, psychiatric hospitalization, school or work involvement, and symptom severity[11].

While many sources of burden are known to impact patients with schizophrenia and their carers[4], few systematic literature reviews (SLRs) have considered the burden of

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disease specifically for patients early in the disease. To complement early intervention in schizophrenia, it is important to identify the aspects of disease burden that are particularly problematic for this group and guide management in a way that addresses those unmet needs.

This SLR aimed to characterize the disease burden for patients "early" in the course of schizophrenia and their caregivers, as observed in naturalistic studies, to better understand and highlight their unmet needs. The aspects of burden investigated in this review span clinical burden (including comorbidities and mortality), economic burden (such as hospitalization and unemployment), and humanistic burden (such as social functioning and quality of life [QoL]). The review set out to make comparisons with healthy controls to identify all sources of burden. Additionally, comparisons were made with chronic schizophrenia and other psychiatric disorders to identify areas that may play a greater role for the early schizophrenia population but could be overlooked if considering schizophrenia or early psychiatric disorders as a whole.

Methods

Search strategy and selection of studies

An SLR was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12]. Searches were conducted in MEDLINE, MEDLINE In-Process, Embase, PsycINFO, and EconLit (last searched 12th April 2019; Supplementary Tables 1 and 2), as well as in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effect, the National Health Service Economic Evaluations Database and the Health Technology Assessment Database (last searched on 11th April 2019; Supplementary Tables 3 and 4). Supplementary searches of major schizophrenia and pharmacoeconomics conferences held between 2014 and 2015 were conducted using the Northern Light Life Sciences Conference Abstracts and Embase databases (Supplementary Table 5). Proceedings of major schizophrenia and pharmacoeconomics congresses held within the last three years (January 2016 through April 2019) were searched by hand (Supplementary Table 6). Conference searches were restricted by date under the assumption that conference presentations not subsequently published as journal articles within the past five years are likely to be of low quality. Finally, hand searches of the bibliographies of all relevant SLRs, network meta-analyses, and all ultimately included, full-text journal articles were undertaken to identify any additional, relevant studies for inclusion in the review.

Titles and abstracts were screened by a single reviewer, with all included articles and a random sample of 10% of excluded articles checked by a second reviewer. Full-texts of all potentially eligible studies identified in the title/abstract screening were reviewed by two independent reviewers. Discrepancies were resolved at all stages by a third independent reviewer when necessary. Studies were eligible for inclusion if they were written in the English language and reported relevant outcomes. Outcomes of interest were those related to clinical, economic, or humanistic burden in early schizophrenia. Studies were required to include patients formally diagnosed with schizophrenia (e.g. according to the International Classification of Diseases [ICD] or Diagnostic and Statistical Manual of Mental Disorders [DSM] criteria). Patients were also required to have early schizophrenia, which was defined as being within the first episode of schizophrenia, being within five years since schizophrenia diagnosis, or being described as early in the course of disease according to the publication itself. Studies of caregivers of patients with early schizophrenia were additionally eligible for inclusion. The SLR was not focused on early-onset schizophrenia, therefore age was not used to define early schizophrenia. A broader definition of early psychosis or undiagnosed schizophrenia was avoided to reduce confounding given the heterogeneous nature of schizophrenia and other psychoses.

Studies were required to include a relevant comparator population (healthy controls, chronic schizophrenia, or other psychiatric disorders). Studies that included patients with early schizophrenia as a subset of a larger population were included only if relevant outcomes were presented separately for these patients. To focus on data more likely to be representative of clinical practice, only observational studies, SLRs, or narrative reviews were included. The review was restricted to articles published in or after 2005 to focus on areas of burden that are relevant to current clinical practice.

Data extraction and analysis

Relevant data from full-text publications and conference proceedings (abstracts, posters, or oral presentations) were extracted into pre-defined extraction tables in Microsoft Excel. Data extraction was performed by a single individual for each included study. A second individual independently verified the extracted information, while a third individual arbitrated any discrepancies. A list of data variables that were extracted is provided in Supplementary Table 7. Quality assessment was performed using the Downs and Black checklist for non-randomized studies[13].

Results

Included studies

After removing duplicates, a total of 5675 citations were identified (Figure 1). From these, 52 publications were included. Twenty publications reported outcomes for early schizophrenia compared with a healthy control population, 18 compared with other psychiatric disorders, 9 compared with chronic schizophrenia, 4 compared with both chronic schizophrenia and other psychiatric disorders, and 1 compared with chronic schizophrenia and a healthy control population (Figure 2). Further characteristics of the included studies are provided in Supplementary Tables 8 and 9. Based on the Downs and Black checklist[13], studies were generally

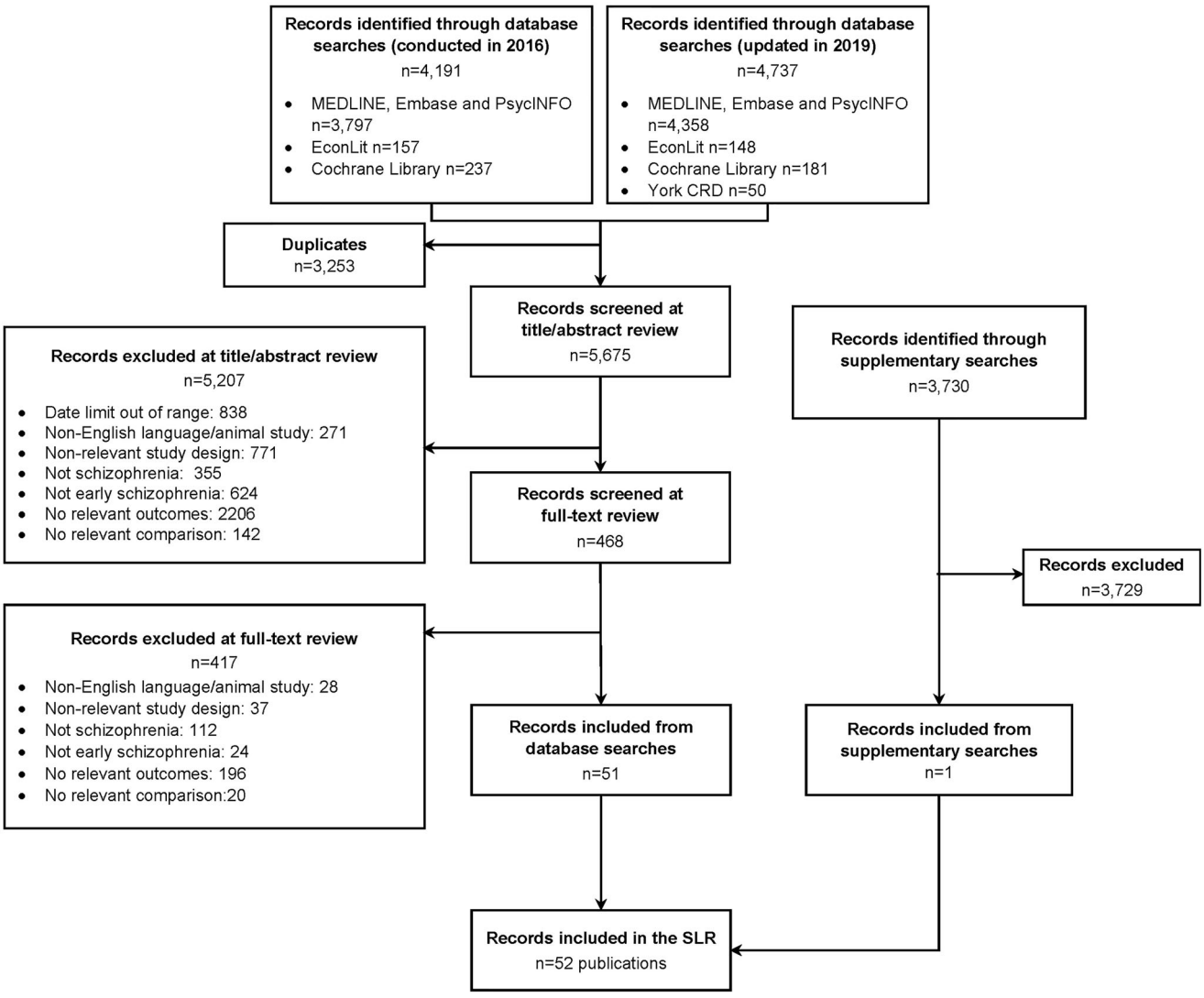

Figure 1. PRISMA study selection schematic. CRD, Centre for Reviews and Dissemination; SLR, systematic literature review.

of good quality. Full results of the quality assessment are provided as in Supplementary Tables 10 and 11.

Clinical burden

Incidence and prevalence

Eight publications reported the incidence or prevalence of early schizophrenia compared with other psychiatric disorders, mostly for regions of England[14–21]. Studies on the incidence of schizophrenia were relatively old, with the most recent reporting data up to 2011[18]. Reported incidence rates of schizophrenia ranged from 4.1 to 13.2 cases per 100,000 person-years, while rates for other non-affective psychoses or schizophrenia spectrum disorders ranged from 3.6 to 17.0 per 100,000 person-years, and rates for affective psychoses from 1.5 to 8.9 per 100,000 person-years[16,18–20].

Four publications reported prevalence as the proportion of first-episode psychosis patients with a diagnosis of schizophrenia[14–16,21]. Variation in the psychiatric disorders reported in these papers, as well as differences in geographical location between studies makes it challenging to determine how the prevalence of schizophrenia compares with other disorders. Nevertheless, there was a general trend towards schizophrenia making up a smaller proportion of psychosis diagnoses in more recent studies (57% of all psychoses before 1980[16]; 31–34% before 2000[16]; 13% up to 2005[14,15] and 11% up to 2011[21]). Kirkbride et al. conducted a longitudinal comparison of schizophrenia rates between 1978 and 1999 and hypothesized this trend may reflect increased reluctance to diagnose schizophrenia on initial presentation, or increased incidence of other non-affective psychoses[16]. No data on the prevalence of early versus chronic schizophrenia were identified.

Mortality

Only one study reported all-cause mortality for early schizophrenia compared with the general population[22]. It found mortality rates to be significantly higher for the schizophrenia group, regardless of the level of antipsychotic exposure (range in hazard ratios: 2.31–9.90)[22]. In contrast, a study of patients with early psychosis found that neither diagnosis of schizophrenia nor diagnosis of brief psychosis at first

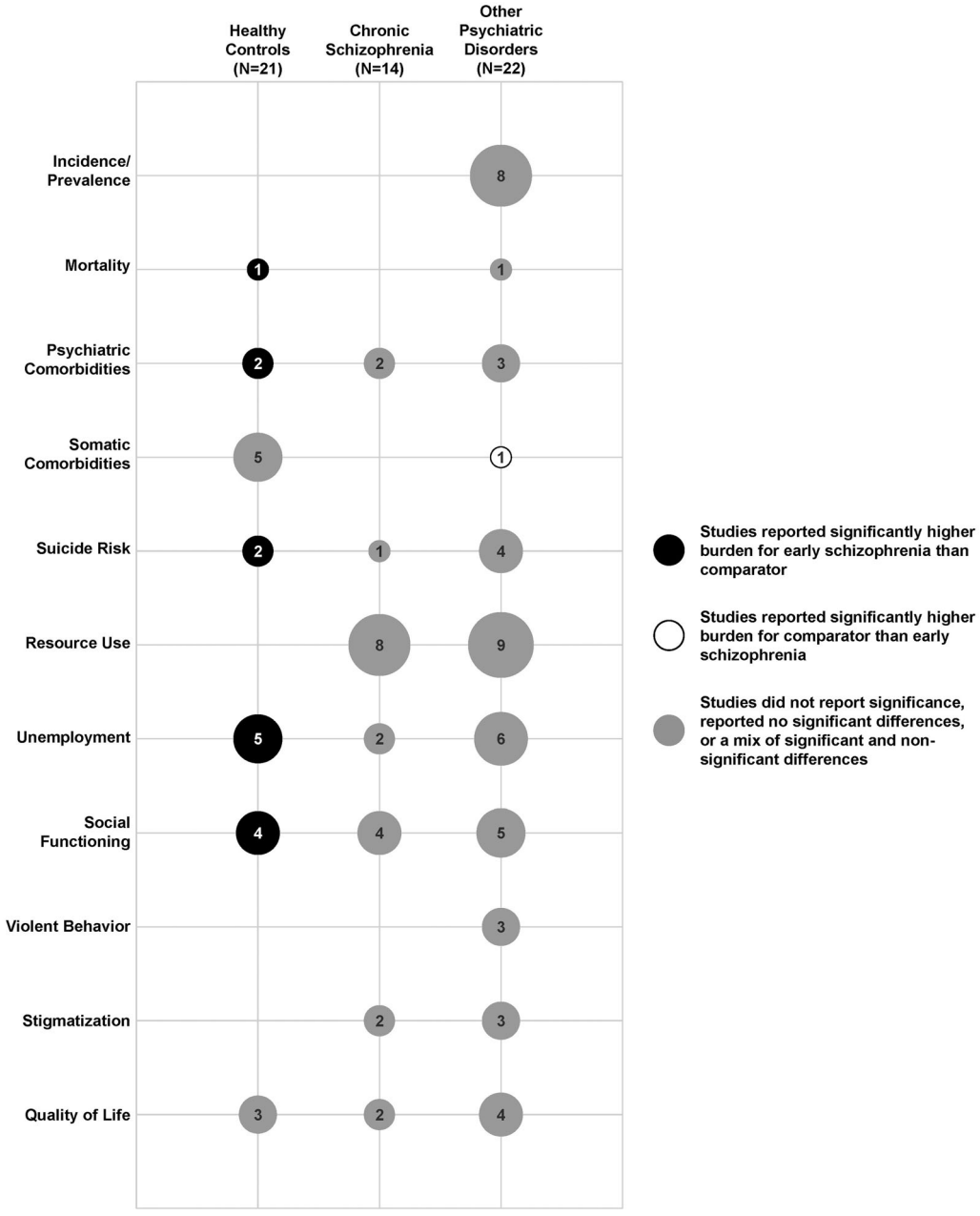

Figure 2. Summary of included outcome comparisons. Numbers indicate the quantity of studies making a comparison between early schizophrenia and the corresponding comparison group for each outcome of interest.

hospitalization were significant risk factors for non-suicide deaths[21].

Psychiatric comorbidities

Comorbid diagnosed depression was not reported in the studies identified in this review, however, two publications assessed depressive symptoms in first-episode schizophrenia using the Hamilton Rating Scale for Depression and Beck's Depression Inventory, respectively[23,24]. They found that patients with first-episode schizophrenia had significantly higher levels of depression than healthy controls ($p < .01$)[23,24]. Compared with chronic schizophrenia, patients with early schizophrenia had higher levels of depression, reaching significance in one study[25], but not in a second study[24].

Findings from comparisons with other psychiatric disorders were mixed. One study found substance use disorder was the most common comorbid disorder in both patients with first-episode schizophrenia (62.9% [178/283]) and first-episode schizoaffective disorder (68.8% [44/64])[26]. Conversely, no significant differences in the rates of comorbid substance use disorder, psychiatric disorder or major depressive disorder were seen between the two groups[26]. A further study using the Calgary Depression Scale reported no significant differences in scores between patients with first-episode psychosis diagnosed with schizophrenia compared with those diagnosed with delusional disorder[27]. On the

other hand, a second study reported a higher frequency of psychiatric comorbidities, particularly affective disorder, in patients with first-episode delusional disorder compared with first-episode schizophrenia ($p = .009$)[28].

Somatic comorbidities

Six studies reported somatic comorbidities in early schizophrenia[15,25,29–32], mostly comparing metabolic or cardiovascular comorbidities in first-episode schizophrenia with healthy controls. Some studies concluded there was a higher risk of comorbidities in patients with early schizophrenia than in healthy controls (impaired glucose tolerance [$p = .002$] and suspected Brugada syndrome [$p < .001$])[29,31]. Conversely, others reported no significant difference (impaired fasting glucose, metabolic syndrome, and cardiovascular risk)[29,30,32], or did not report significance (metabolic syndrome)[32,33]. No studies compared somatic comorbidities between early and chronic schizophrenia, and there was only one study comparing early schizophrenia with another psychiatric disorder[15]. This study found that patients with psychotic depression had a significantly higher prevalence of physical health problems both at presentation and after one year of follow-up compared with those with schizophrenia ($p < .05$)[15].

Risk of suicide

The rates of suicide attempts by patients with early schizophrenia ranged from 8.8% to 20.0%[26,34–36]. Two studies investigated the risk of suicide in early schizophrenia compared with healthy controls, finding the risk of both suicide and suicide attempts to be significantly higher in early schizophrenia ($p < .05$)[36,37]. On the other hand, the only study comparing early and chronic schizophrenia populations found no significant differences in the rate of suicide attempts between the two groups[35]. Amongst the four studies reporting suicide rates in comparison with other psychiatric disorders, two reported no significant differences in suicide attempt rates compared with first-episode schizoaffective disorder or mania with psychotic features[26,34]. The remaining two considered rates of suicide deaths but did not conduct statistical testing[21,37].

Economic burden

Hospitalization and resource use

No studies reported costs associated specifically with early phases of schizophrenia. Nonetheless, hospitalization-related outcomes were reported in several studies comparing early schizophrenia with chronic schizophrenia and other psychiatric disorders (Table 1). Studies comparing early versus chronic schizophrenia showed a trend towards higher mean numbers of hospitalizations for patients with chronic schizophrenia, which reached significance in 3 of 6 studies ($p < .05$)[24,38,39]. The remaining studies did not report statistical analyses or found no significant differences[35,40,41]. One study showed patients with chronic schizophrenia had a significantly longer duration of hospital stay compared with early schizophrenia[42].

The results were mixed when patients with first-episode schizophrenia were compared with those with other psychiatric disorders. Hospitalization-related resource use was reported to be significantly higher for early schizophrenia compared with bipolar disorder ($p < .001$)[43], but lower compared with schizoaffective disorder ($p < .05$)[26]. A further study reported that patients with first-episode psychotic mania had a significantly higher mean number of hospital admissions over three years than patients with first-episode schizophrenia, but significantly fewer readmissions[34,44]. The remaining studies either found no statistically significant differences or did not report statistical significance[14,15,28,45].

No significant differences were reported for the proportions of patients with early schizophrenia using antipsychotics compared with chronic schizophrenia or first-episode delusional disorder[27,28,46], although one study reported some significant differences in the antipsychotics used between early and chronic schizophrenia groups[35]. Regarding outpatient resource use, one study found that 63% of illicit substance users with first-episode schizophrenia and 37% of patients with drug-induced psychosis were in contact with secondary care services in the UK within the first year (statistical significance not reported)[14]. A second study reported a significantly lower rate of outpatient contacts by patients with incident bipolar disorder compared with schizophrenia ($p < .001$)[43].

Unemployment

Unemployment rates for early schizophrenia ranged from 10% to 88% across the 13 studies included in this review. Employment rates were consistently lower for patients with early schizophrenia compared with healthy controls ($p < .01$)[47–51]. Compared with chronic schizophrenia, one study found that unemployment was significantly lower in the early schizophrenia cohort ($p < .001$)[52], whereas a second showed a numerical decrease in unemployment in the early schizophrenia group, although no statistical analysis was performed[40]. Between early schizophrenia and other psychiatric disorders (first-episode major depressive disorder, schizoaffective disorder, and delusional disorder) unemployment rates were relatively consistent[26,27,45], although it was also reported that in comparison with first-episode psychotic mania and schizoaffective disorder, patients with early schizophrenia had a significantly higher rate of unemployment ($p < .05$)[34,44,53].

Humanistic burden

Social functioning

Twelve publications reported social functioning outcomes in early schizophrenia versus healthy controls, chronic schizophrenia, and other psychiatric disorders (Table 2)[28,34,39,42,44,54–60]. Patients with early schizophrenia showed significantly poorer social functioning compared with healthy controls ($p < .05$)[54–56,59]. On the other hand, studies

Table 1. Inpatient hospitalization resource use data in early schizophrenia patient cohorts.

Author and date of publication (Country)	Early schizophrenia and comparator groups (N)	Proportion of patients hospitalized	Mean (SD) number of days hospitalized, per patient	Mean (SD) number of admissions, per patient	Other inpatient hospitalization outcomes
Early vs. Chronic Schizophrenia					
Dubois 2014 (Belgium)[40]	e-STAR cohort ES: ≤3 years since diagnosis (95) C: >3 years since diagnosis (197) TIMORES cohort ES: <4 episodes (23) C: None	NR	NR	NR	e-STAR cohort Mean number of hospital stays per patient at baseline: ES: • 1 year: 1.24 • 2 years: 1.11 CS: • 1 year: 1.05 • 2 years: 1.31 TIMORES cohort Average number of hospital stays per patient at baseline: 0.87 (SD 1.10) No significant difference relative to e-STAR CS group
Garcia-Alvarez 2019 (Spain)[35]	ES: Duration of illness <7 years (35) C: Duration of illness >10 years (69)	ES: 61.8% CS: 82.6% (p=.020)[a]	NR	ES: 1.86 (2.03) CS: 4.79 (5.85) (p=.028)[a]	NR
Kim 2015 (Korea)[39]	ES: Duration of illness <5 years (25) C: Duration of illness >5 years (30)	NR	NR	ES: 2.00 (1.29) CS: 6.24 (5.34) (p<.001)	NR
Leung 2011 (China)[24]	ES: <2 years from first-episode (50) C: Schizophrenia diagnosis ≥5 years (51)	NR	NR	ES: 0.64 (0.67) CS: 3.02 (3.04) (p<.001)	NR
Matsuda 2014 (Japan)[41]	ES: <2 years since psychotic symptom onset (19) C: 5 years since psychotic symptom onset (18)	NR	NR	ES: 0.5 (0.7) CS: 0.8 (1.1)	NR
Mwansisya 2013 (China)[42]	ES: Duration of illness <24 months (197) C: Duration of illness >24 months (392)	NR	ES: 166.38 (397.191) CS: 973.20 (1082.015) (p=.001)	NR	NR
Pawelczyk 2015 (Poland)[38]	ES: Psychotic symptoms for <2 years (42) C: Chronic schizophrenia (44)	NR	NR	ES: 1.26 (0.497) CS: 4.3 (3.359) (p<.0001)	NR
Early Schizophrenia vs. Other Psychiatric Disorders					
Chang 2014 [conference abstract] (Hong Kong, China)[44] Chang 2016 (Hong Kong, China)[34]	ES: 3 years from baseline (374) C: First-episode psychotic mania (46)	NR	ES: 79.4 (SD 121.5) Psychotic mania: 96.1 (70.9) (p=.36)	ES: 1.2 (1.1) Psychotic mania: 1.9 (1.4) (p<.01)	Patients with psychotic mania had significantly fewer readmissions (p < .001) than those with schizophrenia
Corker 2015 (Austria, Croatia, Czech Republic, Poland, Romania, Sweden, Turkey)[45]	ES: First episode (150) C: First-episode major depressive disorder (176)	ES: • 92.6% (at least once in their lifetime) • 35.8% hospitalized involuntarily MDD: • 43.8% (at least once in their lifetime) • 4.8% hospitalized involuntarily	NR	NR	Longest period spent in hospital ES: mean 41.4 days (SD 49.4) MDD: mean 16.1 days (SD 2.1)
Cotton 2013 (Australia)[26]	ES: First episode (283) C: First-episode schizoaffective disorder (64)	ES: 70.7% (inpatient admission) Schizoaffective disorder: 87.5% (p=.008)	NR	ES: 1.6 (1.7) Schizoaffective disorder: 2.2 (1.8) (p=.017)	NR
Crebbin 2008 (UK)[15]	ES: First episode (73) C: First-episode psychotic depression (105)	ES: 64.4% Psychotic depression: 77.1% (p=.76)	ES: 231 Psychotic depression: 124 (p=.78)	NR	NR
Crebbin 2009 (UK)[14b]	ES: First episode (27) C: First-episode drug-induced psychosis (35)	ES: 74.1% Drug-induced psychosis: 62.9%	ES: 88.4 Drug-induced psychosis: 25.7	NR	NR
Hui 2015 (Hong Kong, China)[28]	ES: First episode (71) C: First-episode delusional disorder (71)	ES: 56.3% (at onset) Delusional disorder: 38.0% (at onset) (p=.029)	NR	NR	Median length of stay at onset ES: 34.5 days (IQR 16.3–52.5) (p=.107) Delusional disorder: 21 days (IQR 13.0–36.0)
Laursen 2018 [conference abstract] (NR)[43]	ES: Early-onset (349) C: Early-onset bipolar disorder (365)	NR	NR	NR	Incidence ratio of admissions (bipolar disorder vs. ES) IRR 0.44 (95% CI 0.41–0.48) (p<.001)

Abbreviations. C, comparator; CI, confidence interval; CS, chronic schizophrenia; ES, early schizophrenia; IQR, interquartile range; MDD, major depressive disorder; NR, not reported; SD, standard deviation.
[a]Not significant after adjusting for age.
[b]Subpopulation of the Crebbin 2008 study (injection drug users).

Table 2. Social functioning data in early schizophrenia patient cohorts.

Author and date of publication (Country)	Early schizophrenia and comparator groups (*N*)	Mean (SD) Social and Occupational Functioning Assessment Scale[a]	Mean (SD) Social Functioning Scale[b]	Mean (SD) other social functioning measures
Early Schizophrenia vs. Healthy Controls				
Agid 2012 (Canada)[54]	ES: First episode (31) C: Age and sex-matched controls (29)	• ES in symptomatic remission: 49.8 (7.96) • HC: 84.0 (5.16) ($p<.001$)	NR	NR
Agid 2014 [conference abstract] (Canada)[55]	ES: First episode (65) C: NR (NR)	NR	Patients with ES experienced significant impairment in social engagement, interpersonal communication, recreation, pro-social and enjoyment domains ($p<.05$)	NR
Ballon 2007 (USA)[56]	ES: First episode within last year (16) C: Comparison subjects from the community (34)	NR	NR	Social Adjustment Scale – Self Report[c]: • ES: 2.46 (0.56) • HC: 1.58 (0.28) ($p<.05$)
Jaracz 2007 (Poland)[59]	ES: Up to 13-months' follow-up from first episode (74) C: Age and sex-matched controls (86)	NR	ES: 104.4 (10.6) HC: 117.0 (6.6) ($p<.001$)	NR
Early vs. Chronic Schizophrenia				
Bougie 2017 [conference abstract] (Canada)[57]	ES: Original diagnosis ≤5 years (103) C: Original diagnosis >5 years (52)	Baseline: • ES: 50.3 • CS: 49.8	NR	NR
Garcia-Alvarez 2019 (Spain)[35]	ES: Duration of illness <7 years (35) C: Duration of illness >10 years (69)	NR	NR	Personal and Social Performance Scale: • ES: 47.77 (18.70) • CS: 49.33 (15.50) ($p=.652$)
Higuchi 2017 (Japan)[58]	ES: Duration of illness <1 year (38) C: Duration of illness ≥1 year (135)	• ES: 44.4 (11.7) • CS: 54.9 (14.4) ($p=.11$)	NR	NR
Kim 2015 (Korea)[39]	ES: Duration of illness ≤5 years (25) C: Duration of illness >5 years (30)	NR	NR	Personal and Social Performance Scale: • ES: 60.92 (11.24) • CS: 60.23 (10.42) ($p=.822$)
Early Schizophrenia vs. Other Psychiatric Disorders				
Chang 2014 [conference abstract] (Hong Kong, China)[44]; Chang 2016 (Hong Kong, China)[34]	ES: 3 years from baseline (374) C: First-episode psychotic mania (46)	ES: 62.4 (14.4) Psychotic mania: 68.8 (11.9) ($p<.01$)	NR	NR
Higuchi 2017 (Japan)[58]	ES: Duration of illness <1 year (38) C: Other psychiatric disorders with psychosis (19)	• ES: 44.4 (11.7) • Other psychoses: 42.5 (16.8) ($p=.11$)	NR	NR
Hui 2015 (Hong Kong, China)[28]	ES: First episode (71) C: First-episode delusional disorder (71)	• ES: 57.6 (11.1), • Delusional disorder: 56.6 (15.5) ($p=.673$)	NR	NR
Lee 2016 (Hong Kong, China)[60]	ES: First episode (157) C: First-episode brief psychotic disorder (42)	• ES: 57.06 (12.16), • Brief psychotic disorder: 64.74 (14.31) ($p=.001$)	NR	NR

Abbreviations. C, comparator; CI, confidence interval; CS, chronic schizophrenia; ES, early schizophrenia; HC, healthy control; NR, not reported; SD, standard deviation.
[a]Score ranging from 0–100, with 100 indicating superior functioning in all domains[74].
[b]Composed of 79 items and 7 subscales. Scores range from 55–135 with a higher score representing better functioning[75].
[c]Scale used to measure a person's satisfaction with their social situation, considering work/school role, social/leisure time, family outside of the home, primary relationship, parental role and family unit domains. Higher scores indicate greater social dysfunction[56].

comparing with chronic schizophrenia did not conduct statistical comparisons or found no significant differences[35,39,57,58]. Two studies found that patients with first-episode schizophrenia experienced significantly poorer social functioning when compared with psychotic mania and brief psychotic disorder ($p < .05$)[34,44,60] while further studies found no significant difference versus delusional disorder[28], or other psychiatric disorders with psychosis[58].

Violent behavior

No studies reported on the occurrence of violent behavior in early schizophrenia versus chronic schizophrenia or healthy controls. Two studies found no significant differences for first-episode schizophrenia with current illicit drug use compared with patients with drug-induced psychosis[14], or for first-episode schizophrenia compared with psychotic mania[34], respectively. A third study reported those with early schizophrenia being significantly more likely to have harmed others or property by the time they presented to secondary care compared with patients with psychotic depression ($p < .05$)[15].

Stigmatization

Two publications reported on studies of public opinion in Australia regarding stigmatization of people with early schizophrenia compared with chronic schizophrenia, depression, depression with suicidal thoughts, social phobia, and post-traumatic stress disorder[61,62]. The majority of participants (73.9% [95% CI: 70.7–76.9]) thought patients with early schizophrenia were likely to be discriminated against. The rate was lower compared with those with chronic schizophrenia (73.9% vs 84.1%; $p < .05$), but higher compared with the other psychiatric disorders[61,62]. A third publication reported on interviews with patients with first-episode schizophrenia ($N = 150$) from several European countries including Austria, Croatia, Czech Republic, Poland, Romania, Sweden, and Turkey[45]. Compared with patients with first-episode major depressive disorder, patients with schizophrenia reported a lower total Discrimination and Stigma Scale (DISC-12) score for experienced discrimination ($p = .03$)[45]. More patients with schizophrenia reported negative discrimination from police, however in all other life areas discrimination was more frequent in the group with depression, reaching statistical significance for marriage[45].

Quality of life

Nine studies assessed QoL and happiness in patients with first-episode schizophrenia relative to healthy controls, chronic schizophrenia, or other psychiatric disorders (Table 3)[19,27,39,52–54,63–65]. Two of the three studies comparing QoL or happiness with healthy controls reported no significant differences[54,63], with the remaining study reporting significantly poorer scores on the SF-36 scale for patients with early schizophrenia ($p < .01$)[65]. In comparison with chronic schizophrenia, one study reported no significant difference[39], while the other reported significantly poorer QoL for patients with chronic schizophrenia ($p = .02$)[52]. Findings from studies that compared early schizophrenia with other psychiatric disorders were similarly mixed. One study reported significantly poorer scores for early schizophrenia compared with schizophreniform and schizoaffective disorders ($p < .05$)[64]. A second study using a different QoL measure found no significant differences between early schizophrenia and schizoaffective disorder[53]. A further study reported significantly poorer QoL for early schizophrenia compared with bipolar disorder ($p < .001$), but no significant difference compared with major depressive disorder[19]. The remaining study found no significant differences between first-episode schizophrenia and delusional disorder[27].

Discussion

Disease burden in early schizophrenia

The literature identified by this review illustrates there are multiple sources of burden for patients with schizophrenia compared with healthy controls, even at the early stages of the disease. All-cause mortality, risk of suicide, and psychiatric comorbidities were significantly higher in patients with early schizophrenia compared with the general population, and it has been suggested previously that patients with schizophrenia are at a particularly high risk of suicide in the first few years after diagnosis[66,67]. A thorough assessment of suicide risk is therefore crucial during the early management of schizophrenia. Social functioning outcomes were consistently poorer for patients with early schizophrenia and correspondingly unemployment rates were higher compared with healthy controls. Together, this highlights the disruption that symptoms of schizophrenia can cause even at the onset of disease and the importance of multidisciplinary care involving psychosocial intervention at an early stage.

Comparisons with chronic schizophrenia and other psychiatric disorders were less conclusive, with a high proportion of studies finding no significant differences. Nevertheless, there was a general trend to worsening burden with more chronic disease and poorer social functioning outcomes for patients with early schizophrenia compared with patients with other psychiatric disorders.

Data gaps

Some notable data gaps were identified. No studies assessed the prevalence of early versus chronic schizophrenia, while studies comparing early schizophrenia with other psychiatric disorders were limited to European cohorts only and dominated by historic data with potentially limited relevance today. Additional literature gaps include the lack of data on caregiver burden or comprehensive description of comorbidities, including cardiac and hepatic comorbidities that are important risk factors for early mortality in patients with schizophrenia[68–70]. Furthermore, although QoL was widely reported across the studies, a surprising finding was the large variation in QoL measurements, with only one study

Table 3. Quality of life data in early schizophrenia patient cohorts.

Author and date of publication (Country)	Early schizophrenia and comparator groups (*N*)	Mean (SD) quality of life measures	Mean (SD) happiness measures
Early Schizophrenia vs. Healthy Controls			
Agid 2012 (Canada)[54]	ES: First episode (31) C: Age and sex-matched controls (29)	Satisfaction with Life Scale[a] (5–35): • ES: 24.3 (7.40) • HC: 22.76 (4.81) (p=.349)	Subjective Happiness Scale[b] (1–7): • ES: 5.16 (1.01) • HC: 4.80 (0.68) (p=.113) Single-Item Happiness Question[c] (0–10): • ES: 7.61 (1.67) • HC: 7.21 (0.94) (p=.254) World Values Survey[d] (1–4): • ES: 3.23 (0.76) • HC: 3.03 (0.42) (p=.238)
Agid 2015 (Canada)[63]	ES: First episode (54) C: Age and sex-matched controls (55)	NR	Subjective Happiness Scale[b], score >4 (/7), n (%): • ES: 25 (46) • HC: 34 (62) (p=.09) Satisfaction With Life Scale, score >25 (/35), n (%): • ES: 22 (41) • HC: 31 (57) (p=.09)
Law 2005 (Hong Kong, China)[65]	ES: First episode (117) C: Age-matched controls (117)	SF-36 (Chinese version): Physical function: • ES 88.4 (14.1) • HC 97.1 (6.0) (p<.001) Role-physical: • ES: 46.2 (39.3) • HC: 83.3 (29.9) (p<.001) Bodily pain: • ES: 74.2 (26.7) • HC: 85.6 (21.5) (p<.001) General health: • ES: 52.2 (20.9) • HC: 63.3 (20.5) (p<.001) Vitality: • ES: 49.4 (19.7) • HC: 59.5 (19.6) (p<.001) Social functioning: • ES: 60.6 (30.0) • HC: 87.1 (17.4) (p<.001) Role-emotional: • ES: 37.6 (41.0) • HC: 54.1 (42.9) (p=.003) Mental health: • ES: 48.8 (22.1) • HC: 70.5 (18.8) (p<.001)	NR
Early vs. Chronic Schizophrenia			
Kim 2015 (Korea)[39]	ES: Duration of illness ≤5 years (25) C: Duration of illness >5 years (30)	Schizophrenia Quality of Life Scale: • ES: 42.52 (16.26) • CS: 39.17 (20.36) (p=.509)	NR
Makanjuola 2007 (Nigeria)[52]	ES: Onset of illness (100) C: Illness duration >2 years (100)	WHOQOL-BREF on subjective quality of life, overall quality of life and general health, *n* (%): • ES: Good, 19 (19); Poor, 81 (81) • CS: Good, 7 (7); Poor, 93 (93) (p=.02)	NR

(*continued*)

Table 3. Continued.

Author and date of publication (Country)	Early schizophrenia and comparator groups (*N*)	Mean (SD) quality of life measures	Mean (SD) happiness measures
Early Schizophrenia vs. Other Psychiatric Disorders			
Al-Bataineh 2016 (Europe)[64]	ES: First episode (242) C: First-episode schizophreniform disorder (182) C: First-episode schizoaffective disorder (31)	Manchester Short Assessment of Quality of Life: • Patients with schizophrenia performed significantly worse at 12 months for quality of life compared with schizophreniform disorder ($U = 10{,}176$, $p = .014$) and schizoaffective patients ($U = 1669$, $p = .036$)	NR
Owoeye 2013 (Ireland)[19]	ES: First episode (45) C: First-episode major depressive disorder (28) C: First-episode bipolar disorder (37)	Quality of Life Scale[e] (6–112): • ES: 65.5 (20.6) • MDD: 76.1 (28.0) (p=ns) • Bipolar disorder: 100.3 (22.3) ($p < .001$)	NR
Rowland 2019 (UK)[27]	ES: First episode (227) C: First-episode delusional disorder (36)	EQ-5D health thermometer, baseline: • ES: 61.63 (22.36) • Delusional disorder: 60.00 (24.11) ($p = .689$)	NR
Sim 2007 (Singapore)[53]	ES: First episode (254) C: First-episode schizoaffective disorder (24)	WHOQOL-BREF: Overall quality of life: • ES 3.26 (1.03) • Schizoaffective disorder: 3.25 (1.29) ($p = .78$)	NR

Abbreviations. C, comparator; CS, chronic schizophrenia; EQ-5D, EuroQol 5-dimensions; ES, early schizophrenia; HC, healthy control; MDD, major depressive disorder; NR, not reported; ns, not significant; SD, standard deviation; SF-36, 36-item short form survey; WHOQOL, World Health Organization Quality of Life.
[a]Self-report questionnaire to assess satisfaction with life with a minimum score of 5 (dissatisfied) and a maximum score of 35 (satisfied)[76].
[b]Scale runs from 1 (not happy) to 7 (most happy), averaged over four items[77].
[c]Scale of 0 (not happy) to 10 (most happy)[54].
[d]Scale from 1 (most happy) to 4 (not happy)[54].
[e]Scale ranging from 6–112[78].

utilizing the Schizophrenia Quality of Life Scale, a commonly used scale to assess QoL and functioning in schizophrenia[39].

Further noteworthy data gaps were identified regarding economic burden, as no studies measuring direct or indirect costs attributed to early schizophrenia were found. Some data relating to resource use were identified, however, these were mostly outcomes reported as baseline characteristics, such as inpatient hospital stays and outpatient contacts. Considering literature beyond the scope of this review, a study of USA claims data for schizophrenia spectrum disorder patients found that more patients in their first year of disease were hospitalized compared with chronic patients and that they had significantly higher treatment costs[71]. Costs related to inpatient hospitalization were a major component of overall treatment costs, particularly for those with disease duration of less than one year[71]. A further known aspect of the economic and humanistic burden of schizophrenia is criminal offending, with higher risks of convictions for violent crimes reported for people with schizophrenia than the general population[72], but related data specifically for early schizophrenia were not identified in this review.

Limitations

Some limitations of this research should be noted. Studies were often small and were not always primarily intended to collect data on the disease burden or to make formal comparisons between early schizophrenia and the groups of interest in this review. In addition, a small proportion of the included studies were conference abstracts that may not have been peer reviewed as rigorously as full journal publications.

Metrics used to measure various aspects of burden varied across studies and as a result, few studies reported on any given outcome. Confounding factors such as age and duration of medication exposure could have affected comparisons between the groups of interest, in particular when considering comparisons between early and chronic schizophrenia. Nonetheless, due to the small number of studies identified it was not possible to conduct a quantitative assessment of the impact of these factors. Further variation between studies could be due to differences in diagnostic criteria used, although most studies reported using DSM-IV or ICD-10 (Supplementary Table 8). Furthermore, not all studies reported diagnostic codes to confirm only a "pure schizophrenia" population was included, therefore some studies with mixed schizophrenia disorder populations may have been included in this review inadvertently. Finally, there was wide variation between studies in terms of how early and chronic schizophrenia were defined.

Since this review focused on the burden associated with early schizophrenia, search terms related to "early" were used to refine the searches. These terms were based on a prior review of the literature conducted by our group to identify definitions of early schizophrenia[73]. It is possible, however, that some studies on the incidence of schizophrenia, or studies following patients from the first diagnosis but not specifically concerned with the early stages of

schizophrenia, would not have been identified if they did not use terminology related to "early". Certain aspects of disease burden were not considered in this review. Notably, general functioning scores, including the global assessment of function (GAF) were not extracted. Finally, and particularly when considering the literature gaps, it should be kept in mind that this review only included articles published in or after 2005 and written in the English language.

Conclusions

This review has highlighted several areas of burden for patients with early schizophrenia, including increased mortality, psychiatric comorbidities such as substance abuse and depression, poorer social functioning, and increased levels of unemployment. While the burden of early schizophrenia relative to healthy controls is evident, comparisons with chronic schizophrenia and other psychiatric disorders are less conclusive. Various gaps in available data were uncovered, for example for incarcerations, caregiver burden, and outpatient costs, and even for the more widely reported outcomes there were still few studies identified on each aspect of burden in early schizophrenia overall.

Transparency

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