BMJ Open

Do patterns of mental health care predict treatment failure in young people with schizophrenia? Real-world evidence from Italy

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007140
Article Type:	Research
Date Submitted by the Author:	10-Nov-2014
Complete List of Authors:	Corrao, Giovanni; University of Milano-Bicocca, Department of Statistics and Quantitative Methods Soranna, Davide; University of Milano-Bicocca, Department of Statistics and Quantitative Methods, Laboratory of Healthcare Research and Pharmacoepidemiology Merlino, Luca; Region Lombardy, Operative Unit of Territorial Health Services Monzani, Emiliano; Cà Granda Niguarda Hospital, Viganò, Caterina; , University of Milano, Department of Biomedical and Clinical Sciences Luigi Sacco Lora, Antonio; Lecco Hospital, Department of Mental Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Public health, Epidemiology
Keywords:	Epidemiology < TROPICAL MEDICINE, MENTAL HEALTH, Public health < INFECTIOUS DISEASES

Do patterns of mental health care predict treatment failure in young people with schizophrenia? Real-world evidence from Italy

Giovanni CORRAO[1], Davide SORANNA[1], Luca MERLINO[2], Emiliano MONZANI[3], Caterina VIGANÒ[4], Antonio LORA[5]

1 Department of Statistics and Quantitative Methods, Laboratory of Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy

2 Operative Unit of Territorial Health Services, Region Lombardia, Milan, Italy

3 Cà Granda Niguarda Hospital, Milan, Italy

4 Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milano, Milan, Italy

5 Department of Mental Health, Lecco Hospital, Lecco, Italy

Word Count: 3,725

Address for correspondence: Prof. Giovanni Corrao, Dipartimento di Statistica e Metodi Quantitativi, Sezione di Biostatistica, Epidemiologia e Sanità Pubblica, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milano, Italy. Tel.: +39.02.64485854; Fax: +39.02.64485899; E-mail: giovanni.corrao@unimib.it

Word count:3,725

Key words. Antipsychotic drugs; Database; Real-world evidence; Schizophrenia; Treatment failure

Abstract

Background Little is known about practice predicting community-based care effectiveness of patients affected by schizophrenic disorders. We assessed predictors of treatment failure in a large sample of young people affected by schizophrenia.

Methods. The cohort of 556 patients aged 18-35 years who had firstly diagnosed for schizophrenia during 2005–2009 in a Mental Health Service (MHS) of Italian Lombardy Region was identified. Intensity of mental health care received during the first year after index visit (exposure) was measured by means of regularity of MHS attendance and the length of time covered with antipsychotic drug therapy. Patients were followed from index visit until 2012 for identifying hospital admission for mental disorder (outcome). Proportional hazards model was fitted to estimate hazard ratio (HR), and 95% confidence intervals (CI), for the exposure-outcome association, after adjusting for several covariates. A set of sensitivity analyses was performed in order to account for sources of systematic uncertainty.

Results. During follow-up, 144 cohort members experienced the outcome. Compared with patients on low coverage with antipsychotic drugs (≤4 months), those on intermediate (5-8 months), and high (≥ 9 months) coverage had HRs (95% CI) of 0.94 (0.64 to 1.40), and 0.69 (0.48 to 0.98), respectively. There was no evidence that regular attendance with MHS affected the outcome.

Conclusions. Patients in the early phase of schizophrenia and their familiars should be cautioned about the possible consequences of antipsychotic poor adherence. Physicians and decision makers should strengthen their engagement for improving mental health care.

ARTICLE SUMMARY

Article focus

- Little is known about the practice and patient characteristics that predict effectiveness of community-based care patients affected by schizophrenic disorders.
- The focus of this study is to assess predictors of treatment failure in a large and unselected sample of young people affected by schizophrenia.

Key Message

- Our data on care patterns provided to patients suffering schizophrenic disorders in the real world setting, show poor adherence with antipsychotic drug therapy, as well as with regular attendance of mental health service. In addition, our study showed that a good coverage with antipsychotic therapy already in the first year after the diagnosis of schizophrenia reduces the long-term risk of hospital admission for mental disorders.

Strenghts

- The investigation is based on data from a large unselected population, which was made possible since in Italy a cost-free healthcare system involves practically all citizens.
- Our data reflect routine clinical practice and are not affected by selective participation and recall bias.
- Patients were identified from the point of the initial visit with the mental health service in which diagnosis of schizophrenia was made, and the complete sequence of public or accredited healthcare facilities, including mental health care and other services, was known.
- A number of sensitivity analyses confirmed the robustness of our findings.

Limitations

- Information about private mental health outpatient facilities are not available from our healthcare utilization databases system.
- Evaluation of antipsychotic drug coverage was based on pharmacy-dispensing information. This method assumes that the proportion of days covered by a prescription corresponds to the proportion of days of medication use.
- Although the large sample size, our study was not sufficiently powered to investigate the effect of relatively rare exposures.

Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines schizophrenia as a syndrome characterized by long duration and high relapse rate, with abnormalities in one or more of following five domains: delusions, hallucinations, disorganized thinking (speech) grossly disorganized or abnormal motor behaviour, including catatonia, and negative symptoms, and sometimes a few mood problems [1]. The onset of symptoms typically occurs in adolescence and young adulthood, with a worldwide estimate of its lifetime prevalence and incidence of 1.4–4.6 and 0.16–0.42 per 1,000 persons annually, respectively [2,3]. A recent systematic review indicated that patients diagnosed with this disorder have shorter lifespan than the average general population. They furthermore have increased risk of suicide and physical impairment (e.g., limited exercise, poor diet, and obesity), and reduced access to medical treatment and healthcare services [4].

Antipsychotic medications have been recommended as the mainstream of medical treatment for nearly all patients with schizophrenia, to provide them with a safe and therapeutic environment and effective symptom control [5]. In the last decades, different approaches to psychosocial interventions (e.g., psychotherapy, family therapy, psychoeducation and cognitive–behavioural therapy) have shown to be able to bear positive patient outcomes admitted that they are used as an adjunct to antipsychotics [6-13]. Although their comparative efficacy has been increasingly evaluated in various clinical trials [7,9,11,12], it should be emphasized that patients enrolled in these trials were likely quite motivated as they were consenting to intense monitoring in a structured research program and likely adhered, or were controlled for adherence, with clinical recommendations. Unfortunately, however, how these intervention programs perform in psychiatrically ill patients treated in real-world, naturalistic setting, is little known.

Mental health services play a central role in the treatment of people with schizophrenic disorders, as they act both as direct providers of care and as supporters of primary care practitioners [14]. According with the Italian model of mental health services, as well as with that of most high income countries, a complex network of different types of community mental health teams, and a range of treatment, rehabilitation, employment and residential care facilities, currently operate in in the community [15]. To date, however, little is known about the practice and patient characteristics that predict effectiveness of community-based care patients affected by schizophrenic disorders. This paper is designed to address this need. Our purpose is to assess predictors of treatment failure in a large and unselected sample of young people affected by schizophrenia.

Methods

Healthcare utilization databases of Lombardy

Data used for this study were retrieved from the healthcare utilization databases of Lombardy, a region that accounts for about 16% (more than 9 million inhabitants) of the whole Italian population. In Italy, the population is covered by the National Health Service (NHS) and in Lombardy this has been associated since 1997 with an automated system of databases to collect a variety of information, including: (1) an archive of residents who receive NHS assistance (beneficiaries of NHS practically coincide with the whole resident population), reporting demographic and administrative data; (2) a database on diagnosis at discharge from public or private hospitals of Italy; (3) a database on outpatient drug prescriptions reimbursed by the NHS and delivered by pharmacies of Lombardy; (4) a database on drug prescriptions administered

directly in the outpatient setting and day hospital, and reimbursed by the NHS (the so called file F); and (5) a database of outpatient services, including visits and diagnostic tests respectively performed in specialist ambulatories and laboratories accredited by the NHS. Beside these healthcare utilization databases, that are common to all the Regions of Italy, since 1999 Lombardy Region activated a specific system concerning psychiatric care provided by the regional Departments of Mental Health accredited by the NHS. The system provides demographic information and the ICD-10 diagnoses of all patients in contact with Mental Health outpatient Services (MHS) and records all treatments provided to them (outpatient and home visits, day treatment attendance, and residential facilities). For each patient we linked the above databases via a single identification code. In order to preserve privacy, each identification code was automatically converted to an anonymous code. The inverse process was prevented by deletion of the conversion table.

Through this record linkage process we were able to mark out the complete care pathway of all the citizen of Lombardy beneficiaries of NHS, practically of all residents in the Region, through a long period of observation. This offers the opportunity to design investigations including very large unselected populations, and to generate real-world evidence on several fields of healthcare, including mental health [16,17].

Cohort selection and follow-up

The target population consisted of all beneficiaries of the NHS resident in Lombardy aged 18-35 years. According to the 2011 Italian Census, this population amounted to 1,893,313 individuals. Of these, we identified patients who during the period January 1st, 2005 to December 31st, 2009 had at least a contact with a MHS accredited by the NHS and received in that occasion diagnosis of schizophrenia spectrum disorder (ICD-10 codes 2X.XX). The date of first visit during the considered period was recorded as index visit.

With the aim of favoring the inclusion of only newly treated individuals, patients who within two years prior to the index visit experienced at least a hospital admission for mental disorder (ICD-9 290-319), had at least a contact with a MHS, or even just received at least a prescription of an antipsychotic agent were excluded. Patients who during the first year after index visit did not receive antipsychotic medicaments were also excluded, based on the assumption that in these patients continuous drug treatment might have not been indicated. Finally, patients who did not reach at least 1 year of follow-up were excluded, to ensure at least one year of potential exposure to the care of interest. The remaining patients represented the study cohort.

Each member of the cohort accumulated person-years of follow-up from the index visit until the earliest among the dates of outcome onset (i.e., hospital admission for mental disorder) or censoring (i.e., death from any cause, emigration, or December 31st, 2012).

Characterizing cohort members

For each cohort member data included selected tracts detected at index visit such as gender, age, social tracts, and physical comorbidities. The latter, was measured by means of the Charlson comorbidity index score [18] which was calculated via the diagnostic information available from inpatient charts in the two years prior and one year after the index visit; patients was categorized has having or no having chronic comorbidities. Finally, co-treatments with antidepressive and mood stabilizers during the first year after index visit were considered.

Measuring mental health care

All contacts with MHS experienced by the cohort members during the first year after index visit were identified. Attendance was considered regular if the time-span between two consecutive visits was 60 days or shorter, or discontinuing otherwise. Patients were classified into two mutual exclusive categories of those who had regular attendance with the MHS (i.e., if they did not experience any episode of discontinuation through the first year after the index visit), or

discontinuers otherwise.

Patients were furthermore classified according if they received at least three individual, familiar or group sessions of psychotherapy, family psychoeducational activities or other supports (e.g., social, expressive, practical-manu8al, and physical activities, support to independent living and support to employment).

Data were also regarded in relation to the professionals who supplied care, distinguishing between patients who were seen only by mental health staff (psychiatrists and psychologists) or also by other professionals (educators, social workers, etc…).

Coverage with antipsychotic drug therapy was measured by means of the cumulative number of days during which the medication was available. Patients were accordingly categorized as having at least 4 months, from 5 months to 8 months, and more than 9 months of drug coverage.

Data analysis

The Kaplan-Meier estimator of the cumulative proportion of patients experiencing the outcome was built for the entire cohort, as well as according to selected subgroups. The log-rank test was used to test between group differences. The Cox proportional hazard regression model was fitted to estimate the hazard ratio (HR), and its 95% confidence interval (CI), for the association between the above listed covariates and time of outcome onset. Trends in HRs were tested, when feasible, according to the statistical significance of the regression coefficient of the recoded variables obtained by scoring the corresponding categories.

Sensitivity analyses

Because of the arbitrariness of taking a 60-day time-span to distinguish regular and discontinuing attendance, and to account for at least three psychotherapy sessions to identify patients treated, data were reanalysed according to different criteria, such as 30- and 90-day time-span and one or two sessions of psychotherapy.

The robustness of our findings with regard to potential bias introduced by unmeasured confounders was investigated by using the rule-out approach described by *Schneeweiss* [19]. Let *E* the exposure of interest (e.g., the regular attendance to the MHS contrasted to discontinuation), *O* the outcome (i.e., hospital admission for mental disorder), and *C* a hypothetical unmeasured confounder (e.g., severity of schizophrenia at diagnosis). In applying the rule-out method, we allowed *C* (i) to be present in the study population with a prevalence 50% (e.g., one half of included patients had symptoms of severe schizophrenia at index visit); (ii) to be associated with *O* with risk ratio varying from 1 to 10 (i.e. severe schizophrenics may experience the outcome up to 10-fold more than patients with less severe symptoms); and (iii) to be associated with *E* with odds ratio varying from 1 to 10 (i.e. severe schizophrenics may regularly attend the service up to 10-fold more than others). In its original formulation, rule-out approach aims to detect the extension of confounding required to fully account for the observed exposure-outcome association, so to drag the observed point estimate towards that expected under the null hypothesis. In our application, we extended the use of the rule-out approach at the situations in which the observed association did not reach statistical significance and the interest is to detect the extension of confounding required to make statistically significant the exposure-outcome association. With this aim, we conducted the analysis for the value of the observed higher 95% confidence limit to determine the constellations in which the 95% confidence interval would not cross the expected value under the null hypothesis.

Results

The distribution of the exclusion criteria is shown in Flow chart (**Figure 1**). The 556 who met inclusion criteria accumulated 2,619 person-years of observation, with an average per patient follow up of about 4.7 years. During this period, 144 patients belonging to the cohort members experienced the outcome.

Table 1 provides some characteristics of the included cohort members. At the index visit, almost one half of the patients had aged 30-35 years and 68% of them were men. The most patients had poor education, were never married and lived in family, while almost sixty percent of them were unemployed. Only two patients showed at least of sign of chronic comorbidity. More than one half and one of seven patients were respectively co-treated with antidepressive and mood stabilizers agents. **A**mong the considered covariates, evidence of increased outcome risk issued for patients with poor education, currently unemployed, and who did not receive antidepressive agents.

As far as mental health care provided to cohort members during the first year after index visit, **Table 2** shows that, although only one in five patients had a good coverage with antipsychotic drug therapy, significant reduction of the outcome risk was observed for these patients. The inverse coverage-outcome relationship is depicted in **Figure 2**. In particular the cumulative proportion of patients experiencing the outcome decreased from 34% to 32% and 23% for patients with low, intermediate and high drug coverage, respectively.

Table 2 shows that the most patients received interventions delivered by professionals other than psychiatrics and psychologists, 12% of them received at least three sessions of psychotherapy, and one quarter of patients had regular MHS attendance without any episode of discontinuation

during the first year after index visit. There was no evidence that neither type of treatment or of caregivers, nor regular attendance with MHS affected the outcome risk.

As expected, the proportion of regularly attending patients, as well that of adequately treated patients decreases as less permissive criteria was adopted. **Figure 3** shows that regulars accounted for only 5% by allowing 30 days between two consecutive visits, while 42% of patients had "regular" contacts at least every 90 days. Among the 124 patients who received a first psychotherapy session, only 66 (53%) reached at least three sessions. It should be noticed, however, the lack of evidence of a protective effect of care provided by territorial services even by varying the classification criteria.

The results of the residual confounding analysis obtained by means of the rule-out approach are presented in **Figure 4**. If we assume that patients exposed to the unmeasured confounder have a 4-fold increased outcome risk than those unexposed (i.e., severe schizophrenics experience the outcome 4-fold more than others), then patients exposed to the confounder would increase their exposure of 5.3-fold or more (i.e. severe schizophrenics would regularly attend the service with a odds more than 5-fold higher than others) to drag the effect of regular attendance to be significant protective on the outcome risk. On the other hand, if we assume that patients exposed to the confounder have even higher outcome risk (e.g., severe schizophrenics experience the outcome 10-fold more than others), then a lower discrepancy of the exposure of interest is required for admit protection (i.e., severe schizophrenics would regularly attend the service more than 3-fold higher than others).

Discussion

Our population-based cohort study shows that mental health care provided to young schizophrenic patients is frequently abandoned and/or is not adequately followed since the first year after diagnosis. Consistently with an impressive amount of literature [20], this was observed with regard to antipsychotic drug therapy, since only one in five patients had a good coverage with antipsychotic drug therapy. Furthermore, only one patient in twenty had monthly attendance of territorial MHS, and 58% of schizophrenics had attended the service for less than once every three months.

An important finding of our study, is that in the real-world setting the longer coverage with antipsychotic drug therapy during the first year after diagnosis of schizophrenia, the greater was the reduction in the risk of long-term hospital admission for mental disorder. Thus, our findings suggest that treatment with antipsychotics may favourably affect the risk of hospitalization, a conclusion that expands to a large unselected population the conclusions of several observational studies [21-24] and a recent systematic review of randomized clinical trials [25]. The poor compliance with drug therapy in everyday clinical practice, together with the observed strength of the association between drug coverage and outcome, give a 21% attributable fraction, that is more than one fifth of outcome currently occurring among schizophrenics who received antipsychotic drug therapy at baseline may be prevented if all those patients had good coverage with therapy. Hence, among the investigated factors, poor coverage with antipsychotic drugs appears the more important predictor.

Another important finding of our study, is that, unexpectedly, regular attendance of territorial MHS did not offer evidence of exerting a protective effect on the risk of hospitalization.

Consistently, patients who received psychotherapy, psychoeducational activities, or social supports, as well as multidisciplinary care, did not show evidence of outcome risk reduction. At first sight, this findings seem inconsistent with the current state of psychosocial treatments in the care of schizophrenia [11]. On closer inspection, however, our study suggests that the gap between what is known from clinical efficacy research and the systematic community translation of mental health care programs is still dramatically wide.

Other findings of our study deserve to be mentioned. First, among the considered social tracts, low level of education and unemployment were independent predictors of long-term risk of hospital admission for mental disorders, possibly due to the treatment delay, and then to the greater severity of illness at presentation, among people with low socio-economic status [26]. Second, we observed that almost one half of the included patients co-utilized antidepressants and that these patients were at lower risk of long-term mental disorders hospitalization. This finding confirms recent evidence that antidepressants along with antipsychotics are more effective in treating the negative symptoms of schizophrenia than antipsychotics alone [27].

The present study is unique in several respects. One, the investigation is based on data from a large unselected population, which was made possible since in Italy a cost-free healthcare system involves practically all citizens. Two, our data reflect routine clinical practice and are not affected by selective participation and recall bias. Three, patients were identified from the point of the initial visit with the mental health service in which diagnosis of schizophrenia was made, and the complete sequence of public or accredited healthcare facilities, including mental health care and other services, was known. Four, accurate data are guaranteed from healthcare utilization databases of Lombardy, as documented by several quality checks [28-30]. Finally, a number of sensitivity analyses confirmed the robustness of our findings.

Our study may be limited by some issues. One, information about private mental health outpatient facilities are not available from our healthcare utilization databases system. This involves the following systematic errors. 1) we selectively included patients who had at least a visit with a public structure; 2) we cannot exclude that some of the included patients already had visits with private structures, so that, despite our best efforts, some prevalent cases were selectively included; 3) the pathway of care which we were able to trace lacks for a part of clinical supplies. It should be emphasized, however, that the access to private facilities does not affect our ability to search out drug dispensations. In fact, according with Italian health system organization, free-of-charge drug prescriptions are however ensured (and then recorded in healthcare utilization database) even when they have been prescribed by a private physician. This may explain because, among the investigated health care, only drug therapy showed evidence of effectiveness.

Two, evaluation of antipsychotic drug coverage was based on pharmacy-dispensing information. This method assumes that the proportion of days covered by a prescription corresponds to the proportion of days of medication use. However, data on dispensing history have shown to be consistent with other adherence measures, drug serum levels, and clinical drug effects [31]. Nevertheless, the use of medication dispensing as a measure of coverage remains a source of uncertainty of our estimates.

Three, whether the observed findings are due to our inability to fully account for regular treatment to those patients at higher risk of clinical failure, is a relevant question in interpreting our findings. For example, it is likely that patients with severe schizophrenia at baseline are submitted to greater psychiatric attention than those with less severe symptoms, that is more regular visits, greater care for therapeutic plan and longer drug coverage. Our study addressed confounding by means of the following shrewdness. First, conventional adjustments for a

number of available demographic, therapeutic and clinical characteristics, such as age, gender, social features, and co-treatments, most of them may be considered proxies of disease severity, were performed. Second, we attempted to include patients at their first clinical manifestation of the disease. This was made by excluding patients aged 35 years or more who already received diagnosis of schizophrenia, had contacts with a department mental health, experienced hospitalizations for mental disorder, or even received antipsychotic drug dispensations. The exclusion of prevalent cases, as well as of prevalent drug users, is crucial for healthcare research, since the alternative consists in selectively including those patients who survived their disease status [32]. Third we excluded schizophrenics who did not receive antipsychotic drug dispensations during the first year after the index visit. The latter exclusion criteria, leading to research plans that we called "only user design" [33], have been described as reducing the potential for confounding by indication [34]. We suspect that, due to the nature of the precautions taken, confounding could have biased the effect of regular service attendance, rather than that of antipsychotic medicaments. Our sensitivity analysis accounting for unmeasured confounding, however, showed that, considering severity of schizophrenia as the unmeasured factor, even assuming very high prevalence of severe schizophrenia at presentation (50%) and that severe schizophrenics risk the outcome onset even 10-fold more than others, a strong discrepancy in regularity of service attendance between severe and less severe schizophrenics would need for making statistically significant the association of interest.

Finally, although the large sample size, our study was not sufficiently powered to investigate the effect of relatively rare exposures. For example, if we accept a permissive definition of regularity (e.g., by requiring at least one contact every three months) then our study is able to generate significant evidence admitted that discontinuers experience the outcome at least 1.8-fold more than regulars (with an error of the first type of 5% and a power of 80%). On the other hand, we

do not expect protection from such a permissive criterion. As regularity definition becomes less permissive, however, the observed number of regulars tends to decrease. For example, our study is able to generate significant evidence of outcome protection from monthly attendance admitted that discontinuers experience the outcome at least 5-fold more than regulars. This means that our study has limited chance of highlighting the impact of the proper use of the service, for the simple reason that proper use rarely occurs. Paradoxically, this source of weakness is due to the key message of our study, i.e., the limited use of territorial service.

In conclusion, our data on care patterns provided to patients suffering schizophrenic disorders in the real world setting, show poor adherence with antipsychotic drug therapy, as well as with regular attendance of mental health service. In addition, our study showed that a good coverage with antipsychotic therapy already in the first year after the diagnosis of schizophrenia reduces the long-term risk of hospital admission for mental disorders. Real world psychosocial treatments, as those provided at community level by mental health services in Lombardy in the last decade, should be strengthened to be effective. The development in Lombardy in the last four years of more than twenty projects for the early treatment of psychosis is moving in this direction. It is thus important that mental health professionals and decision makers strengthen their engagement toward improving mental health care in the clinical practice.

Contributorship Statement

AL and GC generated the initial study idea. GC wrote the protocol, and drafted the manuscript. DS and GC prepared the dataset and performed the data analysis and the sensitivity analysis. LM abstracted the data and authorized their utilization. EM assisted in interpreting the results under clinical prospective. All authors interpreted the results.

Competing interests

There are no competing interests

Funding

There are no funding for this study. All authors indicated no financial relationship.

Data sharing

No additional data available

References

[1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013

[2] Dominguez Mde G, Viechtbauer W, Simons CJ, et al. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. Psychol Bull 2009;135:157-71

[3] Jablensky A. Prevalence and incidence of schizophrenia spectrum disorders: implications for prevention. Aust N Z J Psychiatry 2000;34 Suppl:S26–S34; discussion S35–S38

[4] Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 2007;64:1123-31

[5] Chien WT, Yip ALK. Current approaches to treatments for schizophrenia spectrum disorders, part I: an overview and medical treatments. Neuropsychiatric Disease and Treatment 2013;9:1311-32

[6] Bilder RM. Neurocognitive impairment in schizophrenia and how it affects treatment options. Can J Psychiatry 1997;42:255-64

[7] Bustillo J, Lauriello J, Horan W et al. The psychosocial treatment of schizophrenia: an update. Am J Psychiatry 2001;158:163-75

[8] Carpenter WT Jr, Heinrichs DW, Wagman AM et al. Deficit and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 1988;145:578-83

[9] Hogarty GE, Anderson CM, Reiss DJ, et al. Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia. I. One-year effects of a controlled study on relapse and expressed emotion. Arch Gen Psychiatry 1986;43:633-42

[10] Patterson TL, Leeuwenkamp OR. Adjunctive psychosocial therapies for the treatment of schizophrenia. Schizophr Res 2008;100:108-19

[11] Pfammatter M, Junghan UM, Brenner HD. Efficacy of psychological therapy in schizophrenia: conclusions from meta-analyses. Schizophr Bull 2006;32 Suppl 1:S64–S80

[12] Rector NA, Beck AT. Cognitive behavioral therapy for schizophrenia: an empirical review. J Nerv Ment Dis 2001;189:278-87

[13] Tandon R, Targum SD, Nasrallah HA et al; Treatment Effectiveness in Schizophrenia Consortium. Strategies for maximizing clinical effectiveness in the treatment of schizophrenia. J Psychiatr Pract 2006;12:348-63

[14] Lora A, Kohn R, Levav I, et al. Service availability and utilization and treatment gap for schizophrenic disorders: a survey in 50 low- and middle-income. Bull World Health Organ 2012;90:47–5

[15] Tansella M, Thornicroft G, Lempp H. Lessons from Community Mental Health to Drive Implementation in Health Care Systems for People with Long-Term Conditions. Int J Environ Res Public Health 2014;11:4714-28

[16] Conti V, Lora A, Cipriani A et al.. Persistence with pharmacological treatment in the specialist mental healthcare of patients with severe mental disorders. Eur J Clin Pharmacol 2012;68:1647-55

[17] Barbui C, Conti V, Purgato M et al. Use of antipsychotic drugs and mood stabilizers in women of childbearing age with schizophrenia and bipolar disorder: epidemiological survey. Epidemiol Psychiatr Sci 2013;22:355-61

[18] Charlson ME, Charlson RE, Peterson JC, et al. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol 2008;61:1234-40

[19] Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 2006;15:291-303

[20] Marder SR. Monitoring treatment and managing adherence in schizophrenia. J Clin Psychiatry 2013;74:e21

[21] Hui CL, Wong GH, Tang JY, et al. Predicting 1-year risk for relapse in patients who have discontinued or continued quetiapine after remission from first-episode psychosis. Schizophr Res 2013;150:297-302

[22] Uchida T1, Suzuki T, Sakurai H, et al. Ten year outcomes of outpatients with schizophrenia on conventional depot antipsychotics: a systematic chart review. Int Clin Psychopharmacol 2013;28:261-6

[23] Schennach R1, Obermeier M, Meyer S, et al. Predictors of relapse in the year after hospital discharge among patients with schizophrenia. Psychiatr Serv 2012;63:87-90

[24] Subotnik KL, Nuechterlein KH, Ventura J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. Am J Psychiatry 2011;168:286-92

[25] Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 2012;379:2063-71

[26] Mulvany F, O'Callaghan E, Takei N, et al. Effect of social class at birth on risk and presentation of schizophrenia: case-control study. BMJ 2001;323:1398-401

[27] Surendra P, Singh SP, Singh V et al.. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. Br J Psych 2010;197:174–9

[28] Corrao G, Zambon A, Nicotra F, et al. Persistence with oral and transdermal hormone replacement therapy and hospitalisation for cardiovascular outcomes. Maturitas 2007;57:315-24

[29] Corrao G, Zambon A, Conti V, et al. Menopause hormone replacement therapy and cancer risk: an Italian record linkage investigation. Ann Oncol 2008;19:150-5

[30] Corrao G, Parodi A, Zambon A, et al. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. J Hypertens 2010;28:1584-90

[31] Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: Methods, validity, and applications. J Clin Epidemiol 1997;50:105-16

[32] Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915-20

[33] Corrao G, Ghirardi A, Segafredo G, et al, on behalf of the BEST Investigators. User-only design for assessing drug effectiveness in clinical practice: application to bisphosphonates and secondary prevention of fracture. Pharmacoepidemiol Drug Saf 2014. doi: 10.1002/pds.3650

[34] Stürmer T, Funk MJ, Poole C et al. Nonexperimental comparative effectiveness research using linked healthcare databases. Epidemiology 2011;22:298-301

Table 1. Selected tracts of the 556 included patients with diagnosis of schizophrenia and their relationship with the long-term risk of hospital admission for mental disorders. Lombardy Region, Italy, 2005-2012

	N (%)	Rough HR# (95% CI)	Adjusted HR# (95% CI)
DEMOGRAPHICS *			
Male gender	80 (68%)	1.05 (0.74 to 1.49)	1.04 (0.72 to 1.49)
Age (years)			
18-23	144 (26%)	1.00 (reference)	1.00 (reference)
24-29	160 (29%)	0.72 (0.46 to 1.11)	0.75 (0.46 to 1.17)
30-35	252 (45%)	0.83 (0.56 to 1.22)	0.89 (0.60 to 1.33)
p_{trend} ‡		0.269	0.343
SOCIAL TRACTS *			
Education (years)			
≤ 8	323 (58%)	1.00 (reference)	1.00 (reference)
9-14	195 (35%)	0.72 (0.05 to 1.03)	0.80 (0.55 to 1.16)
> 14	38 (7%)	0.49 (0.22 to 1.12)	0.51 (0.26 to 0.99)
p_{trend} §		0.020	0.046
Marital status			
Married	94 (17%)	1.00 (reference)	1.00 (reference)
Never married	462 (83%)	0.95 (0.62 to 1.46)	0.88 (0.55 to 1.42)
Living arrangements			
Alone	34 (6%)	1.00 (reference)	1.00 (reference)
Family	513 (92%)	1.04 (0.51 to 2.12)	0.70 (0.49 to 1.00)
Community	9 (2%)		
Employment			
Currently unemployed	324 (58%)	1.00 (reference)	1.00 (reference)
Currently employed	232 (42%)	0.65 (0.46 to 0.91)	0.74 (0.55 to 0.99)
CO-TREATMENTS AND COMORBIDITIES			
Physical comorbidities †			
None	554 (99%)	-	-
One or more	2 (1%)	-	-
Co-treatments ‡			
Antidepressive	274 (49%)	0.67 (0.48 to 0.93)	0.66 (0.47 to 0.93)
Mood stabilizers	84 (15%)	1.41 (0.93 to 2.14)	1.51 (0.98 to 2.33)

* At baseline (index visit)

† According to diagnostic information available from inpatient charts in the two years prior and one year after the index visit

‡ During the first year after index visit

§ p-value for the trend in the risk of outcome as the category of the corresponding variable increases

Hazard ratio (and 95% confidence interval) for the risk of hospital admission for mental disorders, according to Cox proportional hazard model. Estimates were rough and mutually adjusted for covariates listed in Tables 1 and 2

Table 2. Mental health care provided to the 556 included patients with diagnosis of schizophrenia and its relationship with the long-term risk of hospital admission for mental disorders. Lombardy Region, Italy, 2005-2012

	N (%)	Rough HR# (95% CI) [6]	Adjusted HR# (95% CI) [6]
Coverage with antipsychotic drug therapy *			
1-4 months	303 (55%)	1.00 (reference)	1.00 (reference)
5-8 months	135 (24%)	0.99 (0.67 to 1.45)	0.94 (0.64 to 1.40)
9-12 months	118 (21%)	0.71 (0.51 to 0.99)	0.69 (0.48 to 0.98)
p_{trend} §		0.052	0.043
Attendance of mental health service †,‡			
Discontinue	417 (75%)	1.00 (reference)	1.00 (reference)
Regular	139 (25%)	1.07 (0.74 to 1.55)	0.98 (0.63 to 1.51)
Treatments †			
Patient psychotherapy	124 (22%)	1.08 (0.73 to 1.59)	1.02 (0.66 to 1.56)
Family psychoeducation	319 (57%)	1.18 (0.84 to 1.65)	1.08 (0.76 to 1.55)
Other supports	103 (18%)	1.42 (0.97 to 2.10)	1.35 (0.87 to 2.10)
Caregivers †			
Only mental health professionals	44 (8%)	1.00 (reference)	1.00 (reference)
Also other professionals	512 (92%)	1.41 (0.74 to 2.69)	1.27 (0.65 to 2.47)

* Months with antipsychotic drugs available during the first year after index visit

† During the first year after index visit

‡ Attendance was considered regular if the time-span between two consecutive visits was 60 days or shorter, or discontinue otherwise

§ p-value for the trend in the risk of outcome as the category of the corresponding variable increases

Hazard ratio (and 95% confidence interval) for the risk of hospital admission for mental disorders, according to Cox proportional hazard model. Estimates were rough and mutually adjusted for covariates listed in Tables 1 and 2

Legends of Figures

Figure 1. Flow-chart of inclusion and exclusion criteria. Lombardy Region, Italy, 2005-2012

Figure 2. Cumulative proportion of patients experiencing hospitalization for mental disorders, according with their coverage with antipsychotic drug therapy during the first year since index visit. Lombardy Region, Italy, 2005-2012

Figure 3. Influence of criteria for identifying patients on regular attendance of the mental health service and on psychotherapy on the hazard ratio for hospital admission for mental disorders. Lombardy Region, Italy, 2005-2012

Footnote: Criteria concern the time-span within which two consecutive visits for allowing regular attendance (in box A patients with regular attendance are contrasted with those who experience at least a discontinuing episode) and the cumulative number of psychotherapy sessions (in box B patients with at least a given number of sessions is contrasted with those who experience fewer sessions). Hazard ratio estimated according to Cox proportional hazard model. Estimates are adjusted for covariates listed in Tables 1 and 2

Figure 4. Modelled influence of a hypothetical confounder on the hazard ratio for hospital admission for mental disorders unaccounted for in the adjustments already performed in the main analysis. Lombardy Region, Italy, 2005-2012

Footnote: The graph indicates what combinations of confounder – outcome and confounder – exposure would be required to make significantly protective the observed association between regular attendance of MHS and hospitalization for mental disorders. For an explanation see the "Sensitivity analysis", subsection of the "Methods" section

Figure 1

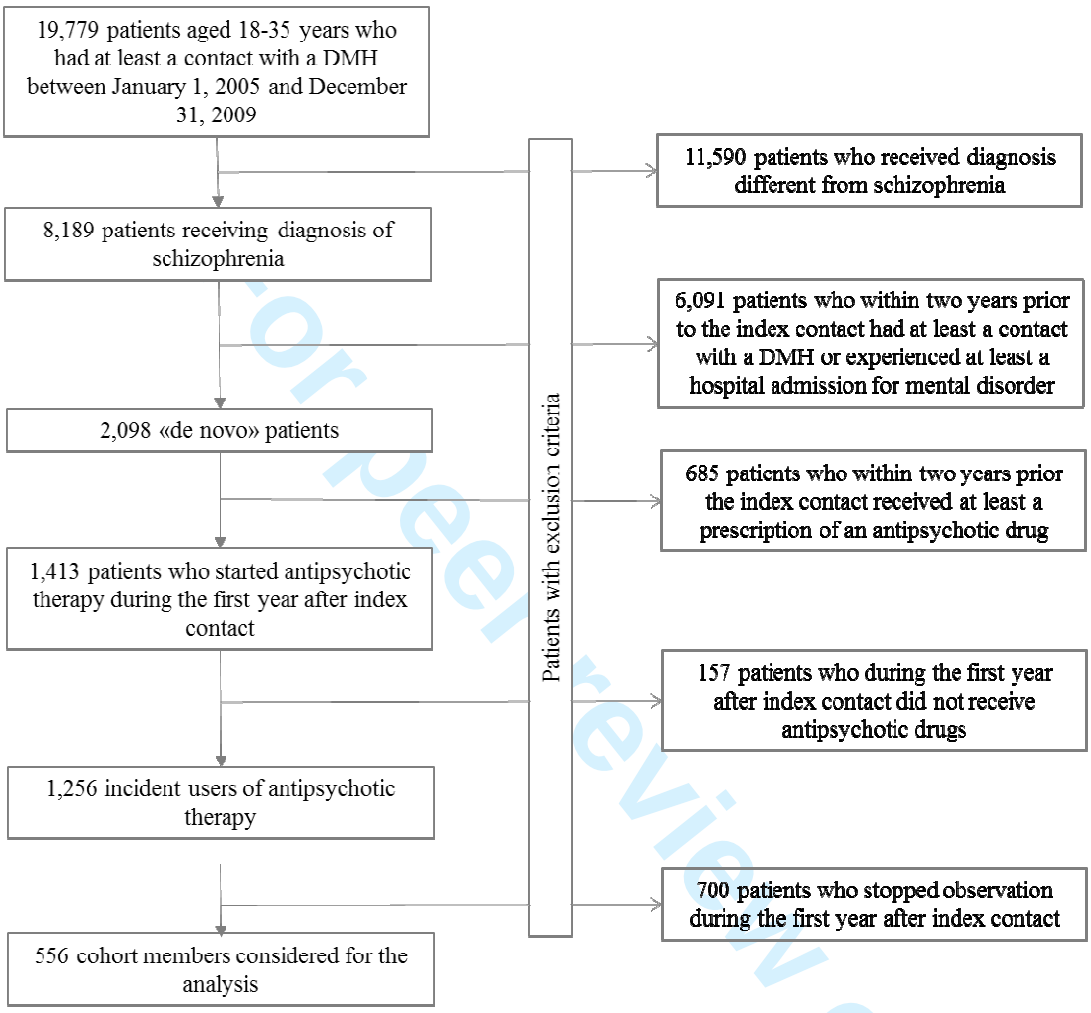


Figure 2

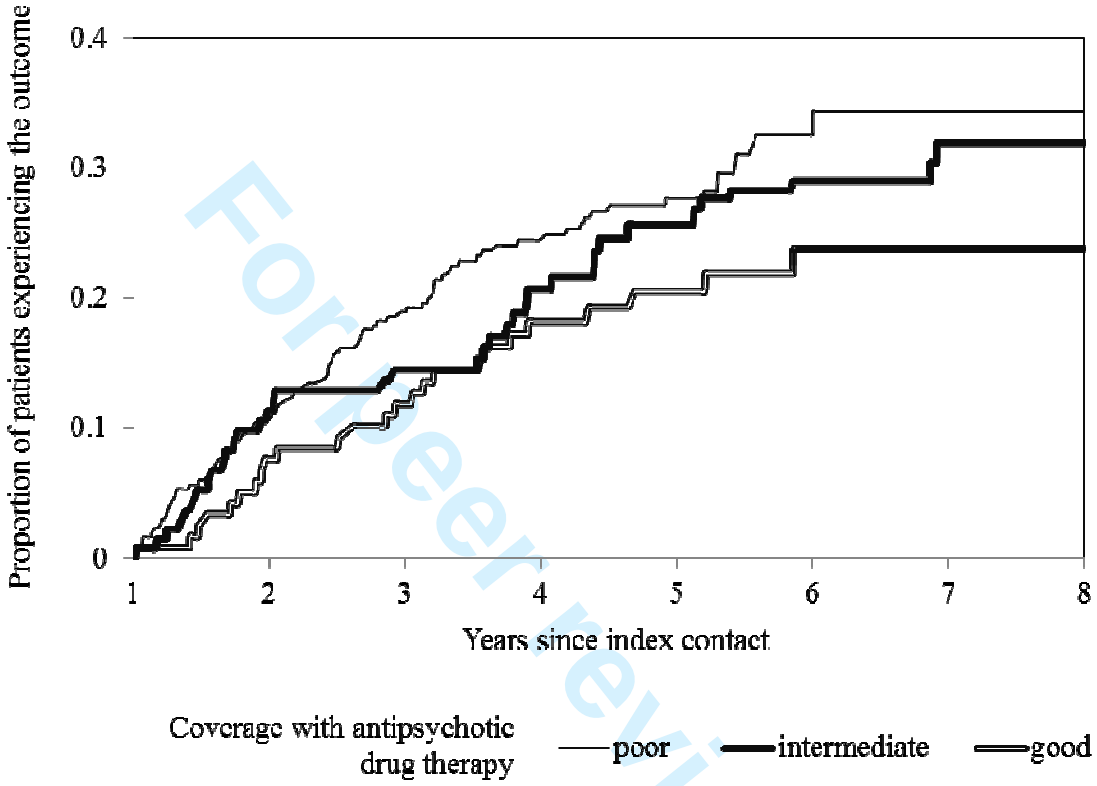


Figure 3

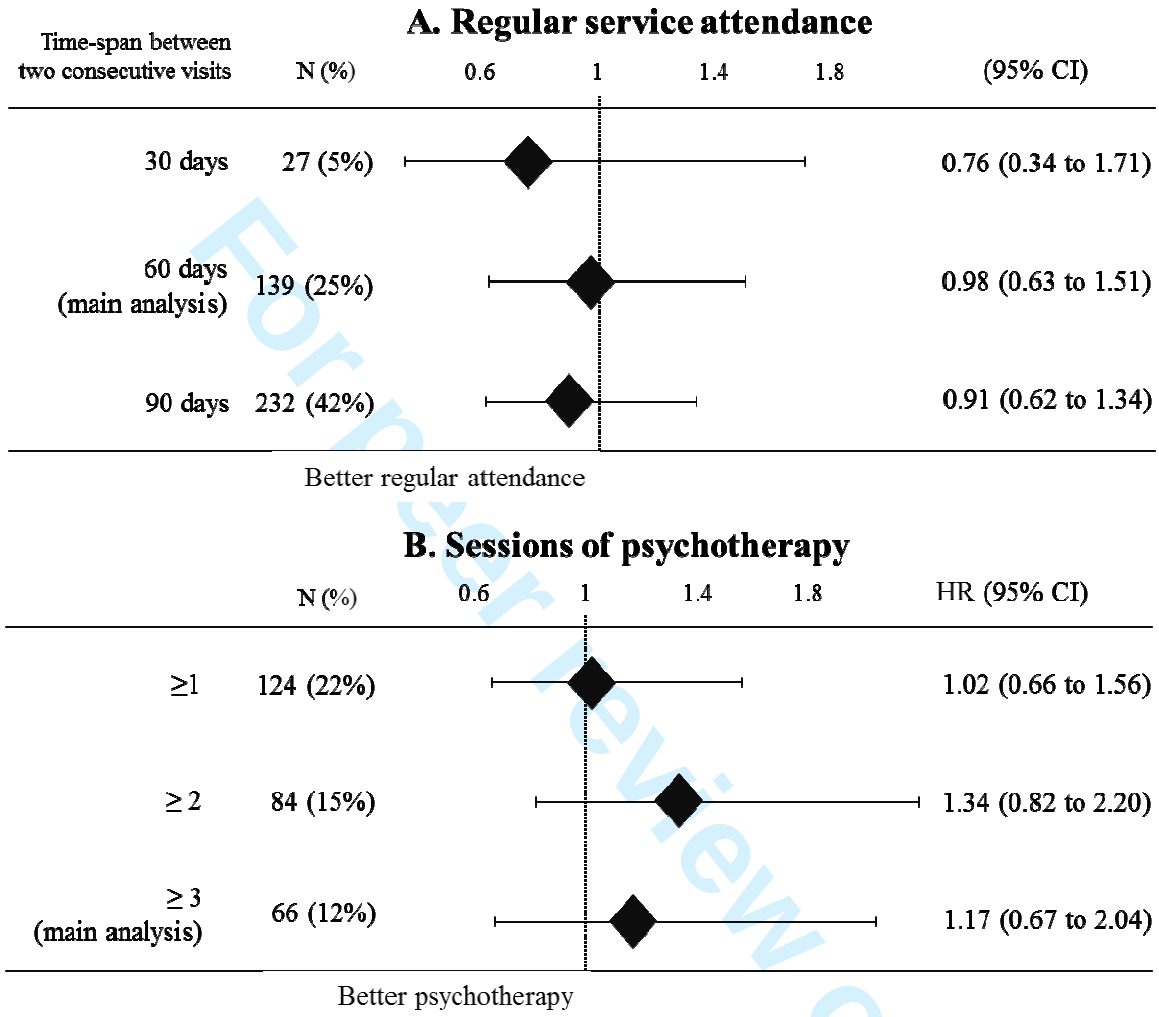
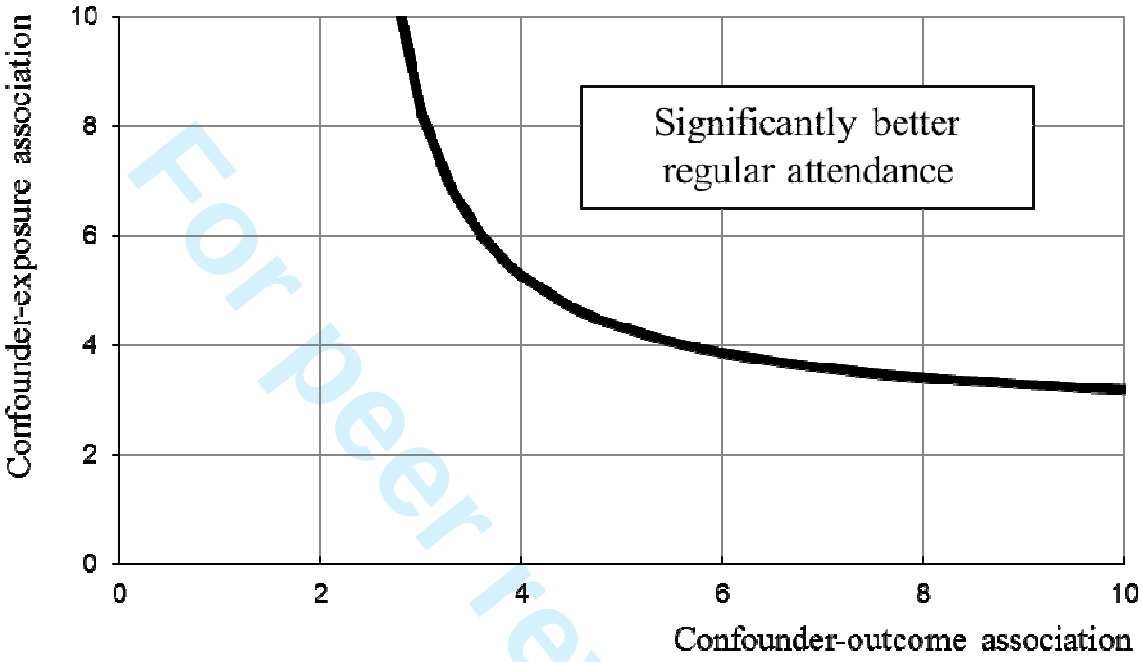


Figure 4



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page 2, line 6)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page2, lines 3-22)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 5, line 3-23)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 5, lines 23-24; Pages 6, lines 1-10)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 7, lines 19-24; Page 8 lines 1-24; Page 9, lines 1-11)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 7, lines 19-24; Page 8 lines 1-24; Page 9, lines 1-11)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page 7, lines 19-24; Page 8 lines 1-24; Page 9)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (NA)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 8, lines 12-24; Page 9, lines 1-11)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Page 8 , line 12-24; Page 9, lines 1-11)
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at (Figure 1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page 9, lines 21-24; Page 10, lines 1-19)
		(*b*) Describe any methods used to examine subgroups and interactions (Page 9, lines 15-19)
		(*c*) Explain how missing data were addressed (NA)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (Page 8, lines 9-11)
		(*e*) Describe any sensitivity analyses (Page 9, lines 21-24; Page 10, lines 1-19)

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Figure 1)
		(b) Give reasons for non-participation at each stage (Figure 1)
		(c) Consider use of a flow diagram (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest (NA)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (Page 11, lines 4-7)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page 11, lines 4-7)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Table 1 , Table 2)
		(*b*) Report category boundaries when continuous variables were categorized (Table 1 , Table 2)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Figure 2, Figure 4)
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page 13, lines 4-24; Page 14, lines 1-14)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page 15, lines 1-24; Page 16, lines 1-24; Page 17, lines 1-7)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 13, lines 4-24; Page 14, lines 1-23; Page 15, lines 1-24; Page 16, lines 1-24; Page 17, lines 1-17)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page 17, lines 8-17)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Page 18, line 2)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

BMJ Open

Do patterns of mental health care predict treatment failure in young people with schizophrenia? Evidence from an Italian population-based cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007140.R1
Article Type:	Research
Date Submitted by the Author:	27-Mar-2015
Complete List of Authors:	Corrao, Giovanni; University of Milano-Bicocca, Department of Statistics and Quantitative Methods Soranna, Davide; University of Milano-Bicocca, Department of Statistics and Quantitative Methods, Laboratory of Healthcare Research and Pharmacoepidemiology Merlino, Luca; Region Lombardy, Operative Unit of Territorial Health Services Monzani, Emiliano; Cà Granda Niguarda Hospital, Viganò, Caterina; , University of Milano, Department of Biomedical and Clinical Sciences Luigi Sacco Lora, Antonio; Lecco Hospital, Department of Mental Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Public health, Epidemiology
Keywords:	Epidemiology < TROPICAL MEDICINE, MENTAL HEALTH, Public health < INFECTIOUS DISEASES

Do patterns of mental health care predict treatment failure in young people with schizophrenia? Evidence from an Italian population-based cohort study

Giovanni CORRAO[1], Davide SORANNA[1], Luca MERLINO[2], Emiliano MONZANI[3], Caterina VIGANÒ[4], Antonio LORA[5]

1 Department of Statistics and Quantitative Methods, Laboratory of Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy

2 Operative Unit of Territorial Health Services, Region Lombardia, Milan, Italy

3 Department of Mental Health, Cà Granda Niguarda Hospital, Milan, Italy

4 Department of Biomedical and Clinical Sciences Luigi Sacco, University of Milano, Milan, Italy

5 Department of Mental Health, Lecco Hospital, Lecco, Italy

Address for correspondence: Prof. Giovanni Corrao, Dipartimento di Statistica e Metodi Quantitativi, Sezione di Biostatistica, Epidemiologia e Sanità Pubblica, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milano, Italy. Tel.: +39.02.64485854; Fax: +39.02.64485899; E-mail: giovanni.corrao@unimib.it

Abstract

Background and objective. Little is known about practice predicting community-based care effectiveness of patients affected by schizophrenic disorders. We assessed predictors of treatment failure in a large sample of young people affected by schizophrenia.

Methods. The cohort of 556 patients aged 18-35 years who had firstly diagnosed for schizophrenia during 2005–2009 in a Mental Health Service (MHS) of Italian Lombardy Region was identified. Intensity of mental health care received during the first year after index visit (exposure) was measured by means of regularity of MHS attendance and the length of time covered with antipsychotic drug therapy. Patients were followed from index visit until 2012 for identifying hospital admission for mental disorder (outcome). Proportional hazards model was fitted to estimate hazard ratio (HR), and 95% confidence intervals (CI), for the exposure-outcome association, after adjusting for several covariates. A set of sensitivity analyses was performed in order to account for sources of systematic uncertainty.

Results. During follow-up, 144 cohort members experienced the outcome. Compared with patients on low coverage with antipsychotic drugs (≤4 months), those on intermediate (5-8 months), and high (≥ 9 months) coverage had HRs (95% CI) of 0.94 (0.64 to 1.40), and 0.69 (0.48 to 0.98), respectively. There was no evidence that regular attendance with MHS affected the outcome.

Conclusions. Patients in the early phase of schizophrenia and their familiars should be cautioned about the possible consequences of antipsychotic poor adherence. Physicians and decision makers should strengthen their engagement for improving mental health care.

Key words. Antipsychotic drugs; Database; Real-world evidence; Schizophrenia; Treatment failure

ARTICLE SUMMARY

Article focus

- Little is known about the practice and patient characteristics that predict effectiveness of community-based care patients affected by schizophrenic disorders.
- The focus of this study is to assess predictors of treatment failure in a large and unselected sample of young people affected by schizophrenia.

Key Message

- Our data on care patterns provided to patients suffering schizophrenic disorders in the real world setting, show poor adherence with antipsychotic drug therapy, as well as with regular attendance of mental health service. In addition, our study showed that a good coverage with antipsychotic therapy already in the first year after the diagnosis of schizophrenia reduces the long-term risk of hospital admission for mental disorders.

Strenghts

- The investigation is based on data from a large unselected population, which was made possible since in Italy a cost-free healthcare system involves practically all citizens.
- Our data reflect routine clinical practice and are not affected by selective participation and recall bias.
- Patients were identified from the point of the initial visit with the mental health service in which diagnosis of schizophrenia was made, and the complete sequence of public or accredited healthcare facilities, including mental health care and other services, was known.
- A number of sensitivity analyses confirmed the robustness of our findings.

Limitations

- Information about private mental health outpatient facilities are not available from our healthcare utilization databases system.
- Evaluation of antipsychotic drug coverage was based on pharmacy-dispensing information. This method assumes that the proportion of days covered by a prescription corresponds to the proportion of days of medication use.
- Although the large sample size, our study was not sufficiently powered to investigate the effect of relatively rare exposures.

Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines schizophrenia as a syndrome characterized by long duration and high relapse rate, with abnormalities in one or more of following five domains: delusions, hallucinations, disorganized thinking (speech) grossly disorganized or abnormal motor behaviour, including catatonia, and negative symptoms, and sometimes a few mood problems [1]. The onset of symptoms typically occurs in adolescence and young adulthood, with a worldwide estimate of its lifetime prevalence and incidence of 1.4–4.6 and 0.16–0.42 per 1,000 persons annually, respectively [2,3]. A recent systematic review indicated that patients diagnosed with this disorder have shorter lifespan than the average general population. They furthermore have increased risk of suicide and physical impairment (e.g., limited exercise, poor diet, and obesity), and reduced access to medical treatment and healthcare services [4].

Antipsychotic medications have been recommended as the mainstream of medical treatment for nearly all patients with schizophrenia, to provide them with a safe and therapeutic environment and effective symptom control [5]. In the last decades, different approaches to psychosocial interventions (e.g., psychotherapy, family therapy, psychoeducation and cognitive–behavioural therapy) have shown to be able to bear positive patient outcomes admitted that they are used as an adjunct to antipsychotics [6-13]. Although their comparative efficacy has been increasingly evaluated in various clinical trials [7,9,11,12], it should be emphasized that patients enrolled in these trials were likely quite motivated as they were consenting to intense monitoring in a structured research program and likely adhered, or were controlled for adherence, with clinical recommendations. Unfortunately, however, how these intervention programs perform in psychiatrically ill patients treated in real-world, naturalistic setting, is little known.

Mental health services play a central role in the treatment of people with schizophrenic disorders, as they act both as direct providers of care and as supporters of primary care practitioners [14]. According with the Italian model of mental health services, as well as with that of most high income countries, a complex network of different types of community mental health teams, and a range of treatment, rehabilitation, employment and residential care facilities, currently operate in in the community [15]. To date, however, little is known about the practice and patient characteristics that predict effectiveness of community-based care patients affected by schizophrenic disorders. This paper is designed to address this need. Our purpose is to assess predictors of treatment failure in a large and unselected sample of young people affected by schizophrenia.

Methods

Departments of Mental Health in Lombardy

Lombardy, the largest and the most affluent Region in Italy with, in 2009, a population of about 9,700,000, lies in the northernmost part of the country. In Lombardy, public Department of Mental Health (DMH) provides mental health care through a network of community services, ranging from acute emergency treatment to long-term rehabilitation; it therefore includes one or more of all the following facilities: Community Mental Health Centers (CMHC), General Hospital Psychiatric Wards (GHPW), Day Care Centers (DCC), Community Residential Facilities (RF). The public DMH is the administrative, financial and organizational entity that is fully responsible for the network of community mental health facilities in the catchment area, including GHPWs and public RFs. It has full governance of all the available facilities in the

Department, and authorizes and controls the admission of DMH patients to private, licensed facilities, like private Residential Facilities [16].

Healthcare utilization databases of Lombardy

In Italy, the population is covered by the National Health Service (NHS) and in Lombardy its management has been associated since 1997 with an automated system of databases to collect a variety of information concerning services provided to beneficiaries of NHS. Information includes data on patients attending public DMH, e.g., demographics, ICD-10 diagnoses, treatments such as outpatient and home visits, day treatment attendance, and residential facilities. Beside the specific system for monitoring the use of mental health services, other automated systems for monitoring healthcare utilization include databases on diagnosis at discharge from public or private hospitals, outpatient drug prescriptions reimbursed by the NHS, drug prescriptions administered directly in the outpatient setting and day hospital, outpatient services, such visits and diagnostic tests respectively performed in specialist ambulatories and laboratories accredited by the NHS. For each patient we linked the above databases via a single identification code. In order to preserve privacy, each identification code was automatically converted to an anonymous code. The inverse process was prevented by deletion of the conversion table.

Through this record linkage process we were able to mark out the complete care pathway of all the citizen of Lombardy beneficiaries of NHS, practically of all residents in the Region, through a long period of observation. This offers the opportunity to design investigations including very large unselected populations, and to generate real-world evidence on several fields of healthcare, including mental health [17,18].

Cohort selection and follow-up

The target population consisted of all beneficiaries of the NHS resident in Lombardy aged 18-35 years. According to the 2011 Italian Census, this population amounted to 1,893,313 individuals.

Of these, we identified patients who during the period January 1st, 2005 to December 31st, 2009 had at least a contact with a MHS accredited by the NHS and received in that occasion diagnosis of schizophrenia spectrum disorder (ICD-10 codes 2X.XX). The date of first visit during the considered period was recorded as index visit.

With the aim of favoring the inclusion of only newly treated individuals, patients who within two years prior to the index visit experienced at least a hospital admission for mental disorder (ICD-9 290-319), had at least a contact with a MHS, or even just received at least a prescription of an antipsychotic agent were excluded. Patients who during the first year after index visit did not received antipsychotic medicaments were also excluded, based on the assumption that in these patients continuous drug treatment might have not been indicated. Finally, patients who did not reach at least 1 year of follow-up were excluded, to ensure at least one year of potential exposure to the care of interest. The remaining patients represented the study cohort.

Each member of the cohort accumulated person-years of follow-up from the index visit until the earliest among the dates of outcome onset (i.e., hospital admission for mental disorder) or censoring (i.e., death from any cause, emigration, or December 31st, 2012).

Characterizing cohort members

For each cohort member data included selected tracts detected at index visit such as gender, age, social tracts, and physical comorbidities. The latter, was measured by means of the Charlson comorbidity index score [19] which was calculated via the diagnostic information available from inpatient charts in the two years prior and one year after the index visit; patients was categorized has having or no having chronic comorbidities. Finally, co-treatments with antidepressive and mood stabilizers during the first year after index visit were considered.

Measuring mental health care

All contacts with MHS experienced by the cohort members during the first year after index visit

were identified. Attendance was considered regular if the time-span between two consecutive visits was 60 days or shorter, or discontinuing otherwise. Patients were classified into two mutual exclusive categories of those who had regular attendance with the MHS (i.e., if they did not experience any episode of discontinuation through the first year after the index visit), or discontinuers otherwise.

Patients were furthermore classified according if they received at least three individual, familiar or group sessions of psychotherapy, family psychoeducational activities or other supports (e.g., social, expressive, practical-manual, and physical activities, support to independent living and support to employment).

Data were also regarded in relation to the professionals who supplied care, distinguishing between patients who were seen only by mental health staff (psychiatrists and psychologists) or also by other professionals (educators, social workers, etc…).

Coverage with antipsychotic drug therapy was measured by means of the cumulative number of days during which the medication was available. Patients were accordingly categorized as having at least 4 months, from 5 months to 8 months, and more than 9 months of drug coverage.

Data analysis

The Kaplan-Meier estimator of the cumulative proportion of patients experiencing the outcome was built for the entire cohort, as well as according to selected subgroups. The log-rank test was used to test between group differences. The Cox proportional hazard regression model was fitted to estimate the hazard ratio (HR), and its 95% confidence interval (CI), for the association between the above listed covariates and time of outcome onset. Trends in HRs were tested, when feasible, according to the statistical significance of the regression coefficient of the recoded variables obtained by scoring the corresponding categories.

Sensitivity analyses

Because of the arbitrariness of taking a 60-day time-span to distinguish regular and discontinuing attendance, and to account for at least three psychotherapy sessions to identify patients treated, data were reanalysed according to different criteria, such as 30- and 90-day time-span and one or two sessions of psychotherapy.

The robustness of our findings with regard to potential bias introduced by unmeasured confounders was investigated by using the rule-out approach described by *Schneeweiss* [20]. Let *E* the exposure of interest (e.g., the regular attendance to the MHS contrasted to discontinuation), *O* the outcome (i.e., hospital admission for mental disorder), and *C* a hypothetical unmeasured confounder (e.g., severity of schizophrenia at diagnosis). In applying the rule-out method, we allowed *C* (i) to be present in the study population with a prevalence 50% (e.g., one half of included patients had symptoms of severe schizophrenia at index visit); (ii) to be associated with *O* with risk ratio varying from 1 to 10 (i.e. severe schizophrenics may experience the outcome up to 10-fold more than patients with less severe symptoms); and (iii) to be associated with *E* with odds ratio varying from 1 to 10 (i.e. severe schizophrenics may regularly attend the service up to 10-fold more than others). In its original formulation, rule-out approach aims to detect the extension of confounding required to fully account for the observed exposure-outcome association, so to drag the observed point estimate towards that expected under the null hypothesis. In our application, we extended the use of the rule-out approach at the situations in which the observed association did not reach statistical significance and the interest is to detect the extension of confounding required to make statistically significant the exposure-outcome association. With this aim, we conducted the analysis for the value of the observed higher 95% confidence limit to determine the constellations in which the 95% confidence interval would not cross the expected value under the null hypothesis.

Results

The distribution of the exclusion criteria is shown in **Figure 1**. The 556 who met inclusion criteria accumulated 2,619 person-years of observation, with an average per patient follow up of about 4.7 years. During this period, 144 patients belonging to the cohort members experienced the outcome.

Table 1 provides some characteristics of the included cohort members. At the index visit, almost one half of the patients had aged 30-35 years and 68% of them were men. The most patients had poor education, were never married and lived in family, while almost sixty percent of them were unemployed. Only two patients showed at least of sign of chronic comorbidity. More than one half and one of seven patients were respectively co-treated with antidepressive and mood stabilizers agents. **A**mong the considered covariates, evidence of increased outcome risk issued for patients with poor education, currently unemployed, and who did not receive antidepressive agents.

As far as mental health care provided to cohort members during the first year after index visit, **Table 2** shows that, although only one in five patients had a good coverage with antipsychotic drug therapy, significant reduction of the outcome risk was observed for these patients. The inverse coverage-outcome relationship is depicted in **Figure 2**. In particular the cumulative proportion of patients experiencing the outcome decreased from 34% to 32% and 23% for patients with low, intermediate and high drug coverage, respectively.

Table 2 shows that the most patients received interventions delivered by professionals other than psychiatrics and psychologists, 12% of them received at least three sessions of psychotherapy, and one quarter of patients had regular MHS attendance without any episode of discontinuation

during the first year after index visit. There was no evidence that neither type of treatment or of caregivers, nor regular attendance with MHS affected the outcome risk.

As expected, the proportion of regularly attending patients, as well that of adequately treated patients decreases as less permissive criteria was adopted. **Figure 3** shows that regulars accounted for only 5% by allowing 30 days between two consecutive visits, while 42% of patients had "regular" contacts at least every 90 days. Among the 124 patients who received a first psychotherapy session, only 66 (53%) reached at least three sessions. It should be noticed, however, the lack of evidence of a protective effect of care provided by territorial services even by varying the classification criteria.

The results of the residual confounding analysis obtained by means of the rule-out approach are presented in **Figure 4**. If we assume that patients exposed to the unmeasured confounder have a 4-fold increased outcome risk than those unexposed (i.e., severe schizophrenics experience the outcome 4-fold more than others), then patients exposed to the confounder would increase their exposure of 5.3-fold or more (i.e. severe schizophrenics would regularly attend the service with a odds more than 5-fold higher than others) to drag the effect of regular attendance to be significant protective on the outcome risk. On the other hand, if we assume that patients exposed to the confounder have even higher outcome risk (e.g., severe schizophrenics experience the outcome 10-fold more than others), then a lower discrepancy of the exposure of interest is required for admit protection (i.e., severe schizophrenics would regularly attend the service more than 3-fold higher than others).

Discussion

Our population-based cohort study shows that mental health care provided to young schizophrenic patients is frequently abandoned and/or is not adequately followed since the first year after diagnosis. Consistently with an impressive amount of literature [21], this was observed with regard to antipsychotic drug therapy, since only one in five patients had a good coverage with antipsychotic drug therapy. Furthermore, only one patient in twenty had monthly attendance of territorial MHS, and 58% of schizophrenics had attended the service for less than once every three months.

An important finding of our study, is that in the real-world setting the longer coverage with antipsychotic drug therapy during the first year after diagnosis of schizophrenia, the greater was the reduction in the risk of long-term hospital admission for mental disorder. Thus, our findings suggest that treatment with antipsychotics may favourably affect the risk of hospitalization, a conclusion that expands to a large unselected population the conclusions of several observational studies [22-25] and a recent systematic review of randomized clinical trials [26]. The poor compliance with drug therapy in everyday clinical practice, together with the observed strength of the association between drug coverage and outcome, give a 21% attributable fraction, that is more than one fifth of outcome currently occurring among schizophrenics who received antipsychotic drug therapy at baseline may be prevented if all those patients had good coverage with therapy. Hence, among the investigated factors, poor coverage with antipsychotic drugs appears the more important predictor.

Another important finding of our study, is that, unexpectedly, regular attendance of territorial MHS for receiving psychotherapy, psychoeducational activities, social supports and multidisciplinary care, did not show evidence of exerting a protective effect on the risk of

hospitalization in our setting. Although it is difficult to draw consistent conclusions from the existing literature on the efficacy of psychological interventions in the therapy of schizophrenic patients, there is however sound evidence for the efficacy of specific psychological approaches, i.e., social skills trainings, cognitive remediation, psychoeducational interventions with families and relatives, and cognitive behavioral therapy of psychotic symptoms [11]. This suggested their implementation into routine care according to several national guidelines [27]. However, the main open question remains the generalizability of RCT findings to routine care. Our study suggests that the gap between what is known from clinical efficacy research and the systematic community translation of mental health care programs is still dramatically wide, at least in the investigated setting.

Other findings of our study deserve to be mentioned. First, we observed that almost one half of the included patients had aged 30-35 years, i.e., they was much older than expected for a group experiencing a first episode of psychosis. This reveals that accessibility public mental health services should be improved for intercepting early onset of schizophrenic disorders. Second, among the considered social tracts, low level of education and unemployment were independent predictors of long-term risk of hospital admission for mental disorders, possibly due to the treatment delay, and then to the greater severity of illness at presentation, among people with low socio-economic status [28]. Finally, we observed that almost one half of the included patients co-utilized antidepressants and that these patients were at lower risk of long-term mental disorders hospitalization. This finding confirms recent evidence that antidepressants along with antipsychotics are more effective in treating the negative symptoms of schizophrenia than antipsychotics alone [29].

The present study is unique in several respects. One, the investigation is based on data from a large unselected population, which was made possible since in Italy a cost-free healthcare system

involves practically all citizens. Two, our data reflect routine clinical practice and are not affected by selective participation and recall bias. Three, patients were identified from the point of the initial visit with the mental health service in which diagnosis of schizophrenia was made, and the complete sequence of public or accredited healthcare facilities, including mental health care and other services, was known. Four, accurate data are guaranteed from healthcare utilization databases of Lombardy, as documented by several quality checks [30-32]. Finally, a number of sensitivity analyses confirmed the robustness of our findings.

Our study may be limited by some issues. One, information about private mental health outpatient facilities are not available from our healthcare utilization databases system. This involves the following systematic errors: 1) we selectively included patients who had at least a visit with a public structure; 2) we cannot exclude that some of the included patients already had visits with private structures, so that, despite our best efforts, some prevalent cases were selectively included; 3) the pathway of care which we were able to trace lacks for a part of clinical supplies. It should be emphasized, however, that the access to private facilities does not affect our ability to search out drug dispensations. In fact, according with Italian health system organization, free-of-charge drug prescriptions are however ensured (and then recorded in healthcare utilization database) even when they have been prescribed by a private physician. This may explain because, among the investigated health care, only drug therapy showed evidence of effectiveness.

Two, evaluation of antipsychotic drug coverage was based on pharmacy-dispensing information. This method assumes that the proportion of days covered by a prescription corresponds to the proportion of days of medication use. Although data on dispensing history have shown to be consistent with other adherence measures, drug serum levels, and clinical drug effects [33], it is likely that in a number of patients the prescribed drugs are not consumed. This implies that the

use of medication dispensing as a measure of coverage remains a source of uncertainty of our estimates. It should be mentioned, however, that this source of misclassification likely leads to an underestimation of the strength of adherence-outcome association [34].

Three, whether the observed findings are due to our inability to fully account for regular treatment to those patients at higher risk of clinical failure, is a relevant question in interpreting our findings. For example, it is likely that patients with severe schizophrenia at baseline are submitted to greater psychiatric attention than those with less severe symptoms, that is more regular visits, greater care for therapeutic plan and longer drug coverage. Our study addressed confounding by means of the following shrewdness. First, conventional adjustments for a number of available demographic, therapeutic and clinical characteristics, such as age, gender, social features, and co-treatments, most of them may be considered proxies of disease severity, were performed. Second, we attempted to include patients at their first clinical manifestation of the disease. This was made by excluding patients aged 35 years or more who already received diagnosis of schizophrenia, had contacts with a department mental health, experienced hospitalizations for mental disorder, or even received antipsychotic drug dispensations. The exclusion of prevalent cases, as well as of prevalent drug users, is crucial for healthcare research, since the alternative consists in selectively including those patients who survived their disease status [35]. Third we excluded schizophrenics who did not receive antipsychotic drug dispensations during the first year after the index visit. The latter exclusion criteria, leading to research plans that we called “only user design” [36], have been described as reducing the potential for confounding by indication [37]. We suspect that, due to the nature of the precautions taken, confounding could have biased the effect of regular service attendance, rather than that of antipsychotic medicaments. Our sensitivity analysis accounting for unmeasured confounding, however, showed that, considering severity of schizophrenia as the unmeasured

factor, even assuming very high prevalence of severe schizophrenia at presentation (50%) and that severe schizophrenics risk the outcome onset even 10-fold more than others, a strong discrepancy in regularity of service attendance between severe and less severe schizophrenics would need for making statistically significant the association of interest.

Finally, although the large sample size, our study was not sufficiently powered to investigate the effect of relatively rare exposures. For example, if we accept a permissive definition of regularity (e.g., by requiring at least one contact every three months) then our study is able to generate significant evidence admitted that discontinuers experience the outcome at least 1.8-fold more than regulars (with an error of the first type of 5% and a power of 80%). On the other hand, we do not expect protection from such a permissive criterion. As regularity definition becomes less permissive, however, the observed number of regulars tends to decrease. For example, our study is able to generate significant evidence of outcome protection from monthly attendance admitted that discontinuers experience the outcome at least 5-fold more than regulars. This means that our study has limited chance of highlighting the impact of the proper use of the service, for the simple reason that proper use rarely occurs. Paradoxically, this source of weakness is due to the key message of our study, i.e., the limited use of territorial service.

In conclusion, our data on care patterns provided to patients suffering schizophrenic disorders in the real world setting, show poor adherence with antipsychotic drug therapy, as well as with regular attendance of mental health service. In addition, our study showed that a good coverage with antipsychotic therapy already in the first year after the diagnosis of schizophrenia reduces the long-term risk of hospital admission for mental disorders. Real world psychosocial treatments, as those provided at community level by mental health services in Lombardy in the last decade, should be strengthened to be effective. The development in Lombardy in the last four years of more than twenty projects for the early treatment of psychosis is moving in this

direction. It is thus important that mental health professionals and decision makers strengthen their engagement toward improving mental health care in the clinical practice.

Contributorship Statement

AL and GC generated the initial study idea. GC wrote the protocol, and drafted the manuscript. DS and GC prepared the dataset and performed the data analysis and the sensitivity analysis. LM abstracted the data and authorized their utilization. EM assisted in interpreting the results under clinical prospective. All authors interpreted the results.

Competing interests

There are no competing interests

Funding

There are no funding for this study. All authors indicated no financial relationship.

Data sharing

No additional data available

References

[1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013

[2] Dominguez Mde G, Viechtbauer W, Simons CJ, et al. Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychol Bull* 2009;135:157-71

[3] Jablensky A. Prevalence and incidence of schizophrenia spectrum disorders: implications for prevention. *Aust N Z J Psychiatry* 2000;34 Suppl:S26–S34; discussion S35–S38

[4] Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007;**64**:1123-31

[5] Chien WT, Yip ALK. Current approaches to treatments for schizophrenia spectrum disorders, part I: an overview and medical treatments. *Neuropsychiatric Disease and Treatment* 2013;**9**:1311-32

[6] Bilder RM. Neurocognitive impairment in schizophrenia and how it affects treatment options. *Can J Psychiatry* 1997;**42**:255-64

[7] Bustillo J, Lauriello J, Horan W, Keith S. The psychosocial treatment of schizophrenia: an update. *Am J Psychiatry* 2001;**158**:163-75

[8] Carpenter WT Jr, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* 1988;**145**:578-83

[9] Hogarty GE, Anderson CM, Reiss DJ, et al. Family psychoeducation, social skills training, and maintenance chemotherapy in the aftercare treatment of schizophrenia. I. One-year effects of a controlled study on relapse and expressed emotion. *Arch Gen Psychiatry* 1986;**43**:633-42

[10] Patterson TL, Leeuwenkamp OR. Adjunctive psychosocial therapies for the treatment of schizophrenia. *Schizophr Res* 2008;**100**:108-19

[11] Pfammatter M, Junghan UM, Brenner HD. Efficacy of psychological therapy in schizophrenia: conclusions from meta-analyses. *Schizophr Bull* 2006;**32** Suppl 1:S64–S80

[12] Rector NA, Beck AT. Cognitive behavioral therapy for schizophrenia: an empirical review. *J Nerv Ment Dis* 2001;**189**:278-87

[13] Tandon R, Targum SD, Nasrallah HA, Ross R; Treatment Effectiveness in Schizophrenia Consortium. Strategies for maximizing clinical effectiveness in the treatment of schizophrenia. *J Psychiatr Pract* 2006;**12**:348-63

[14] Lora A, Kohn R, Levav I, et al. Service availability and utilization and treatment gap for schizophrenic disorders: a survey in 50 low- and middle-income. *Bull World Health Organ* 2012;**90**:47–5

[15] Tansella M, Thornicroft G, Lempp H. Lessons from Community Mental Health to Drive Implementation in Health Care Systems for People with Long-Term Conditions. Int J Environ Res Public Health 2014;11:4714-28

[16] Lora A, Barbato A, Cerati G, Erlicher A, Percudani M. The mental health system in Lombardy, Italy: access to services and patterns of care. *Soc Psychiatry Psychiatr Epidemiol* 2012;**47**:447-54

[17] Conti V, Lora A, Cipriani A, Fortino I, Merlino L, Barbui C. Persistence with pharmacological treatment in the specialist mental healthcare of patients with severe mental disorders. *Eur J Clin Pharmacol* 2012;**68**:1647-55

[18] Barbui C, Conti V, Purgato M, Cipriani A, Fortino I, Rivolta AL, Lora A. Use of antipsychotic drugs and mood stabilizers in women of childbearing age with schizophrenia and bipolar disorder: epidemiological survey. *Epidemiol Psychiatr Sci* 2013;**22**:355-61

[19] Charlson ME, Charlson RE, Peterson JC, et al. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008;**61**:1234-40

[20] Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;**15**:291-303

[21] Marder SR. Monitoring treatment and managing adherence in schizophrenia. *J Clin Psychiatry* 2013;**74**:e21

[22] Hui CL, Wong GH, Tang JY, et al. Predicting 1-year risk for relapse in patients who have discontinued or continued quetiapine after remission from first-episode psychosis. *Schizophr Res* 2013;**150**:297-302

[23] Uchida T1, Suzuki T, Sakurai H, et al. Ten year outcomes of outpatients with schizophrenia on conventional depot antipsychotics: a systematic chart review. *Int Clin Psychopharmacol* 2013;**28**:261-6

[24] Schennach R1, Obermeier M, Meyer S, et al. Predictors of relapse in the year after hospital discharge among patients with schizophrenia. *Psychiatr Serv* 2012;**63**:87-90

[25] Subotnik KL, Nuechterlein KH, Ventura J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. *Am J Psychiatry* 2011;**168**:286-92

[26] Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet* 2012;**379**:2063-71

[27] Gaebel W, Weinmann S, Sartorius N, Rutz W, McIntyre JS. Schizophrenia practice guidelines: international survey and comparison. *Br J Psychiatry* 2005;**187**:248-55

[28] Mulvany F, O'Callaghan E, Takei N, et al. Effect of social class at birth on risk and presentation of schizophrenia: case-control study. *BMJ* 2001;**323**:1398-401

[29] Surendra P, Singh SP, Singh V, Kar N, Chan K. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psych* 2010;**197**:174–9

[30] Corrao G, Zambon A, Nicotra F, et al. Persistence with oral and transdermal hormone replacement therapy and hospitalisation for cardiovascular outcomes. *Maturitas* 2007;**57**:315-24

[31] Corrao G, Zambon A, Conti V, et al. Menopause hormone replacement therapy and cancer risk: an Italian record linkage investigation. *Ann Oncol* 2008;**19**:150-5

[32] Corrao G, Parodi A, Zambon A, et al. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. *J Hypertens* 2010;**28**:1584-90

[33] Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: Methods, validity, and applications. *J Clin Epidemiol* 1997;**50**:105-16

[34] Corrao G, Mancia G. Generating evidence from computerized healthcare utilization databases. *Hypertension* 2015;**65**:490-8

[35] Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;**158**:915-20

[36] Corrao G, Ghirardi A, Segafredo G, et al, on behalf of the BEST Investigators. User-only design for assessing drug effectiveness in clinical practice: application to bisphosphonates and secondary prevention of fracture. *Pharmacoepidemiol Drug Saf* 2014. doi: 10.1002/pds.3650

[37] Stürmer T, Funk MJ, Poole C, Brookhart MA. Nonexperimental comparative effectiveness research using linked healthcare databases. *Epidemiology* 2011;**22**:298-301

Table 1. Selected tracts of the 556 included patients with diagnosis of schizophrenia and their relationship with the long-term risk of hospital admission for mental disorders. Lombardy Region, Italy, 2005-2012

	N (%)	Rough HR[#] (95% CI)	Adjusted HR[#] (95% CI)
DEMOGRAPHICS *			
Male gender	80 (68%)	1.05 (0.74 to 1.49)	1.04 (0.72 to 1.49)
Age (years)			
18-23	144 (26%)	1.00 (reference)	1.00 (reference)
24-29	160 (29%)	0.72 (0.46 to 1.11)	0.75 (0.46 to 1.17)
30-35	252 (45%)	0.83 (0.56 to 1.22)	0.89 (0.60 to 1.33)
p_{trend} ‡		0.269	0.343
SOCIAL TRACTS *			
Education (years)			
≤ 8	323 (58%)	1.00 (reference)	1.00 (reference)
9-14	195 (35%)	0.72 (0.05 to 1.03)	0.80 (0.55 to 1.16)
> 14	38 (7%)	0.49 (0.22 to 1.12)	0.51 (0.26 to 0.99)
p_{trend} §		0.020	0.046
Marital status			
Married	94 (17%)	1.00 (reference)	1.00 (reference)
Never married	462 (83%)	0.95 (0.62 to 1.46)	0.88 (0.55 to 1.42)
Living arrangements			
Alone	34 (6%)	1.00 (reference)	1.00 (reference)
Family	513 (92%)	1.04 (0.51 to 2.12)	0.70 (0.49 to 1.00)
Community	9 (2%)		
Employment			
Currently unemployed	324 (58%)	1.00 (reference)	1.00 (reference)
Currently employed	232 (42%)	0.65 (0.46 to 0.91)	0.74 (0.55 to 0.99)
CO-TREATMENTS AND COMORBIDITIES			
Physical comorbidities †			
None	554 (99%)	-	-
One or more	2 (1%)	-	-
Co-treatments ‡			
Antidepressive	274 (49%)	0.67 (0.48 to 0.93)	0.66 (0.47 to 0.93)
Mood stabilizers	84 (15%)	1.41 (0.93 to 2.14)	1.51 (0.98 to 2.33)

* At baseline (index visit)

† According to diagnostic information available from inpatient charts in the two years prior and one year after the index visit

‡ During the first year after index visit

§ p-value for the trend in the risk of outcome as the category of the corresponding variable increases

Hazard ratio (and 95% confidence interval) for the risk of hospital admission for mental disorders, according to Cox proportional hazard model. Estimates were rough and mutually adjusted for covariates listed in Tables 1 and 2

Table 2. Mental health care provided to the 556 included patients with diagnosis of schizophrenia and its relationship with the long-term risk of hospital admission for mental disorders. Lombardy Region, Italy, 2005-2012

	N (%)	Rough HR[#] (95% CI) [6]	Adjusted HR[#] (95% CI) [6]
Coverage with antipsychotic drug therapy [*]			
1-4 months	303 (55%)	1.00 (reference)	1.00 (reference)
5-8 months	135 (24%)	0.99 (0.67 to 1.45)	0.94 (0.64 to 1.40)
9-12 months	118 (21%)	0.71 (0.51 to 0.99)	0.69 (0.48 to 0.98)
p_{trend} [§]		0.052	0.043
Attendance of mental health service [†,‡]			
Discontinue	417 (75%)	1.00 (reference)	1.00 (reference)
Regular	139 (25%)	1.07 (0.74 to 1.55)	0.98 (0.63 to 1.51)
Treatments [†]			
Patient psychotherapy	124 (22%)	1.08 (0.73 to 1.59)	1.02 (0.66 to 1.56)
Family psychoeducation	319 (57%)	1.18 (0.84 to 1.65)	1.08 (0.76 to 1.55)
Other supports	103 (18%)	1.42 (0.97 to 2.10)	1.35 (0.87 to 2.10)
Caregivers [†]			
Only mental health professionals	44 (8%)	1.00 (reference)	1.00 (reference)
Also other professionals	512 (92%)	1.41 (0.74 to 2.69)	1.27 (0.65 to 2.47)

[*] Months with antipsychotic drugs available during the first year after index visit

[†] During the first year after index visit

[‡] Attendance was considered regular if the time-span between two consecutive visits was 60 days or shorter, or discontinue otherwise

[§] p-value for the trend in the risk of outcome as the category of the corresponding variable increases

[#] Hazard ratio (and 95% confidence interval) for the risk of hospital admission for mental disorders, according to Cox proportional hazard model. Estimates were rough and mutually adjusted for covariates listed in Tables 1 and 2

Legends of Figures

Figure 1. Flow-chart of inclusion and exclusion criteria. Lombardy Region, Italy, 2005-2012

Figure 2. Cumulative proportion of patients experiencing hospitalization for mental disorders, according with their coverage with antipsychotic drug therapy during the first year since index visit. Lombardy Region, Italy, 2005-2012

Figure 3. Influence of criteria for identifying patients on regular attendance of the mental health service and on psychotherapy on the hazard ratio for hospital admission for mental disorders. Lombardy Region, Italy, 2005-2012

Footnote: Criteria concern the time-span within which two consecutive visits for allowing regular attendance (in box A patients with regular attendance are contrasted with those who experience at least a discontinuing episode) and the cumulative number of psychotherapy sessions (in box B patients with at least a given number of sessions is contrasted with those who experience fewer sessions). Hazard ratio estimated according to Cox proportional hazard model. Estimates are adjusted for covariates listed in Tables 1 and 2

Figure 4. Modelled influence of a hypothetical confounder on the hazard ratio for hospital admission for mental disorders unaccounted for in the adjustments already performed in the main analysis. Lombardy Region, Italy, 2005-2012

Footnote: The graph indicates what combinations of confounder – outcome and confounder – exposure would be required to make significantly protective the observed association between regular attendance of MHS and hospitalization for mental disorders. For an explanation see the "Sensitivity analysis", subsection of the "Methods" section

Figure 1

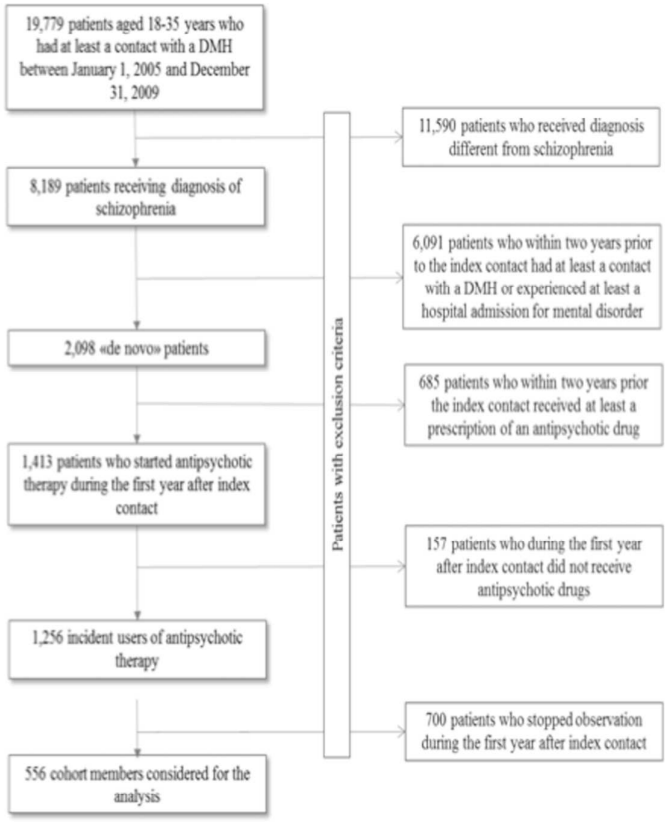


Figure 2

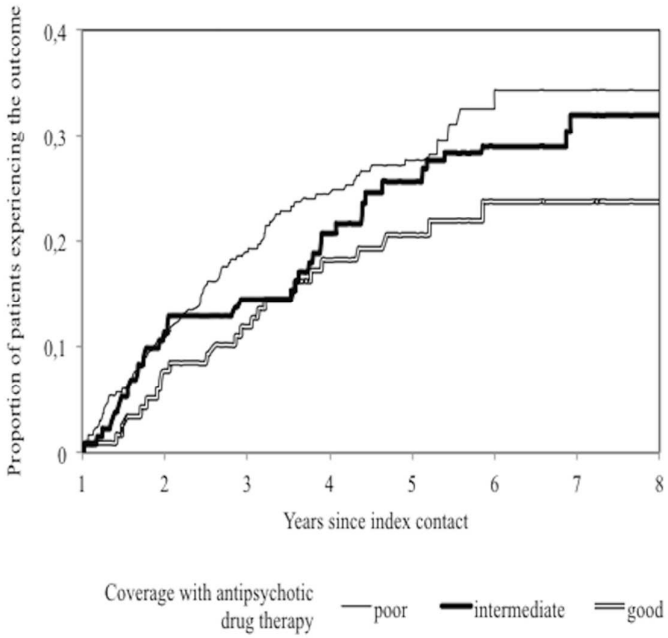


Figure 3

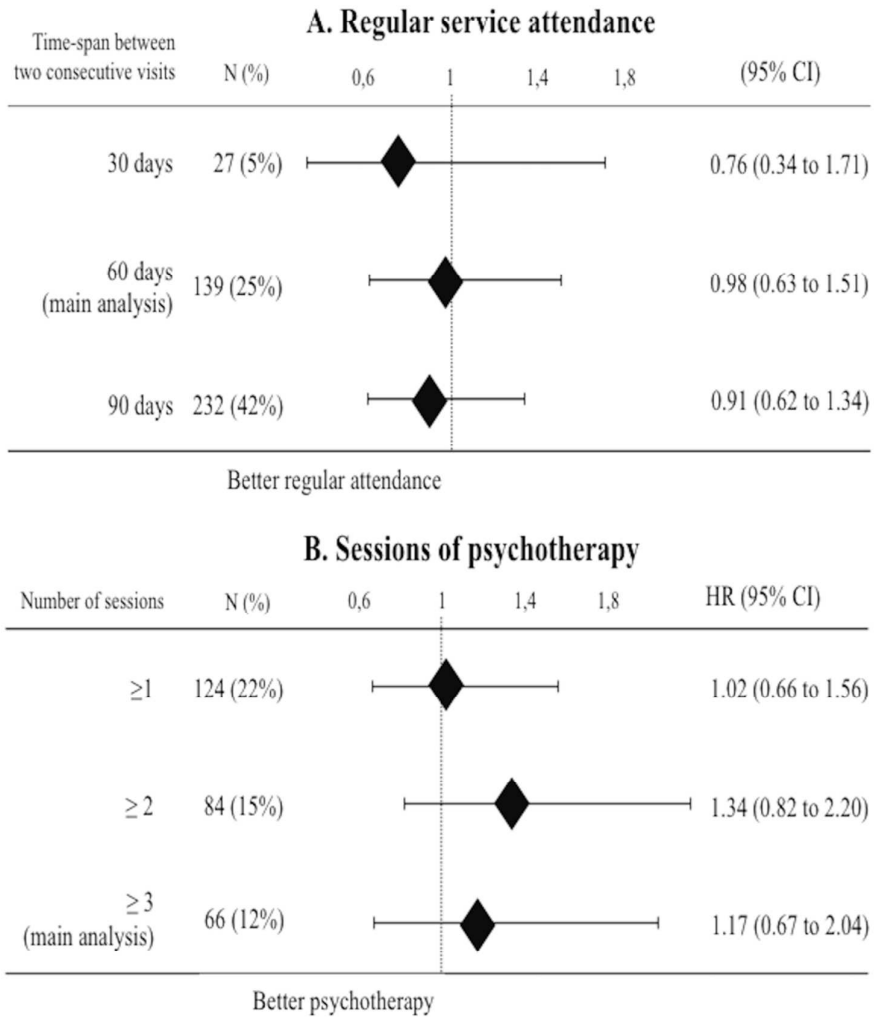
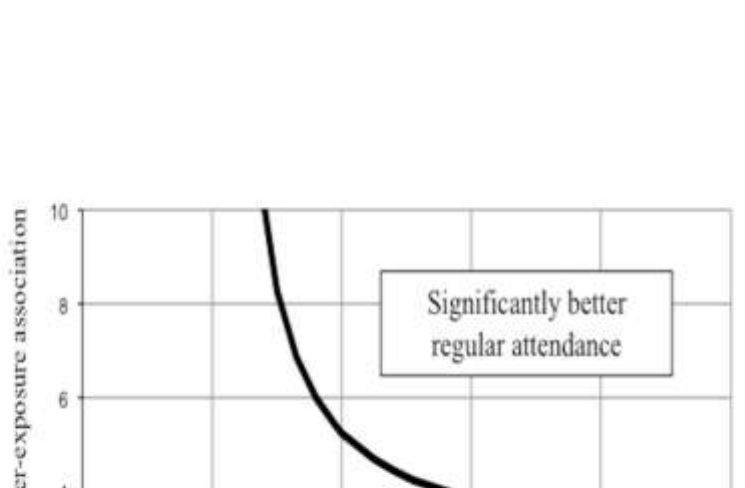


Figure 4


Confounder-exposure association
Confounder-outcome association
Significantly better regular attendance
0
2
4
6
8
10

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page 2, line 6)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Page2, lines 3-22)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 5, line 3-23)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 5, lines 23-24; Pages 6, lines 1-10)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 7, lines 23-24; Page 8 lines 1-24; Page 9, lines 1-15)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 7, lines 23-24; Page 8 lines 1-24; Page 9, lines 1-15)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page 7, lines 19-24; Page 8 lines 1-24; Page 9 lines 1-15)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (NA)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 8, lines 17-24; Page 9, lines 1-15)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Page 8 , line 17-24; Page 9, lines 1-11)
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at (Figure 1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page 9, lines 16-24; Page 10, lines 1-23)
		(*b*) Describe any methods used to examine subgroups and interactions (Page 9, lines 19-23)
		(*c*) Explain how missing data were addressed (NA)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (Page 8, lines 6-8)
		(*e*) Describe any sensitivity analyses (Page 10, lines 1-23)

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Figure 1)
		(b) Give reasons for non-participation at each stage (Figure 1)
		(c) Consider use of a flow diagram (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest (NA)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (Page 11, lines 3-6)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page 11, lines 4-7)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Table 1 , Table 2)
		(*b*) Report category boundaries when continuous variables were categorized (Table 1 , Table 2)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Figure 2, Figure 4)
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page 13, lines 3-24; Page 14, lines 1-22)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page 15, lines 8-24; Page 16, lines 1-24; Page 17, lines 1-24; Page 18 lines 1-2)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 13, lines 3-24; Page 14, lines 1-24; Page 15, lines 1-24; Page 16, lines 1-24; Page 17, lines 1-24; Page 18, lines 1-2)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page 17, lines 17-24; Pag 18 lines 1-2)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Page 18, line 14)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.