European Psychiatry 43 (2017) 73–80

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Chronic physical illnesses in patients with schizophrenia spectrum disorders are independently associated with higher rates of psychiatric rehospitalization; a cross-sectional study in Croatia

I. Filipcic [a,b,c,*,1], I. Simunovic Filipcic [d,1], E. Ivezic [a], K. Matic [a], N. Tunjic Vukadinovic [a], S. Vuk Pisk [a,b], D. Bodor [a], Z. Bajic [e], M. Jakovljevic [c,f], N. Sartorius [g]

[a] Psychiatric Hospital "Sveti Ivan", Zagreb, Croatia
[b] Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
[c] School of Medicine, University of Zagreb, Zagreb, Croatia
[d] Department of psychological medicine, University Hospital Center Zagreb, Zagreb, Croatia
[e] Biometrika Healthcare Research, Zagreb, Croatia
[f] Department of psychiatry, University Hospital Center Zagreb, Zagreb, Croatia
[g] Association for the Improvement of Mental Health Programmes, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 10 November 2016
Received in revised form 29 January 2017
Accepted 22 February 2017
Available online 10 March 2017

Keywords:
Schizotypal
Delusional
Medical comorbidity
Psychiatric comorbidity
Rehospitalization
Severe mental illness

ABSTRACT

Background: Increased physical morbidity in patients with schizophrenia spectrum disorders (SSDs) is well documented. However, much less is known about the association between somatic comorbidities and psychosis treatment outcomes.
Subjects and methods: This cross-sectional study, nested within the larger frame of a prospective cohort study, was done in 2016 at Psychiatric Hospital Sveti Ivan, Zagreb, Croatia. Data were collected on a consecutive sample of 301 patients diagnosed with schizophrenia spectrum disorders who achieved a stable therapeutic dosage. Key outcome was the number of psychiatric rehospitalizations since diagnosis of the primary psychiatric illness. Predictors were number of physical and psychiatric comorbidities. By robust regression, we controlled different clinical, sociodemographic, and lifestyle confounding factors.
Results: The number of chronic somatic comorbidities was statistically significantly associated with a larger number of psychiatric rehospitalizations, even after the adjustment for number of psychiatric comorbidities and large number of other clinical, sociodemographic, and lifestyle variables.
Conclusions: Chronic somatic comorbidities are associated with higher rates of psychiatric rehospitalization independently of psychiatric comorbidities and other clinical, sociodemographic, and lifestyle factors. Therefore, to treat psychosis effectively, it may be necessary to treat chronic somatic comorbidities promptly and adequately. Chronic somatic comorbidities should be considered equally important as the SSD, and should be brought to the forefront of psychiatric treatment and research with the SSD as one entity. The integrative approach should be the imperative in clinical practice.

1. Introduction

Schizophrenia spectrum disorders (SSDs) are among the top 10 causes of disability worldwide [1]. In addition to causing disabling psychiatric symptoms, schizophrenia is associated with frequent physical illness [2,3]. People diagnosed with psychosis have a 2.5 times higher risk of dying than the general population [3,4]. Mortality rates in the population with psychiatric disorders and the difference in mortality between patients diagnosed with psychosis and the general population has been increasing [3–5]. Psychiatric patients die earlier of similar causes than do the general population (e.g., heart disease, cancer, and cerebrovascular and respiratory diseases), and these patients account for more than two thirds of this excess mortality [3–9].

The adverse effects of psychiatric pharmacotherapy, high prevalence of unhealthy lifestyle and modifiable risk factors further increase the risks. Schizophrenia is, however, increasingly recognized as a systemic disorder and these patients face an additional burden in terms of somatic comorbidity implying overlapping and interacting disease mechanisms that involve

* Corresponding author. Psychiatric hospital "Sveti Ivan", Jankomir 11, pp68, 10 090 Zagreb, Croatia.
E-mail address: igor.filipcic@pbsvi.hr (I. Filipcic).
[1] Igor Filipcic and Ivona Simunovic Filipcic have equally contributed to the paper (shared first authorship).

http://dx.doi.org/10.1016/j.eurpsy.2017.02.484
0924-9338/

neurotransmitter, inflammatory, endothelial and hormonal pathways among others [10–13]. Growing body of evidence has demonstrated that people with psychosis are at greatly increased risk of chronic physical comorbidities (cardiovascular disease, metabolic syndrome, diabetes, and respiratory disease) [10,11]. Furthermore, somatic comorbidities in psychiatric patients may be associated with the poor health related quality of life, independently of different sociodemographic, vital and clinical factors [12]. Also, it has been established that somatic comorbidities, as well as the negative association of somatic comorbidities with patients' quality of life, are related to pharmacological treatment of psychosis [12–15]. However, access to preventive interventions, the quality of detection, diagnosis, and adequate treatment are still lower in psychotic than in non-psychiatric patients [5,6,10,16–19]. The prevalent current approach still separates physical and mental health care [20,21].

Despite these facts, less is known about the association of somatic comorbidities with the outcome of treatment of psychosis. Several studies addressed the problem from this "reverse perspective" [22–26], but we have not found conclusive evidence that somatic comorbidities affect symptom exacerbation of schizophrenia spectrum disorders nor the efficacy of their treatment. The objective of this study was to explore whether the number of chronic physical illnesses is associated with a poorer SSD treatment outcome indicated by higher rate of psychiatric rehospitalizations independently of psychiatric comorbidities, and other clinical and sociodemographic parameters.

2. Methods

2.1. Study design

This cross-sectional study enrolled patients during 2016 at Psychiatric Hospital Sveti Ivan, Zagreb, Croatia. The study was nested within the larger frame of a prospective cohort study named, "Somatic comorbidities in psychiatric patients (SCPP)", which has an expected end date of June 2017. The main study protocol was registered at ClinicalTrials.gov (NCT02773108), and it was approved by the Ethics Committee of Psychiatric Hospital Sveti Ivan. Informed consent was obtained from all patients. The study complied with World Medical Association Declaration of Helsinki 2013 [27].

2.2. Study population

The targeted population was patients diagnosed with SSDs (ICD-10; DSM-V) who were treated in a psychiatric hospital and achieved a stable therapeutic dosage. Inclusion criteria were ICD-10 (F20-F29); DSM-V: schizophrenia spectrum disorders, both genders, age $\geq$ 18 years, treated in a psychiatric hospital as inpatients or outpatients, and ability to answer the questionnaire. Exclusion criteria were acute suicidality, dementia, mental retardation, acute psychosis, and intoxication. We chose a consecutive sample of outpatients by the order of their arrival at the exam, and all patients who were hospitalized during the enrollment period.

2.3. Needed sample size

Power analysis was performed before the start of the enrolment as the component of power analysis performed for the main prospective cohort study. A sample size of 231 achieves 90% power to detect an $R^2 \geq 0.05$ attributed to two independent variables: number of physical illnesses and number of psychiatric comorbidities, using a F-test with a significance level (α) of 0.05. The independent variables tested will be adjusted for an additional 10 possible confounding variables with an $R^2 \geq 0.05$. Expecting up to 15% of respondents would have missing data on dependent (number of hospitalizations) and independent variables, the initially needed sample size was determined to be $n = 272$. Power analysis was done in PASS 14 Power Analysis and Sample Size Software (2015) (NCSS, LLC, Kaysville, Utah, USA).

2.4. Outcomes

Our outcome was the number of psychiatric hospitalizations since diagnosis of the primary psychiatric illness. This is not direct measure of clinical success, however, it has been used in many observational studies as an outcome measure to evaluate antipsychotic effectiveness (e.g. [28–31]) and, as Burns concluded, it showed as a good proxy outcome measure in schizophrenia [32]. The number of rehospitalizations was assessed objectively from hospital records archived in Psychiatric Hospital Sveti Ivan. We used the row number and not the standardized one (e.g., average number of hospitalizations annually) because we planned to control duration of illness since diagnosis and patients' age by multivariate analysis.

2.5. Independent variables (predictors)

Our independent variables were number of chronic somatic comorbidities and the number of psychiatric comorbidities. Chronic somatic illness was defined as the non-mental illness that requires medical treatment and lasted for at least six months. Trained psychiatrists recorded all comorbidities after consultation of medical records and clinical interview.

2.6. Possible confounders

Possible confounders whose effect we tried to control by multivariate analysis were sex, age, education, marital status, number of household members, work status, diet, smoking, excessive alcohol consumption, physical activity, duration of primary psychiatric illness, severity at diagnosis measured by the Clinical Global Impression-Severity (CGI-S) scale, antipsychotic drugs used, and treatment with antidepressants and benzodiazepines. Alcohol consumption was measured by self-completion of 2nd wave European Health Interview Survey (EHIS) questions on frequency and number of standard alcoholic drinks [33]. We calculated the average number of standard alcoholic drinks daily based on questions AL2. "Thinking of Monday to Thursday, on how many of these 4 days do you usually drink alcohol?" and AL3. "Number of alcoholic (standard) drinks on average on one of the days (Monday to Thursday)", and the same two questions for the period Friday to Sunday (AL4 and AL5). Excessive alcohol consumption was defined as more than 20 g/day (2 standard units) for men and 10 g/day (1 standard unit) for women [34]. Duration and intensity of average PA was measured by EHIS-PAQ [35]. The instrument was developed for the second wave of European Health Interview Survey (EHIS). According to recent validation, it has good validity and reliability [36]. EHIS-PAQ referent time is "average week". Total PA defined as proportion of individuals being sufficiently physically active in total, that is who are performing $\geq$ 150 minutes of aerobic PA or $\geq$ 2 muscle-strengthening PA weekly [35].

2.7. Statistical analysis

The level of statistical significance was set at $P < 0.05$, and we gave all confidence intervals at 95% level. In all instances, we used two-tailed tests. According to the protocol, it was planned that in

the case of > 5% of participants with missing data, multiple imputation would be done by fully conditional specification of the iterative Markov chain Monte Carlo method, and that we would do a sensitivity analysis. The main analysis was done by robust regression and iteratively reweighted least squares on all variables used simultaneously. We used Huber's method for robust influence function with Huber's default tuning constant of 1.345, and a default median absolute deviation of residuals' scale factor of 0.6745. The criterion for stopping the iteration procedure was set at percent change of 0.001. Regression coefficients and tests of statistical significance were calculated assuming that the robust weights were random, calculated from the sample residuals, and not fixed. Multi-colinearity of independent and confounding variables was tested by tolerance, variance inflation factor (VIF), and eigenvalues/condition numbers. Independence of residuals was tested by the Durbin–Watson test. Normality of distributions was analyzed by Shapiro–Wilk and D'Agostino's omnibus K^2 tests. The model fit to the data was expressed by coefficient of determination (R^2) after robust weighting and by prediction error sum of squares (PRESS). Cases with missing data were omitted from multivariate analysis. No correction for multiple testing was needed, as all analyses were pre-planned, and only one multivariate analysis was interpreted. Sensitivity analysis was done in two ways. First, by repeating the analysis after multiple imputation of confounders' missing data. Second, by repeating the analysis with particular antipsychotics replaced with a binary variable representing long-acting injections vs. oral therapy, and with particular antipsychotics replaced with a number of antipsychotics used. Statistical data analysis was done by NCSS 10 Statistical Software (2015) (NCSS, LLC. Kaysville, Utah, USA).

3. Results

In the main, prospective cohort study, we included 1060 patients treated for any psychiatric condition (Fig. 1). The final sample of 301 patients diagnosed with SSDs was enrolled at the first measurement for the cohort study. Diagnoses of patients were determined by their psychiatrists, according to the ICD-10 diagnostic criteria (WHO, 1992). The percentages of their primary psychiatric diagnoses are showed in Table 1. Primary psychiatric illness duration ranged from < 1 year up to 49 years. Number of hospitalizations was mean (SD) 6.0 (7.61); median (interquartile range) 3.0 (1.0–8.0). Patients' age ranged from 19 to 75 years (Table 2). The most prevalent chronic physical illnesses were endocrine, nutritional and metabolic diseases, and diseases of the circulatory and digestive system (Table 3). The most prevalent psychiatric comorbidities were disorders of adult personality and behavior, mental and behavioral disorders due to psychoactive substance use, mood (affective) disorders, and neurotic, stress-related, and somatoform disorders (Table 3).

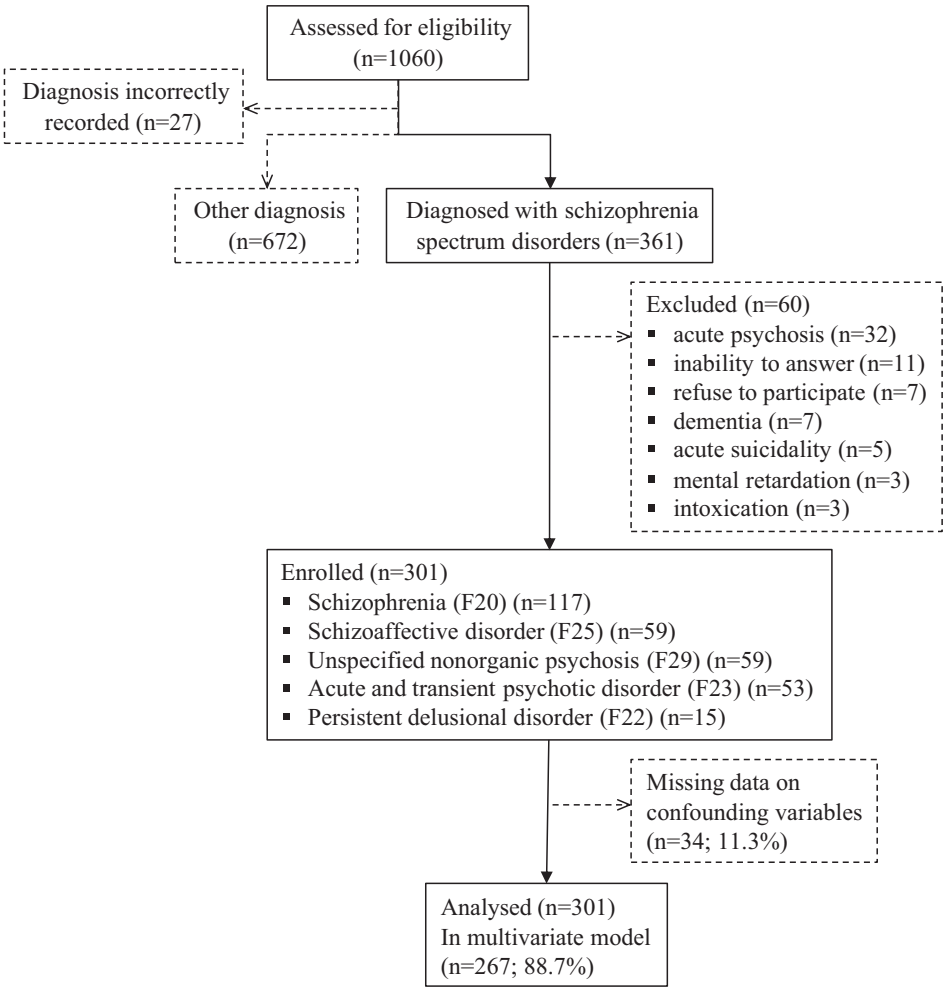

Fig. 1. Study flow.

Table 1
Patients' clinical characteristics ($n = 301$).

	n	(%)
Outpatients	159	(52.8)
Hospitalized	142	(47.2)
Primary psychiatric illness		
Schizophrenia (F20)	117	(38.6)
Acute and transient psychotic disorder (F23)	53	(17.5)
Schizoaffective disorder (F25)	59	(19.5)
Unspecified nonorganic psychosis (F29)	59	(19.5)
Persistent delusional disorder (F22)	15	(5.0)
Duration of primary psychiatric illness (years), $\bar{x}$ (SD)	11	(10.1)
Clinical global impression-severity scale (CGI-S) at diagnosis		
Up to mildly ill	48	(16.2)
Moderately ill	94	(31.6)
Significantly ill	99	(33.3)
Severely ill	56	(18.9)
Antipsychotics[a]		
Monotherapy	149	(49.5)
Combination	152	(50.5)
1st generation	118	(39.2)
Fluphenazine	53	(17.6)
Promazine	44	(14.6)
Haloperidol	33	(11.0)
Zuclopentixol	14	(4.7)
Levomepromazine	10	(3.3)
2nd generation	248	(82.4)
Amisulpirid	8	(2.7)
Aripiprazole	30	(10.0)
Quetiapine	52	(17.3)
Olanzapine	94	(31.2)
Paliperidone	29	(9.6)
Risperidone	53	(17.6)
Sertindole	2	(0.7)
Sulpiride	10	(3.3)
Ziprasidone	47	(15.6)
Clozapine	51	(16.9)
Antidepressants	126	(41.9)
Benzodiazepines	230	(76.4)
Number of chronic physical illness, $\bar{x}$ (SD)	0.9	(1.21)
Number of chronic physical illness		
None	152	(50.5)
1	81	(26.9)
≥ 2	68	(22.6)
Number of psychiatric comorbidities, $\bar{x}$ (SD)	1.5	(0.78)
Number of psychiatric comorbidities		
None	187	(62.1)
1	75	(24.9)
≥ 2	39	(13.0)
Number of hospitalizations, $\bar{x}$ (SD)	6.1	(7.76)

Data are presented as number (percentage) of participants if not stated otherwise. $\bar{x}$: arithmetic mean; SD: standard deviation. Data were missing for duration of primary psychiatric illness 2 (0.7%), CGI-S 4 (1.3%) of participants.
[a] Sum exceeds 100% because of combination therapies.

Table 2
Patients' sociodemographic and lifestyle characteristics ($n = 301$).

	n	(%)
Sex		
Male	163	(54.2)
Female	138	(45.8)
Age (years), $\bar{x}$ (SD)	44	(12.8)
Education		
Primary	39	(13.0)
Secondary	186	(61.8)
University	76	(25.2)
Marital status		
Single	182	(60.7)
Married	71	(23.7)
Widowed or divorced	47	(15.7)
Number of household members, $\bar{x}$ (SD)	1.4	(1.04)
Monthly income per household member (EUR), $\bar{x}$ (SD)	434	(344.3)
Work status		
Employed	119	(39.9)
Unemployed	80	(26.8)
Retired	99	(33.2)
Diet		
Having a breakfast		
Up to once a week	51	(17.3)
Several times a week	55	(18.7)
Every day	188	(63.9)
Eating fruits every day	93	(31.7)
Eating vegetables every day	93	(31.8)
Sufficient physical activity[a]	195	(64.8)
Smoking tobacco	167	(55.5)
Excessive alcohol consumption[b]	8	(2.7)

Data are presented as number (percentage) of participants if not stated otherwise. $\bar{x}$: arithmetic mean; SD: standard deviation. Data were missing for marital status 1 (0.3%), number of household members 6 (2.0%), work status 3 (1.0), having a breakfast 7 (2.3), eating fruits 8 (2.7), eating vegetables 9 (3.0) of participants.
[a] Sufficient physical activity was defined as aerobic physical activity ≥ 150 min/week or ≥ 2 muscle-strengthening physical activity weekly.
[b] Excessive alcohol consumption was defined as > 20 g/day men; > 10 g/day women.

Final multivariate analysis was done per protocol with the list-wise deletion of cases with missing data on the sample of 267 (89%) patients with complete data. We had no missing data on the dependent nor on the independent variables. According to Little's MCAR test, our data were not missing completely at random ($P = 0.001$). Robust regression criterion for stopping the iteration procedure was achieved in 14 iterations. Multi-colinearity was not indicated, as tolerances of all variables were > 0.84, and variance inflation factors for all variables were < 3.1. The smallest eigenvalue was 0.15 with condition number of 22.4. The largest correlation was found between age and duration of illness ($r = 0.48$; $r^2 = 0.23$; $P < 0.001$). Distribution of residuals was symmetric and was not significantly different from the normal one: Shapiro–Wilk test, $P = 0.092$, D'Agostino Omnibus K^2 test, $P = 0.085$. The Durbin–Watson test statistic was 2.0, indicating no serial correlation of residuals. Several outliers were detected. Association of number of rehospitalizations with the number of physical illnesses and number of psychiatric diagnoses was not significantly deviated from linear ($P = 0.260$ and $P = 0.714$, respectively).

Univariate analysis showed significant positive correlation between the number of rehospitalizations and number of chronic physical illnesses ($\beta = 0.20$; $P < 0.001$). (Table 4, Fig.2). After adjustment for all clinical, sociodemographic and lifestyle characteristics by multivariate robust regression, the number of chronic physical illnesses was independently, significantly correlated with a larger number of psychiatric rehospitalizations ($\beta = 0.16$; $P = 0.009$) (Table 4). Having two or more chronic physical illnesses was associated with an increase of one psychiatric rehospitalization. The overall model was significant ($P < 0.001$) with coefficient of determination after robust weighting, $R^2 = 0.54$. The prediction error sum of squares (PRESS) coefficient of determination indicated low-to-moderate predictive validity (prediction $R^2 = 0.15$).

Sensitivity analysis after the multiple imputation of confounders' missing data resulted in the comparable pooled independent association of chronic somatic illness with the number of psychiatric rehospitalizations ($\beta = 0.15$). Repeating the regression analysis with specific antipsychotics replaced with a binary variable representing long-acting injections vs. oral therapy, the relative importance of number of somatic illnesses further increased ($\beta = 0.18$). The same happened when we replaced specific drugs with the total number of antipsychotics used ($\beta = 0.21$).

4. Discussion

Our study has shown significant and clinically relevant correlation of number of psychiatric rehospitalizations with the

Table 3
Chronic physical illnesses and psychiatric comorbidities ($n = 301$).

	n	(%)
Chronic physical illnesses		
IV Endocrine, nutritional and metabolic diseases (E00-E90)	102	(33.9)
IX Diseases of the circulatory system (I00-I99)	36	(12.0)
XI Diseases of the digestive system (K00-K93)	22	(7.3)
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	12	(4.0)
X Diseases of the respiratory system (J00-J99)	12	(4.0)
VI Diseases of the nervous system (G00-G99)	9	(3.0)
XIII Diseases of the musculoskeletal system and connective tissue (M00-M99)	10	(3.3)
II Neoplasms (C00-D48)	5	(1.7)
XII Diseases of the skin and subcutaneous tissue (L00-L99)	3	(1.0)
XIV Diseases of the genitourinary system (N00-N99)	3	(1.0)
Other diseases > 1% each[a]	5	(1.7)
Psychiatric comorbidities		
Disorders of adult personality and behavior (F60-F69)	36	(12.0)
Mental and behavioral disorders due to psychoactive substance use (F10-F19)	26	(8.6)
Mood (affective) disorders (F30-F39)	23	(7.6)
Neurotic, stress-related and somatoform disorders (F40-F48)	21	(7.0)
Organic, including symptomatic, mental disorders (F00-F09)	15	(5.0)
Behavioral syndromes associated with psychological disturbances and physical factors (F50-F59)	5	(1.7)
Intentional self-harm (X60-X84)	3	(1.0)
Disorders of psychological development (F80-F89)	1	(0.3)
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90-F98)	1	(0.3)

[a] Other diseases: I Certain infectious and parasitic diseases (A00-B99), VII Diseases of the eye and adnexa (H00-H59), VIII Diseases of the ear and mastoid process (H60-H95), XIX Injury, poisoning, and certain other consequences of external causes (S00-T98).

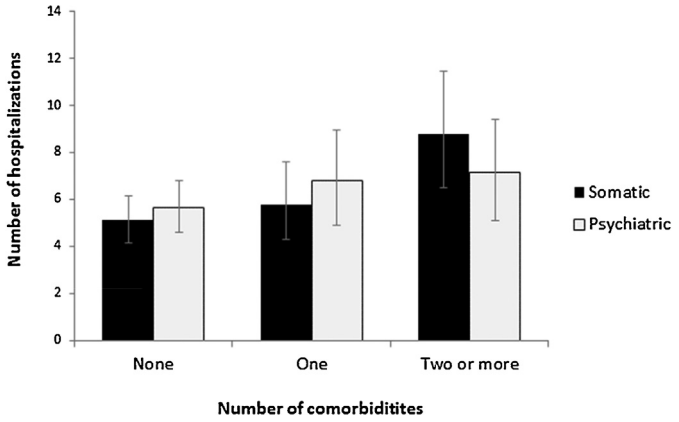

Fig. 2. Number of previous psychiatric hospitalizations by number of chronic somatic and psychiatric comorbidities; error lines represent 95% confidence intervals ($n = 301$).

number of chronic physical illnesses in patients diagnosed with SSDs independently of psychiatric comorbidities, and other relevant clinical, sociodemographic, and lifestyle parameters.

Number of chronic physical illnesses may affect treatment outcome in different ways. First, more physically ill patients may have higher incidences of therapy discontinuation due to polypharmacy, increased risk of drugs interactions, and lower tolerability of antipsychotic medication [37–39]. In addition, it is possible that patients sometimes erroneously recognize physical illness symptoms for the side effects of psychiatric therapy, which may jeopardize their adherence and lower efficacy, or somatic therapies' adverse events may interfere with psychiatric treatment. Consequently, serious, chronic somatic illnesses may cause lower adherence and more frequent absence from psychotherapy sessions. Second, the activation of immune responses caused by physical illness may cause the worsening of the clinical picture [40,41]. Third, capacity for productive participation in psychotherapy may be weaker because of somatic illnesses and subjective focus on their symptoms instead of on psychotherapy and treatment of the SSD. Fourth, chronic physical illnesses are associated with a higher probability of rehospitalization, what indicates higher relapse rates [42,43]. Increase in number of relapses increases the risk of development of resistance to the antipsychotic treatment [44]. Therefore, we may hypothesize the association of chronic physical illnesses with resistance to the antipsychotic treatment mediated by relapse rates.

To the best of our knowledge, only a few studies addressed the problem of the association of somatic comorbidities with the outcomes of treatment of psychosis. These studies used different outcome measures, compared to our research, but the prevalence of patients with chronic somatic comorbidities and the main guiding principles were similar to ours. It is important to note the high rates of somatic comorbidities among patients with SSDs, considering higher mortality rates compared to general population [3–5], the adverse effects of physical illnesses on patients' quality of life, lower quality of somatic healthcare and inadequate healthcare strategies for patients with mental illnesses [5,12]. The percentage of patients with chronic somatic comorbidities in our study (50%) was exactly the same as what was found in the study by Douzenis et al. [45] and similar to that of Chwastiak et al. [24] (58%) but, it was higher compared to what was found by Lyketsos et al. [23] (21%), possibly due to the fact that Lyketsos et al. studied the general population of psychiatric patients, and patients diagnosed with SSDs made up only 16% of their sample. Also, Lyketsos et al. included inpatients only, whereas our sample comprised both inpatients and outpatients.

The main conclusion of Lyketsos et al. [23] was comparable to ours. After the adjustment for illness severity at hospital admission, in their study, somatic comorbidities were significantly associated with higher psychiatric symptom ratings at discharge [45]. If the evidences of increase in somatic comorbidities incidence in patients diagnosed with psychosis over the last two decades are correct [3–5], the 10-year difference between the Lyketsos et al. and Douzenis et al. studies, as well as the 16-year separation from our study, should be taken into account.

Our findings are apparently contrary to the results of the study conducted by Chwastiak et al. in 2006 [24]. They found no significant association between number of chronic physical illnesses and severity of psychiatric symptoms measured by PANSS score in patients diagnosed with schizophrenia. Both of our

Table 4
Robust regression on number of previous psychiatric hospitalizations ($n = 267$).

	Univariate		Multivariate			
	β_{unw}	P_{unw}	B	β_{adj}	t	P
Number of chronic physical illnesses	0.20	< 0.001	0.52	0.16	2.59	0.010
Number of psychiatric comorbidities	0.12	0.082	0.10	0.02	0.29	0.769
Confounders controlled						
Sex (female vs. male)	0.05	0.450	−0.12	−0.02	−0.26	0.797
Age (years)	0.11	0.115	−0.00	−0.01	−0.12	0.904
Education						
Secondary vs. primary	−0.04	0.669	0.54	0.07	0.81	0.421
University vs. primary	−0.13	0.160	0.52	0.06	0.68	0.497
Marital status						
Married vs. single	−0.05	0.454	−0.11	−0.01	−0.17	0833
Widowed or divorced vs. single	0.12	0.084	0.32	0.03	0.46	0.648
Number of household members	−0.04	0.584	−0.05	−0.01	−0.20	0.845
Monthly income per household member	−0.21	0.002	−7.88	−0.01	−0.12	0.904
Work status						
Unemployed vs. employed	0.23	0.002	0.83	0.10	1.49	0.137
Retired vs. employed	0.30	< 0.001	1.01	0.13	1.75	0.081
Diet						
Having a breakfast several times a week[a]	−0.04	0.640	0.87	0.09	1.21	0.229
Having a breakfast every day	0.03	0.743	0.63	0.08	1.11	0.268
Eating fruits every day	−0.01	0.860	0.71	0.09	1.38	0.170
Eating vegetables every day	−0.03	0.661	−0.43	−0.05	−0.87	0.385
Sufficient physical activity[b]	−0.01	0.868	0.03	0.00	0.07	0.946
Smoking tobacco	0.23	0.001	1.48	0.19	3.26	0.001
Excessive alcohol consumption[c]	0.04	0.541	−1.21	−0.05	−0.94	0.348
Treated as outpatient vs hospitalized	−0.49	< 0.001	−2.57	−0.34	−5.31	< 0.001
Diagnosis (referent: schizophrenia (F20))						
Acute and transient psychotic disorder (F23)	−0.26	< 0.001	0.05	0.01	0.07	0.944
Schizoaffective disorder (F25)	0.13	0.081	0.97	0.10	1.52	0.131
Unspecified nonorganic psychosis (F29)	−0.12	0.088	−1.02	−0.11	−1.48	0.142
Persistent delusional disorder (F22)	−0.09	0.172	−0.37	−0.02	−0.36	0.722
Duration of primary psychiatric illness (years)	0.30	< 0.001	0.06	0.16	2.25	0.025
Clinical global impression- severity scale (CGI-S) at diagnosis	0.44	< 0.001	0.16	0.04	0.57	0.567
Antipsychotics						
1st generation						
Fluphenazine	0.10	0.127	−0.14	−0.01	−0.22	0.827
Haloperidol	−0.01	0.893	−1.20	−0.09	−1.44	0.151
Levomepromazine	0.03	0.629	−1.44	−0.07	−1.11	0.269
Promazine	0.35	< 0.001	2.03	0.18	3.10	0.002
Zuclopentixol	0.12	0.078	1.02	0.05	0.86	0.390
2nd generation						
Amisulpirid	0.03	0.711	−2.15	−0.09	−1.56	0.119
Aripiprazole	0.07	0.274	−0.17	−0.01	−0.21	0.833
Quetiapine	0.04	0.541	−0.88	−0.09	−1.26	0.211
Olanzapine	−0.06	0.380	0.06	0.01	0.10	0.924
Paliperidone	0.08	0.212	0.25	0.02	0.30	0.763
Risperidone	−0.12	0.069	−1.10	−0.11	−1.56	0.120
Sertindole	0.02	0.764	2.38	0.05	0.94	0.349
Sulpiride	−0.05	0.499	−1.41	−0.08	−1.38	0.168
Ziprasidone	−0.02	0.763	−0.19	−0.01	−0.15	0.879
Clozapine	0.15	0.024	−0.35	−0.03	−0.52	0.601
Antidepressants	0.08	0.219	1.76	0.20	3.13	0.002
Benzodiazepines	0.37	< 0.001	1.31	0.17	2.68	0.008

β_{unw}: standardized regression coefficient in univariate analysis; P_{unw}: two-tailed test statistical significance of univariate regression coefficient; β_{adj}: unstandardized multivariate (adjusted) regression coefficient; β_{adj}: standardized multivariate (adjusted) regression coefficient; t: t-test statistic with $n–p–1$ degrees of freedom where p is total number of parameters in the model; P: two-tailed test statistical significance of multivariate regression coefficient.

[a] Referent value was: up to once a week.

[b] Sufficient physical activity was defined as aerobic physical activity ≥ 150 min/week or ≥ 2 muscle-strengthening physical activity weekly.

[c] Excessive alcohol consumption was defined as > 20 g/day men; > 10 g/day women.

studies were cross-sectional. However, whereas our key outcome was the number of psychiatric hospitalizations since diagnosis, Chwastiak et al. used the outcome measure that could not reflect the change in psychopathology. They used PANSS score at baseline in a randomized control trial of antipsychotic efficacy in treatment of schizophrenia [46]. In addition, several important physical illnesses were excluded from their study: myocardial infarction in the previous 6 months, history of or current QTc prolongation, uncompensated congestive heart failure, sustained cardiac arrhythmia, first-degree heart block, and complete left bundle branch block.

Sim et al. in 2006 found the opposite effect of physical illnesses in patients with first episode schizophrenia [22]. At 24-month follow-up, patients with physical comorbidity had a significantly greater reduction in total PANSS score: 53% vs. 42% in the group of patients with no somatic illnesses. However, their study population was younger (28 years SD 6.7 years vs. 44 SD 12.9 years in our sample). Any somatic comorbidity was found in 22% vs. 38% in our sample. Finally, their study population was patients in the first episode schizophrenia, whereas the average duration of illness in our sample was 11 (SD 10.1) years. For these reasons, the two studies are not comparable, but the difference in our findings may

lead to new hypotheses for future research. It is possible that association of physical illnesses with psychiatric treatment outcomes is different in first and in recurrent episodes.

Our study findings are in line with the findings of Köhler et al. [25]. In their study, an increased risk of schizophrenia 2-year relapse was significantly associated with somatic comorbidity and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) in painful and inflammatory states, particularly acetylsalicylic acid and diclofenac, except for patients with a prior hospital diagnosis for a musculoskeletal disease, which had a lower risk of relapse.

It is possible that psychiatrists generally pay more attention to mental illnesses and are less sensitive to physical health [5,47]. Our study indicates that such position would be wrong even from the perspective of treatment of psychosis. Olivares et al.'s systematic literature review from 2013 showed a similar tendency among researchers in schizophrenia. Physical illnesses are rarely analyzed as the possible predictors of schizophrenia relapse [48]. Our results indicate that this should not be so, but we should certainly take into account the association of chronic physical illnesses and optimal treatment outcome in patients with SSDs. Unfortunately, our experience in clinical practice over the years indicates that the diagnostic habits in Croatia have not changed very much, which further emphasizes the relevance of our study.

4.1. Limitations of the study

First, our results should not be treated as representative for the total population of Croatian patients diagnosed with SSDs. It is reasonable to assume that the quality of both psychiatric and somatic medicine is better in the center where we enrolled patients than what is the case in provincial hospitals with more sparse resources and less experienced, although not less dedicated, health care professionals. However, this source of bias would probably promote the null hypothesis of no association between number of chronic somatic comorbidities and number of psychiatric rehospitalizations. If so, this limitation would actually strengthen the reliability of our findings. Second, our key independent variable was number of diagnosis of chronic somatic illnesses regardless of the illness severity or type. It is possible that in many somatic illnesses there are moderating effects of severity, illness type, illness duration, and somatic therapy on the association of the number of comorbidities with psychiatric rehospitalizations. Third, we measured only the number of hospital admissions and not the duration nor the reasons for hospitalizations. As Psychiatric Hospital Sveti Ivan, Zagreb is a specialized psychiatric institution, all patients were hospitalized due to psychiatric indication, but we could not differentiate whether the reason for particular rehospitalization was the worsening of the primary psychiatric illness, or because of psychiatric comorbidity. Within the limited time span, number and duration of hospitalizations may even be negatively correlated. Also, no other clinical variables relevant to clinical or treatment outcome were included in this study. However, the number of hospital admissions is a simple and universally understood outcome. As Tom Burns pointed out in 2007, "This understanding may, of course, be more illusory than real; the threshold for admission. . .may be very different in inner-city London and in a small town in Switzerland" [32]. Fifth, we have not collected the data on the possible confounding effect of antipsychotic doses, although a dosing schedule may be associated with the both: somatic health state and psychosis treatment outcomes. Sixth, no patients' adherence was analyzed while it may be associated with a larger number of somatic and psychiatric illnesses and a higher rate of psychiatric rehospitalizations. We tried to minimize the consequences of missing data on patients' adherence by sensitivity analysis where particular antipsychotics were replaced with the binary variable representing long-acting injections vs. oral therapy. Finally, we used a consecutive, and not the random sample from our targeted population what increased the risk of a sampling bias. The strength of our study is that we controlled a relatively large number of possible confounders and we approached the problem from a relatively novel perspective of chronic somatic comorbidities' impact on the psychosis treatment outcome and not vice versa.

5. Conclusion

Chronic physical illnesses in patients diagnosed with SSDs are associated with the higher rates of psychiatric rehospitalizations independently of psychiatric comorbidities and other clinical and sociodemographic factors. We need to pay more attention to the treatment of chronic physical illnesses in psychiatric patients not only because of somatic health consequences and patients' quality of life but also for the effectiveness of psychiatric therapy. The integrative, multidisciplinary approach should be the imperative in clinical practice. "Multimorbidities are indifferent to medical specialties" [40]. Future studies are needed with more rigorously defined and direct psychiatric treatment outcomes and prospective cohort designs that may establish the temporal order of occurrences.

Funding

The study was funded by Psychiatric Hospital Sveti Ivan, Zagreb, Croatia.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

Authors wish to acknowledge the work of all patients, physicians, and medical nurses who took part in the data collection.

References

[1] WHO. The world health report: mental health: new understanding. Geneva: WHO; 2001.
[2] Nasrallah HA, Harvey PD, Casey D, Csoboth CT, Hudson JI, Julian L, et al. The management of schizophrenia in clinical practice (MOSAIC) registry: a focus on patients, caregivers, illness severity, functional status, disease burden and healthcare utilization. Schizophr Res 2015;166(1–3):69–79.
[3] 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(10):1123–31.
[4] Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015;72(4):334–41.
[5] Björkenstam E, Ljung R, Burström B, Mittendorfer-Rutz E, Hallqvist J, Weitoft GR. Quality of medical care and excess mortality in psychiatric patients – a nationwide register-based study in Sweden. BMJ Open 2012;2:e000778.
[6] Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Annu Rev Clin Psychol 2014;10:425–48.
[7] Lasić D, Bevanda M, Bošnjak N, Uglešić B, Glavina T, Franić T. Metabolic syndrome and inflammation markers in patients with schizophrenia and recurrent depressive disorder. Psychiatr Danub 2014;26(3):214–9.
[8] Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatry 2015;72(12):1172–81.
[9] Kim J-H, Chang SM, Bae JN, Cho S-J, Lee J-Y, Kim B-S, et al. Mental-physical comorbidity in Korean adults: results from a nationwide general population survey in Korea. Psychiatry Invest 2016;13(5):496–503.
[10] De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 2011;10(1):52–77.

[11] Gardner-Sood P, Lally J, Smith S, Atakan Z, Ismail K, Greenwood KE, et al. Cardiovascular risk factors and metabolic syndrome in people with established psychotic illnesses: baseline data from the IMPaCT randomized controlled trial. Psychol Med 2015;45(12):2619–29.
[12] Filipčić I, Filipčić IŠ, Matić K, Lovretić V, Ivezić E, Bajić Ž. et al. Somatic comorbidities are independently associated with the poor health-related quality of life in psychiatric patients. Psychiatr Danub 2016;28(3):284–92.
[13] Abraham KM, Miller CJ, Birgenheir DG, Lai Z, Kilbourne AM. Self-efficacy and quality of life among people with bipolar disorder. J Nerv Ment Dis 2014;202(8):583–8.
[14] Baumeister H, Balke K, Härter M. Psychiatric and somatic comorbidities are negatively associated with quality of life in physically ill patients. J Clin Epidemiol 2005;58(11):1090–100.
[15] Miller CJ, Abraham KM, Bajor LA, Lai Z, Kim HM, Nord KM, et al. Quality of life among patients with bipolar disorder in primary care versus community mental health settings. J Affect Disord 2013;146(1):100–5.
[16] Briskman I, Bar G, Boaz M, Shargorodsky M. Impact of co-morbid mental illness on the diagnosis and management of patients hospitalized for medical conditions in a general hospital. Int J Psychiatry Med 2012;43(4):339–48.
[17] Mai Q, Holman CDJ, Sanfilippo FM, Emery JD. The impact of mental illness on potentially preventable hospitalisations: a population-based cohort study. BMC Psychiatry 2011;11:163.
[18] Munk Laursen T, Munk-Olsen T, Gasse C. Chronic somatic comorbidity and excess mortality due to natural causes in persons with schizophrenia or bipolar affective disorder. PLoS One 2011;6(9).
[19] Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015;14(2):119–36.
[20] Fleischhacker WW, Cetkovich-Bakmas M, De Hert M, Hennekens CH, Lambert M, Leucht S, et al. Comorbid somatic illnesses in patients with severe mental disorders: clinical, policy, and research challenges. J Clin Psychiatry 2008;69(4):514–9.
[21] Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. BMJ Open 2013;3(4).
[22] Sim K, Chan YH, Chua TH, Mahendran R, Chong SA, McGorry P. Physical comorbidity, insight, quality of life and global functioning in first episode schizophrenia: a 24-month, longitudinal outcome study. Schizophr Res 2006;88(1–3):82–9.
[23] Lyketsos CG, Dunn G, Kaminsky MJ, Breakey WR. Medical comorbidity in psychiatric inpatients: relation to clinical outcomes and hospital length of stay. Psychosomatics 2002;43(1):24–30.
[24] Chwastiak LA, Rosenheck RA, McEvoy JP, Keefe RS, Swartz MS, Lieberman JA. Interrelationships of psychiatric symptom severity, medical comorbidity, and functioning in schizophrenia. Psychiatr Serv 2006;57(8):1102–9.
[25] Köhler O, Petersen L, Benros ME, Mors O, Gasse C. Concomitant NSAID use during antipsychotic treatment and risk of 2-year relapse – a population-based study of 16,253 incident patients with schizophrenia. Expert Opin Pharmacother 2016;17(8):1055–62.
[26] Dixon L, Postrado L, Delahanty J, Fischer PJ, Lehman A. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999;187(8):496–502.
[27] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310(20):2191–4.
[28] Conley RR, Kelly DL, Love RC, McMahon RP. Rehospitalization risk with second-generation and depot antipsychotics. Ann Clin Psychiatry 2003;15(1):23–31.
[29] Lin C-H, Lin S-C, Chen M-C, Wang S-Y. Comparison of time to rehospitalization among schizophrenic patients discharged on typical antipsychotics, clozapine or risperidone. J Chin Med Assoc 2006;69(6):264–9.
[30] de Castro APW, Elkis H. Rehospitalization rates of patients with schizophrenia discharged on haloperidol, risperidone or clozapine. Rev Bras Psiquiatr 2007;29(3):207–12.
[31] Herceg M, Jukić V, Vidović D, Erdeljić V, Celić I, Kozumplik O, et al. Two-year rehospitalization rates of patients with newly diagnosed or chronic schizophrenia on atypical or typical antipsychotic drugs: retrospective cohort study. Croat Med J 2008;49(2):215–23.
[32] Burns T. Hospitalisation as an outcome measure in schizophrenia. Br J Psychiatry Suppl 2007;50:s37–41.
[33] EUROSTAT.. European Health Interview Survey (EHIS wave 2). Methodological manual [Internet]; 2013 Available from:https://www.google.hr/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwi3mveGsvbPAhWFvhQKHbg9ANsQFggnMAA&url=http%3A%2F%2Fec.europa.eu%2Feurostat%2Fdocuments%2F3859598%2F5926729%2FKS-RA-13-018-EN.PDF%2F26c7ea80-01d8-420e-bdc6-e9d5f6578e7c&usg=AFQjCNHLe.
[34] Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the Europea. Atherosclerosis 2016;253:281–344.
[35] Finger JD, Tafforeau J, Gisle L, Oja L, Ziese T, Thelen J, et al. Development of the European Health Interview Survey – Physical Activity Questionnaire (EHIS-PAQ) to monitor physical activity in the European Union. Arch Public Health 2015;73:59.
[36] Baumeister SE, Ricci C, Kohler S, Fischer B, Töpfer C, Finger JD, et al. Physical activity surveillance in the European Union: reliability and validity of the European Health Interview Survey-Physical Activity Questionnaire (EHIS-PAQ). Int J Behav Nutr Phys Act 2016;13:61.
[37] Owen-Smith A, Stewart C, Green C, Ahmedani BK, Waitzfelder BE, Rossom R, et al. Adherence to common cardiovascular medications in patients with schizophrenia vs. patients without psychiatric illness. Gen Hosp Psychiatry 2016;38:9–14.
[38] Kansagara D, Englander H, Salanitro A, Kagen D, Theobald C, Freeman M, et al. Risk prediction models for hospital readmission: a systematic review. JAMA 2011;306(15):1688–98.
[39] Viktil KK, Blix HS, Moger TA, Reikvam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. Br J Clin Pharmacol 2007;63(2):187–95.
[40] Jakovljević M, Ostojić L. Comorbidity and multimorbidity in medicine today: challenges and opportunities for bringing separated branches of medicine closer to each other. Psychiatr Danub 2013;25(Suppl. 1):18–28.
[41] Kalakonda B, Koppolu P, Baroudi K, Mishra A. Periodontal systemic connections-novel associations – A review of the evidence with implications for medical practitioners. Int J Health Sci (Qassim) 2016;10(2):293–307.
[42] Boyer L, Millier A, Perthame E, Aballea S, Auquier P, Toumi M. Quality of life is predictive of relapse in schizophrenia. BMC Psychiatry 2013;13:15.
[43] Šprah L, Dernovšek MZ, Wahlbeck K, Haaramo P. Psychiatric readmissions and their association with physical comorbidity: a systematic literature review. BMC Psychiatry 2017;17(1):2.
[44] Kane JM. Treatment adherence and long-term outcomes. CNS Spectr 2007;12(10 Suppl. 17):21–6.
[45] Douzenis A, Seretis D, Nika S, Nikolaidou P, Papadopoulou A, Rizos EN, et al. Factors affecting hospital stay in psychiatric patients: the role of active comorbidity. BMC Health Serv Res 2012;12:166.
[46] Stroup TS, McEvoy JP, Swartz MS, Byerly MJ, Glick ID, Canive JM, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophr Bull 2003;29(1):15–31.
[47] Kopp M, Fleischhacker WW, Stürz K, Ruedl G, Kumnig M, Rumpold G. Poor health behaviour and reduced quality of life of people treated with psychotropic drugs. Hum Psychopharmacol 2011;26(2):161–7.
[48] Olivares JM, Sermon J, Hemels M, Schreiner A. Definitions and drivers of relapse in patients with schizophrenia: a systematic literature review. Ann Gen Psychiatry 2013;12(1):32.