Cost-Sharing Increase, Medication Adherence, and Hospitalizations in Schizophrenia Patients: A Natural Experiment

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Increases in medication cost-sharing rates remain a controversial system-wide cost-containment measure for chronic mental health patients. The objective was to investigate the effects of cost-sharing increases on adherence to prescribed antipsychotic medication and psychiatric hospitalizations among patients with schizophrenia. In July 2012, a Spanish National Law raised the cost-sharing rate from 0 to 10% for pensioner outpatient medication while cost-sharing remained at 0% for other socioeconomic groups. To estimate the effects of the reform, we analyzed the prevalent adult schizophrenic population of Valencia, Spain, followed up 1 year before and after the Law took effect. We used a quasi-experimental design with a patient fixed-effects difference-in-differences regression to evaluate the reform effects on antipsychotic medication adherence, prescription, and hospitalization rates. A total of 5,672 included patients were exposed to the reform, whereas 5,545 were not. There were no differences in adherence, prescription, or hospitalization rates between exposed and nonexposed patients prior to its implementation. The odds ratio of exposed patients remaining adherent to issued prescriptions after the reform took effect were 0.70 99% confidence interval (CI 0.66–0.75), in relation to the nonexposed group. Additionally, the reform was associated with a reduction in exposure to antipsychotic medication (odds ratio (OR) 0.85, 99%CI 0.83–0.88) and an increase in hospitalization risk (OR 1.13, 99% CI 1.05–1.23) during the first year after implementation. Policies raising the cost-sharing rate of medication for patients with schizophrenia are simultaneously associated with unintended effects. We report decreases in antipsychotic exposure and increases in hospitalization rates that lasted for 1 year after follow-up.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Cost-sharing increases in medication have been associated with decreases in adherence, however, no causal link between raises and hospitalization events has been proven.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Is a free-to-fee (0 to 10%) cost-sharing increase in antipsychotic medication associated with poorer adherence and hospitalization events for patients with schizophrenia?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Cost-sharing increases for vulnerable mental health populations have severe unintended effects leading to psychiatric hospitalizations.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Cost-sharing increases for psychiatric patients should be avoided or specific countermeasures of patient surveillance should be adopted and evaluated simultaneously.

Schizophrenia is a serious psychiatric syndrome characterized by psychotic events, negative symptoms, and cognitive deficits.[1] It entails severe consequences and a heavy societal burden for patients and their families.[2] Because of impaired function, interpersonal relationships, stigmatization, unemployment, and poverty, patients with schizophrenia represent one of the most vulnerable social groups.[3–5] Although antipsychotic medication is effective in reducing positive symptoms,[6] current practice is to continue treatment indefinitely, even when the patient remains stable, in order to avoid relapses.[7] However, due to side effects or other motives, many patients discontinue treatment, the most important risk factor for relapse. Nonadherence to antipsychotic medication and psychotic events requiring subsequent hospitalization has been widely documented.[8,9]

Raises in medication cost-sharing rates are a two-edged healthcare policy. Classic economic theory predicts that for low-value treatments, small price increases will produce significant reductions in consumption, while remaining constant for their higher-valued counterparts.[10] However, these predictions are not always consistent with the available evidence.[11,12] Larger inconsistencies are found among mental health patients,[13–15] for whom critical economic assumptions, such as individual rationality are not met,[16] and an increase in patient cost-sharing seems to be associated with poorer medication adherence and outcomes.[17–19] Additionally, relative price changes (i.e., from 10 to 20%) are known to produce smaller consumption reductions than free-to-fee increases (i.e., 0 to 10%).[20]

We explored these questions with a quasi-experimental design by taking advantage of a natural experiment in Spain. In July 2012, and in the context of a severe economic recession, the cost-sharing rate of medication for pensioners was raised from 0 to 10% while for other socioeconomic groups it remained free.

The objective of the present study is to estimate the association between a free-to-fee change in cost-sharing of antipsychotic medication, adherence, and hospitalization outcomes in a population of patients with schizophrenia in Spain.

METHODS

Setting

The study was conducted within the Valencia Health System (VHS), a comprehensive structure of hospitals, primary care facilities, and other public resources managed by the Government of the region of Valencia, Spain, with more than 5 million inhabitants registered in 2010 (~ 11% of Spain and 1% of Europe's population). The VHS is part of the Spanish National Health System (NHS), a public healthcare system with universal health coverage in which each region is responsible for the financing and provision of healthcare, in an analogous way to Medicare and Medicaid duties. However, the central Government holds central competencies in healthcare regulation, including the definition and price bargaining of the public portfolio of treatments.[21] Most of the care is free for users, including all in-hospital and primary care costs. Cost-sharing is only present for pharmacy-dispensed out-of-hospital prescriptions, making the Spanish NHS one of the most generous systems in the European Union.[22]

Intervention

In 2012, Spain was in a deep economic recession sustained since 2009, with a sky-rocketing unemployment rate of 24% and a public deficit of 10.5%.[22] In March of the same year, the Spanish Government announced a structural healthcare reform through a new urgent law (the Royal Decree Law (RDL) 16/2012) which, among other "cuts," modified the cost-sharing of prescribed outpatient medicines. The legislative reform, compulsory for all regional healthcare systems, was announced in March 2012, being effective nationwide in July of the same year.

The cost-sharing scheme of medicines was modified by socioeconomic groups.[22] Pensioners saw their coinsurance (as the percentage of the retail price) raised from 0% to 10% (or 60% for a small group -< 1%- of pensioners with income over 100,000 euros per year) with a monthly stop loss of 8 or 18 euros per month (or 60€ for high-income pensioners), depending upon their income bracket (see Supplementary Material **Table S1**). They were therefore defined as the exposed group in our work. Disabled, noncontributive pensioners, individuals with social integration income aid, and long-term idle workers who lost unemployment benefits were exempted from the reform and their cost-sharing rate remained inexistent, and were defined as the nonexposed group in our work.

Data sources

Data were obtained from the Valencia Health System Integrated Databases (VID).[23] The VHS is widely computerized with homogeneous systems in all its health centers since 2008, and data are collected routinely by a wide variety of healthcare providers that operate within the public health system. VID is the result of the linkage, by means of a single personal identification number, of publicly owned population-wide healthcare, clinical, and administrative electronic databases in the whole region. The VID includes sociodemographic and administrative information (sex, age, nationality, etc.) and healthcare information, such as diagnoses, procedures, laboratory data, pharmaceutical prescriptions and dispensations, hospitalizations, mortality, healthcare utilization, and public health data. It also includes a set of specific associated databases with population-wide information on significant care areas, such as cancer, rare disease, vaccines, or imaging data.

Study population

We defined a cohort of patients with schizophrenia with 2-years of follow-up, from July 2011 to July 2013, 1 year before and after implementation of the new law. Our initial sample included all 26,913 adult patients from the source population database with a confirmed schizophrenia diagnosis before cohort entry, see diagnostic categories in **Supplementary Material**. There were 1,135 (4.2%) patients who were excluded due to their decease before the outset of the follow-up, 9,080 (33.7%) were neither eligible for the pensioner (exposed) nor exempt (nonexposed) groups as they were employed and working, 4,360 (16.2%) were diagnosed at age 60 years or older (likely misdiagnosed to prescribe antipsychotic medication for dementia patients), and 1,121 (4.1%) patients with an incident schizophrenia diagnosis were also omitted. A final sample of 11,217 patients (41.7%) was included in the analysis, as seen in the selection algorithm displayed in **Figure 1**.

Outcomes and exposures

Outcomes of interest were weekly adherence, prescription, and exposure to antipsychotic medication, as well as hospitalizations (all-cause and psychiatric). Because VID has information about the prescription made by doctors and the dispensations actually picked-up by patients in pharmacies, it was possible to know when the patient stopped taking a drug (adherence), when the doctor stopped prescribing it (prescription), and the real quantities of medication actually dispensed (exposure).

Adherence mas measured as a binary indicator following a previously published pinpointed approach.[22] This method considers both issued and dispensed prescriptions; hence, adherence is only assessed during periods with valid prescriptions. Prescription was measured as a binary indicator of whether the patient has an antipsychotic prescription for the week. Exposure to antipsychotic medication was measured as the interaction between the two previous binary outcomes, where 1 indicated a patient-week with an issued and dispensed prescription, and 0 indicated a patient-week with no issued or issued but not dispensed prescription. Furthermore, different antipsychotic drugs were considered interchangeable. Hospitalization was measured by means of the inpatient database, accounting for the causes, hospitalization wards, and length of stay. All-cause hospitalization was measured as a binary patient-week indicator of whether the individual had an inhospital stay of at least one night, independently of the diagnostic and the hospitalization ward. Psychiatric hospitalizations were also measured as a patient-week binary indicator inhospital stay of at least one night in the psychiatric ward.

The exposure to the reform was defined as the interaction between having a pensioner status and March 2012.
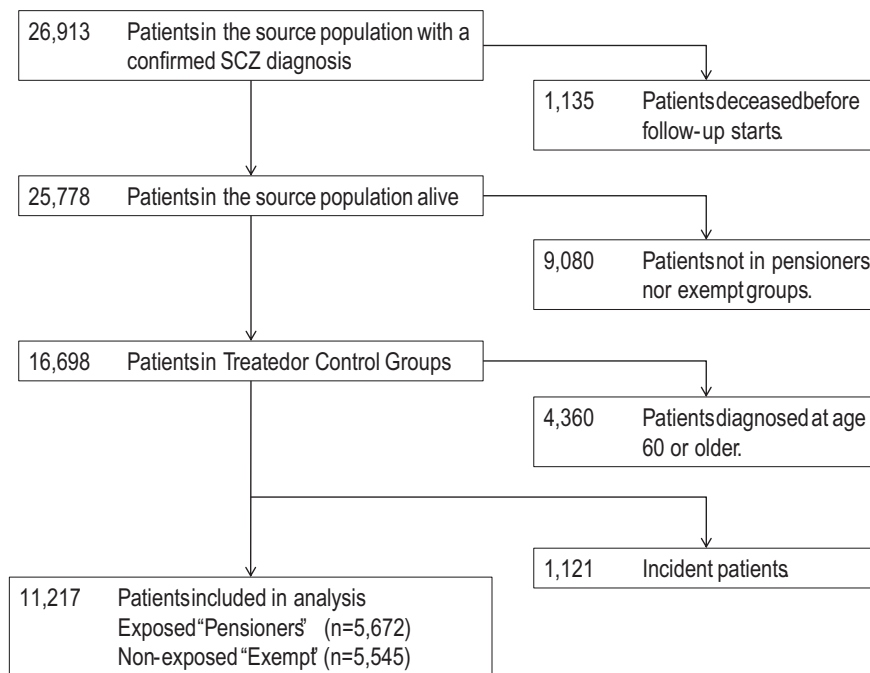
Figure 1 Patient selection flowchart. SCZ, schizophrenia.

Ethical aspects

Our study was observational in design and used retrospective data that was pseudo-anonymized before being transferred to the research team, in compliance with Spanish and European laws on data protection for health research (Spanish Act 3/2018 and 2015 European Data Protection Regulation). The study was classified by the Spanish Agency for Drugs and Medical Products (Ref. SAL-SUL-2015-01), approved by the Institutional Review Board of the Public Health General Directorate of the Valencia Health Authority and the Center for Public Health Research (Ref. 20150724), and the Regulatory Commission of Access to Ambulatory Care Information of the Valencia Health Authority approved the cession of the anonymized data.

Statistical analyses

We evaluated the association between cost-sharing increase using a difference-in-differences approach. The method compares changes in the outcome of interest between exposed and nonexposed groups before and after the implementation of the policy, in our case, the RDL16/2012 Decree-law. We adopted a lag-lead approach,[24] which facilitated the inspection of the underlying assumptions of the model. The main premise is that in absence of the policy, the exposed group's trend in outcome would have remained parallel to its unexposed counterpart (i.e., the parallel trends assumption). Our design formally tests whether the monthly difference in outcomes remained stable across pre-intervention periods. The main exposure of interest was a dummy interaction indicating whether the patient had been exposed to the reform at a month-year level. We used the announcement of the reform, March 2012, as the reference level in our model's estimation. Our primary model was a generalized linear regression model with patient fixed effects, meaning that each patient in our study has an individual risk parameter. We also included additional time-varying control variables at a weekly basis, which are described in detail in the **Supplementary Material**. We defined a statistical confidence level of 99%.

To assess the robustness of our results, we conducted extensive sensitivity analyses, namely the inclusion of patient-specific trends, matching of patients through propensity score, and alternative specifications (described in detail in the robustness checks section of the **Supplementary Material**).

RESULTS

The final sample included 11,217 patients followed-up from 1 year before (July 2011) the reform and up to 1 year after (July 2013) or upon death. There were 5,672 patients who were exposed to the reform and 5,545 were not. The average age at follow-up entry was 42.9 years, 32.4% patients were women, 14.7% had diabetes mellitus, 18.7% presented obesity, 8.9% had drug dependence, and at least 34.8% had a drug abuse episode diagnosis at cohort entry. The median number of distinct medications consumed before cohort entry was 3 interquartile range (IQR; 2–4). Table 1 presents the baseline characteristics of the included cohorts.

Compared to the year before implementation, the reform was, 1 year after implementation, associated with a reduction in adherence to antipsychotic prescribed medication (odds ratio (OR) 0.70, 99% confidence interval (CI) 0.66–0.75) of those affected, in relation to those not affected by the raise. The reform was also associated with a reduction in antipsychotic prescription (OR 0.91, 99% CI 0.88–0.93), and a reduction in effective exposure to antipsychotic drugs (OR 0.86, 99% CI 0.84–0.88). See **Supplementary Tables S4.1–S4.4** for alternative specifications.

Figure 2 shows the generalized additive model smoothed rates and monthly model estimates of exposed and nonexposed patients for (i) adherence, (ii) prescription, and (iii) exposure of antipsychotic medication. Prior to implementation, trends in all three outcomes were parallel across exposed and nonexposed schizophrenic groups. Compared to the reference month, March 2012, only 1 period out of

Table 1 Baseline patient cohort characteristics

	All	Non-exposed	Exposed
	N = 11,217	*N* = 5,545	*N* = 5,672
Demographics			
Foreign	745 (6.64%)	412 (7.43%)	333 (5.87%)
Female	3,634 (32.4%)	2,031 (36.6%)	1,603 (28.3%)
Age at documented diagnosis	38.7 [31.7–45.2]	36.1 [29.5–42.9]	40.9 [34.2–46.8]
Age at cohort entry	42.9 [36.1–49.5]	40.5 [34.1–47.0]	45.2 [38.7–51.2]
Comorbidities			
Diabetes mellitus	1,652 (14.7%)	707 (12.8%)	945 (16.7%)
Obesity	2,098 (18.7%)	1,050 (18.9%)	1,048 (18.5%)
Hypertension	2,072 (18.5%)	891 (16.1%)	1,181 (20.8%)
Pulmonary	818 (7.29%)	509 (9.18%)	309 (5.45%)
Depression	1,644 (14.7%)	743 (13.4%)	901 (15.9%)
Borderline personality	818 (7.29%)	509 (9.18%)	309 (5.45%)
Drug dependence	997 (8.89%)	500 (9.02%)	497 (8.76%)
Drug abuse episode	3,899 (34.8%)	1,866 (33.7%)	2,033 (35.8%)
Prescriptions			
Polypharmacy	3.00 [2.00–4.00]	3.00 [2.00–4.00]	3.00 [2.00–4.00]
Most prescribed drug			
Amisulpride	668 (5.96%)	323 (5.83%)	345 (6.08%)
Aripiprazole	949 (8.46%)	442 (7.97%)	507 (8.94%)
Clozapine	574 (5.12%)	332 (5.99%)	242 (4.27%)
Haloperidol	619 (5.52%)	296 (5.34%)	323 (5.69%)
Levomepromazine	629 (5.61%)	314 (5.66%)	315 (5.55%)
Olanzapine	1,865 (16.6%)	989 (17.8%)	876 (15.4%)
Paliperidone	1,021 (9.10%)	509 (9.18%)	512 (9.03%)
Quetiapine	1,105 (9.85%)	554 (9.99%)	551 (9.71%)
Risperidone	2,159 (19.2%)	1,027 (18.5%)	1,132 (20.0%)

IQR, interquartile range.
Numbers expressed as *N* (%) or median [IQR].

33 differed from the null, pre-implementation. Implementation was associated with a systematic reduction in the OR of adherence, ranging from 0.53 (99% CI 0.43–0.66) 5 months later to 0.76 (99% CI 0.62–0.95) 10 months afterward. Moreover, both the OR of having an antipsychotic prescription and the by-product of prescription and adherence decreased significantly after implementation. **Table 2** presents the numeric estimates of the figure.

In terms of hospitalization risk, the reform was associated with a significant increase in all-cause hospitalizations (OR 1.13, 99% CI 1.05–1.23) during the follow-up. More specifically, the OR of being hospitalized with a specific schizophrenic decompensation diagnosis was higher (OR 1.18, 99% CI 1.08–1.29).

Figure 3 presents the generalized additive model smoothed rates and monthly model estimates of exposed and nonexposed patients for (i) all-cause hospitalizations and (ii) schizophrenic-specific hospitalizations. Prior to implementation, trends in both outcomes were parallel across exposed and nonexposed schizophrenic groups. Compared to the reference month, March 2012, no period differed from the null, pre-implementation. Implementation was associated with an immediate increase in the OR of hospitalization during the first 2 months, July (OR 1.34, 99% CI 1.02–1.76) and August (OR 1.37, 99% CI 1.05–1.79). Moreover, these differences were persistent across the follow-up period at a relatively smaller OR and were mainly driven by schizophrenic-specific hospitalizations, as displayed in **Figure b3**. The results did not change upon the inclusion of additional controls or alternative statistical specifications, as shown in the **Supplementary Material Section 2**. **Table 3** presents the numeric estimates of the figure.

The estimates were not sensitive to additional robustness checks, namely controlling for patient-specific trends, matching patients by propensity score of pertaining to either exposed or nonexposed groups, or a linear probability model specification, see **Figures S1– S6**, and **Tables S4** and **S5** of the Supplementary Material.

DISCUSSION

The present study approximated the causal effect of a 0 to 10% cost-sharing increase in antipsychotic medication, on medication utilization patterns, and hospitalizations for a population of patients with schizophrenia. Our results suggest harmful unintended effects, with decreases in adherence to prescriptions,
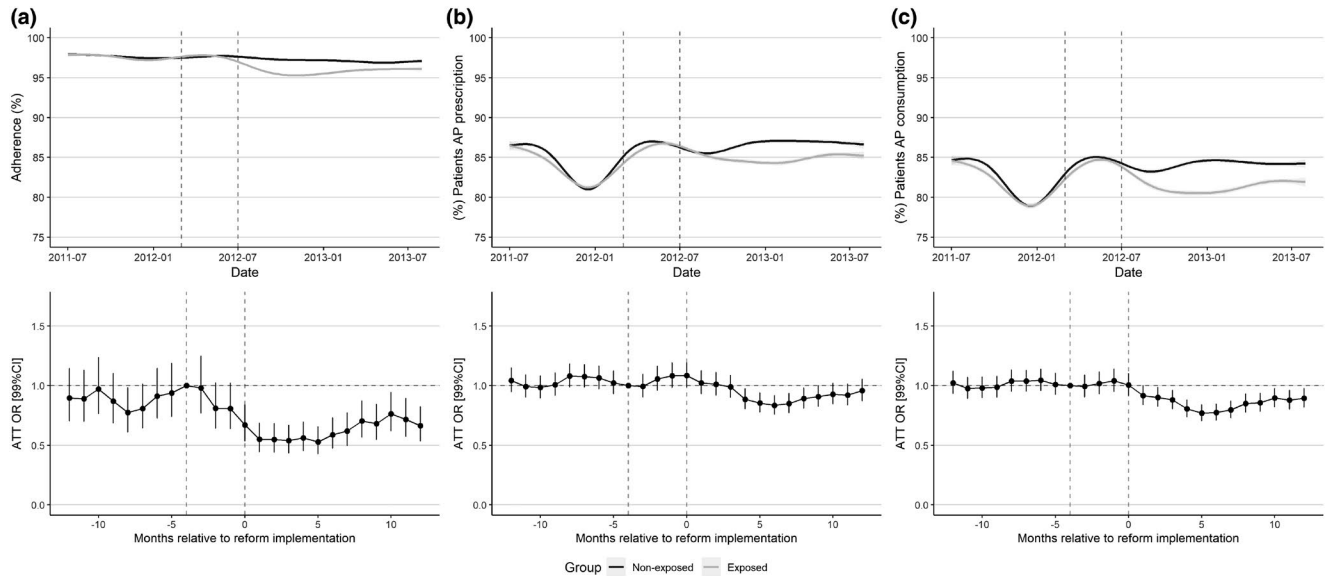
Figure 2 Generalized additive model-smoothed trends in medication outcomes and difference-in-differences estimates. Notes: panel (**a**) presents antipsychotic (AP) medication adherence, (**b**) presents AP medication prescription, and (**c**) presents AP medication consumption. Upper panel represents trends in rates between exposed and control populations, while lower panel presents model estimates in odds ratios (ORs) with 99% confidence interval (CI).

Table 2 Medication outcomes estimates

Month	Adherence OR	99% CI		Prescription OR	99% CI		Psychiatric hospitalization OR	99% CI	
−12	0.90	0.70	1.15	1.04	0.95	1.15	1.02	0.93	1.12
−11	0.89	0.70	1.13	0.99	0.90	1.09	0.98	0.89	1.07
−10	0.97	0.76	1.24	0.98	0.90	1.08	0.98	0.90	1.07
−9	0.87	0.69	1.10	1.01	0.92	1.11	0.99	0.90	1.08
−8	0.78	0.61	0.98	1.08	0.99	1.18	1.04	0.95	1.13
−7	0.81	0.64	1.02	1.08	0.98	1.18	1.04	0.95	1.13
−6	0.91	0.73	1.15	1.06	0.97	1.17	1.04	0.96	1.14
−5	0.94	0.74	1.19	1.02	0.93	1.12	1.01	0.92	1.10
−4	Reference level OR = 1								
−3	0.98	0.77	1.25	1.00	0.90	1.10	0.99	0.91	1.09
−2	0.81	0.64	1.02	1.06	0.96	1.16	1.02	0.93	1.12
−1	0.81	0.64	1.02	1.08	0.98	1.19	1.04	0.95	1.14
0	0.67	0.53	0.84	1.08	0.99	1.19	1.01	0.92	1.10
1	0.55	0.44	0.69	1.02	0.93	1.12	0.92	0.84	1.00
2	0.55	0.44	0.68	1.01	0.92	1.11	0.90	0.82	0.99
3	0.54	0.43	0.67	0.99	0.90	1.09	0.88	0.81	0.96
4	0.56	0.45	0.70	0.89	0.81	0.97	0.81	0.74	0.88
5	0.53	0.43	0.66	0.85	0.78	0.94	0.77	0.70	0.84
6	0.59	0.47	0.73	0.83	0.76	0.92	0.77	0.71	0.85
7	0.62	0.50	0.77	0.85	0.77	0.94	0.80	0.73	0.87
8	0.70	0.57	0.87	0.89	0.81	0.98	0.85	0.78	0.93
9	0.68	0.55	0.84	0.91	0.83	1.00	0.86	0.78	0.94
10	0.76	0.62	0.95	0.93	0.84	1.02	0.90	0.82	0.98
11	0.72	0.58	0.89	0.92	0.84	1.01	0.88	0.80	0.96
12	0.66	0.53	0.82	0.96	0.87	1.05	0.89	0.82	0.98

CI, confidence interval; OR, odds ratio.
Generalized linear model estimated odds ratios of the interaction between being affected by the reform and month with respect to reform announcement.
Controls for: patient fixed-effects, month fixed-effects, region-fixed-effects, sex, nationality, age, and time-varying comorbidities.
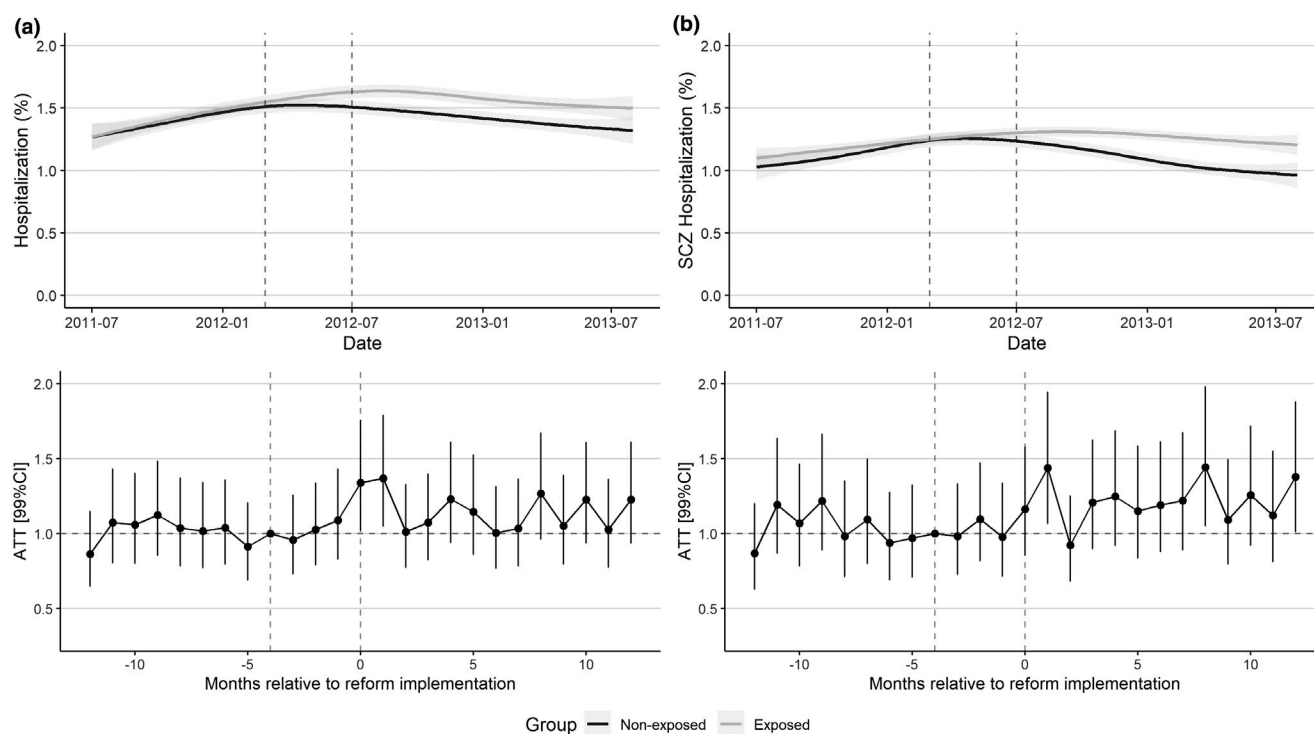
Figure 3 Generalized additive model-smoothed trends in hospitalization rates and difference-in-differences estimates. Notes: panel (**a**) presents all-cause hospitalization, and (**b**) presents psychiatric-specific hospitalization. Upper panel represents trends in rates between exposed and control populations, while lower panel presents model estimates in odds ratios with 99% confidence interval (CI). SCZ, schizophrenia.

overall exposure to antipsychotic agents, and a significant increase in decompensation events as measured by hospital admissions. Our results are in line with previous studies documenting the negative effects of outpatient medication cost-containment policies in patients with schizophrenia. In a recent study comparing utilization patterns of antipsychotic drugs among four countries (Italy, Spain, the United Kingdom, and the United States), discontinuation of treatment at 1 year was high among all populations, ranging from 70% in Italy to 55% in Spain.[25] Therefore, insurers and policy makers should be extremely careful in applying copayment schemes with regard to patients with schizophrenia. The particularities of our setting, with the regulation acting directly through prices instead of monthly caps, in a universally insured population offers further insights for insurers and policy makers.

The novel message of the present study relates to the longer-term association between a small cost-sharing increase (10% with a stop loss of 8 or 18 euros per month) and a persistent decompensation of a subset of very frail patients with schizophrenia. A similar effect size with regard to adherence has been recently reported in the United States,[26] and smaller but significant effect size were already reported in the early 2000s.[27] Moreover, given the institutional context of the Spanish NHS, and to the best of our knowledge, this is the first study to explore the relation among medication cost-sharing, adherence, prescription, and hospitalization of patients with schizophrenia in a universal coverage health system.

Our analyses estimate the effect of the reform, before and after its implementation, between adherence and exposure to antipsychotic medication with hospitalizations among exposed and unexposed

patients with schizophrenia. Thanks to the unique nature of the reform, as well as to novel data resources and measurements, we can address several limitations of previous studies that studied this association.[19,28,29] The similarity between exposed and unexposed patients, all residing within the same region, the precise measurement of adherence by means of a new pinpointed approach, in addition to the explicit testing of our assumptions and the application of extensive sensitivity analyses, allows us to abstract from some documented biases.

The strengths of our study relate to three main categories. First, the piece of legislation passed in Spain in 2012 was unique in having both exposed and unexposed social groups, rendering a natural experiment. The reform was applied countrywide, hence both exposed and non-exposed social groups resided in the same regions, enabling us to abstract from unmeasured geographical secular trends. Second, the integrated database resource used in the analyses provides a unique comprehensive set of previously unobserved variables, such as the link between prescription and dispensation, allowing us to abstract from common measurement error biases and observe the lagged effect on reduced medication prescription. Third, we explicitly test our validating assumptions, providing suggestive evidence of their validity and unbiasedness of the reported associations. This study is not without limitations. Namely, the piece of Spanish reform was unique and unlikely to be repeated in similar settings. Second, the generosity of the Spanish NHS may jeopardize the external validity of our results, as healthcare systems in other countries might already be on higher copayment levels. Additionally, the

Table 3 Hospitalization outcomes estimates

Month	All-cause hospitalization			Psychiatric hospitalization		
	OR	99% CI		OR	99% CI	
−12	0.86	0.65	1.15	0.87	0.63	1.20
−11	1.07	0.81	1.43	1.19	0.87	1.64
−10	1.06	0.80	1.40	1.07	0.78	1.47
−9	1.12	0.85	1.48	1.22	0.89	1.66
−8	1.04	0.78	1.37	0.98	0.71	1.35
−7	1.02	0.77	1.34	1.09	0.80	1.50
−6	1.04	0.79	1.36	0.94	0.69	1.28
−5	0.91	0.69	1.21	0.97	0.71	1.33
−4	Reference level					
−3	0.96	0.73	1.26	0.98	0.73	1.33
−2	1.03	0.79	1.34	1.10	0.82	1.47
−1	1.09	0.83	1.43	0.98	0.71	1.34
0	1.34	1.02	1.76	1.16	0.86	1.58
1	1.37	1.05	1.79	1.44	1.07	1.94
2	1.01	0.77	1.33	0.92	0.68	1.25
3	1.07	0.82	1.40	1.21	0.90	1.62
4	1.23	0.94	1.61	1.25	0.92	1.69
5	1.15	0.86	1.53	1.15	0.84	1.58
6	1.00	0.77	1.31	1.19	0.88	1.61
7	1.03	0.78	1.36	1.22	0.89	1.67
8	1.27	0.96	1.67	1.44	1.05	1.98
9	1.05	0.80	1.39	1.09	0.80	1.50
10	1.23	0.93	1.61	1.26	0.92	1.72
11	1.03	0.77	1.36	1.12	0.81	1.55
12	1.23	0.94	1.61	1.38	1.01	1.88

CI, confidence interval; OR, odds ratio.
Generalized linear model estimated odds ratios of the interaction between being affected by the reform and month with respect to reform announcement. Controls for: patient fixed-effects, month fixed-effects, region-fixed-effects, sex, nationality, age, and time-varying comorbidities.

relatively short window of our cohort analysis, 1 year pre-post, could be extended in time, and a full economic assessment carried considering not only the additional revenue provided by the policy and the hospitalization costs, but also indirect costs as well as its effects on patient's quality of life.

All in all, small increases in cost-sharing rates of antipsychotic medication for patients with schizophrenia were simultaneously associated with unintended effects, such as nonadherence and long-term decompensation among patients with schizophrenia.

CONFLICT OF INTEREST
M.S.B. reports research grants from the European Commission H2020 program and from the EiT Health program, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
M.S.B., I.H., G.S.G., A.G.S., and S.P. wrote the manuscript. M.S.B. and S.P. designed the research. M.S.B. and I.H. performed the research. M.S.B, analyzed the data.

ETHICAL APPROVAL
The study was classified by the Spanish Agency for Drugs and Medical Products (Ref. SAL-SUL-2015-01), approved by the Institutional Review Board of the Public Health General Directorate of the Valencia Health Authority and the Center for Public Health Research (Ref. 20150724), and the Regulatory Commission of Access to Ambulatory Care Information of the Valencia Health Authority approved the cession of the anonymized data.

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