Effect of copayment policies on initial medication non-adherence according to income: a population-based study

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ABSTRACT

Objective Copayment policies aim to reduce the burden of medication expenditure but may affect adherence and generate inequities in access to healthcare. The objective was to evaluate the impact of two copayment measures on initial medication non-adherence (IMNA) in several medication groups and by income level.

Design A population-based study was conducted using real-world evidence.

Setting Primary care in Catalonia (Spain) where two separate copayment measures (fixed copayment and coinsurance) were introduced between 2011 and 2013.

Participant Every patient with a new prescription issued between 2011 and 2014 (3 million patients and 10 million prescriptions).

Outcomes IMNA was estimated throughout dispensing and invoicing information. Changes in IMNA prevalence after the introduction of copayment policies (immediate level change and trend changes) were estimated through segmented logistic regression. The regression models were stratified by economic status and medication groups.

Results Before changes to copayment policies, IMNA prevalence remained stable. The introduction of a fixed copayment was followed by a statistically significant increase in IMNA in poor population, low/middle-income pensioners and low-income non-pensioners (OR from 1.047 to 1.370). In high-income populations, there was a large statistically non-significant increase. IMNA decreased in the low-income population after suspension of the fixed copayment and the introduction of a coinsurance policy that granted this population free access to medications (OR=0.676). Penicillins were least affected while analgesics were affected to the greatest extent. IMNA to medications for chronic conditions increased in low/middle-income pensioners.

Conclusion Even nominal charge fixed copayment may generate inequities in access to health services. An anticipation effect and expenses associated with IMNA may have generated short-term costs. A reduction in copayment can protect from non-adherence and have positive, long-term effects. Copayment scenarios could have considerable long-term consequences for health and costs due to increased IMNA in medication for chronic physical conditions.

INTRODUCTION

Medication represents one of the highest costs to healthcare systems. In 2014, medication expenditure accounted for 7%–30% of health spending in Organisation for Economic Co-operation and Development countries.[1] In most of these countries, medication costs per capita have increased steadily over recent decades and pharmaceutical expenditure doubled between 1997 and 2009.[2] Pressure on governments to reduce public spending led to the adoption of new, or tougher, medication copayment measures.[3 4]

Medication copayment could be considered a twofold strategy: it reduces government expenditure on medication and promotes rational use of medicines.[5] Copayment policies have been shown to decrease purchases of medication in countries with diverse health systems.[6 7] Some authors explain this as an improvement in responsible use of medicines.[5 6] However, very few studies have explored the effect of copayment policies on health outcomes and the long-term impact of these outcomes on health expenditure.[7] Furthermore, copayment policy design may create healthcare inequities by imposing a higher relative burden on low-income patients.[8 9]

Previous studies showed that increasing copayment often decreases adherence to medical treatment,[3 10] especially among pensioners and low-income populations.[4 11 12] Medication non-adherence is known to negatively affect health and costs.[13 14] Initial medication non-adherence (IMNA)—not filling a prescription

for a newly prescribed medication—is a prevalent behaviour[15 16] associated with higher costs. These costs are mainly generated by productivity losses, which suggests worse disease progress.[17 18] Since patients are prescribed the medication for the first time, they would probably not have these prescription drugs at home (eg, drugs for chronic conditions or antibiotics).[19 20] Therefore, increases in IMNA are unlikely to be a consequence of more rational use of medicines. Wang *et al*[21] assessed the impact of fixed copayment followed by introduction of an income-based copayment on IMNA to antidepressants in a population of retirees in British Columbia (Canada) between 2002 and 2003. They observed that both measures increased IMNA to antidepressants compared with the period when drugs were free of charge and that the impact of fixed copayment was greater than that of income-based coinsurance. In the same population, Dormuth *et al*[22] showed that both measures increased IMNA to inhaled medications compared with the period when this medication was free. However, these studies offered no information on how these policies affected IMNA according to income or on treatments for prevalent chronic and acute physical conditions such as cardiovascular diseases or infections.

In 2012, new copayment policies were implemented in Spain: a fixed copayment policy in which patients had to pay a fixed amount per each prescription filled irrespective of the kind of drug or patient profile (which we refer to as fixed copayment throughout the paper) and an income-based coinsurance copayment in which patients had to pay a percentage of the drug price according to the patient's annual income and the drug profile (which we refer to as coinsurance throughout the paper). These policies may have affected IMNA and generated inequities in access to medical treatment. We evaluated the impact of the introduction of fixed copayment and coinsurance contributions on IMNA for the most prevalent and/or expensive pharmacologic groups in economically vulnerable and non-vulnerable population groups using a natural experiment. Additionally, we explored the impact of these policies on key medication groups.

METHODS

Study design

This was a natural experiment using real-world evidence.

Setting

This study sample consisted of all patients receiving care at any of the publicly managed primary care (PC) centres in Catalonia (Spain). The healthcare system in Spain is funded through taxes and provides universal coverage, mostly free at the point of use, for citizens and foreign nationals. The central government is responsible for pharmaceutical policies such as medication pricing[23] and health planning, while public health and management of health services are decentralised to the regional governments of Spain's 17 autonomous communities, including Catalonia. PC acts as the gatekeeper to the healthcare system. In Catalonia, 5.8 million inhabitants (80% of the population) receive care at public PC centres managed by the Institut Català de la Salut.[24]

Events of interest

Between 2011 and 2013, abrupt changes to copayment conditions were introduced by the central (Spanish) and regional (Catalan) governments. Prior to this, reimbursement rules had remained virtually unchanged since the late '70s.

In Catalonia, four specific events occurred that could have affected IMNA. We divided the time around these four changes into five interrupted periods to observe the effects of each. Table 1 shows these five periods, when and how they began and ended and the changes in cost-sharing policies in Catalonia.

1. Initial period (initial coinsurance): Pensioners had free medications while non-pensioners were subject to coinsurance based on medication type. They paid 40% of general medications and 10% of reduced contribution medications (most chronic treatments).

2. Awareness after news publication (initial coinsurance): In October 2011, news of a pharmaceutical fixed copayment measure was released (event 1). We considered this period separately as we hypothesised that the announcement would trigger stockpiling during this period. The original coinsurance scheme continued in effect.

3. Fixed copayment + initial coinsurance: A fixed copayment scheme (€1 per prescription) was introduced by the regional government in June 2012 (event 2). This copayment was added to the original coinsurance scheme (initial coinsurance).

4. Fixed copayment + new coinsurance: In August (non-pensioners) and September 2012 (pensioners), the Spanish government modified the coinsurance payment to an income-based scheme (event 3). Coinsurance rates increased from 40% to 50% and 60% for medium/high-income non-pensioners, respectively. Pensioners were subject to a coinsurance scheme of 10% in all medications with a ceiling based on patient income. The poor population was exempt from coinsurance.

5. New coinsurance: Finally, in January 2013, the €1 per prescription (regional) copayment measure was suspended (event 4).

Population profiles

Following the insurance scheme introduction in 2012, the population was classified into five profiles (table 1):

1. Exempt from copayment (the poor): includes beneficiaries of very low pensions (between €1288 and €5100/year), the unemployed without benefits, those

Table 1 Events and periods under study and copayment schemes

Period	First week of period	Last week of period	Termination event	Fixed copayment	Coinsurance
1. Initial period	1 (3 January 2011)	41 (16 October 2011)	First press report on regional copayment	None	*Pensioners* 0% All medications *Non-pensioners* 40% Regular medicines 10% Reduced contribution medicines (€2.64 ceiling per prescription)
2. Awareness after news publication	42 (17 October 2011)	77 (24 June 2012)	Introduction of the regional fixed €1 per prescription copayment	None	*Pensioners* 0% All medications *Non-pensioners* 40% Regular medicines 10% Reduced contribution medicines (€2.64 ceiling per prescription)
3. Fixed copayment	78 (25 June 2012)	Non-pensioner profiles: 82 (23 July 2012) Pensioner profiles: 87 (26 August 2012) 0% copayment profile: 85 (13 August 2012)	Introduction of the changes in national coinsurance rates	€1 per prescription for all medications over €1.67* Annual limit: €61 per patient	*Pensioners* 0% All medications *Non-pensioners* 40% Regular medicines 10% Reduced contribution medicines (€2.64 ceiling per prescription)
4. Fixed copayment + new coinsurance rate	Non-pensioner profiles: 83 (30 July 2012) Pensioner profiles: 88 (3 September 2012) 0% copayment profile: 86 (20 August)	107 (20 January 2013)	Suspension of regional fixed copayment	€1 per prescription for all medications over €1.67* Annual limit: €61 per patient	*Poor population*† 0% All medications *Low/middle-income pensioners* 10% All medications with monthly limits per patient based on income‡ *Low-income non-pensioners* 40% Regular medicines 10% Reduced contribution medicines (€4.13 ceiling per prescription) *Middle-income non-pensioners* 50% Regular medicines 10% Reduced contribution medicines (€4.13 ceiling per prescription) *High-income population (pensioners§ and non-pensioners)* 60% Regular medicines 10% Reduced contribution medicines (€4.13 ceiling per prescription)
5. New coinsurance rate	108 (21 January 2013)	183 (30 June 2014)		None	*Poor population*† 0% All medications *Low/middle-income pensioners* 10% All medications with monthly limits per patient based on income‡ *Low-income non-pensioners* 40% Regular medicines 10% Reduced contribution medicines (€4.13 ceiling per prescription) *Middle-income non-pensioners* 50% Regular medicines 10% Reduced contribution medicines (€4.13 ceiling per prescription) *High-income population§ (pensioners and non-pensioners)* 60% Regular medicines 10% Reduced contribution medicines (€4.13 ceiling per prescription)

*Population at risk of exclusion was not subject to copayment.
†Population excluded from coinsurance: minimum integration copayment, non-contributory income, unemployed without benefits and analogous situations.
‡Patient monthly limit based on patient income of €8 (<€18 000/year) and €18 (€18 000–€100 000/year).
§Pensioner patients had a monthly limit of €60.

receiving social integration income (around €5000/year) and analogous situations;

2. 10% low/middle-income pensioners (≈€5000–€100 000/year): pensioners with annual income under €100 000 that do not fulfil criteria for full coverage;

3. 40% low-income non-pensioners (≈€5000–€18 000/year): non-pensioners with annual income lower than €18 000 that do not fulfil criteria for full coverage;

4. 50% middle-income non-pensioners (€18 000–€100 000/year): non-pensioners with annual income between €18 000 and €100 000;

5. 60% high-income population (>€100 000/year): pensioners and non-pensioners with annual income over €100 000.

Information on patients' annual income was not available in our database but could be calculated based on the percentage of coinsurance in non-reduced contribution drugs. We estimated the mean percentage of coinsurance for drugs dispensed per patient in the October 2012 to June 2014 timespan when new coinsurance was in force and grouped patients according to coinsurance profile.

Initial medication non-adherence

We obtained data on all PC patients (>14 years old) prescribed a new medication—from the 10 most prescribed pharmacotherapeutic subgroups and/or the 7 most costly in 2014 (see table 2)—at a public PC centre between January 2011 and June 2014. Data were gathered from the public Primary Healthcare System database in Catalonia (SIDIAP).[24 25]

Our dependent variable, IMNA, was defined as not filling a prescription for a newly prescribed medication in the month it was prescribed or the following month. To identify newly prescribed medicines, we considered a 3-month preperiod (time with no prescriptions for drugs from the same pharmacotherapeutic group) (1 month for penicillins).[16] Information was collected on prescriptions and used to estimate IMNA. New prescriptions were included for all drugs and specific groups based on pharmacologic profile: medication for physical chronic conditions, analgesics and penicillins. (Medicines included in these profiles are detailed in table 2.) Penicillins and analgesics are acute treatments but analgesics can be prescribed 'as needed' while penicillins, like medication for chronic conditions, are only prescribed when essential.

Covariates

Patient, family physician (FP) and PC centre characteristics have shown to be predictors of IMNA. Therefore, information on patients, FPs and PC centres associated with each new prescription was obtained from the database and used for adjustment.[16]

We gathered sociodemographic and clinical data from patients, including sex, age, place of origin (Spain, Europe, Africa, Americas and Asia-Oceania),

Table 2 Prescription, patient, family physician and primary care centre characteristics included in the study (January 2011 to June 2014)

Prescriptions	n=10 652 213	%
Total new prescriptions for all medications*	10 652 213	100
Medication subgroups		
Medication for chronic physical conditions†	1 230 371	11.55
Analgesics (anilides and propionic acid derivatives)	5 323 761	49.98
Penicillin	1 258 577	11.82
PPIs	1 293 904	12.15
Benzodiazepines	950 890	8.93
SSRIs	389 967	3.66
Other antiepileptics	204 743	1.92
Patients	n=3 075 364	**%**
Gender (female)	1 679 893	54.62
Age (mean±SD)	50.61	18.90
Copayment grade		
Poor population (0%)	205 006	6.67
Low-middle income pensioners (10%)	962 622	31.30
Low-income non-pensioners (40%)	1 349 222	43.87
Middle-income non-pensioners (50%)	505 597	17.86
High-income population (60%)	9271	0.30
Area socioeconomic status		
Urban 1	449 117	14.60
Urban 2	498 001	16.19
Urban 3	512 450	16.66
Urban 4	524 855	17.07
Urban 5	516 091	16.78
Rural	574 772	18.69
Nationality		
Spaniard	2 463 220	80.10
American	250 906	8.16
Asian/Oceanian	65 527	2.13
Other European	123 248	4.01
African	172 385	5.61
Active diseases†		
Allergy	73 823	2.40
Pain	1 086 049	35.32
Respiratory disease	252 758	8.22
Disability	506 422	16.47
Cardiovascular	1 551 824	50.46
Mental disorder	688 581	22.39
Neurological	249 993	8.13
Diabetes mellitus	302 175	9.83
Digestive system disorder	392 931	12.78
Thyroid gland-related disease	177 456	5.77
Number of grouped comorbidities (mean±SD)	1.72	1.48

Continued

Table 2 Continued

Prescriptions	n=10 652 213	%
Family physician characteristics	n=10 936	%
Gender (female)	7514	68.71
Age (mean±SD)	42.95	10.29
Assigned FPs	3767	34.45
Primary care centre characteristics	n=295	%
Teaching centre	72	24.41

*All medications include (ATC code): insulins and analogues for injection; long-acting (A10AE); platelet aggregation inhibitors excluding heparin (B01AC); ACE inhibitors, plain (C09AA); HMG CoA reductase inhibitors (C10AA); adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics (R03AK); anticholinergics (R03BB); PPIs (A02BC); propionic acid derivatives (M01AE); anilides (N02BE); other antiepileptics (N03AX); selective serotonin reuptake inhibitors (N06AB); benzodiazepine derivatives (N05BA); and penicillin with extended spectrum (J01CA).
†Medication for chronic physical conditions includes: long-acting insulins and analogues for injection; platelet aggregation inhibitors excluding heparin; plain ACE inhibitors; HMG CoA reductase inhibitors; adrenergics in combination with corticosteroids or other drugs excluding anticholinergics; anticholinergics.
FP, family physician; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.

socioeconomic status (five categories, from low to high for urban areas, and a rural category) and comorbidities (recorded in the International Classification of Diseases, 10th Revision, and grouped into most prevalent pathologies[16]). Month and week of prescription were also used as covariates. Patients were included multiple times if they were prescribed several drugs during the study period but covariates (eg, patient age) were different for each prescription.

FP sex, age, type (assigned or substitute/resident), and PC centre type (resident training centre or other) were also registered. All these data were obtained from SIDIAP.

Statistical analysis

Missing data

Five covariables had missing values in different proportions: socioeconomic status (4%), nationality (42%), copayment profile (26%), and FP age and gender (both 10%). Several patient characteristics (eg, patient age and gender and most comorbidities) were associated with a higher or lower probability of missingness, suggesting that the missing data mechanism was not missing completely at random. FP age was missing only for FPs not assigned to patients, that is, substitutes and/or residents. These FPs are younger than the FP sample registered in the database. Consequently, FP age missing values were assumed to be 32.5, which corresponds to the mean age of substitutes and residents. To deal with the remaining missing values, one database was imputed using multivariate imputation with chained equations using all the available variables in the model. Due to the high computational cost, single imputation was used. To assess the reliability of the imputation model, as described in a previous paper,[16 17] we randomly eliminated the same proportion of missing values from the database without missing data and ran the imputation model. Subsequently, imputed values were compared with the original values. Erroneous imputation values were around 5% in all four variables. A sensitivity analysis without imputation was developed. The results were in line with those from the model with imputed missing data (see online supplementary table 1).

Impact of copayment policies on IMNA

To show a representation of raw trends in IMNA, weekly IMNA prevalences from 3 January 2011 to 30 June 2014 (183 weeks) were estimated and plotted for all medications (see figure 1A) and specific pharmacologic groups in populations with distinct copayment profiles (see online supplementary figures 1–3).

To test one-off level changes (ie, immediate increase/decrease in IMNA) after the events related to the new copayment policies (described in table 1) as well as trend changes in the weeks following the events of interest (ie, increase/decrease in the slope of IMNA per week), we used adjusted segmented logistic regression (SLR). Segmented regression analyses estimate level and trend in the pre-event segment and changes in level (immediate increase/decrease in IMNA) and trend (increase/decrease in the slope of IMNA) after the events.[26]

The unit of analysis was IMNA for each prescription, which had a set of associated variables including information from the prescription, the patient, FP and PC centre where the prescription was written up. The dependent variable in the SLR model was IMNA to prescriptions (Yes/No) and the main independent variable was *time* (time in weeks from the start of the study period (3 January 2011) until the end of follow-up (30 June 2014) (183 weeks)). The model also included four binary *event* variables, one for each event of interest; four continuous *time after the event* variables, indicating time in weeks after each event of interest, which were all 0 for the weeks before the event; and potential confounding variables. The model was adjusted for all patient, FP and PC centre characteristics, and variables to control for seasonality (month of the year (January to December) and week of the month (first to fifth)).

The effects of the events on weekly IMNA rates were estimated using the following model:

$$\begin{aligned} logit\left(\frac{p(IMNA)}{1-p(IMNA)}\right) &= \beta_0 + \beta_1 * time_w + \beta_2 * 1^{st}\ event_w \\ &+ \beta_3 + time\ after\ 1^{st}\ event_w + \beta_4 \\ &* 2^{nd}\ event_w + \beta_5 * time\ after\ 2^{nd}\ event_w \\ &+ \beta_6 * 3^{rd}\ event_w + \beta_7 \\ &* time\ after\ 3^{rd}\ event_w + \beta_8 * 4^{th}\ event_w \\ &+ \beta_9 * time\ after\ 4^{th}\ event_w \\ &+ \beta_i\ counfounding\ variable_i + e_w \end{aligned}$$

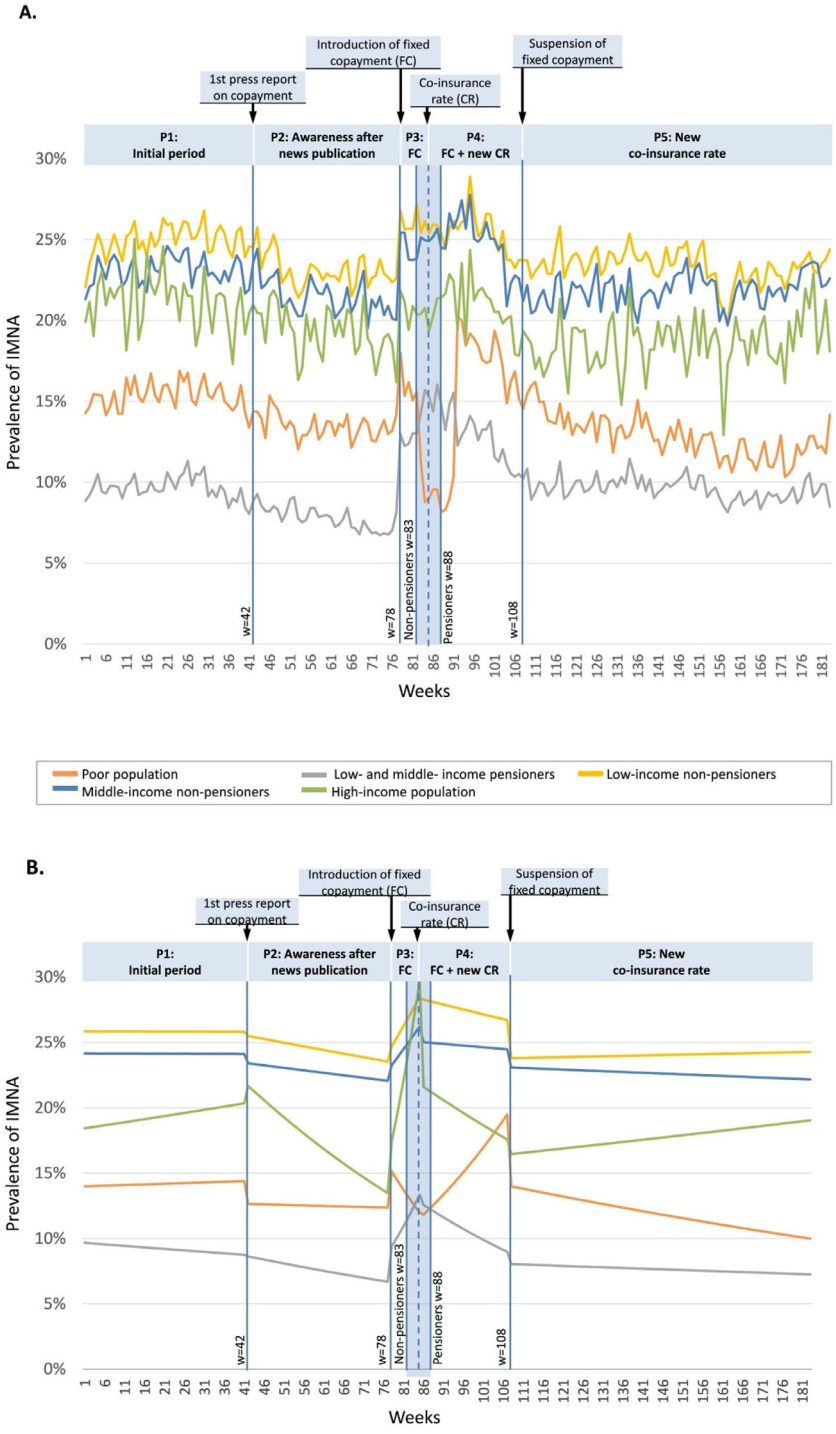

Figure 1 IMNA weekly prevalence of new prescriptions for all medicines during the period of study stratified by coinsurance rate. (A) IMNA weekly prevalence based on raw data. (B) IMNA weekly prevalence based on the segmented logistic regression model. IMNA, initial medication non-adherence.

where β_0 estimates the baseline level of the outcome at time 0; β_1 estimates the week-to-week change in the IMNA rate before the first event of interest (the baseline trend); β_2 estimates the IMNA rate level change immediately after the first event (IMNA rate in the week following the news release compared with the week prior to the news release); β_3 estimates the change in the long-term IMNA trend after the first event of interest, compared with the trend before the event; β_4 estimates the IMNA level change immediately after the second event (IMNA rate in the week following the implementation of the fixed copayment compared with the week prior to the implementation of the fixed copayment); β_5 estimates the change in the long-term IMNA trend after the second event of interest (implementation of the fixed copayment), compared with the trend before the event (after news release); β_6 estimates

the IMNA level change immediately after the third event (IMNA rate in the week following the changes in coinsurance scheme compared with the week prior to changes in coinsurance scheme); β_7 estimates the change in the long-term IMNA trend after the third event of interest (changes in coinsurance scheme), compared with the trend before the event; β_8 estimates the IMNA level change immediately after the fourth event (IMNA rate in the week following the suspension of the fixed copayment compared with the week prior to the suspension of the fixed copayment); β_9 estimates the change in the long-term IMNA trend after the fourth event of interest (suspension of the fixed copayment), compared with the trend before the event; β_i estimates the IMNA level changes caused by confounding variables; and e_w is the error term at week w representing variability not explained by the model. Online supplementary tables 2 and 3 show the logistic segmented regression model coefficients.

The estimates of change in the long-term trend in IMNA after the events of interest (β_3, β_5, β_7 and β_9) are measuring the interaction of time with each of the events of interest. The indicator variables for each period apply to all times after the event, therefore level and slope changes are cumulative. To facilitate the interpretation of results, we estimated the week-to-week change in the IMNA rate (IMNA trend) in each study period and tested whether there were statistically significant differences between each period slope and the initial period slope. Level changes and slope changes were reported as ORs and p values of these changes were calculated for a confidence probability of 95%. Predicted IMNA prevalence based on the SLR model was also plotted (see figure 1B).

All analyses were performed with Stata MP V.13.1.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or study implementation. No patients were asked to advise on interpretation or writing up of the results. The results will be disseminated via mass media, social networks and institutional websites to the relevant patient community, clinicians and decision-makers.

RESULTS

Prescription, patient, FP and PC centre characteristics are shown in table 2. This study included 3 075 364 patients and 10 652 213 new prescriptions, mainly analgesics (50%), treatments for chronic conditions (12%) and penicillins (12%). Patients were mainly low-income non-pensioners (44%), low/middle-income pensioners (31%) and middle-income non-pensioners (18%).

Copayment impact on IMNA prevalence for all medications

Figure 1 shows weekly IMNA rates for all medications throughout the study period. Figure 1A shows raw data while figure 1B shows predicted data based on the regression model. Table 3 shows the level change in IMNA prevalence (OR)—that is, the increase/decrease in IMNA prevalence immediately after the event—as well as the trend (slope) change (OR) after each event of interest, compared with the trend in the initial period.

Initial period

Prior to the news release, IMNA prevalence remained stable in all populations except low/middle-income pensioners, where it decreased (OR=0.997, 95% CI 0.997 to 0.998). IMNA prevalence ranged from 9.7% to 24.9% in the initial period, with population groups containing higher proportions of older people[16] showing lower IMNA levels.

Awareness after news publication

When information on new copayment measures was released, an immediate level and/or a long-term trend reduction in IMNA prevalence occurred in all population groups, indicating an anticipation effect (stockpiling).

Fixed copayment

The establishment of fixed copayment caused an immediate large IMNA increase in the poor population and low/middle-income pensioners. The odds of not initiating medication in the week when the fixed copayment was established were 1.3 times higher with respect to the previous week in low/middle-income pensioners (OR=1.370, 95% CI 1.319 to 1.423) and the poor (OR=1.315, 95% CI 1.216 to 1.422). A small increase occurred in low-income non-pensioners while the high-income population experienced a large statistically non-significant increase. In the weeks following this event, compared with the trend per week before the news release, the IMNA prevalence trend increased among all population groups but the poorest patients (OR per week=0.962, 95% CI 0.948 to 0.976) (ie, as the weeks progressed, the chances of initiating the medication increased in the poorest population).

Fixed copayment + new coinsurance rate

The modification of the coinsurance copayment was followed by an immediate small reduction in IMNA in low/middle-income pensioners and low-income non-pensioners, which was followed by a declining IMNA trend in low/middle-income pensioners and middle-income non-pensioners. Large immediate and

Table 3 Immediate and long-term effects of the events under study based on segmented logistic regression models (OR and 95% CI)*

	Poor population†		Low/middle-income pensioners		Low-income non-pensioners		Middle-income non-pensioners		High-income population†	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Baseline level of IMNA (intercept, $e^{\beta 0}$)	**0.311**	**0.297 to 0.325**	**0.241**	**0.235 to 0.246**	**0.243**	**0.240 to 0.247**	**0.243**	**0.238 to 0.249**	**0.251**	**0.207 to 0.303**
Baseline trend per week of IMNA (preintervention slope, $e^{\beta 1}$)‡	1.001	0.999 to 1.002	**0.997**	**0.997 to 0.998**	1.000	0.999 to 1.001	1.000	0.999 to 1.001	1.003	0.996 to 1.010
News release										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 2}$)§	**0.862**	**0.819 to 0.907**	0.992	0.966 to 1.019	**0.963**	**0.947 to 0.980**	0.986	0.957 to 1.015	1.102	0.850 to 1.428
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3}$)¶	0.999	0.997 to 1.001	**0.992**	**0.991 to 0.993**	**0.998**	**0.997 to 0.998**	**0.997**	**0.996 to 0.998**	**0.984**	**0.975 to 0.993**
Introduction of the fixed copayment**										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 4}$)§	**1.315**	**1.216 to 1.422**	**1.370**	**1.319 to 1.423**	**1.047**	**1.015 to 1.079**	1.038	0.985 to 1.093	1.231	0.804 to 1.882
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5}$)¶	**0.962**	**0.948 to 0.976**	**1.058**	**1.052 to 1.064**	**1.023**	**1.015 to 1.030**	**1.028**	**1.015 to 1.041**	**1.104**	**1.020 to 1.194**
Change in coinsurance scheme**										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 6}$)§	0.957	0.882 to 1.039	**0.949**	**0.907 to 0.993**	**0.941**	**0.901 to 0.983**	0.994	0.922 to 1.073	0.659	0.415 to 1.048
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5+\beta 7}$)¶	**1.029**	**1.025 to 1.032**	**0.982**	**0.980 to 0.985**	0.999	0.997 to 0.999	**0.996**	**0.994 to 0.998**	0.988	0.969 to 1.008
Suspension of fixed copayment										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 8}$)§	**0.676**	**0.642 to 0.711**	**0.883**	**0.865 to 0.912**	**0.927**	**0.912 to 0.942**	**0.856**	**0.833 to 0.880**	0.922	0.720 to 1.180
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5+\beta 7+\beta 9}$)¶	**0.995**	**0.994 to 0.995**	**0.999**	**0.998 to 0.999**	**0.999**	**0.999 to 0.999**	1.000	1.000 to 1.001	1.002	1.000 to 1.005

*Models were adjusted for the characteristics of patients, FPs and PC centres as well as for seasonality (week of the month and month of the year).
†Includes pensioners and non-pensioners.
‡Bold numbers indicate statistically significant difference from zero.
§This row reports the level change in IMNA prevalence (OR)—that is, the increase/decrease in IMNA prevalence—immediately after the event week; bold numbers indicate statistically significant differences (95% confidence probability).
¶This row reports the period trend in OR per 1-week increase. Bold numbers indicate statistically significant differences between each period slope and initial period slope.
**The end of the third period and the beginning of the fourth period are not the same for all population profiles. For non-pensioner only profiles (40% and 50%) the period change was in the 83rd week, for pensioner only profiles (40%) the period change was in the 88th week, and for pensioner and non-pensioner profile groups the period change was in the 85th week.
FP, family physician; IMNA, initial medication non-adherence; PC, primary care.

long-term statistically non-significant decreases in IMNA were observed in the high-income population.

In poor patients, extreme values were observed between weeks 83 and 92 (figure 1A). After full insurance was granted to poor non-pensioners (week=83), IMNA abruptly decreased. When coinsurance policies for pensioners were applied (week=88), IMNA abruptly increased in the poor population, although coverage for poor pensioners did not change.

New coinsurance rate

Suspension of fixed copayment was followed by an immediate decrease in IMNA in all populations (statistically non-significant in the high-income population), followed by a decreasing IMNA trend in the poor population and low/middle-income pensioners (although this decrease had a smaller effect than was initially observed, ie, the slope was less pronounced than the initial period slope).

Copayment impact on IMNA prevalence by medication profiles

Table 4 shows the level and trend changes after each study event. Online supplementary figures 1–3 show IMNA weekly prevalence by medication group.

Initial period

Before the news release, prevalence of IMNA to chronic condition medication was declining or stable. There was no evidence of prevalence change in IMNA to analgesics and penicillins for all population groups but the poor, which showed an increasing INMA trend.

Awareness after news publication

Following the news release, with few exceptions, a statistically significant anticipation effect was observed in analgesics and medication for chronic conditions. In penicillins, an immediate large statistically significant decrease was observed in the poor population while an immediate large statistically non-significant decrease was observed in the high-income population.

Fixed copayment

Overall, the establishment of fixed copayment caused an increase in IMNA to analgesics. IMNA also increased for penicillins and medication for chronic physical conditions in low/middle-income pensioners. In the poor population, an immediate increase was followed by a decreasing IMNA trend. In the high-income population, a large statistically non-significant increase was observed in all medication groups.

Fixed copayment + new coinsurance rate

The modification of coinsurance rates was followed by an IMNA decrease to analgesics in low/middle-income pensioners and to medication for chronic conditions in low/middle-income pensioners and the high-income population. In the poor population, an increasing IMNA trend in medication for chronic conditions and analgesics was seen.

New coinsurance rate

Overall, compared with the previous period, the suspension of fixed copayment was followed by a level and/or trend decrease in IMNA in all population groups. However, compared with the initial period (before any changes made to the copayment scheme), the decreasing IMNA trend in medication for chronic conditions was less pronounced in low/middle-income pensioners and low-income non-pensioners.

DISCUSSION

This study demonstrates a correlation between copayment policies and IMNA that differs according to medication group. We observed a greater effect of copayment measures on the poor and pensioners. Copayment measures had two main effects on IMNA: an anticipation effect following news of the copayment measures and an increase in IMNA as a consequence of the establishment of fixed copayment measures. IMNA rates reverted to previous values for some populations and medication groups after their suspension.

Our results show that even a small copayment (€1) that did not consider patients' purchasing power had an impact on IMNA, especially in the poor population and low/middle-income pensioners. This might have increased healthcare access inequities although lack of statistical significance on the impact of IMNA in high-income populations may be due to small sample size. Furthermore, the effect is more pronounced in medications with a high impact on health-related quality of life in the short term (analgesics) and long term (medications for chronic physical conditions).[27] In the medium term, IMNA to these treatments is associated with increased costs, mainly due to higher sick leave costs,[17 18] and may also be related to higher long-term costs.[28] Therefore, copayment policies could increase costs as a result of both the impact on non-adherence and the anticipation effect (stockpiling), which artificially reduced IMNA and increased pharmaceutical spending, even in high-income population groups.

A recent study in Spain showed a decrease in medication purchases after the introduction of copayment policies.[6] The authors attributed this to a reduction in drug abuse although they had no prescription information and could not discern whether the reduction in purchases caused an increase in non-adherence. Another study, which linked prescription and dispensing information, assessed the impact of the coinsurance rate on non-adherence to acute coronary syndrome drugs. In line with our results, the study showed an increase in non-adherence to costly drugs and this was especially pronounced in the pensioner population.[12] IMNA occurs when a first prescription of a new treatment is not dispensed, and rational use

Table 4 Immediate and long-term effects of the events under study for specific pharmacologic groups based on segmented logistic regression models (OR and 95% CI)*

	Poor population†		Low/middle-income pensioners		Low-income non-pensioners		Middle-income non-pensioners		High-income population†	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Medication for chronic conditions										
Baseline level of IMNA (intercept, $e^{\beta 0}$)	**0.233**	**0.206 to 0.264**	**0.176**	**0.166 to 0.187**	**0.193**	**0.181 to 0.206**	**0.167**	**0.152 to 0.184**	**0.188**	**0.109 to 0.324**
Baseline trend per week of IMNA (preintervention slope, $e^{\beta 1}$)‡	**0.994**	**0.990 to 0.998**	**0.991**	**0.989 to 0.993**	**0.996**	**0.994 to 0.998**	0.999	0.995 to 1.002	1.011	0.990 to 1.033
News release										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 2}$)§	**0.808**	**0.703 to 0.928**	1.034	0.971 to 1.101	0.955	0.880 to 1.035	0.967	0.858 to 1.092	1.275	0.632 to 2.572
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3}$)¶	**1.006**	**1.002 to 1.011**	**0.998**	**0.996 to 1.001**	**1.002**	**0.999 to 1.004**	1.001	0.997 to 1.005	**0.971**	**0.949 to 0.994**
Introduction of the fixed copayment**										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 4}$)§	**1.379**	**1.127 to 1.687**	**1.271**	**1.166 to 1.386**	1.068	0.935 to 1.220	0.966	0.795 to 1.176	1.512	0.566 to 4.041
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5}$)¶	**0.918**	**0.885 to 0.952**	**1.036**	**1.023 to 1.050**	1.004	0.973 to 1.036	1.035	0.989 to 1.083	1.208	1.018 to 1.434
Change in coinsurance scheme**										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 6}$)§	1.007	0.820 to 1.236	**0.849**	**0.762 to 0.946**	0.909	0.760 to 1.088	0.799	0.616 to 1.036	**0.336**	**0.118 to 0.956**
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5+\beta 7}$)¶	**1.032**	**1.021 to 1.043**	0.988	0.983 to 0.994	0.997	0.990 to 1.002	0.998	0.988 to 1.007	0.972	0.918 to 1.028
Suspension of fixed copayment										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 8}$)§	**0.669**	**0.581 to 0.771**	**0.832**	**0.779 to 0.888**	0.932	0.861 to 1.010	**0.883**	**0.787 to 0.992**	0.954	0.484 to 1.879
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5+\beta 7+\beta 9}$)¶	0.997	0.995 to 0.999	**0.998**	**0.998 to 0.999**	**0.997**	**0.996 to 0.998**	**0.998**	0.997 to 0.999	1.003	0.997 to 1.009
Analgesics										
Baseline level of IMNA (intercept, $e^{\beta 0}$)	**0.361**	**0.340 to 0.384**	**0.262**	**0.253 to 0.270**	**0.283**	**0.279 to 0.289**	**0.298**	**0.290 to 0.307**	**0.302**	**0.231 to 0.396**
Baseline trend per week of IMNA (preintervention slope, $e^{\beta 1}$)‡	**1.002**	**1.000 to 1.004**	0.999	0.999 to 1.000	1.001	0.999 to 1.001	1.000	0.999 to 1.001	1.006	0.996 to 1.017
News release										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 2}$)§	**0.860**	**0.802 to 0.922**	0.999	0.962 to 1.038	**0.968**	**0.947 to 0.989**	0.974	0.938 to 1.012	1.031	0.711 to 1.495
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3}$)¶	1.000	0.998 to 1.003	**0.990**	**0.989 to 0.992**	**0.997**	**0.997 to 0.998**	**0.997**	**0.996 to 0.999**	**0.986**	**0.972 to 0.999**
Introduction of the fixed copayment**										

Continued

Table 4 Continued

	Poor population†		Low/middle-income pensioners		Low-income non-pensioners		Middle-income non-pensioners		High-income population†	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 4}$)§	**1.289**	**1.152 to 1.435**	**1.459**	**1.380 to 1.542**	**1.06**	**1.018 to 1.103**	1.044	0.974 to 1.120	1.285	0.633 to 2.492
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5}$)¶	**0.968**	**0.948 to 0.988**	**1.067**	**1.059 to 1.076**	**1.032**	**1.022 to 1.042**	**1.038**	**1.020 to 1.056**	1.046	0.922 to 1.187
Change in coinsurance scheme**										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 6}$)§	0.946	0.843 to 1.062	0.976	0.915 to 1.041	**0.929**	**0.877 to 0.984**	1.015	0.916 to 1.124	1.085	0.514 to 2.287
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5+\beta 7}$)¶	**1.031**	**1.025 to 1.036**	**0.983**	**0.979 to 0.985**	**0.998**	**0.997 to 1.000**	**0.996**	**0.993 to 0.998**	0.990	0.963 to 1.018
Suspension of fixed copayment										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 8}$)§	**0.654**	**0.610 to 0.701**	**0.859**	**0.828 to 0.891**	**0.887**	**0.869 to 0.906**	**0.789**	**0.762 to 0.817**	0.829	0.587 to 1.172
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5+\beta 7+\beta 9}$)¶	**0.994**	**0.994 to 0.995**	0.998	0.998 to 0.999	**0.999**	**0.999 to 0.999**	1.000	1.000 to 1.001	1.001	0.998 to 1.005
Penicillins										
Baseline level of IMNA (intercept, $e^{\beta 0}$)	**0.157**	**0.134 to 0.183**	**0.116**	**0.106 to 0.126**	**0.097**	**0.093 to 0.103**	**0.105**	**0.096 to 0.114**	**0.112**	**0.052 to 0.243**
Baseline trend per week of IMNA (preintervention slope, $e^{\beta 1}$)†	**1.006**	**1.001 to 1.011**	0.998	0.996 to 1.001	0.999	0.998 to 1.001	0.997	0.994 to 1.001	1.020	0.990 to 1.051
News release										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 2}$)§	**0.739**	**0.617 to 0.885**	0.955	0.862 to 1.058	0.943	0.887 to 1.003	1.019	0.912 to 1.138	0.623	0.195 to 1.992
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3}$)¶	1.002	0.995 to 1.008	**0.995**	**0.991 to 0.998**	0.999	0.996 to 1.001	0.996	0.992 to 1.000	0.983	0.942 to 1.025
Introduction of the fixed copayment**										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 4}$)§	1.245	0.952 to 1.627	0.918	0.781 to 1.079	1.089	0.974 to 1.218	1.107	0.900 to 1.362	2.155	0.453 to 10.248
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5}$)¶	0.963	0.914 to 1.015	**1.058**	**1.033 to 1.084**	0.993	0.966 to 1.021	0.985	0.957 to 1.059	1.094	0.797 to 1.502
Change in coinsurance scheme**										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 6}$)§	1.020	0.745 to 1.396	**0.952**	**0.786 to 1.154**	1.106	0.940 to 1.302	1.007	0.739 to 1.341	0.524	0.070 to 3.907
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5+\beta 7}$)¶	1.021	1.008 to 1.035	0.984	0.975 to 0.993	0.997	0.993 to 1.002	1.001	0.993 to 1.008	0.994	0.923 to 1.071

Continued

Table 4 Continued

	Poor population†		Low/middle-income pensioners		Low-income non-pensioners		Middle-income non-pensioners		High-income population†	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Suspension of fixed copayment										
Immediate effect of the event (level change in IMNA rate from previous week, $e^{\beta 8}$)§	**0.706**	**0.594 to 0.838**	0.966	0.876 to 1.065	1.025	0.968 to 1.022	**0.900**	**0.816 to 0.993**	0.516	0.205 to 1.299
Long-term effect of the event (gradual change in slope, per week, $e^{\beta 1+\beta 3+\beta 5+\beta 7+\beta 9}$)¶	**0.995**	**0.993 to 0.997**	0.999	0.998 to 1.000	0.999	0.999 to 0.999	**1.002**	**1.001 to 1.003**	**1.009**	**1.000 to 1.018**

*Models were adjusted for the characteristics of patients, FPs and PC centres as well as for seasonality (week of the month and month of the year).
†Includes pensioners and non-pensioners.
‡Bold numbers indicate statistically significant difference from zero.
§This row reports the level change in IMNA prevalence (OR)—that is, the increase/decrease in IMNA prevalence—immediately after the event week; bold numbers indicate statistically significant differences (95% confidence probability).
¶This row reports the period trend in OR per 1-week increase. Bold numbers indicate statistically significant differences between each period slope and initial period slope.
**The end of the third period and the beginning of the fourth period are not the same for all population profiles. For non-pensioner only profiles (40% and 50%) the period change was in the 83rd week, for pensioner only profiles (40%) the period change was in the 88th week, and for pensioner and non-pensioner profile groups the period change was in the 85th week.
FP, family physician; IMNA, initial medication non-adherence; PC, primary care.

of medicines is not relevant, although it could partially explain IMNA in analgesics.[16] The only two studies that assessed a similar situation[21 22] observed that fixed copayment followed by an income-based copayment caused an increase in IMNA in antidepressant and inhaled medications compared with the period when this medication was free of charge and that the impact of the fixed copayment was greater than that of the coinsurance measure. This finding is similar to our results in medication for chronic physical conditions.

As seen in previous studies, copayment policies had an impact on populations with limited resources.[11 29] Special attention should be paid to vulnerable populations when designing copayment policies. The poor and low/middle-income pensioners experienced the largest statistically significant increases in IMNA following introduction of fixed copayment. Following its suspension, there was a reduction in IMNA in the poor population.

The new coinsurance policy introduced in June 2012, which took into account patients' income, had less impact on IMNA. We expected to see reductions in IMNA rates in the poor population (then exempt from payment) and increases in IMNA rates in low/middle-income pensioners and low-income non-pensioners after the introduction of the new coinsurance scheme. However, this policy was implemented shortly after the introduction of the fixed copayment, which had already produced considerable changes in IMNA rates and could have limited our capacity to detect the impact of the new coinsurance scheme on IMNA. In fact, when the €1 per prescription fixed copayment was eliminated and coinsurance based on income was the only copayment policy, we observed differences in IMNA rates in comparison with the initial period. Poor non-pensioners no longer had to pay for medicines and there was a protective effect on this population. This effect was already shown in previous studies, where copayment reduction generated an increase in adherence, especially to chronic treatments.[30 31] This suggests that equitable copayment policies could be used as a strategy to increase adherence in vulnerable populations. For instance, the 10% coinsurance for low/middle-income pensioners caused an increase in the IMNA trend at the end of the study compared with the period where they had free medicines. This is especially worrying in drugs for chronic physical conditions where adherence reductions could have long-term health and economic consequences.

The income-based coinsurance policy brought together a highly heterogeneous population in the low/middle-income pensioner group. This population group, which moved from full insurance to 10% cost-sharing, includes pensioners with annual income ranging from €5000 to €100 000/year. Considering that middle-income pensioners are likely to behave similarly to middle-income non-pensioners, we may have underestimated the impact of copayment policies

on IMNA in low-income pensioners. It is possible that increases in IMNA on low/middle-income pensioners are mainly explained by a higher burden on low-income pensioners.

The large changes (technically known as *wild data points*[26]) observed in the fourth period (weeks 88–91) for the poorest individuals could be explained by an initial and temporary erroneous classification of patients according to income after the policy implementation for pensioners (week 88). While this erroneous classification should have affected all populations, these patients could have been affected to a greater extent since they may not have been able to afford the prescription charge. As distinct from penicillins and medications for chronic conditions, copayment news led to a clear anticipation effect for analgesics. This could be explained by stockpiling of these treatments.[32]

The primary strength of this study is its representativeness. This study contains every single new prescription for the main pharmacotherapeutic groups issued in the entire Catalonian public PC system for 3.5 years. However, it has several limitations. First, consideration of at least 12 data points before and after each event is recommended to conduct segmented regression analysis. The number of data points per period ranged from 5 to 10, depending on the population group. As such, focused on improving precision and working with weekly prevalence, we had a limited sample size when evaluating specific populations (high-income population) which may have limited our capacity to detect statistically significant impacts on these populations. Second, dispensation does not necessarily imply consumption, even though the number of prescriptions dispensed is widely used to assess adherence[15 16] and this method provides reliable estimates.[33] Third, several variables, including the copayment profile, had missing information. The computational cost prevented us from doing multiple imputations so we used simple imputation techniques to deal with this issue. We also presented a sensitivity analysis without imputation. Fourth, the high-income population represented only 0.3% (n=9271) of the total sample, accounting for 24 981 prescriptions. Although the sample size is large, it may have limited our power to detect statistically significant effects of the policies in this population group, especially when specific pharmacologic groups were modelled. Therefore, results in this population group should be interpreted with caution. Finally, as the two copayment policies overlapped, we could not explore the isolated effect of each one.

CONCLUSIONS

IMNA increases resulting from the introduction of copayment measures need to be considered when debating new copayment policies. The goal of these kinds of policies is to reduce pharmaceutical spending, mainly caused by stockpiling. However, the anticipation effect increased pharmaceutical spending which, added to the costs associated with IMNA increases as a consequence of copayment measures, might have caused suffering to patients in addition to the short/medium-term economic losses. In future studies, the long-term effects on health expenditure and negative effects on health need to be explored, especially in medication for chronic conditions.

Health policymakers should consider these findings when designing new copayment strategies. Coinsurance policies seemed fairer than fixed copayment policies. Moreover, based on the protective effect seen in the poor population, the low-income population (pensioners and non-pensioners) could benefit from more equitable policies. Thresholds for coinsurance level should be carefully reviewed in Spain.

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