Pediatric Medication Non-Initiation in Spain

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Abbreviations:

- PADRIS – Public Data Analysis for Health Research and Innovation Program
- ATC – Anatomical Therapeutic Chemical classification system
- PC – Primary care
- SC – Secondary care
- ICH – International Council for Harmonization guidance
- ICD-10 – International Statistical Classification of Diseases and Related Health Problems
- PPI – Proton Pump Inhibitor
- OR – Odds Ratio
- CI – Confidence Interval
- prn - *pro re nata*

Article summary: Through linkage of prescription and dispensing databases, this study captures prevalence and explanatory factors of medication non-initiation in the pediatric population.

What's Known on This Subject: Medication non-initiation is a complex behavior, influenced by multiple determinants, which is well documented in the adult population but few studies have assessed it in pediatric patients, with overall prevalence rates up to 22%.

What This Study Adds: An extensive analysis of non-initiation in pediatrics was carried out focusing on more than 20 medication groups and a set of explanatory factors. Results of this study offer a broad perspective of non-initiation, which allows health planners to prioritize future actions.

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Authors' contribution:

Ms Carbonell-Duacastella acquired, analyzed and interpreted the data, carried out the statistical analysis, drafted the initial manuscript, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Drs Aznar-Lou and Rubio-Valera conceptualized and designed the study, obtained funding, acquired, analyzed and interpreted the data, carried out the statistical analysis, supervised the study, had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Ms Peñarrubia-María, Dr Pasarín, Dr Garcia-Cardenas and Ms Marqués-Ercilla conceptualized and designed the study and obtained funding.

All authors critically reviewed the manuscript for important intellectual content, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives: To estimate medication non-initiation prevalence in the pediatric population and to identify the explanatory factors underlying this behavior.

Methods: Observational study of patients (<18 years old) receiving at least one new prescription (28 pharmaceutical subgroups) (July 2017-June 2018) in Catalonia (Spain). A prescription was considered new when there was no prescription for the same pharmaceutical subgroup in the previous 6 months. Non-initiation occurred when a prescription was not filled within 1 month or 6 months (sensitivity analysis). Prevalence was estimated as the proportion of total prescriptions not initiated. To identify explanatory factors, a multivariable multilevel logistic regression model was used and adjusted Odds ratios were reported.

Results: Overall, 1,539,003 new prescriptions were issued to 715,895 children. Overall prevalence of 1-month non-initiation was 9.0% (ranging from 2.6% (oral antibiotics) to 21.5% (proton-pump inhibitors)) and prevalence of 6-month non-initiation was 8.5%. Non-initiation was higher in the youngest and oldest population groups, in children from families with a 0% copayment rate (vulnerable populations) and those with conditions from external causes. Out-of-pocket costs of drugs increased the odds of non-initiation. The odds of non-initiation were lower when the prescription was issued by a pediatrician (compared to a primary or secondary care clinician).

Conclusions: The prevalence of non-initiation of medical treatments in pediatrics is high and varies according to patients' ages and medical groups. Results suggest that there are inequities in access to pharmacological treatments in this population that must be taken into account by healthcare planners and providers.

INTRODUCTION

Medication non-adherence is widespread in the pediatric population and has a negative impact on health and health care utilization[1–3] but to date the effects of pediatric non-initiation have not been fully assessed. Medication non-initiation, or initial medication non-adherence, occurs when a patient does not take the first dose of a prescribed medication[4]. Non-initiation and its consequences are well documented in the adult population[5–11] with the few studies assessing it in pediatric patients, having prevalence rates in the latter up to 22%[12–16]. Most of these studies did not establish time frames that accurately define non-initiation[17]: the pre-period (i.e., time-span to consider a prescription as new) and the follow-up period (i.e., time-span to consider a prescription initiated). Only two studies assessed non-initiation in various medication groups[12,14] with the lowest non-initiation prevalence seen for antibiotics (4.2% and 5.6%) and the highest for nutritional treatments (29.3%)[14] and pain medications (28.6%)[12]. Studies conducted on anti-infectives, antidepressants and asthma medications showed rates of 11.1%[18], 16.9%[19] and 10.6%[20], respectively.

Medication non-adherence is complex and influenced by multiple determinants which are often classified into five dimensions[21]: socio-economic (e.g., socioeconomic status); healthcare team and system-related (e.g., patient-provider relationship); condition-related (e.g., severity of symptoms); therapy-related (e.g., side-effects); and patient-related factors (e.g., forgetfulness)[18,22–26]. Factors influencing non-initiation may differ from those affecting implementation and discontinuation. In the USA, non-initiation was found to be associated with gender, age and the socioeconomic status of the residential area[14]. To the best of our knowledge, no further determinants of this complex behavior have been identified in the pediatric population. A deeper understanding of

this phenomenon is needed; characterizing the pediatric non-initiator may assist in the development of targeted strategies and interventions.

The aims of this study were, first, to estimate the prevalence of non-initiation of prescribed medications in the pediatric population and, second, to identify the explanatory factors underlying this behavior.

METHODS

The STROBE statement and the ESPACOMP Medication adherence Reporting Guideline (EMERGE) were followed in the reporting of this research[27,28] .

STUDY DESIGN AND SETTING

This was an observational study of a cohort of pediatric patients receiving at least one new prescription (July 2017-June 2018) in Catalonia (Spain). Data (July 2016-December 2018) were obtained from the PADRIS real world database[29], which has data from all providers in the public health system, including information on the use of healthcare resources, clinical information, and medication prescription and dispensing.

The Catalan public health system provides universal healthcare to all residents (around 7.5 million) and is organized into health areas (smaller territories that manage healthcare provision). Supplementary File 1 gives a detailed description of the characteristics of the healthcare system. All citizens have a unique individual identification number which grants access to the whole public health system in Catalonia and Spain. It is funded through taxes and free-of-charge at the point of use except for prescription medications, which are subjected to a co-payment contribution ranging from 0 to 60% according to the type of medication, level of income and status

as a pensioner[30]. An electronic prescription system registers all electronic prescriptions and dispensing of publicly financed medications, which are dispensed in community pharmacies using the Anatomical Therapeutic Chemical (ATC) classification system. Patients can get prescriptions from private providers but these are not funded by the Catalan public health system nor registered in the databases. Primary care (PC) is the gateway to the system and provides access to secondary care (SC).

Data were anonymized and no informed consent was needed from participants. The Fundació Sant Joan de Déu Ethics Committee approved the study (PIC-118-18).

SAMPLE

The study included patients (<18 years old) who were prescribed a new pharmacological treatment. The most prescribed and clinically relevant pharmaceutical subgroups were included (Table 1). The prescription was considered new when there were no prescription records for the same pharmaceutical subgroup in the previous 6 months (pre-period). Consequently, the same patient could be included a maximum of two times for the same pharmaceutical subgroup. No other inclusion criteria were applied.

VARIABLES

For time-dependent variables, information recorded at the time of prescription was used.

Non-Initiation. Initiation is a time-to-event variable with a well-defined time origin (prescription) and an easily identifiable end-point (dispensing)[4]. A prescription was considered non-initiated if there was no dispensing record during the follow-up period (1-month). As a sensitivity analysis, the follow-up period was extended to 6 month.

188 **Age.** In Catalonia, patients are considered pediatric until they reach the age of 15 yo in
189 PC and 18 yo in SC. The study population was stratified into age categories according
190 to International Council for Harmonization (ICH) guidance[31] although the *Adolescents*
191 age-group was divided into 2 categories: 0–1 yo; 2–4 yo; 5–11 yo; 12–14 yo; 15–17 yo.

192 **Copayment level.** Patients were classified based on their copayment level (assigned to
193 the parent/legal guardian) for the year of prescription as defined by the Spanish
194 Government[32]: 0% (pensioner and non-pensioner, annual income up to ≈5,000€); 10%
195 (pensioner, annual income ≈5,000-100,000€); 40% (non-pensioner, annual income
196 ≈5,000-18,000€); 50% (non-pensioner, annual income 18,000€-100,000€); 60%
197 (pensioner and non-pensioner, annual income >100,000€). There is a monthly income-
198 based ceiling for pensioners (i.e., when a pensioner reaches the ceiling, the cost of
199 subsequent dispensed medications is 0€). Some drugs (such as chronic treatments) have
200 reduced contribution (10% co-payment capped at 4.26€ per prescription)[30,32]. Patients'
201 copayment level was estimated based on their contribution to the cost of the medication.

202 **Medication costs.** The proportion of medication costs assumed by the patient was
203 categorized based on the distribution of the variable (Supplementary File 2) (0€; >0 to
204 2€; >2€). The public health system (partially/totally) covers the cost of medications
205 prescribed to patients and implements policies to reduce the cost of medication
206 (Supplementary File 1). Patients with different copayment levels may contribute the
207 same (e.g., patients from different copayment groups purchasing reduced contribution
208 medications or patients who reached the monthly ceiling).

209 **Diagnoses.** Active diagnoses at the time of prescription were considered based on the
210 International Statistical Classification of Diseases and Related Health Problems (ICD-

10). The ICD-10 chapter code was used to define the category of all diagnoses, except for diabetes mellitus, behavioral and emotional disorders with onset in childhood, and asthma (Table 2) that were considered separately (based on their exact coding) due to their clinical relevance.

Other variables included were patient's sex; appointments with the PC social worker (during the study period (July 2017 – June 2018)); number of new prescriptions, visits to a PC clinician and visits to a PC nurse (the latter three variables refer to the year prior to the new prescription assessed); specialty of the prescribing clinician (pediatrician [including PC and SC], PC clinician [includes general practitioners and family physicians] or SC clinician); characteristics of the center (PC center, after hours PC center or SC center); and health area.

ANALYSIS

Analyses were conducted using Stata/MP 13.1.

The unit of analysis was the prescription. Prevalence of overall non-initiation was expressed as the proportion of new prescriptions not filled within 30 days (1-month non-initiation) and 180 days (6-month non-initiation) of the date of the prescription. Prevalence of non-initiation by pharmaceutical subgroup and age group was also estimated. When the number of new prescriptions was less than 50, prevalence in that age group was not estimated.

To identify non-initiation explanatory factors, all available variables were included in a mixed-effects logistic regression model in which level one was prescription and level two was health area, using the "melogit" command, which fits mixed-effects models for

binary and binomial responses. In this model, prescriptions were clustered within health areas. One-month non-initiation was the dependent variable. With the exception of medication cost, where the reference category was "0€" to ease interpretation, for categorical independent variables, the category with the highest sample size was used as the reference group. The strength and direction of the association were reported using adjusted Odds ratios (ORs) and 95% confidence intervals (CIs). Due to the large sample size, most explanatory factors are statistically significant at 95%. Associations were considered clinically relevant when they were statistically significant ($p<0.05$) and showed high effect size: in categorical variables (OR <0.9 or >1.1), in continuous variables (OR <0.99 or >1.01).

When no dispensing records or only reduced contribution drugs (fixed at 10%) were dispensed the year when the prescription was issued, co-payment level was missing (4.16% patients). To deal with this, when available, we assigned the level of co-payment from the previous or subsequent year (1.66% of cases). When this was not possible, we imputed the median copayment level of the patients' health area (2.5% of cases). Furthermore, 18.71% of prescriptions had no active diagnosis related to the prescription recorded at the moment of prescription (Supplementary File 2). These data were considered to be missing at random. An imputed database was generated using multivariate imputation with chained equations using all the available variables in the model.

RESULTS

SOCIODEMOGRAPHIC CHARACTERISTICS

A total of 1,539,003 new prescriptions were issued to 715,895 children, consisting of almost equal numbers of boys and girls aged 0-1 yo (8.7%), 2-4 yo (19.8%), 5-11 yo (38.8%), 12-14 yo (14.6%) and 15-17 yo (18.1%). Tables 2-4 detail the characteristics of the sample.

PREVALENCE OF NON-INITIATION

Table 1 presents the prevalence of non-initiation. The overall prevalence of 1-month non-initiation was 9.0% while the prevalence of 6-month non-initiation was slightly lower (8.5%).

By pharmaceutical subgroups (Table 1), the highest 1-month non-initiation prevalence was observed in proton pump inhibitors (PPIs) (21.5%) and benzodiazepine derivatives (19.4%), while the lowest was observed in oral antibiotics (2.6% in penicillins with extended spectrum; 3.9% in macrolides) and 3.9% in oral glucocorticoids.

Table S2.1 (Supplementary File 2) shows 1-month non-initiation prevalence by age groups.

NON-INITIATION EXPLANATORY FACTORS

Table 5 shows the non-initiation explanatory factors based on data gathered from electronic health records.

Patient-related factors: Children aged 5-11 years showed the lowest non-initiation risk while 15-17-year-olds showed the highest (OR=1.50; 95% CI 1.48; 1.53).

Socioeconomic factors: Patients who had a 10% (OR=0.45; 95% CI 0.44; 0.47), 50% (OR=0.76; 95% CI 0.75; 0.77) or 60% copayment level (OR=0.73; 95% CI 0.67; 0.80)

showed lower non-initiation odds than patients co-paying 40%, while those with a 0% copayment level (OR=5.18; 95% CI 4.16; 6.45) showed higher odds.

Therapy-related factors: Prescriptions that were free of charge were less likely to be non-initiated and patients who received a higher number of new prescriptions during the year prior to the index prescription had a lower probability of non-initiation (OR=0.92; 95% CI 0.91; 0.92).

Condition-related factors: Children suffering from diseases of the respiratory system excluding asthma (OR=0.75; 95% CI 0.75; 0.76) and diseases of the eye and adnexa; of the ear and mastoid process (OR=0.87; 95% CI 0.86; 0.88), had a lower probability of non-initiation, while those suffering from conditions due to external causes had a higher probability of non-initiation (OR=1.22; 95% CI 1.19; 1.24).

System-related factors: Prescriptions issued in a SC (OR=1.53; 95%CI 1.50; 1.55) were less likely to be initiated than those issued in a PC center, while prescriptions made by a pediatrician were more likely to be initiated than ones issued by a PC clinician (OR=1.16; 95% CI 1.15; 1.18) or a SC clinician (OR=1.55; 95% CI 1.51; 1.59).

DISCUSSION

Our study involved an extensive overall analysis of pediatric non-initiation in several medication groups showing different prevalence between them. The prevalence of non-initiation of anti-inflammatory medications was in line with previous studies[12], while the prevalence of antidepressant, antimicrobial and antiasthmatic non-initiation in other studies was almost 5 times higher[12,18–20,33]. Differences in setting (e.g., organization of

300 the healthcare system and low out-of-pocket medication cost for patients in Catalonia)
301 or study methodologies (e.g., pre-period, sample size and study length) could explain
302 these figures. Poor definition of the parameters that define adherence (initiation,
303 implementation or persistence) leads to heterogeneous adherence figures that are open
304 to interpretation[26].

305 Pediatric non-initiation in the current study showed lower rates than in adults for most
306 medication groups[10]. Parents' greater concern for their children's health may explain
307 lower non-initiation rates in this population[34,35] and, additionally, some medicines for
308 children (such as syrups) have shorter expiration dates, preventing accumulation of
309 surplus medications[36]. Finally, children's medicines are sometimes prescribed *pro re*
310 *nata (prn)* which may partially explain the high rates of non-initiation of
311 benzodiazepine derivatives in children up to 5 years old, commonly used to treat
312 feverish convulsions[37].

313 In line with studies in adults[8,11], overall non-initiation barely decreased when the
314 follow-up period was extended to 6 months and this may be due to greater
315 representation of medication for acute conditions. Non-initiation rates of chronic
316 treatments such as antipsychotics, psychoanaleptics and antidiabetics noticeably
317 diminished when the follow-up period was extended (sensitivity analysis), indicating a
318 period when caregivers/patients consider acceptance of the medication. In
319 psychoanaleptics and antipsychotics, this may be related to stigma and caregiver
320 preference for non-pharmacological interventions[38,39].

321 Fear of side-effects, preference for non-pharmacological interventions and stigma may
322 also explain the decrease in 6-month non-initiation of oral antidiabetics, which are

indicated in the pediatric population with overweight associated with hyperandrogenemia, polymicrocystic ovary syndrome, and, as an "off-label", to treat early puberty in 5- to 11-year-old girls[40,41]. In insulins, however, the decrease in non-initiation over time may be because clinicians usually provide the first unit of insulin pens. Therefore, 6-month non-initiation rates may be a more reliable prevalence measure for chronic pharmaceutical treatments.

A curvilinear relationship between age and non-initiation was observed with the higher rates of non-initiation in the youngest and oldest population groups. In the youngest, this could be influenced by the fear of exposing infants to the occasional toxic effects of medications and/or by a preference for complementary alternative medicines, which are perceived as safer[42]. Higher rates of non-initiation prevalence in adolescents, who showed similar rate of non-initiation to adults[10], may be explained by a lower perception of disease severity threat, their own beliefs about the need for medication and stigma[43].

The medication cost share was the variable with the greatest impact on non-initiation and cost of treatment has consistently been reported as a factor that can lead to non-adherence[26,32]. In line with previous studies[32], our study showed that even small co-payments were associated with increased odds of non-initiation. Patients who did not pay for their prescriptions could be those who were exempt from contributions or those who already reached their monthly cost ceiling[30]. In our data, 86.7% of free-of-charge prescriptions were issued to patients in the 0% co-payment group and 13.3% to other co-payment groups. Having controlled for the cost share, patients exempt from copayment showed the highest probability of non-initiation. In other words, although

these patients do not have to contribute to the treatment cost, they have the highest risk of non-initiation. To facilitate interpretation of these results, supplementary regression models were fitted (Supplementary File 3). When the effect of copayment on non-initiation was explored in a bivariate analysis, patients exempt from copayment showed the lowest odds of non-initiation. When this association was adjusted for medication cost assumed by the patient, the odds of non-initiation attributed to the medication cost increased and patients exempt from copayment showed the highest odds of non-initiation. We hypothesize that this occurred because the protective effect of payment exemption in this profile of patients was controlled. Patients with 0% copayment are patients with a low socioeconomic status, which may be associated with a lower educational level and a higher risk of social isolation. The association found between appointments with a social worker and the risk of non-initiation might support previous arguments. In Sweden, non-initiation was associated with socioeconomic disadvantages, in the same way as lack of trust in health care and a long-term illness[44].

Prescriptions issued by pediatricians were more likely to be initiated than those issued by PC clinicians and SC clinicians, which may be explained by the existing bond of trust with the prescribing professional[39,44,45].

As far as we know, this is the largest study to assess the prevalence of non-initiation and its determinants in the pediatric population and the first study to analyze non-initiation by not yet studied pharmaceutical subgroups, age groups, and multiple follow-up periods. It is also the first to identify multiple non-initiation explanatory factors related to age, copayment level, cost assumed by the patient, and clinician specialty.

The main strengths of this study are its representativeness and sample sizes in terms of population and medication, which improves its external validity. Moreover, the wide range of drugs studied may allow prioritization in future interventions.

LIMITATIONS

The study presents some limitations that should be considered. First, non-initiation could have been underestimated since dispensed medication may not have been consumed and, conversely, it may have been overestimated if the patient had surplus medication from previous prescriptions or when prescriptions were *prn*. Migrations could have caused an overestimation of the prevalence of 6-month non-initiation although only 0.69% of children 0-14 yo emigrated in 2019[46,47]. Second, some variables that have been described as affecting adherence, such as nationality or medication beliefs [35,48], were not available in the database. A sensitivity analysis extending the follow-up period to 6 months was conducted to quantify the possible impact of these variables. Variables related to the caregiver are very likely to influence non-initiation in the pediatric population although it should be pointed out that the children could not be linked to their caregivers in our database. Third, there could be some collinearity between co-payment level and medication cost as well as between specialty of prescribing clinician and center where the prescription was issued. Sensitivity analyses were conducted to explore the impact of excluding one of these variables at a time (Supplementary File 3) and the interpretation of results was slightly affected. Fourth, this study was performed in a specific healthcare context, so the generalizability of the results to other countries should be done with caution due to possible differences within the healthcare system and the socio-demographic context. Fifth, the variable medication

cost assumed by the patient showed different results based on how it is modeled (Supplementary File 2), therefore these results should be interpreted carefully. Finally, some data related to co-payment and diagnoses were missing and this can be understood as a consequence of the inherent limitations of working with real world data.

CONCLUSIONS

The prevalence of non-initiation of medical treatments in pediatrics varies according to patients' age and medical groups and is noticeably high in Catalonia. Non-initiation rates of chronic medications diminished significantly from 1 to 6-month follow-up. Factors related to the patient, such as age or copayment level, or to the healthcare system, such as type of prescriber or healthcare center, increase the risk of non-initiation. Results suggest that there are inequities in access to pharmacological treatments in this population that must be taken into account by healthcare planners and providers. Physicians should be alert to non-initiation of chronic treatments, emphasizing the relevance of early adherence and resolving patients' and parents' doubts at the moment of prescription. Further research should focus on understanding the root causes of non-initiation, including those related to the physician-patient relationship and the clinical and economic impact of non-initiation in the pediatric population must be explored and axes of inequalities assessed.

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Table 1. One and 6-month non-initiation prevalence by pharmaceutical subgroup; and total number and proportion of new prescriptions by pharmaceutical subgroup, between July 2017 and June 2018 in Catalonia.

		Prevalence of non-initiation (%)		**Prescriptions**	
Pharmaceutical subgroups	**ATC code**	**1-month**	**6-months**	**N[a]**	**Proportion of total prescriptions (%)**
Drugs used in diabetes					
Insulins and analogues for injection (fast-acting)	A10AB	5.59	2.06	340	0.02
Insulins and analogues for injection (long-acting)	A10AE	7.77	3.49	373	0.02
Biguanides	A10BA	16.95	7.46	295	0.02
Psycholeptics and psychoanaleptics					
Other antipsychotics	N05AX	11.15	6.61	2,843	0.18
Benzodiazepine derivatives	N05BA	19.35	18.22	6,268	0.41
Non-selective monoamine reuptake inhibitors	N06AA	12.90	9.11	527	0.03
Selective serotonin reuptake inhibitors	N06AB	8.70	5.01	3,035	0.20
Other antidepressants	N06AX	10.45	8.86	440	0.03
Centrally acting sympathomimetics	N06BA	9.72	4.63	5,081	0.33
Endocrine therapy					
Gonadotropin releasing hormone analogues	L02AE	5.85	3.31	393	0.03
Drugs for obstructive airway diseases					
Selective beta-2-adrenoreceptor agonists	R03AC	5.82	4.90	106,257	6.90
Symptomatic treatments					
Proton pump inhibitors	A02BC	21.46	21.12	14,509	0.94
Propionic acid derivatives	M01AE	10.15	9.50	322,026	20.92
Anilides	N02BE	11.93	11.39	253,133	16.45
Diphenylmethane derivatives	N05BB	15.10	14.82	36,576	2.38
Corticosteroids[b]	R01AD	13.24	10.95	42,173	2.74
Substituted alkylamines	R06AB	13.45	13.14	27,525	1.79

Piperazine derivatives	R06AE	15.46	13.88	29,952	1.95
Other antihistamines for systemic use	R06AX	11.46	9.98	63,230	4.11
Other antiallergics	S01GX	11.55	10.34	18,713	1.22
Corticosteroids for systemic use					
Oral glucocorticoids	H02AB	3.87	3.80	101,416	6.59
Antibacterials for systemic use					
Penicillins with extended spectrum	J01CA	2.56	2.54	200,359	13.02
Macrolides	J01FA	3.87	3.85	56,642	3.68
Antiinfectives and corticosteroids by other administration routes					
Imidazole and triazole derivatives	D01AC	8.11	7.96	40,188	2.61
Other antifungals for topical use	D01AE	11.43	10.43	8,833	0.57
Other antibiotics for topical use	D06AX	10.74	10.73	67,651	4.40
Corticosteroids, potent (group III)	D07AC	11.10	10.75	54,772	3.56
Ophthalmic antibiotics	S01AA	8.25	8.18	75,453	4.90
Overall		**9.01**	**8.46**	**1,539,003**	**100**

[a] *"N prescriptions" is the denominator used to estimate the 1and 6-month prevalence of non-initiation.*
[b] *Decongestants and other nasal preparations for topical use.*

Table 2. Active diagnoses (ICD-10) at the moment of prescription stratified by patient and prescription-level, between July 2017 and June 2018 in Catalonia.

Diagnoses (ICD-10 code groups)	**Patient-level (N = 715,895)**		**Prescription-level (N = 1,539,003)**	
	N	**%**	**N**	**%**
Certain infectious and parasitic diseases (A-B)	164,338	22.96	295,024	19.17
Neoplasms (C-D48)	34,128	4.77	74,068	4.81
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	20,030	2.80	43,438	2.82
Diabetes mellitus (E10 – E14)	1,307	0.18	2,673	0.17
Other endocrine, nutritional and metabolic diseases (E)	73,233	10.23	152,554	9.91
Behavioral and emotional disorders with onset in childhood (F90, F91, F93-F95)	39,775	5.56	80,254	5.21
Other mental and behavioral disorders (F)	75,912	10.60	157,187	10.21
Diseases of the nervous system (G)	20,440	2.86	43,059	2.80
Diseases of the eye and adnexa; of the ear and mastoid process (H)	271,281	37.89	500,895	32.55
Diseases of the circulatory system (I)	110,213	15.40	230,795	15.00
Asthma (J44-J46, J82)	44,039	6.15	103,925	6.75
Other diseases of the respiratory system (J)	447,194	62.47	890,962	57.89
Diseases of the digestive system (K)	307,781	42.99	596,489	38.76
Diseases of the skin and subcutaneous tissue (L)	354,843	49.57	690,427	44.86
Diseases of the musculoskeletal system and connective tissue (M)	130,775	18.27	252,301	16.39
Diseases of the genitourinary system (N)	61,282	8.56	121,441	7.89
Pregnancy, childbirth and the puerperium (O)	1,679	0.23	3,394	0.22
Certain conditions originating in the perinatal period (P)	25,905	3.62	56,797	3.69
Congenital malformations, deformations and chromosomal abnormalities (Q)	89,335	12.48	197,586	12.84
Symptoms, signs and abnormal clinical and laboratory findings, not	370,847	51.80	698,404	45.38

elsewhere classified (R)				
External causes (S, T, V, X, Y)[a]	79,449	11.10	139,263	9.05

[a]*Including injury, poisoning and certain other consequences of external causes.*

Table 3. Sample demographic characteristics stratified by patient and prescription-level, between July 2017 and June 2018 in Catalonia.

Demographic characteristics of the sample	**Patient-level (N = 715,895)**		**Prescription-level (N = 1,539,003)**	
	N/mean	**%/SD**	**N/mean**	**%/SD**
Sex (female), N (%)	345,795	48.30	735,236	47.77
Age at the moment of the new prescription*, mean (±SD)	9.14	5.28	8.60	5.27
Age groups*, N (%)				
0-1 year old	62,192	8.69	138,308	8.99
2-4 years old	141,615	19.78	371,369	24.13
5-11 years old	277,781	38.80	579,648	37.66
12-14 years old	104,725	14.63	200,229	13.01
15-17 years old	129,582	18.10	249,449	16.21
Copayment level (patient profile)*, N (%)				
0% (pensioner and non-pensioner, annual income up to ≈5,000€ per year)	35,188	4.92	82,364	5.35
10% (pensioner, annual income ≈5,000€-100,000€)[a]	28,712	4.01	63,045	4.10
40% (non-pensioner, annual income ≈5,000€-18,000€)	426,922	59.63	915,046	59.46
50% (non-pensioner, annual income 18,000€-100,000€)	221,480	30.94	471,948	30.67
60% (pensioner and non-pensioner, annual income >100,000€)	3,593	0.50	6,600	0.43
Medication cost assumed by the patient (range 0–174.93)[b], N (%)	NA	NA		
0€			94,879	6.16
>0 to 2€			1,166,418	75.79
>2€			277,706	18.04
Number of new prescriptions* (range 0–14)[c], mean (±SD)	NA	NA	1.64	1.68

Abbreviations: NA: not applicable, as these only refer to patient or prescription characteristics; PC: primary care; SC: secondary care.
** Information recorded at the time of prescription was used for time-dependent variables.*
[a] Pensioners up to 100,000 €/annual income have a ceiling cap based on annual income.
[b] The amount (in €) to be paid by the patient in the pharmacy to obtain the prescribed medication.
[c] New prescriptions (excluding the index prescription) during the year prior to the new prescription assessed.

Table 4. Descriptive variables related to healthcare services stratified by patient and prescription-level, between July 2017 and June 2018 in Catalonia.

	Patient-level (N = 715,895)		**Prescription-level (N = 1,539,003)**	
	N/mean	**%/SD**	**N/mean**	**%/SD**
Use of PC healthcare services made by the patient*				
Visits to a clinician, mean (±SD)[a]	NA	NA	6.08	6.02
Visits to a nurse, mean (±SD)[a]	NA	NA	3.00	3.63
Appointments with a social worker, N (%)[b]	11,633	1.62	27,578	1.79
Specialty of the prescribing clinician, N (%)	NA	NA		
Pediatrician [including PC and SC]			907,364	58.96
PC clinician [includes general practitioners and family physicians]			560,277	36.41
SC clinician			71,362	4.64
Characteristics of the center where the prescription was issued, N (%)	NA	NA		
PC center			1,137,032	73.88
After hours PC center[c]			163,486	10.62
SC center			238,485	15.50

Abbreviations: NA: not applicable, as these only refer to patient or prescription characteristics; PC: primary care; SC: secondary care.
** Information recorded at the time of prescription was used for time-dependent variables.*
[a] During the year prior to the new prescription assessed.
[b] During the study period (July 2017 – June 2018).
[c] This group includes only those specific emergency ambulatory care centers: Centre d'Urgències d'Atenció Primària (CUAP), Atenció Continuada i de les Urgències de base Territorial (ACUT), Centre d'Atenció Continuada (CAC), Punts d'Atenció Continuada (PAC) and dispositius d'atenció urgent aïllats o de muntanya. For the other two types of centers (PC or SC) we cannot differentiate whether the visit was scheduled or urgent/unscheduled.

Table 5. Explanatory factors of 1-month medication non-initiation in the pediatric population based on the multilevel multivariate regression model: Odds ratios (ORs) and 95% confidence intervals.

	OR	**95% CI**
Female sex (vs. male)	1.01	0.99; 1.02
Age groups		
0-1 year old	**1.29**	**1.26; 1.32**
2-4 years old	**1.29**	**1.27; 1.31**
5-11 years old	Ref.	
12-14 years old	**1.21**	**1.19; 1.23**
15-17 years old	**1.50**	**1.48; 1.53**
Copayment level (patient profile)*		
0% (pensioner and non-pensioner, annual income up to ≈5,000€)	**5.18**	**4.16; 6.45**
10% (pensioner, annual income ≈5,000€-100,000€)[a]	**0.45**	**0.44; 0.47**
40% (non-pensioner, annual income ≈5,000€-18,000€)	Ref.	
50% (non-pensioner, annual income 18,000€-100,000€)	**0.76**	**0.75; 0.77**
60% (pensioner and non-pensioner, annual income >100,000€)	**0.73**	**0.67; 0.80**
Medication cost assumed by the patient[b]		
0€	Ref.	
>0 to 2€	**16.11**	**12.97; 20,00**
>2€	**11.71**	**9.43; 14.54**
Number of new prescriptions (continuous)[c]	**0.92**	**0.91; 0.92**
Active diagnoses (ICD-10) at the moment of prescription (vs. not active)		
Certain infectious and parasitic diseases (A-B)	1.03	1.01; 1.04
Neoplasms (C-D48)	0.97	0.94; 0.99
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	0.93	0.90; 0.97
Diabetes mellitus (E10 – E14)	0.96	0.84; 1.09
Other endocrine, nutritional and metabolic diseases (E)	0.92	0.90; 0.94

Behavioral and emotional disorders with onset in childhood (F90, F91, F93-F95)	1.02	0.99; 1.04
Other mental and behavioral disorders (F)	0.96	0.94; 0.98
Diseases of the nervous system (G)	1.01	0.97; 1.04
Diseases of the eye and adnexa; of the ear and mastoid process (H)	**0.87**	**0.86; 0.88**
Diseases of the circulatory system (I)	1.02	1.00; 1.04
Asthma (J44-J46, J82)	1.02	1.00; 1.05
Other diseases of the respiratory system (J)	**0.75**	**0.75; 0.76**
Diseases of the digestive system (K)	0.94	0.93; 0.95
Diseases of the skin and subcutaneous tissue (L)	1.01	1.00; 1.02
Diseases of the musculoskeletal system and connective tissue (M)	1.00	0.98; 1.01
Diseases of the genitourinary system (N)	0.98	0.96; 1.01
Pregnancy, childbirth and the puerperium (O)	1.00	0.89; 1.12
Certain conditions originating in the perinatal period (P)	0.95	0.93; 0.98
Congenital malformations. deformations and chromosomal abnormalities (Q)	0.97	0.96; 0.99
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R)	1.00	0.98; 1.01
External causes (S, T, V, X, Y)[d]	**1.22**	**1.19; 1.24**
Use of PC healthcare services made by the patient		
Appointments with a PC social worker (vs. no attendance)[e]	1.05	1.00; 1.09
Visits to a PC clinician (continuous)[c]	0.99	0.99; 0.99
Visits to a PC nurse (continuous)[c]	1.00	1.00; 1.01
Specialty of the prescribing clinician		
Pediatrician [including PC and SC]	Ref.	
PC clinician [includes general practitioners and family physicians]	**1.16**	**1.15; 1.18**
SC clinician	**1.55**	**1.51; 1.59**
Characteristics of the center		
PC center	Ref.	

After hours PC center[f]	1.04	1.02; 1.06
SC center	**1.53**	**1.50; 1.55**

Abbreviations: (PC) primary care; (SC) secondary care
Prescription was the unit of analysis.
***Bold numbers** indicate a statistically significant (p<0.05) and clinically significant association between the independent variable and 1-month non-initiation: in categorical variables (OR <0.9 or >1.1), in continuous variables (OR <0.99 or >1.01).*
** Information recorded at the time of prescription was used for time-dependent variables.*
[a] *Pensioners up to 100,000€/annual income have a ceiling cap based on annual income.*
[b] *The amount (in €) to be paid by the patient in the pharmacy to obtain the prescribed medication.*
[c] *New prescriptions (excluding the index prescription) during the year prior to the new prescription assessed.*
[d] *Including injury, poisoning and certain other consequences of external causes.*
[e] *During the study period (July 2017 – June 2018).*
[f] *This group includes only those specific emergency ambulatory care centers: Centre d'Urgències d'Atenció Primària (CUAP), Atenció Continuada i de les Urgències de base Territorial (ACUT), Centre d'Atenció Continuada (CAC), Punts d'Atenció Continuada (PAC) and dispositius d'atenció urgent aïllats o de muntanya. For the other two types of centers (PC or SC) we cannot differentiate whether the visit was scheduled or urgent/unscheduled*