

## **Title**

A retrospective and prospective 12 month observational study of the socioeconomic burden of moderate to severe Irritable Bowel Syndrome with Constipation in Spain

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## **Abstract**

The socioeconomic burden of irritable bowel syndrome with constipation (IBS-C) has never been formally assessed in Spain.

This 12 month (6-month retrospective and prospective periods) observational, multicentre study assessed the burden of moderate to severe IBS-C in Spain. Patients were included if they had been diagnosed with IBS-C (Rome III criteria) within the last 5 years and had moderate-to-severe IBS-C (IBS Symptom Severity Scale score  $\geq 175$ ) severity at inclusion. The primary objective was to assess the direct cost to the Spanish healthcare system (HS).

A total of 112 patients were included, 64 (57%) of which had severe IBS-C at inclusion. At baseline, a high degree of patients reported abdominal pain and distention (80% in both cases). Patient quality of life (QoL), measured by the IBS-C QoL and EQ-5D instruments, was found to be impaired with a mean score of 59 and 57 (0-100, worst-best), respectively. Over the 6-month prospective period the mean IBS severity, measured using the IBS-Symptom Severity Scale (IBS-SSS) showed some improvement (315 to 234 [0-500, best-worst]). During the year, 80% of patients used prescription drugs for IBS-C was substantial, being laxatives the most frequently-prescribed (63%). The direct cost to the HS was €1,067, and to the patient was €568 per year. The total direct cost for moderate to severe IBS-C was €1,635.

Almost all patients reported continued IBS-C symptoms despite over three-quarters taking medication to treat their IBS-C; overall healthcare resource use and direct costs were asymmetric with a small subset of patients consuming the most resources.

### **Keywords:**

IBS, IBS-C, direct costs, healthcare resource utilisation, Spain.

## Introduction

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder with an estimated prevalence of 12% in Spain and between 5% - 20% worldwide.<sup>1-3</sup> It is characterised by recurrent symptoms of abdominal pain accompanied by altered bowel function.<sup>4</sup> Subdivision of IBS by the Rome III criteria lists four subtypes: IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), mixed IBS (IBS-M), and unsubtyped IBS (IBS-U).<sup>5</sup> Disease activity can vary over time, with periods of high disease activity followed by periods of remission.<sup>6</sup> Similarly, symptoms can change over time and almost half (40%) of IBS patients can transition from one subtype to another.<sup>7</sup>

Irritable bowel syndrome has been shown to negatively impact quality of life (QoL), for example, affecting sleep, diet, personal/work relationships, and sexual function.<sup>5,8</sup> The more severe end of the spectrum, moderate to severe IBS, is thought to account for approximately 60% of all IBS cases and previous studies have shown a substantial economic burden to society through direct medical costs and indirect societal costs.<sup>9-11</sup>

According to the Rome III criteria, the diagnostic criteria for IBS is recurrent abdominal pain or discomfort present for at least three days/month in the last three months accompanied by two or more of the following: improvement with defecation, onset associated with a change in stool frequency, or a change in stool form.<sup>12</sup> For IBS-C, these characteristics are accompanied by  $\geq 25\%$  of bowel movements being hard or lumpy stools and  $< 25\%$  of bowel movements being loose or watery stools. The IBS-C subtype is characterised by constipation, and commonly underdiagnosed due to its similarity to chronic constipation as it shares similar defecation patterns accompanied by occasional abdominal discomfort.<sup>13</sup> Nevertheless, it is thought that IBS-C affects about 30% of the IBS population.

Some studies suggest that the current burden of illness for IBS is quite significant.<sup>8,14-16</sup> Traditional therapies including laxatives, prokinetics, antispasmodics, and bulking agents (such as dietary fibres) are useful for treating constipation in some patients, however, their use is limited due to low overall efficacy and tolerability that is compounded by the fact that as individual treatments they do not treat all the key IBS-C symptoms.<sup>17,18</sup> Thus, there remains a clear need for more effective therapeutic agents for the treatment of IBS-

C. To date, linaclotide - a guanylate cyclase-C agonist, is the only licensed pharmacological treatment in Europe for the treatment of IBS-C.<sup>19</sup>

Therefore, the aim of this study was to describe the socioeconomic burden of moderate to severe IBS-C. Here we report the quality of life of patients with IBS-C, the evolution of IBS-C severity over time, and the direct economic costs of IBS-C in Spain.

## **Patients and Methods**

The study was an observational, 12 month, multicentre study with 6-month retrospective and 6-month prospective components conducted in 6 European countries. Here we report the results of the Spanish population. Patients were included in the study if they were  $\geq 18$  years of age, diagnosed with IBS-C in the last 5 years using the Rome III criteria, and had moderate to severe IBS-C at inclusion: defined as an Irritable Bowel Syndrome Symptom Severity Scale (IBS-SSS) score  $\geq 175$ . The IBS-SSS score was obtained by the sum of the five equally-weighted questions related to pain, distention, bowel dysfunction, and general well-being; each question was scored out of 100 and moderate severity is defined as an overall score of  $\geq 175$ -300; severe severity:  $>300$ .<sup>20</sup> Patients were excluded if they had participated in a clinical trial involving an experimental IBS-C treatment in the six months prior to starting the observational period, or they had an acute or chronic condition that, in the investigator's opinion, would impact the patient's ability to complete the study. This study was conducted in accordance with the Declaration of Helsinki as well as in compliance with ICH GCP guidelines. All ethics committees approved the trial protocol and its amendments.

Patients were screened using medical records in primary and specialist care. Baseline and retrospective data of patients enrolled in the study were obtained from patient interviews and patient medical records, respectively. Demographic, clinical, and QoL data were collected at baseline. Assessment of QoL was performed using the IBS-QoL<sup>21</sup> and EQ-5D<sup>22</sup> instruments. The IBS-QoL included an overall score and eight subscale scores, with 0 indicating the worst QoL and 100 indicating the highest possible QoL. The EQ-5D was a generic measure of health status and consisted of two parts. The first part consisted of five categorical dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; these were scored on a 3-point Likert scale. The second part consisted

of a visual analogue scale (VAS) where 0 indicated the worst health state and 100 indicated the best health state.

Symptom severity was collected using the IBS-SSS at baseline, 3, and 6 months. Healthcare resource utilisation (HRU) data related to IBS-C (medical consultations, hospitalisations, diagnostic tests, therapies, management of adverse reactions) were collected using a questionnaire (specifying whether the costs were public or private). A maximum of 6 months' direct HRU costs were collected at baseline retrospectively. Prospective HRU data were collected during routine follow-up at 3 months ( $\pm 0.5$  months) and 6 months ( $\pm 1$  month) /Early Termination. All HRU data were calculated in patients that used the resource.

Direct costs were calculated for the Spanish healthcare system (HS) and the patient's perspective. Consultations, physician visits, and diagnostic tests were estimated from the Listados de Boletines Oficiales de tarifas de Comunidades Autónomas (2005-2011) Hospitalisation costs were estimated from Grupos Relacionados con el Diagnóstico (GRD/DRG) correspondientes and estadísticas. Ministerio de Sanidad, Servicios Sociales e Igualdad (Tarifa AP25, 2008), and Listados de Boletines Oficiales de tarifas de Comunidades Autónomas (2005-2011). Drug costs were estimated from the Ministerio de Sanidad, Servicios Sociales e Igualdad (Nomenclator Digitalis-Integra) and the Consejo General de Colegios Oficiales de Farmacéuticos (Bot Plus, Portalfarma). For the patient's perspective, only the sum of non-prescription medication, complementary therapies, the percentage of HS medications, consultations, hospitalisations, and diagnostic procedures paid for by the patient in each country were taken into account; costs of private consultations and diagnostic procedures were not included.

Exploratory analyses were performed and no confirmatory statistical tests were performed. Demographics, baseline characteristics, HRU characteristics and productivity losses were summarised using descriptive statistics based on non-missing observations. Costs were calculated as a mean with 95% confidence interval (calculated using 1000 bootstrap samples).

The retrospective, prospective, and combined data periods were analysed separately. The separate analyses were then compared to determine whether there was any statistical difference between them. The data presented here is derived from the combined analysis.

## Results

A total of 112 patients were enrolled in the study from 4 primary care centres and 12 specialist centres in Spain (Table 1). Over the six month prospective follow up period there were 7 (6.3%) discontinuations; 6 (5.4%) lost to follow-up and 1 (0.9%) withdrawal due to serious illness.

### *Demographic, lifestyle and clinical characteristics at baseline*

From the 112 patients that were enrolled in the study, 25 (22.3%) were recruited from GP centres (all public centres), and 87 (77.7%) were recruited from specialist centres (59 [52.7%] from public centres). Baseline patient demographics are shown in Table 1. The average time since IBS-C diagnosis was 2.3 years and patients suffered from IBS-C symptoms for around 10 years. Almost one in five patients had undergone a prior appendectomy/cholecystectomy, and almost one quarter of the total patients had some other form of abdominal surgery.

### *IBS-C symptoms and quality of life at baseline*

At baseline almost all patients (96.4%) reported current IBS symptoms (Table 2). Constipation, abdominal pain, and abdominal distention were the most frequently reported symptoms, affecting over three quarters of all patients. Over half of all patients also reported suffering from bloating and abdominal discomfort. Using the IBS-QoL instrument, the most affected domains were food avoidance and health worry. The overall impact of IBS-C on QoL was similar for the IBS-QoL and EQ-5D questionnaires, 59.0 and 56.8 respectively. In addition, over three quarters of patients reporting moderate-to-severe pain/discomfort and over half reported moderate-to-severe anxiety/depression using the EQ-5D categorical dimensions.

### *Evolution of severity using the IBS-SSS questionnaire*

The severity of the patients IBS-C was assessed three times over the prospective period at three month intervals. The number of patients reporting current abdominal pain and current abdominal distention decreased from 95.5% and 92.9% (respectively) at baseline to 85.6% at 6 months for both categories (Table 3). Using the IBS-SSS VAS the severity of abdominal pain showed the least reduction over 6 months, from mean  $\pm$  SD  $56.5 \pm 21.4$

at baseline to  $45.5 \pm 20.4$  at 6 months. By contrast the number of days with abdominal pain and the severity of abdominal pain exhibited the largest reduction, from  $5.7 \pm 2.8$  days and  $65.0 \pm 23.6$  to  $4.4 \pm 2.6$  days and  $50.3 \pm 21.7$ , respectively. Overall, the total score was observed to decrease by 26%, from  $515.4 \pm 82.2$  to  $233.9 \pm 97.8$ , thus the mean severity decreased from “severe” at baseline to “moderate” at 6 months. Categorically, this observation is demonstrated by the overall reduction in patients with severe IBS-C severity – from 57.1% of patients at baseline to 20.2% of patients at 6 months. By contrast, both the number of patients with moderate and mild severity at baseline and 6 months increased from 42.0% to 53.8% and 0.0% to 21.2%, respectively.

### *Medication use*

Overall, 84.8% of patients took some form of prescription medication over the 12 months (Table 4). Almost four out of five patients (79.5%) took prescription medication to treat their IBS-C whereas under half (42.0%) of all patients took prescription medication to treat another disease. The most frequently prescribed medication class for IBS-C was laxatives, which were prescribed to almost two thirds of all patients. Antispasmodics and prokinetics were the second and third most prescribed medication classes at 34.8% and 22.3% of all patients, respectively. In terms of individual medications, the most frequently prescribed medication was plantago ovata, followed by otilonium bromide, and macrogol plus electrolytes. A high proportion of patients also took some form of non-prescription drug or complementary therapy. Non-prescription drugs were taken by over half of the study population whereas almost a third sought complementary therapies.

### *Direct cost of IBS-C*

The direct cost of IBS-C was estimated for the HS and for the patient (Table 5). For the HS the largest cost drivers were hospitalisations and medical consultations, which accounted for 50.8% and 23.3% of the total costs, respectively. By contrast, pharmacological medications and complementary therapies were the largest drivers for costs to the patients, at 81.2% and 18.7% of the total (€567.6), respectively. Overall, pharmacological medications and hospitalisations accounted for 35.3% and 33.1% of the total direct costs. The total cost of moderate to severe IBS-C included €1,635 of direct costs, with patients paying 34.7% of these costs (**Fout! Verwijzingsbron niet**



gevonden.). A comparison of retrospective and prospective data revealed no significant differences between the retrospective and prospective periods.

## Discussion

This is the first study to directly evaluate the socioeconomic impact of moderate to severe IBS-C in Spain. As defined by the Rome III criteria, a positive diagnosis requires IBS-C symptoms to be present for three days per month every three months. During enrolment we observed that almost all patients were currently reporting one or more IBS-C symptom, thus indicating that more severe patients have a high symptom frequency. In terms of QoL, moderate to severe IBS-C patients reported a greater overall QoL impairment compared to studies of IBS patients of all subtypes and severities.<sup>8,16,23</sup> Studies that predominantly included moderate or severe IBS patients showed the largest similarity in overall QoL score.<sup>24-26</sup> Assessment of the individual IBS-QoL instrument questions reflected previous observations that the largest impairments in QoL were manifested in terms of dietary restrictions and concern about health.<sup>8,16,23-25</sup> Similar to the IBS-QoL, the mean score in the EQ-5D VAS was at the lower end of that previously reported for IBS patients (55.3-61.4).<sup>8,16,27</sup> For the categorical items, similar to the aforementioned studies, few patients reported problems with self-care. Similarly, the most frequently reported problems were pain/discomfort and anxiety/depression.<sup>27</sup> Combined with the high degree of health worry from the IBS-QoL instrument, the high proportion of patients reporting anxiety or depression provides support to the disorder having an important psychological impact.

At baseline, the mean IBS-SSS score indicated a great severity with an interference with life in general and a dissatisfaction with bowel habits being the most severely affected categories; an observation reflected by the categorical scores from an all-subtype IBS study with a similar overall IBS-SSS score.<sup>28</sup> Over follow-up, improvements in IBS-C severity were similar to previous studies.<sup>29,30</sup> The most likely reason for improvement without a specific change in intervention reflects a regression toward the mean and the waxing and waning nature of the disorder.

Prescription drug use was also high for moderate-to-severe IBS-C patients. Surprisingly, IBS-C related medication use was only slightly higher than that reported for moderate to severe all-subtype IBS patients, and yet marginally lower than that reported for IBS

patients of all subtypes and severities.<sup>24</sup> Non-prescription drugs were also taken by over half of the patients and an additional third sought complementary therapies, thus suggesting dissatisfaction with current prescription medications.

The largest cost driver for the HS was hospitalisations/ER visits, which was two-fold above the second cost driver – medical consultations – and over three-fold above other costs. Hospitalisations account for 50% of HS costs, approximately two-fold higher than those previously reported for mixed-severity/all-subtype French IBS patients.<sup>14</sup> Thus, this suggests that moderate-to-severe IBS-C patients require more inpatient care compared to all-severity patients, however, further comparisons from other countries will be necessary to verify this observation.

Costs to the patient were lower, at approximately half the HS' direct costs. The largest direct costs paid by the patient were medication costs (81.2%), followed by complementary therapies (18.7%). Approximately two-thirds of the total direct costs for IBS-C in Spain were attributable to the HS, with the remaining third being attributable to the patient. The largest drivers of total direct costs for IBS-C in moderate-to-severe patients were medication costs (35.3%), hospitalisations/ER visits (33.1%), and consultation costs (15.2%). Overall, the costs for hospitalisations/ER visits accounted for a larger proportion of costs than previously reported for mixed-severity IBS/IBS-C patients.<sup>3,14,15</sup> It is worth noting that the proportion of overall costs attributable to each cost component varied widely between studies and are most likely explained by both the differences in therapeutic management and in reimbursement policies.

In comparison to previous European studies for IBS patients across all severities costs related to moderate-severe patients shown here were substantially higher.<sup>3,11,14-16</sup>

The main limitations of this study were the possibility of healthcare resource underestimation due to approximately three quarters of patients being recruited from specialist care centres. Cost estimations may also be underestimated due to the exclusion of private consultation and diagnostic procedure costs. Furthermore, the partially retrospective nature of the study may be associated with some recall bias.

## **Conclusion**

In this study we observed a high socioeconomic impact of moderate to severe IBS-C in Spain. Despite over three-quarters of patients taking medication to treat their IBS-C, almost all patients reported continued IBS-C symptoms. This negatively impacted QoL with a large percentage of patients reporting pain/discomfort and anxiety/depression. The variety of medications prescribed to patients, in combination with a high degree of non-prescription medication and complementary therapy use, suggest that patients are not controlled with currently available therapeutic medications. From an economic perspective, the overall direct cost was highly asymmetrical with few patients consuming a large proportion of healthcare resources. Together, poor QoL and high resource use demonstrates the high socioeconomic cost of this chronic functional bowel disorder.

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### *Declaration of personal interests:*

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### *Declaration of author contributions:*

F. Mearin was the coordinating investigator in Spain and J. Tack was the lead coordinator of the study. AM. Caballero, J. Serra, C. Brotons Cuixart, A. Tantiña, E. Fort-Martorell, F. Martínez-Cerezo, A. Perelló, G. Sánchez-Antolín, E. Rey, R. Angós Musgo, R. Berdier, B. Gómez-Rodríguez, P. Clavé, M. Garcia-Alonso, and P. Torán-Monserrat contributed to clinical data collection. All authors contributed to the creation of the manuscript and all authors revised and approved the final version of the manuscript.

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## TABLES

Table 1: Patient Demographics

	<i>N</i>	<i>112</i>
Age (years), mean (SD)		46.8 (13.7)
Female, n (%)		96 (85.7)
Highest level of education, n (%)		
	None	1 (0.9)
	Lower education	25 (22.3)
	Intermediate education	56 (50.0)
	Higher education	30 (26.8)
Level of physical exercise*, n (%)		
	Low	67 (59.8)
	Intermediate	33 (29.5)
	High	12 (10.7)
Consumes alcohol, n (%)		22 (19.6)
Current smoker, n (%)		26 (23.2)
Patients who follow a diet, n (%)		48 (42.9)
Type of diet, n (%)		
	Rich in fibre	27 (24.1)
	Hypocaloric	10 (8.9)
	Low sodium	9 (8.0)
	Low carbohydrate	7 (6.3)
	Low in fibre	4 (3.6)
	Other	6 (5.4)
Time since IBS-C diagnosis (years), mean (SD)		2.3 (2.8)
Symptom duration (years) , mean (SD)		9.6 (9.9)
GI clinical history, n (%)		
	Proctology Problems	48 (42.9)
	Cathartic colon or other	13 (11.6)
	Diverticulitis or chronic condition associated with abdominal pain	11 (9.8)
	Faecal impaction that required hospitalisation	11 (9.8)
	Peptic ulcer disease	9 (8.0)
	Dyspepsia	4 (3.6)
	Diseases or condition associated with constipation	4 (3.6)
	Other GI diseases <sup>†</sup>	22 (19.6)
Previous GI surgery, n (%)		
	Appendectomy/cholecystectomy	20 (17.9)
	Other abdominal surgery	27 (24.1)

\*Low level: Sports activities 0-1 times a week/ walk less than ½ hour per day; Medium level: Sports activities 2-3 times per week/ walk at least ½ hour per day; High level: sports activities at least 4 times per week. <sup>†</sup>Cumulative value of GI diseases affecting <3.6% of the study population. SD: standard deviation; GI: gastrointestinal.



Table 2: IBS-C symptoms and quality of life at baseline

	<i>N</i>	<i>112</i>
IBS-C symptoms questionnaire, n (%)		
Any IBS-C symptom	108 (96.4)	
Constipation	94 (83.9)	
Abdominal pain	89 (79.5)	
Abdominal distention	89 (79.5)	
Bloating	66 (58.9)	
Abdominal discomfort	65 (58.0)	
Straining	30 (26.8)	
Swollen stomach	29 (25.9)	
Diarrhoea	13 (11.6)	
Other*	4 (3.6)	
IBS-QoL questionnaire score, mean (SD) <sup>†</sup>		
Food Avoidance	39.6 (24.2)	
Health Worry	45.4 (26.9)	
Dysphoria	56.5 (25.8)	
Interference with Activity	59.1 (23.2)	
Body Image	61.1 (23.8)	
Social Reaction	68.9 (27.8)	
Sexual concern	73.5 (32.9)	
Relationships	76.5 (24.4)	
Overall	59.0 (21.2)	
Number of patients with impairment in EQ-5D categorical domains, n (%)		
Mobility	20 (17.9)	
Self-care	4 (3.6)	
Usual activities	34 (30.4)	
Pain/discomfort	96 (85.7)	
Anxiety/Depression	70 (62.5)	
EQ-5D total score, mean (SD) <sup>†</sup>	56.8 (20.9)	

\*Cumulative value of symptoms affecting <3.6% of the study population. <sup>†</sup>Scale: 0-100 worst to best. QoL: quality of life; EQ-5D: EuroQol 5 dimension questionnaire; SD: standard deviation.

Table 3: Evolution of IBS-C severity

	<i>N</i>	Baseline <i>112</i>	Visit 2 <i>108</i>	Visit 3 <i>104</i>
IBS-SSS categorical item scores, n (%)				
Current abdominal pain		107 (95.5)	89 (82.4)	89 (85.6)
Current abdominal distention		104 (92.9)	91 (84.3)	89 (85.6)
IBS-SSS VAS and overall scores, mean (SD)				
Severity of abdominal pain <sup>*1</sup>		56.5 (21.4)	47.7 (20.1)	45.5 (20.4)
Number of days with abdominal pain <sup>†2</sup>		5.7 (2.8)	4.8 (2.8)	4.4 (2.6)
Severity of abdominal distention <sup>*3</sup>		65.0 (23.6)	55.7 (22.3)	50.3 (21.7)
Dissatisfaction with bowel habits <sup>*</sup>		77.9 (19.6)	60.8 (22.0)	60.6 (22.8)
Interference with life in general <sup>*</sup>		71.4 (21.0)	59.4 (21.8)	56.3 (23.3)
IBS-SSS total score <sup>‡</sup>		315.4 (82.2)	240.4 (99.3)	233.9 (97.8)
Categorical severity of IBS-C (IBS-SSS), n (%)				
Mild (<175)		0 (0)	18 (16.7)	22 (21.2)
Moderate (175≤300)		47 (42.0)	54 (50.0)	56 (53.8)
Severe (>300)		64 (57.1)	30 (27.8)	21 (20.2)

\*0-100; best to worst. †in every 10 days. ‡0-500; best to worst. <sup>1</sup>N=99/81/87. <sup>2</sup>N=107/85/84. <sup>3</sup>N=103/90/89. IBS-SSS: IBS-symptom severity scale; VAS: visual analogue scale; SD: standard deviation.

Table 4: Medication use over 12 months

	<i>N</i>	<i>112</i>
Any prescription drug, n (%)		95 (84.8)
IBS-C prescription drug, n (%)		89 (79.5)
Prescription drug for other diseases, n (%)		47 (42.0)
IBS-C prescription medication group, n (%)		
	Laxatives	70 (62.5)
	Antispasmodics	39 (34.8)
	Prokinetics	25 (22.3)
	Antidepressants	4 (3.6)
	Analgesics	3 (2.7)
	Other*	10 (8.9)
Individual IBS-C prescription drugs n (%)		
	Plantago ovata	33 (34.7)
	Otilonium bromide	21 (22.1)
	Macrogol plus electrolytes	12 (12.6)
	Cinitapride tartrate	9 (9.5)
	Magnesium hydroxide	8 (8.4)
	Mebeverine	8 (8.4)
	Lactulose	6 (6.3)
	Macrogol	5 (5.3)
	Pinaverium bromide	5 (5.3)
	Agiolax	4 (4.2)
	Bisacodyl	4 (4.2)
	Domperidone	4 (4.2)
	Flatoril	4 (4.2)
	Hyoscine butylbromide	4 (4.2)
	Mebeverine hydrochloride	4 (4.2)
	Prucalopride succinate	4 (4.2)
	Other†	50 (54.2)
Non-prescription drugs for IBS-C, n (%)		63 (56.3)
Complementary therapies, n (%)		33 (29.5)

\*Includes medications not prescribed as analgesics, antidepressants, antispasmodics, laxatives or prokinetics. †Includes medications used by <4.2% of patients.

Table 5: Direct costs of IBS-C

	<i>N</i>	HS <i>112</i>	Patient <i>112</i>	Total <i>112</i>
Medical consultations (€)				
Mean (95% CI)		249.0 (198.3 , 311.7)	0.0 (0.0 , 0.0)	249.0 (198.3 , 311.7)
Min-Max		0.0 – 2,311.0	0.0 - 0.0	0.0 – 2,311.0
Median		153.0	0.0	153.0
Hospitalisations (€)				
Mean (95% CI)		541.9 (285.9 , 849.8)	0.0 (0.0 , 0.0)	541.9 (285.9 , 849.8)
Min-Max		0.0 – 8,614.0	0.0 - 0.0	0.0 – 8,614.0
Median		0.0	0.0	0.0
Diagnostic tests (€)				
Mean (95% CI)		159.4 (109.5 , 215.2)	0.0 (0.0 , 0.0)	159.4 (109.5 , 215.2)
Min-Max		0.0 – 1,474.0	0.0 - 0.0	0.0 – 1,474.0
Median		0.0	0.0	0.0
Pharmacological medications (€)				
Mean (95% CI)		116.5 (34.5 , 227.6)	460.9 (239.5 , 716.8)	577.3 (328.5 , 848.3)
Min-Max		0.0 – 4,772.0	0.0 – 7,372.0	0.0 – 7,372.0
Median		0.0	61.5	123.0
Complementary therapies (€)				
Mean (95% CI)		0.0 (0.0 , 0.0)	106.3 (57.9 , 178.8)	106.3 (57.9 , 178.8)
Min-Max		0.0 - 0.0	0.0 – 2,640.0	0.0 – 2,640.0
Median		0.0	0.0	0.0
Adverse reactions (€)				
Mean (95% CI)		0.6 (0.0 , 1.9)	0.5 (0.0 , 1.3)	1.1 (0.0 , 2.7)
Min-Max		0.0 - 71.0	0.0 - 36.0	0.0 - 71.0
Median		0.0	0.0	0.0
<b>TOTAL DIRECT COSTS (€)</b>				
<b>Mean (95% CI)</b>		<b>1,067.3 (729.6 , 1,446.6)</b>	<b>567.6 (333.1 , 840.7)</b>	<b>1635.0 (1,226.0 , 2,061.4)</b>
<b>Min-Max</b>		<b>0.0 – 9,680.0</b>	<b>0.0 – 8,092.0</b>	<b>0.0 – 10,782.0</b>
<b>Median</b>		<b>262.5</b>	<b>103.5</b>	<b>518.5</b>

HS: Healthcare system; 95% CI: 95% confidence interval.