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Social economic costs of type 1 diabetes mellitus in pediatric patients in Spain: CHRYSTAL observational study

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ABSTRACT

Aims: To estimate the social-economic costs of Type 1 Diabetes Mellitus (T1DM) in patients aged 0–17 years in Spain from a social perspective.

Methods: We conducted a cross-sectional observational study in 2014 of 275 T1DM pediatric outpatients distributed across 12 public health centers in Spain. Data on demographic and clinical characteristics, healthcare utilization and informal care were collected from medical records and questionnaires completed by clinicians and patients' caregivers.

Results: A valid sample of 249 individuals was analyzed. The average annual cost for a T1DM patient was €27,274. Direct healthcare costs were €4070 and direct non-healthcare cost were €23,204. Informal (familial) care represented 83% of total cost, followed by medical material (8%), outpatient and primary care visits (3.1%) and insulin (2.1%). Direct healthcare cost per patient statistically differed by glycated haemoglobin (HbA1c) level [mean cost €4704 in HbA1c $\geq 7.5\%$ (≥ 58 mmol/mol) group vs. €3616 in HbA1c $< 7.5\%$ (< 58 mmol/mol) group]; and by the presence or absence of complications and comorbidities (mean cost €5713 in group with complications or comorbidities vs. €3636 in group without complications or comorbidities).

Conclusions: T1DM amongst pediatric patients incurs in considerable societal costs. Informal care represents the largest cost category.

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1. Introduction

Epidemiologic studies suggest that the incidence rate of type 1 diabetes mellitus has been growing worldwide, especially amongst young children [1]. In Spain, the prevalence of type 1 diabetes is 1.1–1.44 per 1000 people under 15, with annual incidence rates of between 11.5 and 27.6 per 100,000 people in children under 15 [2].

Along with health effects, type 1 diabetes in the pediatric population has a major economic impact for patients, health services and society in general, for several reasons. First, these patients take insulin-replacement therapies throughout their lifetimes. Second, the disease entails a high risk of hospitalization due to severe hypoglycemic or ketoacidosis events as well as type 1 diabetes associated illnesses [3]. Third, the time dedicated to childcare because of diabetes can be considerable. In these cases, the burden of care and the opportunity cost of time spent on informal care can be a highly relevant cost from the perspective of society [4]. Moreover, families are also likely to spend extra resources (on drugs, private medical visits, monitoring systems, home education, sport activities, transport, etc.) due to the disease [5,6]. Lastly, as any chronic illness, type 1 diabetes may impact negatively on several dimensions of children parents' well-being [5,7].

Measuring the social costs of type 1 diabetes in children is a rather uncommon practice. However, it may be relevant for healthcare decision-makers, as it provides useful information to assess the real magnitude of the benefits of different intervention programs that target the disease. Moreover, it offers a baseline for planning prevention policies in relation to future complications and for allocating health and social care and research resources. Finally, it provides essential evidence and information as regards the performance of new treatments for the disease or any of its complications in economic evaluations.

In Spain, the National Health System guarantees universal coverage, free of charge to anyone living in Spain. Even if private healthcare is available, if not all, close to 100% of patients with type 1 diabetes are treated by the National Health System. The core package includes public health services, pharmaceuticals, out-patient health services (primary and specialized health care) and in-patient services. These services are fully publicly funded and co-payment for the user is zero, except for prescribed medicines. As all patients with a chronic or life threatening condition, type 1 diabetes patients pay a 10% co-payment for outpatient prescribed medicines, with a maximum co-payment of 4.46€ per prescription.

The objective of this study was to estimate the direct healthcare costs and the direct non-healthcare costs (including informal care) of type 1 diabetes in patients aged 0–17 years old in the outpatient setting during 2014 in Spain.

2. Subjects

The CHRYSTAL (Costs and Health Related quality of life Study for Type 1 diabetes mellitus pediatric patients in Spain) study is a multicenter, cross-sectional observational study of pediatric population (0–17 years of age) diagnosed with type 1 diabetes who receive outpatient care by the Spanish public healthcare system in pediatric endocrinology specialized centers within the hospital area, as is customary to treat type 1 diabetes pediatric outpatients in Spain.

Children with type 1 diabetes in Spain may be treated in large centers (treating at least 150 diabetes pediatric patients), medium centers (treating 50–149 diabetes pediatric patients) and small centers (treating 49 diabetes pediatric patients or less) [8]. In order to obtain a representative sample of type 1 diabetes children and adolescents as they are being treated in Spain, a three-stage stratified sampling was carried out. In the first stage, a randomized sample representative of 0–17 years old population diagnosed with type 1 diabetes at the national level ($n = 275$, 90% confidence level, 5% sampling error) was collected based on the prevalence of type 1 diabetes in the population under 18 in Spain. In the second stage, three age group quotas (0–5, 6–11, 12–17 years old) were established within the sample in order to represent different age groups of prevalence in Spain [9]. In parallel, we grouped the Autonomous Communities of Spain into 8 regions based on population size and proximity: Madrid, Catalonia, North-west (Galicia, Asturias, Cantabria, Castilla y León), North (Aragón, Navarra, La Rioja, País Vasco), East (Valencia, Baleares), Center (Castilla-la Mancha, Extremadura), South (Andalucía, Murcia, Ceuta, Melilla), and Canary Islands. In the third stage, we randomly selected 12 centers across these regions, out of a list of 90 public hospitals in Spain that are known to provide care to at least 20 type 1 diabetes patients under the age of 18 [8]. Selected centers were representative of the distribution of center sizes per region, which allows accounting for any differences in resource availability (such as number of beds, medical or nursing staff and medical equipment) that may be associated with center size, and for possible variations in clinical practice across geographical regions. The number of patients to enroll and age quotas were assigned to each center trying to replicate the previously described distribution of pediatric patients with type 1 diabetes in Spain in large, medium, and small centers [8]. Inclusion criteria were patients under 18 years of age who had been diagnosed with type 1 diabetes for at least 12 months, implying that the youngest age group under study was actually limited to children 1–5 years of age. Patients diagnosed with any other type of diabetes, patients participating in clinical trials and inpatients, were excluded. Each center selected patients fulfilling inclusion criteria as they were attending their previously scheduled usual appointments until all age quotas were completed.

The patient's primary caregivers (defined as the adult responsible for controlling the patient's diabetes most of the

time) were informed about the study objectives and data confidentiality. The primary caregivers and patients 12 years old and over provided their informed assent to participate in the study and to release information, according to the Spanish legislation, and the study was approved by the hospitals' Ethics Committees in accordance with national and regional regulations.

3. Materials and methods

3.1. Data collection

Data were collected between March and August 2014, at one single time for each patient, by the investigators of each center (pediatric endocrinologists or diabetes specialist nurses). A Case Report Form (CRF) was completed by clinical experts using the patient's medical record and one questionnaire was filled by the patient's primary caregiver ("Caregiver's Questionnaire"). Data covered the 12-month period prior to the date of collection. In order to minimize recall bias some data were collected for the previous month, 3 months or 6 months, depending on the frequency of use of each resource, and extrapolated to 12 months in order to obtain annual costs.

The CRF included patient's demographics (sex, age, height, weight), date of first insulin injection, puberty status, HbA1c level, diabetes related acute and chronic complications (hypoglycaemia, ketosis without acidosis, ketoacidosis, dawn phenomenon, retinopathy, nephropathy and peripheral neuropathy) and common comorbidities (hypothyroidism and celiac disease), and healthcare resource utilization related to diabetes (medication, outpatient visits, hospitalizations, emergency services, and medical tests).

The caregiver's questionnaire included utilization of diabetes related medical material and supplies (glucose meters, insulin injection pumps, glucose monitoring sensors, lancets, blood strips), visits to private healthcare providers, caregiver's socio-demographic data (age, sex, level of education, occupation), extra expenditures due to diabetes (on transportation, food, and sports activities), time devoted to diabetes surveillance activities both by the primary caregiver and by other caregivers, work status, and work problems associated to providing informal care.

3.2. Cost methodology

We estimated direct healthcare costs (those borne by the Spanish National Health System), and direct non-healthcare costs (out of pocket expenditures borne by families, and cost equivalence of the time devoted to caregiving). We used a prevalence approach to value health and social resources consumed during a given year. This includes all healthcare resources used to control the disease and to treat its complications, familial (informal) care and other non-healthcare resources employed within a whole year. This approach is particularly relevant when estimating the burden of chronic conditions requiring long-term treatment [9–12]. We used a bottom-up costing approach to estimate average annual costs per patient [13]. The base year for all costs was 2014.

3.3. Direct healthcare costs

Direct healthcare costs included medications related to diabetes or diabetes derived conditions (insulin and other medications), medical tests, outpatient and primary healthcare visits, acute hospitalizations due to type 1 diabetes, medical material and supplies, and use of emergency services.

The cost of insulin was calculated as cost per average daily dose according to the patient's information registered on his/her notebook in the past three months and extrapolated to 12 months. The cost of insulin was also calculated by the caregivers' recall using the number of vials and pens that they collected from the pharmacy. Given that the latter is subject to recall bias, in the calculation of total costs we opted for a conservative approach and considered the cost of insulin according to average daily dose used. The annual cost of other drugs was calculated according to medical records and the regimen followed by the patient (dose, frequency, and days of treatment in the past 12 months). All drug costs were obtained from the list of approved drugs in Spain [14]. Official price discounts published by the Spanish Ministry of Health were applied [15].

The cost of healthcare resources (other than medication) used by patients was calculated by multiplying resource quantities by the average of all available official regional unit costs [16]. Hospitalization costs were obtained by their main Diagnosis-Related Group in Spain [17].

3.4. Direct non-healthcare costs

Direct non-healthcare costs include the costs of families' expenditure on transportation, special food (e.g. carbohydrate dietary supplements), physical activities undertaken because of the child's diabetes, and informal care provided by the primary and other caregivers. Informal care was defined as the performance of tasks that help maintain or enhance the patient's health, carried out by non-professional caregivers [18]. The primary caregiver was defined as the person who carried out these tasks the majority of the time. Informal care included daily time spent on glucose control, insulin administration, special food preparation, and monthly time spent on healthcare visits and travelling to health centers, administrative tasks and diabetes surveillance, both by the primary caregiver and by other caregivers.

A conservative approach was taken regarding the maximum number of caregiving hours per patient that was allowed for analysis. This approach responds to the notion that when caregiving time is not censored, a joint-production bias may arise, as it will often be the case that part of the time people spend on caregiving can be spent on other simultaneous tasks such as housework or leisure [19]. We used a limit of 8 h of caregiving time per day per caregiver (primary caregiver or "other caregivers") as the baseline (when the care time reported per caregiver type exceeded this number of hours) and increased it to 12 and 16 h per day per caregiver in the sensitivity analysis. This means that, at the baseline, the total maximum number of hours that a child may receive is 16 h per day (8 h for primary caregiver and 8 h for other caregivers).

We estimated the cost of informal care using the proxy good method, which uses the cost of a professional caregiver as a proxy for the time provided by informal caregivers, considering that if the later were not to provide these services, they would have to be replaced by a professional caregiver [19]. We used the official hourly wage of a professional caregiver provided by the Ministry of Health and Social Policies as a proxy for the hourly cost of informal care [20].

Other non-healthcare costs (out of pocket expenditure on transportation, special food, and sports activities) were directly provided by the caregiver's questionnaire.

3.5. Empirical analysis

Based on the general consensus about level of glycemic control in pediatric populations [21], we estimated costs according to different levels of HbA1c, considering a cut point of $<7.5\%$ (<58 mmol/mol) vs. $\geq 7.5\%$ (≥ 58 mmol/mol). We analyzed whether costs vary significantly depending on HbA1c level and the existence of diabetes related complications and comorbidities, using gender and age of patients as control variables. When the distribution of costs was markedly asymmetrical and very different from a Normal distribution, multivariate regression analysis by Generalized Linear Model (GLM) was implemented using a Gamma link function due to the similarity with the distribution observed in the cost data [22–24].

4. Results

A total of 275 questionnaires were collected, 26 of whom were excluded because of incomplete information for calculating all the resources identified. The valid sample for analysis amounted to 249 (90.5% of all). The main characteristics of our sample are shown in Table 1.

4.1. Healthcare utilization

Analysis of healthcare resource utilization showed that the patients made an average of 3.04 public primary care visits per year (0.06 to general practitioner, 1.41 to general pediatrician and 1.56 to nurse -non-diabetes education purpose-), 3.35 visits to diabetes educator nurses, and 5.45 visits to public specialists (including endocrinologists, pediatricians, and other). According to the type of insulin used by children, 53.3% were rapid-acting insulin, 40.8% were long-acting, 3.6% biphasic and 2.4% intermediate-acting. Most of the insulin consumption was an analog origin (90.8%). Overall, 99.2% of the children required tests or examinations, 12.4% used insulin pumps (standard criteria for prescribing insulin pumps are: children over the age of 2, with frequent severe hypoglycemic events, and/or who, in spite of having received optimal diabetes education on insulin multi-dose therapy and adequate medical follow-up, have not yet achieved an adequate metabolic control), 6.8% used CGM systems in the past year, 92.4% did not require hospitalization during the entire 12-month period, and 7.6% were admitted once or more times due to diabetes related problems (the mean number of annual hospital admissions per patient who was hospitalized was

1.4). Emergency care was provided at least once to 20.48% of total patients: 6.02% in primary care emergency services, 16.87% in hospital emergency departments, and 2.01% in medical transport (ambulance) in the form of on-site emergency intervention.

4.2. Non-healthcare resources involved

With regard to other resources, 62.1% of patients received special food and 38.0% incurred in expenditures related to sports activities due to their disease (i.e. the caregivers reported enrolling their child in paid activities such as swimming, football, dance, etc., as part of type 1 diabetes control). As expected in children, informal care was required by 100% of the patients. In 35% of the cases one single caregiver was identified and in the remaining 65% more than one caregiver was identified. In 99% of the cases, the primary caregiver was the child's mother or father. In the base case, the total average time of caregiving provided by all caregivers was 33 h per week.

4.3. Costs assessment

The estimated average annual cost per patient in 2014 was €27,274 (Table 2). Annual average costs have an inverted U-shaped depending on the age of the child: 31,040€ for children 1 to 5 years old vs. 33,090€ for children 6–11 ($p < 0.05$), vs. 21,291€ for children 12–17 years of age ($p < 0.05$); but do not significantly differ by center size (these results not shown in tables). Direct non-healthcare costs represented the largest proportion, with 85.1% of the total average cost per patient (€23,204). Average direct healthcare costs were estimated in €4070 (14.9% of total costs). The most important categories of direct healthcare costs were medical material and supplies, which accounted for almost 50% of healthcare costs and 7.46% of total costs, followed by outpatient and primary healthcare visits (20.67% of direct healthcare costs and 3.08% of total costs) and insulin (14.9% of healthcare costs and 2.12% of total costs). The most relevant category of direct non-healthcare cost was informal care, with an average cost of €22,618 (97.47% of direct non-healthcare cost and 82.93% of total costs) (Table 2). The cost related to the time spent on diabetes care by primary caregivers represented 74% of direct non-healthcare cost and 61% of total costs. Fig. 1 shows the distribution of direct healthcare and non-healthcare costs in terms of percentage over total costs, and percentage over their own cost category.

Depending on the scenario chosen to assess informal care (maximum admitted caregiving time set at 8, 12 and 16 h per caregiver), the estimated mean annual cost ranged from €27,274 (base case) to €31,058 (scenario 2) and €33,056 (scenario 3) (Table 3).

Direct healthcare cost differences between patients with HbA1c $\geq 7.5\%$ (≥ 58 mmol/mol; €4704) and patients with $<7.5\%$ (<58 mmol/mol; €3616) were statistically significant ($p < 0.01$). After controlling for age and gender, we found significant differences in the costs of insulin, hospitalization, emergency services, and the total direct healthcare costs of these two patient groups. In all these categories, a level of HbA1c $\geq 7.5\%$ (≥ 58 mmol/mol) was associated with higher costs. Non-

Table 1 – Sample characteristics (patients included in the costs analysis n = 249, unless specifically mentioned) Mean (SD).

Patients characteristic	HbA1c < 7.5% (<58 mmol/mol) (n = 145)	HbA1c ≥ 7.5% (≥58 mmol/mol) (n = 104)	Absence of CC (n = 197)	Presence of CC (n = 52)	Full sample (n = 249)
Patient age	10.51 (3.84)	11.78 (3.83) <i>p</i> < 0.01	10.78 (3.96)	12.03 (3.40)	11.04 (3.88)
Age at time of diagnosis	5.34 (3.62)	5.90 (3.65)	5.41 (3.61)	6.19 (3.69)	5.58 (3.64)
Sex (% of males)	53.10%	52.88%	55.84%	42.31%	53.01%
Hba1C% [mmol/mol]	6.82 (0.43) [51.1 (4.6)]	8.26 (0.89) <i>p</i> < 0.001 [66.8 (9.7)]	7.35 (0.82) [56.9 (9.0)]	7.68 (1.36) [60.5 (14.9)]	7.42 (0.97) [57.7 (10.6)]
Number of hypoglycemic episodes in the last month	12.55 (8.69)	10.22 (11.29) <i>p</i> < 0.01	11.28 (8.85)	12.69 (13.22)	11.58 (9.91)
Number of severe hypoglycemic episodes in the last 12 months	0.11 (0.37)	0.11 (0.46)	0.09 (0.33)	0.17 (0.61)	0.11 (0.41)
Caregiver's age (n = 235)	42.36 (6.32)	43.24 (6.06)	42.50 (6.19)	43.54 (6.32)	42.72 (6.22)
Total informal care hours per week (primary caregiver plus other caregivers) ^a	34.12 (30.16)	31.37 (27.81)	33.39 (29.76)	31.38 (27.08)	32.97 (29.18)
Total informal care hours per week (primary caregiver plus other caregivers) ^b	39.90 (41.28)	36.51 (36.25)	39.12 (39.85)	36.11 (37.01)	38.49 (39.22)
Total informal care hours per week (primary caregiver plus other caregivers) ^c	43.29 (48.34)	38.77 (40.54)	42.37 (46.39)	37.73 (40.65)	41.40 (45.21)
Informal care hours per week – primary caregiver ^a	24.41 (19.87)	24.23 (20.91)	24.36 (20.52)	24.22 (19.48)	24.33 (20.27)
Informal care hours per week – primary caregiver ^b	29.05 (28.16)	29.02 (29.01)	29.27 (28.95)	28.13 (26.76)	29.04 (28.46)
Informal care hours per week – primary caregiver ^c	32.22 (34.96)	31.27 (33.91)	32.37 (35.42)	29.76 (30.76)	31.82 (34.46)
Informal care hours per week – other caregivers ^a	9.71 (15.59)	7.13 (12.51) <i>p</i> = 0.02	9.03 (14.9)	7.15 (12.45)	8.64 (14.42)
Informal care hours per week – other caregivers ^b	10.85 (19.34)	7.49 (14.12) <i>p</i> = 0.02	9.84 (17.79)	7.96 (15.94)	9.45 (17.41)
Informal care hours per week – other caregivers ^c	11.07 (20.24)	7.49 (14.12) <i>p</i> = 0.02	10.00 (18.52)	7.96 (15.94)	9.57 (18.00)

SD: Standard Deviation; CC: complications and/or comorbidities related to type 1 diabetes.

^a Informal caregiving censured to a maximum of 8 h per day (base case).^b Informal caregiving censured to a maximum of 12 h per day.^c Informal caregiving censured to a maximum of 16 h per day.

Table 2 – Average costs per patient (EUR year 2014) (n = 249).

Costs categories (bold type) and subcategories	Mean (SD)	% over subcategory ^a	% over total costs ^b
Direct healthcare cost			
Medication: insulin (measured through average daily dose used, included in subtotal costs)	577.41 (370.07)	14.19%	2.12%
Medication: insulin (measured through vials and pens collected from the pharmacy, not included in subtotal costs)	819.59 (676.86)	–	–
Medication: other drugs	18.14 (19.56)	0.45%	0.07%
Tests	57.59 (40.63)	1.41%	0.21%
Outpatient and primary health care visits	841.39 (1243.33)	20.67%	3.08%
Hospitalization due to type 1 diabetes related problems	452.75 (2074.34)	11.12%	1.66%
Medical material and supplies (insulin pumps, CGM systems, glucose meters, lancets, blood strips, and other glucose control material)	2034.70 (1550.58)	49.99%	7.46%
Emergency services	88.06 (318.67)	2.16%	0.32%
Direct healthcare cost subtotal	4070.08 (3223.77)	100.00%	14.92%
Direct non-healthcare cost			
Non healthcare transportation	63.15 (150.50)	0.27%	0.23%
Special food	423.78 (661.19)	1.83%	1.55%
Physical activities	99.47 (205.40)	0.43%	0.36%
Caregiver's time costs (informal care)	22617.8 (20015.85)	97.47%	82.93%
Primary caregiver	16691.77 (13906.43)	73.80%	61.20%
Other caregivers	5926.02 (9891.07)	26.20%	21.73%
Direct non-healthcare cost subtotal	23204.21 (20224.6)	100.00%	85.08%
Total cost (Direct healthcare plus direct non-healthcare costs)	27274.29 (20713.61)		100.00%

SD: Standard Deviation.
^a Percentage over corresponding cost subcategory.
^b Percentage over TOTAL COST (Direct healthcare plus direct non-direct healthcare costs).

healthcare costs showed no statistically significant differences (indicating no significant differences in the caregiving time received by the patients), nor did total costs (Table 4). Table 4 also compares the average costs per patient depending on whether the child experienced any type of diabetes related complication and/or comorbidity (CC) or not (in this analysis CCs included ketosis without acidosis, ketoacidosis, dawn phenomenon, retinopathy, nephropathy and peripheral neuropathy). Overall, 52 patients (20.9%) suffered from some kind of CC during the 12-month period and the remaining 197 patients did not report to experience any type of CC. Patients without CCs had lower average direct healthcare costs than patients with CC (€3636 vs. €5713; $p < 0.001$). After controlling for age and gender, we found statistically significant differences in the costs of tests, healthcare visits, hospitalization, and in total healthcare costs. As with HbA1c level, non-healthcare costs (with the exemption of special food) and total costs showed no statistically significant differences.

4.4. Caregiver's lost working hours

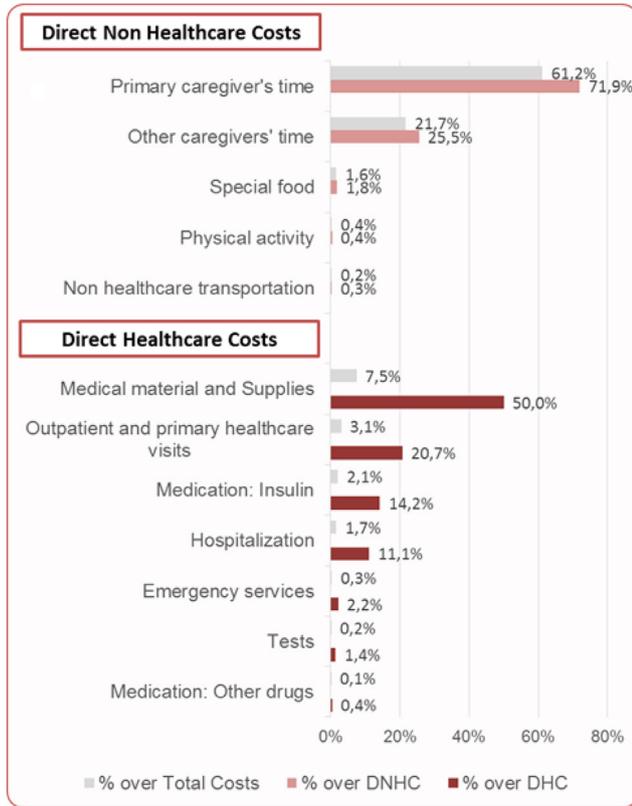
Although we have not translated into monetary values the labor problems reported by the principal caregivers, our results show that 111 people (44.6% of the principal caregivers) indicated that the care of their children had caused them some problems at work. Of these, 26 caregivers lost an

average of 21 working hours in the past year (3.5 h for 6 working days on average) and 42 indicated that they had missed at least one day of work because of childcare (4.5 days loss on average in the past year). In addition, 17 caregivers reported having to leave their job in order to look after their children with diabetes.

5. Discussion

To our knowledge, this is the first study that estimates the economic impact of informal caregiving of type 1 diabetes among pediatric patients. Also, this is the first attempt to approximate the economic healthcare costs of type 1 diabetes in Spain, which National Health System offers full health coverage with well-developed free care at point of delivery.

The research on the economic burden of type 1 diabetes in pediatric population is scarce in the scientific literature. Previous estimations of healthcare costs in other countries range between €1570 and €4852 (current euros of 2014) per young patients annually [25–29]. Our results show similar healthcare costs but significantly higher total costs than in previous works, as a result of considering the non-health resources involved in patient care (particularly informal care). In addition, our results indicate that direct healthcare costs of young people with type 1 diabetes are substantial, mainly due to the use of medical material and supplies, healthcare visits, and



DNHC: Direct Non-Healthcare Costs; DHC Direct Healthcare Costs

Fig. 1 – Distribution of Direct Healthcare Costs and Direct Non-Healthcare Costs: percentage over total costs, and percentage over same cost category.

insulin. These resources are covered almost entirely by the Spanish National Health System. Although increases in these costs are unlikely because healthcare prices are strictly regulated and negotiated in Spain, any increase in the costs of medical supplies, healthcare visits and insulin would be likely to have an impact on the national budget.

Our results indicate that metabolic control is relatively good among children and adolescents, with 60% of children having an HbA1c level under 7.5%. To our knowledge this is the first study that estimates average HbA1c levels at the national level in the pediatric population in Spain. According

to our estimates, a poor glycemic control of the disease (HbA1c $\geq 7.5\%$ or 58 mmol/mol) is associated with a 28% increase in the direct healthcare costs (€4704 per patient vs. €3616 for patients with HbA1c $< 7.5\%$ or 58 mmol/mol). The relationship between poor glycemic control and higher healthcare costs among children with diabetes has also been found in previous studies [26–29]. This relationship is not exclusive to children with type 1 diabetes, as it has been also confirmed for adults with type 1 or type 2 diabetes [30–32]. Aagren (2011) found that a 1-percentage-point increase in HbA1c levels will, on average, lead to a 6.0% and 4.4% increase in diabetes-related medical costs for type 1 and type 2 diabetes, respectively [30].

We also proved that, in line with other studies, the existence of acute and chronic CC related to diabetes (ketosis without acidosis, ketoacidosis, dawn phenomenon, retinopathy, nephropathy, peripheral neuropathy, hypothyroidism and celiac disease) increases direct healthcare costs. Indeed, those patients who suffered diabetes related CC during the considered period consumed healthcare resources valued at €5713, which is 57% higher than the average healthcare cost of patients without CC (€3636). The 1-year prevalence approach and the retrospective nature of our study impedes considering the long-term effects of chronic complications, which are considered the most harmful and costly [33]. Of course, the fact that this study focuses on pediatric population, in which the evolution of the disease is shorter than in the adult population, can partially explain the relatively low prevalence of CC compared to adults.

One of the strongest findings of our paper is the estimation of informal care costs associated with type 1 diabetes. Although the estimation of informal care is uncommon in cost of diabetes studies, the growing scientific literature on this subject shows the relevance of this social resource in the case of many diseases and injuries [34–36]. To our knowledge, this is the first study that estimates the economic impact of informal caregiving among pediatric type 1 diabetes patients. Our results show that, from a social perspective, the costs of informal care far exceed direct healthcare expenditure. According to the average time of care provided by the patient's environment, the cost of informal care amounts to an average of €22,618 per patient per year.

In our analysis, we censored the maximum number of hours of caregiving time using three different scenarios (8 h,

Table 3 – Sensitivity analysis of the average costs per patient.

	Base case ^a Mean (SD)	Scenario 2 ^b Mean (SD)	Scenario 3 ^c Mean (SD)
1. Direct healthcare cost	4070.08 (3223.77)	4070.08 (3223.77)	4070.08 (3223.77)
2. Direct non-healthcare cost other than informal care	586.41 (733.81)	586.41 (733.81)	586.41 (733.81)
3. Caregiver's time costs (informal care)	22617.8 (20015.85)	26401.79 (26903.78)	28399.17 (31013.19)
3.1. Primary caregivers	16691.77 (13906.43)	19918.28 (19523.88)	21829.45 (23637.02)
3.2. Other caregivers	5926.02 (9891.07)	6483.505 (11938.85)	6569.717 (12346.42)
4. Direct non-healthcare cost (2 + 3)	23204.21 (20224.60)	26988.2 (27079.81)	28985.58 (31177.96)
5. Total cost (1 + 4)	27274.29 (20713.61)	31058.27 (27475.44)	33055.66 (31505.76)

^a Informal caregiving censored to a maximum of 8 h per day (base case).

^b Informal caregiving censored to a maximum of 12 h per day.

^c Informal caregiving censored to a maximum of 16 h per day.

Table 4 – Average costs per patient by HbA1c level and in the presence or absence of type 1 diabetes related complications and/or comorbidities (CC). (EUR year 2014) (n = 249).

	HbA1c level		In the presence or absence of type 1 diabetes related CC					
	HbA1c < 7.5% (<58 mmol/mol) Mean (n = 145)	HbA1c ≥ 7.5% (≥58 mmol/mol) Mean (n = 104)	Differences of means ^a (CI)	Adjusted differences of means ^b (CI)	Absence of CC Mean (n = 197)	Presence of CC Mean (n = 52)	Differences of means ^c (CI)	Adjusted differences of means ^b (CI)
Direct health care cost								
Medication: insulin	538.89	631.10	92.21 (–0.92 to 185.35)	41.65 (0.45–82.84)	560.79	640.38	79.59 (–33.83 to 193.02)	25.92 (–45.65 to 97.51)
Medication: other drugs	16.69	20.16	3.47 (–1.47 to 8.41)	4.48 (–0.44 to 9.41)	17.28	21.42	4.13 (–1.86 to 10.13)	2.41 (–4.41 to 9.23)
Tests	55.01	61.18	6.17 (–4.10 to 16.44)	4.33 (–5.93 to 14.61)	54.21	70.36	16.14 (3.81–28.48)	15.67 (1.53–29.82)
Outpatient and primary health care visits	790.07	912.95	122.88 (–192.05 to 437.82)	109.82 (–181.72 to 401.36)	751.79	1180.85	429.06 (50.28–807.83)	356.16 (–57.87 to 770.19)
Hospitalization due to type 1 diabetes related problems	109.92	930.74	820.82 (304.91–1336.73)	798.70 (274.72–1322.68)	184.36	1469.54	1285.17 (667.55–1902.78)	1259.27 (630.21–1888.34)
Medical material and supplies	2059.33	2000.37	–58.96 (–452.13 to 334.20)	9.23 (–391.45 to 409.91)	2012.09	2120.38	108.29 (–368.62 to 585.21)	78.69 (–435.71 to 593.11)
Emergency services	45.66	147.18	101.51 (21.71–181.32)	108.77 (27.82–189.72)	55.78	210.35	154.56 (58.44–250.68)	152.9 (–15.75 to 321.57)
Subtotal	3615.6	4703.71	1088.11 (282.01–1894.22)	1050.53 (255.54–1845.52)	3636.32	5713.3	2076.97 (1119.79–3034.16)	1982.8 (819.02–3146.58)
Direct non health care cost								
Non health care transportation	50.06	81.41	31.34 (–6.61 to 69.31)	31.09 (–8.63 to 70.82)	56.65	87.77	31.11 (–15.03 to 77.26)	34.72 (–22.05 to 91.49)
Special food	398.52	459	60.47 (–107.03 to 227.98)	84.43 (–84.82 to 253.68)	375.80	605.53	229.73 (28.33–431.13)	288.41 (24.71–552.11)
Physical activities	89.13	113.88	24.74 (–27.25 to 76.74)	9.43 (–37.12 to 56.00)	100.94	93.903	–7.04 (–70.23 to 56.15)	–2.94 (–66.51 to 60.61)
Caregiver's time costs (informal care)	23406.01	21518.86	–1887.15 (–6957.75 to 3183.45)	–406.75 (–5080.87 to 4267.36)	22906.23	21525.09	–1381.13 (–7537.52 to 4775.25)	2656.41 (–3196.19 to 8509.03)
Primary caregivers	16740.75	16623.48	–117.27 (–3643.97 to 3409.43)	607.47 (2673.67–3888.61)	16711.26	16617.94	–93.32 (–4372.27 to 4185.63)	3028.15 (–1250.19 to 7306.49)
Other caregivers	6665.25	4895.37	–1769.88 (–4268.47 to 728.71)	1031.53 (–641.80 to 2704.86)	6194.97	4907.15	–1287.81 (–4326.99 to 1751.35)	–577.42 (–2586.07 to 1431.21)
Subtotal	23943.73	22173.15	–1770.57 (–6894.83 to 3353.67)	–198.86 (–4942.68 to 4526.95)	23439.64	22312.3	–1127.33 (–7348.78 to 5094.11)	2925.67 (–3009.76 to 8861.11)
Total cost	27559.33	26876.87	–682.45 (–5934.83 to 4569.91)	1036.86 (–3960.06 to 6033.77)	27075.97	28025.61	949.64 (–5422.76 to 7322.05)	4134.79 (–2206.13 to 10475.73)

CI: confidence interval.

^a Positive values indicate that children with HbA1c ≥7.5% consumed significantly more resources than children with HbA1c <7.5%.^b Adjusted differences of means by sex and age using General Linear Models.^c Positive values indicate that children with CC consumed significantly more resources than children without CC.

12 h and 16 h a day). This censorship is common to avoid overestimates of time devoted to care where joint production activities may be performed [37]. Censorship in our study affects only 5% of caregivers. In the remaining caregivers (95%), the valuation was made on the amount of time caring for the different activities mentioned by the surveyed caregivers. However, as can be seen, the cost of informal care ranges between 22,618 euros (censorship 8 h per day), 26,402 euros (censorship 12 h) and 28,399 euros (censorship 16 h per day). This implies that a small number of caregivers referred a large amount of time devoted to diabetes care, which significantly influences the estimated cost of informal care. Future research could study whether the costs of informal care vary depending on the type of revelation system used for collecting time devoted to care. For example, combining questionnaires (recall method, which was used in our study) with a diary where caregivers carefully indicate the diabetes care related tasks performed and the time spent on each of them, may result in a more accurate calculation of the real time spent on caregiving activities and therefore on a more precise estimation of the costs of informal care.

Our study adopts the societal perspective. However, it does not imply that all relevant costs have been included in the analysis. The productivity losses of the primary caregivers, who often need to reduce working hours because of the time they need to spend as the child's caregiver, is one of them. However, in order to avoid assigning double costs to the time devoted to diabetes care productivity losses have not been included. There are several methods of valuation of informal care that have been used in the literature [19]. In this work, we have estimated the informal care using the proxy good method or market cost method where time spent on informal care is valued as the (labor) market prices of a close market substitute.

A further analysis of labor problems of caregivers exceeds the scope of this article. However, it is a very important line of research for future work, which would help shed light into the real impact of diabetes in pediatric patients. Similarly, although we have not made a monetary valuation, lost school time attributable to diabetes for children is a very relevant variable from a social point of view. Our estimates show that school-age children lost an average of 5.61 annual school days [4.04 in children with HbA1c <7.5% (<58 mmol/mol) and 7.83 with HbA1c ≥7.5% (≥58 mmol/mol)]. According to Tao et al. (2010), children with type 1 diabetes miss school 3.7 days yearly, 9.3 times more than children who do not have diabetes [38]. Therefore, the socioeconomic impact of type 1 diabetes goes beyond the figures estimated in our study. Our analysis can be considered as a useful first step, since it is the first work that shows the cost of type 1 diabetes in Spanish children. However, it is necessary to deepen the analysis of other social costs that help to reveal the true impact of type 1 diabetes on the wellbeing of children and caregivers.

Additionally, it must be recognized that an ideal study would follow a prospective longitudinal cohort of type 1 diabetes pediatric population where the long-term impact of the disease's complications over health can be taken into account. However, this type of study was beyond our means.

In spite of its limitations, we believe that this study represents the most complete and realistic costing of the burden of

type 1 diabetes patients performed to date in Spain. The main strength of the study lies in the bottom-up approach to costing. In addition, the costs were estimated for a period of 1 year, therefore they provide an accurate picture of the medium-term burden of type 1 diabetes.

As is the case with most chronic prevalent conditions associated to acute and chronic complications, type 1 diabetes exerts a great impact on public health resources, which justifies the attention received from health authorities and society in general [39]. The control and consequences of the disease also result in relevant costs to patients and caregivers. Because decision-makers consider information about the financial impact of diseases to be a useful input for program planning, the governments of many countries continue to encourage researchers to carry out cost-of-illness analysis [40,41].

In conclusion, the results from the CHRYSTAL study highlight the importance of analyzing the economic consequences of type 1 diabetes from a societal perspective. Our results provide insights into the distribution of the costs of type 1 diabetes and the impact of this disease on national expenditures for healthcare, and show that healthcare and social costs of type 1 diabetes pediatric patients are considerable in Spain. We identified statistically significant differences in healthcare costs associated with HbA1c level and with the presence of complications. Our results also suggest that any program, strategy or policy on health promotion and care for type 1 diabetes pediatric patients cannot overlook the importance of informal support networks. A clear understanding of the current patterns of resource use and costs in type 1 diabetes patients is needed from the social perspective in order to inform health services planning appropriately.

Conflict of interest

MPN, TD, and JR are employees and stockholders of Eli Lilly and Company. DJ and LAV are former employees and stockholders of Eli Lilly and Company.

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.diabres.2017.02.033>.

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