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ORIGINAL PAPER

Social/economic costs and health-related quality of life in patients with fragile X syndrome in Europe

Karine Chevreul[1,2,3] · Coralie Gandré[1,2,3] · Karen Berg Brigham[1,4] · Julio López-Bastida[5,6] · Renata Linertová[6,7] · Juan Oliva-Moreno[6,8] · Pedro Serrano-Aguilar[6,9] · Manuel Posada-de-la-Paz[10] · Domenica Taruscio[11] · Arrigo Schieppati[12] · Georgi Iskrov[13,14] · László Gulácsi[15] · Johann Matthias Graf von der Schulenburg[16] · Panos Kanavos[17] · Ulf Persson[18] · Giovani Fattore[19] · BURQOL-RD Research Network

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Abstract
Objective To estimate the social/economic costs of fragile X syndrome (FXS) in Europe and to assess the health-related quality of life (HRQOL) of patients and caregivers.
Methods A cross-sectional study was conducted in a sample of European countries. Patients were recruited through patients' associations. Data on their resource use and absence from the labour market were retrospectively obtained from an online questionnaire. Costs were estimated by a bottom-up approach and the EuroQol-5 Domain (EQ-5D) questionnaire was used to measure patients' and caregivers' HRQOL.
Results Five countries were included in the analysis. The mean annual cost of FXS per patient varied from €4951 in Hungary to €58,862 in Sweden. Direct non-healthcare costs represented the majority of costs in all countries but there were differences in the share incurred by formal and informal care among those costs. Costs were also shown to differ between children and adults. Mean EQ-5D utility score for adult patients varied from 0.52 in France ($n = 42$) to 0.73 in Hungary ($n = 2$), while for caregivers this score was consistently inferior to 0.87.
Conclusion Our findings underline that, although its prevalence is low, FXS is costly from a societal perspective. They support the development of tailored policies to

Members of the BURQOL-RD Research Network listed in the Supplementary Annex 1.

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✉ Karine Chevreul
karine.chevreul@urc-eco.fr

1 URC Eco Ile de France, AP-HP, Paris, France
2 Université Paris Diderot, Sorbonne Paris Cité, ECEVE, UMRS 1123, Paris, France
3 INSERM, ECEVE, U1123, Paris, France
4 Université Paris Est, Créteil, France
5 University of Castilla-La Mancha, Talavera De La Reina, Toledo, Spain
6 Red de Investigación en Servicios Sanitarios en Enfermedades Crónicas (REDISSEC), Madrid, Spain
7 Fundación Canaria de Investigación Sanitaria (FUNCANIS), Las Palmas de Gran Canaria, Spain
8 University of Castilla-La Mancha, Toledo, Spain
9 Evaluation and Planning Service at Canary Islands Health Service, Santa Cruz de Tenerife, Spain
10 Institute of Rare Diseases Research, ISCIII, SpainRDR & CIBERER, Madrid, Spain
11 National Center for Rare Diseases, Istituto Superiore di Sanità (ISS), Rome, Italy
12 Centro di Ricerche Cliniche per Malattie Rare Aldo e Cele Daccò, Istituto di Ricerche Farmacologiche Mario Negri, Ranica (Bergamo), Italy
13 Institute of Rare Diseases, Plovdiv, Bulgaria
14 Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria
15 Department of Health Economics, Corvinus University of Budapest, Budapest, Hungary
16 Centre for Health Economics Research Hannover (CHERH), Leibniz Universität Hannover, Hannover, Germany
17 Department of Social Policy and LSE Health, London School of Economics and Political Science, London, UK

reduce the consequences of FXS on both patients and their relatives.

Keywords Fragile X syndrome · Economic burden · Cost analysis · Quality of life

Introduction

Fragile X syndrome (FXS) is the leading cause of inherited intellectual disability and results from mutations on the fragile mental retardation 1 (FMR1) gene of the X chromosome [1]. These mutations are associated with reduced levels of the *FMR* protein, triggering manifestations that vary widely from patient to patient [2] but often result in intellectual disability, as well as cognitive and behavioural impairments and, in particular, autism spectrum disorder for which FXS is the leading monogenic cause [3]. In addition, individuals affected by FXS often display identifiable features with a long narrow face, prominent ears and high-arched palate [4]. This disease affects males more often and more severely than females, with an estimated incidence of 1 in 5000 males and 1 in 9000 females [5]. In Europe, the overall prevalence of the disease is estimated at 20 per 100,000 inhabitants [6], with a prevalence reaching 22.6 per 100,000 habitants in the UK [7].

Despite the low incidence of FXS, previous research suggests that the societal impact of rare diseases deserves wider attention [8] and that FXS has significant consequences for both patients and caregivers. It is indeed estimated that only 10 % of adult male patients live on their own [9] and that one in three caregivers of FXS patients visit a health professional for anxiety and depressive symptoms each year. Moreover, 79 % of families of FXS patients report financial difficulties linked to the disease [10]. Apart from a French analysis [11], very little information is available on the cost incurred by FXS for health and social care systems. No study has assessed this cost on a large scale using data from several countries, nor has any study conjointly determined the impact of this disease on the health-related quality of life (HRQOL) of patients and caregivers through the use of standardised quantitative tools.

In this context, the objectives of this article were to estimate the social/economic costs (direct healthcare costs, direct non-healthcare costs and labour productivity losses) of FXS in European countries in 2012, to assess the HRQOL of patients with FXS and their caregivers and to describe variations between countries.

[18] The Swedish Institute for Health Economics, Lund, Sweden

[19] Centre for Research on Health and Social Care Management (CERGAS), Bocconi University, Milan, Italy

Methodology

Research design and subjects

Within the BURQOL-RD project, we conducted a cross-sectional survey of people diagnosed with FXS who received outpatient care and were living in the community. They were recruited from associations and registries specific to FXS in eight European countries (Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden and the UK). All patients and caregivers were informed about the objectives of the study and the confidentiality of their data. Their agreement to participate was then collected through an online form or by post. Complete anonymity of the collected data was guaranteed as recruitment was carried out by patient organisations and no form of identification was present in the data sent to researchers.

Data were collected between September 2011 and April 2013. Questionnaires were administered by e-mail and postal surveys through patient organisations. Different questionnaires were available to patients depending on their age group: children (under 18) and adults. For children, their legal representative completed the questionnaire for them. In the case of FXS adult patients with intellectual disability, relatives could also fill in the questionnaire on the patient's behalf. For patients with informal caregivers, the principal caregiver, defined as the person who spent the most hours helping the patient, was also asked to complete a separate questionnaire.

Information gathered at a specific point in time is commonly used in cost and HRQOL studies [12, 13]. This was the approach we selected, with a questionnaire that was detailed enough to reduce either exaggeration or underestimation. It covered a 6-month period prior to the study, with the exception of hospital admissions for which the annual frequency was collected. Data were then extrapolated over a 1-year period. The information compiled from patients included socio-demographic characteristics, use of healthcare services, formal and informal care as well as quantitative data regarding absence from the labour market (temporary and permanent sick leave or early retirement). Principal caregivers were asked to provide information regarding their demographic characteristics, relationship to the patient, number of hours spent on informal care and resulting work limitations.

Costing methodology

Costs were estimated from a societal perspective during a given year. We considered all healthcare resources used for prevention, treatment and rehabilitation, as well as additional resources used (through formal and informal care) or

lost (through loss of labour productivity) within that year as a consequence of the illness considered [14]. Total and average annual costs were estimated through a bottom-up approach, which is the most accurate method for cost estimation and allows evidence-based decision-making [14, 15]. Three categories of costs were considered: direct healthcare costs (all goods and services directly linked to the diagnosis and treatment of the disease), direct non-healthcare costs including formal costs (professional caregivers, social services and non-healthcare transport) and informal costs (informal care provided by the patient's relatives), and loss of labour productivity resulting from sick leave and early retirement from the labour market due to the illness.

Direct healthcare costs

Frequency of healthcare utilisation in terms of drugs, medical devices, medical tests, visits to health professionals, healthcare-related transportation, emergency visits and hospital admissions was derived from the questionnaire. Unit costs for each resource were obtained from healthcare cost databases at a national level and multiplied by the number of units of each resource used (see Supplementary Annex 2). Drug cost was calculated by determining the daily cost for each of the products used (based on the cost of each pack dispensed and the dose taken) and then multiplying by the duration of use. When no information concerning the number of units per pack was available, we assumed the largest pack size was dispensed.

Direct non-healthcare costs

Formal non-healthcare included care provided by social services at home or in institutions as well as non-healthcare transport. The number of hours of care by professional caregivers (defined as any home caregivers who are paid for their services) needed by patients was extracted from the questionnaire and valued using the mean wage of a professional home caregiver. Daily tariffs were used for services provided in institutions.

Informal non-healthcare is the provision of care by non-professional caregivers, such as a patient's relative, friend or neighbour. Information about informal care was obtained from the items of the questionnaire concerning the time spent helping the patient with his/her basic activities of daily living (recall method). As a conservative criterion, and to prevent joint production, we censored the time of care to a maximum of 16 h per day (112 h per week) when the time of care reported exceeded this figure.

Costs were then computed through the proxy good method, which assumes that if these persons were not assisting the patient, a professional caregiver would have to be hired instead [16, 17]. We therefore computed the costs that would result from the substitution of an informal caregiver by a paid professional using the hourly wage of a health aide.

Loss of labour productivity

Costs linked to loss of productivity (including early retirement) were estimated by valuing the total number of hours not worked due to FXS using the human capital approach [18]. In this approach, the gross average earnings of a worker are used as a proxy for loss of labour productivity [19]. The total number of hours away from work due to the disease was extracted from the questionnaire and converted into monetary units. Our calculations were based on average gross wage figures from the National Wage Structure Surveys of the participating countries for the year 2012.

Patient and caregiver outcomes

Patient and caregiver outcomes were obtained by means of self-administered questionnaires: the EQ-5D, the Barthel Index and the Zarit Burden Interview. The EQ-5D is a simple generic instrument developed by a multidisciplinary group of researchers [20], which has been validated in many countries in Europe and is commonly used in economic evaluations and health technology assessments [21]. Previous studies carried out on developmental disorders have used this tool for both patients [22] and caregivers [23]. The questionnaire is divided into five items (mobility, self-care, daily activities, pain and discomfort, anxiety and depression) and it produces utility scores developed from general population-based valuation studies, reflecting societal preferences. Utility scores are on a scale of 0 (death) to 1 (perfect health), although negative scores are possible for states worse than death. A visual analogue scale (VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health) is also part of the EQ-5D and provides a quantitative measure of health outcome as judged by the individual respondents. Country-specific adult value sets were used when they were available. When they were not, other value sets were used (Danish value set for Sweden, Spanish for Italy, French for Hungary and British for Bulgaria) [24]. Because FXS results in intellectual disability, caregivers most often filled in the patient's EQ-5D questionnaire. Despite the limitations of proxy assessment of a patient's HRQOL by a relative [25, 26], previous research has shown that a caregiver can estimate the point of view of a patient with intellectual disability in a valid and reliable manner [27].

To obtain a quantitative estimate of a patient's degree of dependence, we used the Barthel Index, which is widely used to assess the level of functioning through ten items related to activities of daily living [28, 29]. The scores for

Table 1 Characteristics of the study participants (all)

	France	Hungary	Italy	Spain	Sweden	UK
Patients						
No. of responses	95	12	41	76	17	2
Mean age, years (SD)	19.4 (13.1)	9.2 (6.0)	14.6 (9.5)	18.4 (12.0)	25.2 (12.8)	24.5 (0.7)
Mean age at diagnosis, years (SD)	7.6 (8.7)	3.9 (2.5)	5.3 (6.5)	5.5 (4.6)	10.3 (10.6)	0 (−)
Female (%)	12.6	0.0	12.2	10.5	23.5	0.0
Informal caregivers						
No of responses	56	4	15	28	6	1
Mean age, years (SD)	47.9 (11.8)	37.5 (7.0)	36.9 (20.0)	44.7 (8.7)	38.2 (10.5)	58.0 (−)
Female (%)	89.3	100.0	66.7	67.9	66.7	0.0
Relationship to patient (%)						
Parent	82.1	100.0	13.3	96.4	100.0	100.0
Other relative	17.9	0.0	86.7	3.6	0.0	0.0
Partner or other	0.0	0.0	0.0	0.0	0.0	0.0
Informal caregivers: mean number of hours per week (SD)	34.1 (34.9)	43.2 (28.1)	54.7 (30.9)	61.2 (39.1)	46.4 (44.5)	0.0 (−)
Health outcomes						
Utilities (adult patients) (SD)	0.522 (0.255)	0.730 (−)	0.674 (0.237)	0.728 (0.245)	0.606 (0.251)	0.622 (0.179)
Utilities (caregivers) (SD)	0.754 (0.239)	0.874 (0.106)	0.791 (0.183)	0.853 (0.157)	0.734 (0.035)	–
VAS (adult patients) (SD)	67.6 (20.1)	90.0 (−)	76.7 (23.5)	69.9 (22.5)	66.5 (18.3)	82.5 (24.7)
VAS (caregivers) (SD)	74.9 (16.7)	87.5 (8.7)	75.0 (11.0)	74.6 (15.4)	82.5 (12.6)	–
Barthel Index (patients) (SD)	82.3 (12.3)	84.2 (16.9)	80.4 (24.9)	84.7 (14.7)	14.7 (3.0)[a]	19.0 (0.0)
Zarit scale (caregivers) (SD)	39.9 (16.0)	–	34.5 (11.4)	38.6 (13.7)	36.0 (16.6)	26.0 (−)

[a] Barthel Index out of 20 and not out of 100

each item are generally summed to give a score between 0 (total dependence) and 100 (independence) [28]. This method was used in all countries except Sweden and the UK, where the Barthel Index was assessed on a scale of 0–20 [30].

Caregivers also completed the Zarit Burden Interview (22-item version), which assesses the impact of a patient's disabilities on his/her caregiver's physical and emotional health as well as the repercussions on social and financial aspects. Each item is a statement that the caregiver is asked to respond to using a 5-point scale, indicating how often he/she has felt the suggested feeling, with options ranging from 0 (never) to 4 (nearly always). The total score is obtained by adding the responses of the individual items and ranges from 0 to 88, with a higher score indicating a higher perceived burden [31].

Results

Patients' characteristics

Among the eight countries participating in the BURQOL-RD project, only five (France, Hungary, Italy, Spain and Sweden) provided enough valid questionnaires to be included in the analysis. Our sample was comprised of 241 patients with valid questionnaires, with 101 adults and 140 children under 18. Mean age was 18.1 and mean age at diagnosis was 6.5. The large majority of our population (88 %) was male and 66 % required a caregiver. Detailed patient characteristics by country are presented in Table 1. Consistently across countries, most adult patients were single (90.5–100 %) and less than 20 % worked regularly. Depending on the country, the majority of children either attended specialised schools (France) or regular schools with personalised support (Italy and Spain). Only data from countries where there were at least ten respondents were included in the overall analysis to ensure the representativity of the results. Results from all participating countries can be seen in the tables.

Costs

The mean total annual cost per FXS patient was €4951 in Hungary, €21,586 in Italy, €31,008 in Spain, €35,737 in France and €58,862 in Sweden (Table 2). Healthcare costs ranged from €110 in Hungary to €2675 in France. The main items were medical visits, followed by

Table 2 Average annual costs per patient, all patients (2012 €)

Costs € 2012	France[a]		Hungary[a]		Italy[a]		Spain[a]		Sweden[a]		UK	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Drugs	55	157	4	14	98	222	307	459	86	246	62	87
Medical tests	74	154	31	91	37	149	64	111	15	45	0	0
Medical visits	1160	1514	50	53	1899	2567	537	985	613	703	348	492
Hospitalizations	902	4717	20	46	264	731	29	149	42	171	0	0
Medical devices	70	111	4	9	148	226	12	22	52	83	0	0
Healthcare transport	415	2408	0	0	40	258	0	0	146	600	0	0
Direct healthcare costs	2675	5519	110	127	2485	3099	948	1213	953	998	410	579
Professional caregiver	4987	44,831	0	0	1902	12,182	448	2746	20,523	44,615	0	0
Non-healthcare transport	357	774	92	178	411	1209	82	319	112	277	21	29
Social services	13,859	20,723	6	16	1364	4412	4562	28,783	18,906	22,942	0	0
Direct non-healthcare formal costs	19,202	48,018	98	177	3677	12,729	5093	28,910	39,542	56,261	21	29
Main informal caregiver	10,478	16,455	3617	6490	10,108	16,337	15,871	26,647	14,316	29,558	0	0
Other informal caregivers	2108	6771	1127	2659	4917	10,436	9092	20,256	4052	12,299	0	0
Direct non-healthcare informal costs	12,586	20,176	4743	8917	15,025	24,498	24,963	41,526	18,367	35,671	0	0
Direct non-healthcare costs	31,788	52,955	4841	8891	18,702	26,155	30,056	51,729	57,909	60,873	21	29
Direct costs	34,463	53,448	4951	8849	21,187	26,993	31,004	52,126	58,862	61,357	430	608
Sick leave[b]	226	1913	0	0	20	125	4	34	0	0	0	0
Early retirement[b]	1047	5831	0	0	379	1695	0	0	0	0	0	0
Labour productivity losses patients	2880	8973	0	0	1486	3118	4	34	0	0	0	0
Total costs	35,737	53,202	4951	8849	21,586	26,969	31,008	52,124	58,862	61,357	430	608

[a] Country included in the description and analysis

[b] Excluding children

hospitalisations and drugs. Direct non-healthcare costs ranged from €4841 in Hungary to €57,909 in Sweden, with informal care being the most important item except in France and Sweden. Loss of labour productivity was very low with values close to zero except in France and Italy where they nonetheless still represented a small part of the total costs of FXS.

When looking specifically at the costs incurred by adults, the data of only four countries were included in the analysis based on the sample size (France, Italy, Spain and Sweden). Mean annual costs ranged from €13,596 per patient in Italy to €64,005 in Sweden (Table 3). In all considered countries, direct healthcare costs represented less than 7 % of total costs. They resulted mainly from medical visits, except in France where hospitalisation costs were the highest. Loss of labour productivity similarly contributed to a minimal part of total costs (less than 11 %). For all countries, the main costs were direct non-healthcare costs. For France and Sweden, non-healthcare formal costs represented the majority of costs, accounting for 58 and 85 % respectively of total costs while, for Italy and Spain, the majority of costs resulted from informal care (51 and 63 % of total costs, respectively) (Fig. 1).

For the paediatric patients, four countries were included in the analysis based on the sample size (France, Hungary, Italy and Spain). Mean annual costs ranged from €5295 per patient in Hungary to €38,368 in France (Table 4). In all countries, direct healthcare costs consistently represented less than 13 % of total costs (Fig. 2). The majority of those direct costs resulted from medical visits (Table 4). In Hungary, Italy and Spain, direct non-healthcare informal costs represented the majority of costs (96, 73 and 93 %, respectively) while in France direct non-healthcare formal costs were the most significant (Fig. 2), similar to what was observed for adult patients.

Outcomes

Patients

Mean utility scores for adult patients varied from 0.52 in France to 0.73 in Spain, while mean VAS scores varied from 66.5 in Sweden to 76.7 in Italy (Table 3).

Regarding the level of functioning, the mean Barthel Index varied from 81.5 in France (corresponding to moderate dependency) to 93.9 in Italy (slight dependency) in adult patients (Table 3), and from 73.9 in Italy to 84.0 in

Table 3 Adults with FXS: costs (2012 €) and HRQOL

Country, *n* (% with HRQOL data)	France[a], 42 (93 %)		Hungary, 2 (50 %)		Italy[a], 11 (82 %)		Spain[a], 34 (79 %)		Sweden[a], 12 (83 %)		UK, 2 (100 %)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Drugs	52	164	0	0	99	207	150	341	1	4	62	87
Medical tests	117	168	0	0	8	14	61	95	7	23	0	0
Medical visits	439	453	72	102	556	819	299	645	668	786	348	492
Hospitalizations	1507	6905	0	0	76	251	39	166	59	204	0	0
Medical devices	42	90	0	0	0	0	6	16	44	80	0	0
Healthcare transport	150	963	0	0	0	0	0	0	206	714	0	0
Direct healthcare costs	2307	6960	72	102	738	839	555	830	986	1097	410	579
Professional caregiver	10,400	67,400	0	0	0	0	1002	4070	29,074	51,226	0	0
Non-healthcare transport	104	427	25	36	101	290	131	467	109	315	21	29
Social services	8353	15,633	27	38	4384	7846	9073	42,861	25,527	24,411	0	0
Direct non-healthcare formal costs	18,858	67,866	52	74	4484	7962	10,206	42,927	54,711	61,183	21	29
Main informal caregiver	7157	10,662	3108	4395	4449	8057	9947	20,899	4373	15,149	0	0
Other informal caregivers	1215	2803	0	0	2439	5939	8368	20,243	3936	13,634	0	0
Direct non-healthcare informal costs	8372	12,324	3108	4395	6888	12,334	18,315	37,820	8309	28,783	0	0
Direct non-healthcare costs	27,230	68,409	3160	4321	11,372	12,762	28,521	60,277	63,020	68,253	21	29
Direct costs	29,537	68,204	3232	4219	12,110	13,371	29,076	60,357	64,005	68,856	430	608
Sick leave	511	2871	0	0	73	242	0	0	0	0	0	0
Early retirement	2369	8646	0	0	1413	3145	0	0	0	0	0	0
Labour productivity losses patients	2880	8973	0	0	1486	3118	0	0	0	0	0	0
Total costs	32,417	67,941	3232	4219	13,596	14,192	29,076	60,357	64,005	68,856	430	608

HRQOL	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Utilities	0.522	0.255	0.730	–	0.674	0.237	0.728	0.245	0.606	0.251	0.622	0.179
VAS	67.6	20.1	90.0	–	76.7	23.5	69.9	22.5	66.5	18.3	82.5	24.7
Barthel Index	81.5	10.5	85.0	–	93.9	7.8	89.0	13.7	14.9	3.1	19.0	0.0

[a] Country included in the description and analysis for adult patients only

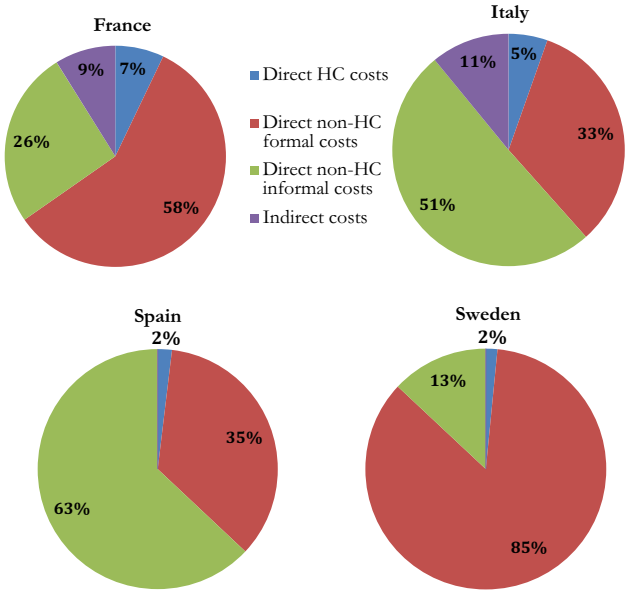

Fig. 1 Repartition of costs by country for adult FXS patients

Hungary in paediatric patients, both corresponding to a moderate level of dependency (Table 4). In Sweden, where the Barthel Index was assessed on a scale of 0–20, the mean Barthel Index was 14.9 for adult patients and 14.3 for paediatric patients, corresponding to slight dependency (Tables 3 and 4).

Caregivers

Mean age of caregivers ranged from 36.9 in Italy to 47.9 in France. The vast majority were female (66.7–100 % of all caregivers). In all countries considered, more than 50 % were still working. Their mean utility score ranged from 0.734 in Sweden to 0.874 in Hungary, while the mean VAS score ranged from 74.6 in Spain to 87.5 in Hungary. The mean Zarit burden measure was available in only three countries. Its value was 34.5 in Italy, 36.0 in Sweden and 39.9 in France, corresponding to a mild-to-moderate burden (Table 1).

Table 4 Children with FXS: costs and HRQOL

Country, *n* (% with HRQOL data)	France[a], 53 (79 %)		Hungary[a], 10 (50 %)		Italy[a], 30 (63 %)		Spain[a], 42 (62 %)		Sweden, 5 (60 %)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Drugs	57	154	5	16	98	230	434	505	291	411
Medical tests	39	133	38	100	47	174	66	124	34	77
Medical visits	1731	1797	46	46	2391	2815	729	1164	480	496
Hospitalizations	423	1449	24	50	333	835	21	135	0	0
Medical devices	92	122	5	9	202	244	17	26	71	97
Healthcare transport	626	3106	0	0	55	301	0	0	0	0
Direct healthcare costs	2967	4081	117	135	3126	3379	1266	1380	876	811
Professional caregiver	697	2978	0	0	2600	14,241	0	0	0	0
Non-healthcare transport	557	921	106	193	525	1392	42	85	119	186
Social services	18,222	23,233	2	5	257	947	911	2525	3016	4419
Direct non-healthcare formal costs	19,476	23,158	107	193	3382	14,188	953	2535	3135	4421
Main informal caregiver	13,110	19,592	3719	7019	12,183	18,143	20,667	29,911	38,178	43,072
Other informal caregivers	2816	8691	1352	2881	5826	11,614	9678	20,493	4329	9681
Direct non-healthcare informal costs	15,925	24,298	5070	9712	18,009	27,221	30,345	44,009	42,507	42,184
Direct non-healthcare costs	35,401	36,732	5178	9684	21,390	29,318	31,298	44,351	45,642	41,771
Direct costs	38,368	38,225	5295	9640	24,516	30,011	32,565	45,084	46,518	41,841
Total costs	38,368	38,225	5295	9640	24,516	30,011	32,572	45,079	46,518	41,841
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Barthel index	83.0	13.8	84.0	18.8	73.9	27.7	80.0	14.6	14.3	3.1

[a] Country included in the description and analysis for children patients only

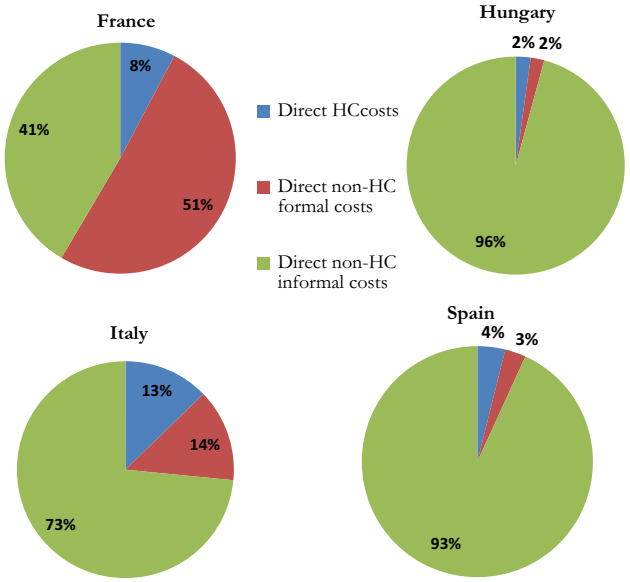

Fig. 2 Repartition of costs by country for paediatric patients

Discussion

The economic burden of FXS in Europe is significant, with a mean annual cost per patient reaching up to €58,862. It represented 39 % of the gross domestic product per capita in Hungary in 2012, 64 % in Italy, 90 % in France, 107 % in Sweden and 110 % in Spain [32]. In each of the countries considered, the main contributors to the economic burden for adult patients were direct non-healthcare costs, either formal in France and Sweden or informal in Italy and Spain. Direct non-healthcare costs also represented the predominant share of costs for children. In addition, the impact of FXS on health-related quality of life was considerable for both patients and caregivers.

Distribution of FXS direct non-healthcare costs varied from country to country. For adult patients in the most Northern countries (France and Sweden), main costs were attributable to formal care, while main costs in Southern countries (Italy and Spain) were attributable to informal care. These differences have been highlighted in other studies and may be explained by stronger family ties in Southern European countries [33, 34]. In addition, France and Sweden had the highest gross domestic product among the study countries [35] and may therefore have been able to invest more in the development of social services than the others. Previous studies have also underlined that richer households were more likely to delegate care of dependent relatives than less wealthy households [36]. The same situation was observed for paediatric patients. Both French and Swedish paediatric patients mainly attended

specialised schools, which may support the hypothesis that those two countries have developed more specialised services for FXS patients, even if the sample size was particularly small for children in Sweden.

There is currently very little literature on the cost of FXS. One study estimated the lifetime costs of FXS at USD 958,000 for men and USD 534,000 for women [37] (€1,113,000 and €620,000, respectively, after conversion to 2012 euros using the purchasing power parities [38, 39]). When dividing those costs by the life expectancy of patients [40, 41], they amounted to €14,089 annually for men and €7470 for women, which is lower than in all the countries we considered, except Hungary. However, the study dates back to 1998, and reported costs referred only to residential institutions. The most recent study, a cost-effectiveness analysis of a prenatal population-based fragile X carrier screening programme, was based on a lifetime cost estimate of USD 615,000 in 2004 (€632,000 in 2012, corresponding to an annual cost per patient of €8208), which was derived from a population of patients suffering from Down's syndrome [42]. However, this study likely underestimates the real lifetime costs of FXS if one assumes that FXS patients have a life expectancy similar to the general population [43]. A recent publication reported the cost to society of patients with intellectual disability in Australia and found an annual cost per patient of AUD 60,000 (€43,000 in 2012) [44]. When subtracting allowances and costs resulting from education to increase comparability with our study, the remaining amount represented AUD 53,000 (€38,000 in 2012), which is within the range reported here. This would seem to confirm the validity of our findings, although differences in methods and populations limit this comparison.

To our knowledge, the HRQOL of FXS patients and their caregivers has never been measured. In our study, mean EQ-5D utility scores for FXS adult patients were lower than the mean values observed in the general population in both France and Hungary, where references are available [45, 46]. In Italy, mean VAS score for adult FXS patients was lower than that measured in a sample representative of the Italian general population [47] and lower than the mean value for patients affected by HIV [48], similar to what was observed in Spain [49]. In Sweden, the mean utility score for adult FXS patients was lower than for patients suffering from a broad range of disorders, including diabetes, asthma, mental distress, hypertension, angina pectoris and neck/shoulder pain [50]. There have also been no studies on the burden borne by caregivers of FXS patients. However, our findings are consistent with the mean utility score of 0.81 found in female caregivers of children with autism [51]. As with HRQOL, our study is the first to report the burden for caregivers of FXS patients through the Zarit Burden Interview, and we found the score to be significantly higher than any Zarit burden measure reported for other diseases with relatively comparable functional impairment in the three countries for which we had data. The highest score reported in the literature was 35.6 and was measured in caregivers of patients with Alzheimer's disease in Brazil [52], while a recent study found a mean score of 29.3 in Japanese mothers of children with intellectual disability [53]. In addition, the substantial burden documented here is consistent with a study reporting that a considerable proportion of caregivers were injured in the past year by their child with FXS [10]. It might also be linked to a depressive disposition in some women carrying the genetic permutation [54, 55].

The strengths of this study are based on its bottom-up approach, which enabled inclusion of all types of costs associated with FXS, including some less visible, such as informal costs and loss of labour productivity. A top-down approach would not have been as informative as it can only allocate a portion of a known expenditure to the disease [14]. Furthermore, to our knowledge, this study is the first to estimate both the cost incurred by FXS and the impact on HRQOL for FXS patients and caregivers. This study is also unique in taking a European perspective and in including countries from Northern, Central, Southern and Eastern Europe.

However, our findings should be interpreted in light of the following limitations. The intangible costs [56] linked to the loss of quality of life were not included in the cost analysis, leading to an underestimation of the economic burden of FXS. Further research should be carried out in that regard. In addition, there is a high degree of variability from country to country in our sample, as reflected by the standard deviation for the total annual cost per patient, which ranged from €8849 in Hungary to €61,357 in Sweden. Moreover, in three countries involved in the BURQOL-RD project (Bulgaria, Germany and the UK) data were insufficient for analysis.

The main shortcoming of using a retrospective online survey is the risk of recall bias. Indeed patients may not remember their use of healthcare resources accurately and may simply guess, leading to an under- or overestimation of costs [14]. It should also be noted that some of the cost estimations may have been more sensitive than others to recall bias as patients are more likely to remember large or recurrent expenses than small or rare ones [57]. The use of an online questionnaire may also skew the patient or caregiver population towards younger, better educated, healthier and wealthier individuals with easy access to the Internet, and we cannot therefore rule out a degree of selection bias in our study. Moreover, we only considered the loss of labour productivity for patients who had once worked, while some patients who had never worked may not have done so as a result of their disease. It was not

possible to identify those patients based on the information collected in the questionnaire and it is therefore possible that we underestimated the share of loss of labour productivity in the total costs. Finally, costs of schooling were not considered, while they potentially could be significant in France and Sweden, where children predominantly attended specialised schools.

Despite the limitations we acknowledge here, and based on the available data, we believe that our study represents a reasonable estimate of costs in the range of true FXS patient costs in Europe. It is the first study to provide a framework to determine such costs using standardised quantitative tools and it underlines the high cost of the disease from a societal perspective, despite its low prevalence. Our description of the previously undocumented burden of FXS supports the development of tailored policies to reduce the consequences of FXS on both patients and their caregivers. Services developed for FXS patients should in particular account for the high burden on caregivers by offering them social support alongside patient care.

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Compliance with ethical standards

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