

# Out-of-Pocket Healthcare Expenditures of Households Living With Rare Diseases

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## Research Article

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# Abstract

**Background:** Economic impact of rare diseases for both individuals and family members, in addition to many expenditures such as disease-related medication, use of healthcare, access to treatment, special medical and nutritional requirements; it also causes indirect effects such as loss of productivity, loss of wages, health insurance and inability to find work. In this study, it is aimed to determine the out-of-pocket health expenditures and economic burden of households where individuals with rare diseases live in Turkey.

**Methods:** The research population consists of registered members of associations that are members of the Rare Diseases Network. The questionnaire was developed based on literature review and expert opinion and the online survey was made available between 01.05.2020- 31.05.2020. After obtaining data on out-of-pocket expenditures in rare diseases, the necessary analysis was carried out through the Microsoft Office Excel application. In addition to the general analysis involving all participants, expenditures on the basis of disease group and disease were calculated. The costs calculated in Turkish Liras (₺/TL) have been converted to Euros (€) according to the average exchange rate for 2020.

**Results:** 456 participants were included in the analysis. Accordingly, 233 patients were included in the metabolic diseases category, 178 in the neuromuscular system diseases category and 41 in the others category. It was determined that special nutrition were the highest expenditure group and emergency department were the lowest expenditure group. The lowest amount of out-of-pocket expenditure is in the metabolic diseases group. It has been observed that 47.35% of all participants allocate more than 10% of the annual average household income and 4.65% more than 100% of the annual average household income for medical expenses. It is seen that the average out-of-pocket expenses in DMD, SMA, cystinosis and cystic fibrosis diseases are close to each other.

**Conclusion:** Since individuals with rare diseases are often unable to work, out-of-pocket expenditures related to the disease lead to financial difficulties and even impoverishment. Their already difficult lives get even more difficult by the financial sacrifices made for treatment. Treatments for rare diseases need to go beyond special exclusivity for patient access and reimbursement.

## Introduction

Rare diseases are life-threatening, serious, genetic, chronic, complex, demanding and low prevalence diseases [1–3]. Rare diseases other than genetic ones are generally cancer, autoimmune diseases, degenerative and proliferative diseases or diseases caused by infection and infestation [4]. Although definitions of rare diseases vary; diseases affecting less than 200.000 people in America, 50,000 in Japan, and 2,000 in Australia are considered as rare diseases [1, 3, 5]. Yet according to the report published by the World Health Organization (WHO) in 2013, if the number of people affected is less than 5 out of 10,000, the disease is considered a rare disease [2].

It is estimated that there are more than 7,000 different types of rare diseases. This number makes up 6–10% of all diseases in the world [6]. However, epidemiological data in the world are constantly changing and a new rare disease is being discovered every week. A disease that was considered rare in the past can become an epidemic/widespread disease today. Similarly, the diseases that are considered rare in one region may not be so in another region [1].

Rare diseases that negatively affect the patient's quality of life and dramatically reduce life expectancy manifest themselves by serious mental and physical disorders [7]. Since they are not well known, occur in unusual ways and often in comorbidities; rare diseases are also difficult to diagnose. On the other hand, diagnostic methods and possibilities are not available for many rare diseases. In addition, the number of doctors who can diagnose and treat rare diseases are quite limited [8]. Only 1% of known rare diseases have been approved for orphan drug treatment [9]. For these reasons, rare diseases with difficulties in diagnosis, treatment and follow-up require to be handled differently from other diseases [7].

Turkey's definition of rare diseases is 50 times less common than the European Union and the United States, and diseases with a prevalence of roughly 0.1–9% for every 100,000 people are considered rare. In this context, it can be said that fewer diseases are considered rare in Turkey than in the European Union [10–11].

Turkey is a country where rare diseases are frequently seen because of inbreeding and different ethnic structures. Due to inbreeding, the prevalence of rare diseases in Turkey is higher. While the rate of inbreeding in European Union countries is 3–10‰, the proportion of inbreeding in Turkey is 12–17%. Therefore, it is likely that approximately 5–7 million people in Turkey suffer from rare diseases [12].

Economic impact of rare diseases for both individuals and family members, in addition to many expenditures such as disease-related medication, use of healthcare, access to treatment, special medical and nutritional requirements; it also causes indirect effects such as loss of productivity, loss of wages, health insurance and inability to find/leave work [13]. The loss of income caused by the inability of individuals with rare diseases to participate in the working life and the fact that one of the households quits their job to care for the individual with the rare disease brings with it the individual and social economic burden [14].

As in many countries of the world, there are problems in Turkey due to lack of knowledge about rare diseases, lack of specialist physicians in these fields, high costs of treatment of the diseases and lack of legal regulation regarding rare diseases and orphan drugs [12]. In particular, the low number of individuals with rare diseases causes not to be given priority in the health system and the public, and this results in problems in accessing health services [14]. Rare diseases differ from other diseases with their characteristics such as disease-specific drugs, treatments, medical tests, special nutrition programs, medical devices and consumable requirements [2]. However, every patient has equal rights when it comes to the right to health. Due to the rarity of diseases and limited demand for the treatment of these diseases, government support is very limited [3].

Recently, there has been a growing awareness all over the world, including Turkey, about the quality of life of individuals with rare diseases, the availability of orphan drugs and the cost of medicines. However, most countries have not studied the use of healthcare, drug use and the economic burden on the specific needs of individuals with rare diseases [15]. Health expenditures of people with rare diseases that are not covered by the government and have to be paid out-of-pocket place a great burden to the individuals and families [16]. Out-of-pocket health expenditures include payments made by individuals for the healthcare they receive and are not reimbursed by any person or institution [17].

In this study, it is aimed to determine the out-of-pocket health expenditures and economic burden of households where individuals with rare diseases live in Turkey.

## **Method**

In order to carry out the research, the necessary permission documents have been obtained from the Social and Human Sciences Research Ethics Committee of Ondokuz Mayıs University.

## **Research Population**

The research population consists of registered members of associations that are members of the Rare Diseases Network. Although there are approximately 4,000 individuals with rare diseases registered in the Rare Disease Network, no sample was selected from the research population and it was aimed to reach the entire population. Only individuals with rare diseases and willing to participate in the research were included in the study. In cases such as the fact that the individual with rare diseases is a child, is illiterate, does not have the necessary information; the necessary data were obtained from their parents.

## **Research Questionnaire**

Within the scope of the study, a questionnaire was used by individuals with rare diseases and their families as the data collection tool to determine out-of-pocket expenditures related to the disease in the last 1 year. The questionnaire was developed based on literature review and expert opinion.

The first part consists of 14 questions to determine the demographic characteristics of the individual with rare diseases, the second part consists of 11 questions about the rare disease which the person has, and the last part consists of 30 questions about the financial expenditures caused by the disease.

## **Data Collection**

The questionnaire was finalized by working with the members of the Board of Directors of the Rare Disease Network. After conducting the pilot study with a certain number of households, the necessary arrangements were made, and the online survey was made available between 01.05.2020–31.05.2020. In order to access the online survey, households have been given the necessary announcements and information by the Board of Directors of the Rare Diseases Network via e-mail.

## **Data Analysis**

After obtaining data on out-of-pocket expenditures in rare diseases, the necessary analysis was carried out through the Microsoft Office Excel application. In addition to the general analysis involving all participants, expenditures on the basis of disease group and disease were calculated. The costs calculated in Turkish Liras (₺/TL) have been converted to Euros (€) according to the average exchange rate for 2020.

*The average expenditure*

$$= \frac{\textit{Total expenditure}}{\textit{Total number of participants} - \textit{Number of people who did not respond}}$$

*Medical expenditures*

$$= \textit{special nutrion} + \textit{medicine} + \textit{laboratory and imaging tests} \\ + \textit{medical devices and supplies} + \textit{emergency} + \textit{hospitalization} \\ + \textit{specialist physician visit}$$

$$\textit{Non - medical expenditures} = \textit{Transportation/Food/Accommodation} + \\ \textit{patient care} + \textit{non - medical supplies} + \textit{traditional/complementary medicine}$$

*Medical expenditure rate in annual household income*

$$= \frac{\textit{out of pocket medical expenditures} - \textit{amount of reimbursed}}{\textit{annual household income}}$$

*Non - medical expenditure rate in annual household income*

$$= \frac{\textit{out of pocket non - medical expenditures} - \textit{amount of reimbursed}}{\textit{annual household income}}$$

## Findings

### Descriptive Findings

Among those submitted questionnaires, the number of households with rare diseases who participated in the study was 472. Following the examinations, the appropriate and complete fillings were detected and

the answers of 452 participants were included in the analysis. Estimated respond rate was calculated as 11.8%.

However, since there are 2 individuals with rare diseases in 4 households, the total number of individuals with rare diseases was 456. The first part of the research questionnaire contains demographic information about the individual with rare diseases. Data on the demographic information of individuals with rare diseases participating in the survey are presented in Table 1. The average age was 11.7 for the group of participants with rare diseases, the youngest of whom was 1 and the oldest was 70 years old.

Table 1  
Demographic Findings Regarding  
Participants

<b>Age</b>	<b>n</b>	<b>%</b>
1-4	99	21.71
5-9	155	33.99
10-14	87	19.08
15-19	49	10.75
20-24	20	4.39
25-29	14	3.07
30-34	10	2.19
35-39	5	1.10
40-44	6	1.32
45-49	2	0.44
50-54	3	0.66
55-59	2	0.44
60-64	1	0.22
65+	1	0.22
Unspecified	2	0.44
Total	456	100
<b>Sex</b>	<b>n</b>	<b>%</b>
Women	137	30.04
Men	316	69.30
Unspecified	3	0.66
Total	456	100
<b>Marital Status</b>		
Married	21	4.61
Single	435	95.4
Total	456	100
<b>Education Status</b>		

<b>Age</b>	<b>n</b>	<b>%</b>
Illiterate	185	40.57
Primary school	189	41.44
High school	53	11.62
University	20	4.39
Graduate	5	1.10
Unspecified	4	0.88
Total	456	100
<b>Health Insurance</b>		
General Health Insurance	421	92.32
Private Health Insurance	13	2.85
Both	22	4.82
Total	456	100
<b>Employment Status</b>		
Unemployment	426	93.42
Employee	26	5.70
Retired	4	0.88
Total	456	100

Among the total participants in the questionnaire, the occupational information about the occupational fields and annual income of 30 individuals with rare diseases who are working and retired are presented in Table 2.

Table 2  
Occupational Information on Participants

<b>Job Distribution</b>	<b>n</b>	<b>%</b>
Retired	4	13.33
Student	2	6.67
Laborer	7	23.33
Banker	1	3.33
Officer	12	40.00
Programmer	1	3.33
Electronic Repair	1	3.33
Self-employment	2	6.67
Total	30	100
<b>Inability to Work Due to Illness</b>		
Yes	22	73.33
No	8	26.67
Total	30	100
<b>Loss of Income Due to Illness</b>		
Yes	15	68.18
No	7	31.82
Total	22	100
<b>Annual income of the patient</b>		
	<b>₺</b>	<b>€</b>
Minimum	1,200	152
Maximum	60,000	7,590
Average (SD)	33,608 (± 15,678)	4,251 (± 1,983)
<b>Annual Loss of Income</b>		
Minimum	500	63
Maximum	36,000	4,554
Average (SD)	7,583 (± 9,686)	959 (± 1,225)

<b>Job Distribution</b>	<b>n</b>	<b>%</b>
<b>Annual income of the household where the patient lives</b>		
Minimum	8,000	1,012
Maximum	264,000	33,396
Average (SD)	41,489 (± 25,854)	5,248 (± 3,270)

## Findings About the Diseases

In the second part of the questionnaire, there are questions about the rare disease that individuals who participated in the research have. Rare diseases identified were examined under the category of metabolic diseases, neuromuscular system diseases and others according to the type of the disease. Accordingly, 233 patients were included in the metabolic diseases category, 178 in the neuromuscular system diseases category and 41 in the others category. Information on the diagnosis of the rare disease that the participants have is presented in Table 3.

Table 3  
Rare Disease Distribution Regarding Participants

<b>Metabolic Diseases</b>	<b>n</b>	<b>%</b>
Addison's Disease (Adrenal Insufficiency)	1	0.22
Maple Syrup Urine Disease (MSUD)	3	0.66
Albinism	26	5.70
Celiac Disease	1	0.22
Fabry Disease	1	0.22
Phenylketonuria	97	21.27
HPA	1	0.22
Cystic fibrosis	69	15.13
Lipid storage disease (Goser)	1	0.22
Mucopolysaccharidosis	5	1.10
Ornithine Transcarbamylase (OTC) Deficiency	1	0.22
Paroxysmal Nocturnal Hemoglobinuria (PNH)	1	0.22
Cystinosis	24	5.26
Sotos Syndrome	1	0.22
Tyrosinemia Type 1	1	0.22
Multiple Disease*	3	0.66
<b>Subtotal</b>	<b>236</b>	<b>51.75</b>
<b>Muscular and Nervous System Diseases</b>		
Amyotrophic Lateral Sclerosis (ALS) (Motor Neuron Disease)	2	0.44
Ankylosing spondylitis	1	0.22
Ataxia Telangiectasia	6	1.32
Becker Muscular Dystrophy	4	0.88
Duchenne Muscular Dystrophy (DMD)	133	29.17
Juvenile NCL Type III (Batten's Disease)	3	0.66
Limb-Girdle Muscular Dystrophies (LGMD)	1	0.22
NCL Type V	1	0.22
Neurofibromatosis Type 1	1	0.22

<b>Metabolic Diseases</b>	<b>n</b>	<b>%</b>
Ohtahara Syndrome	1	0.22
Autism	1	0.22
Autosomal Recessive Limb-Girdle Muscular Dystrophy Type 2A	1	0.22
Pantothenate Kinase Associated Neurodegeneration (PKAN)	1	0.22
Sandhoff Disease	1	0.22
Cerebellar Ataxia- Hypogonadism Syndrome	1	0.22
Cerebral Palsy	1	0.22
Spinal Muscular Atrophy (SMA)	17	3.73
Wolf-Hirschhorn Syndrome	1	0.22
Multiple Disease*	2	0.44
<b>Subtotal</b>	<b>179</b>	<b>39.25</b>
<b>Other</b>		
Cri du Chat Syndrome	1	0.22
Dlf508	1	0.22
Eisenmenger Syndrome	1	0.22
Ekstrophy Vesika	13	2.85
Glycogen Storage Disease	3	0.66
Pulmonary Arterial Hypertension	4	0.88
Scleroderma	6	1.32
Treacher Collins Sendromu	1	0.22
Treacher Collins Syndrome	9	1.97
Multiple Disease*	2	0.44
<b>Subtotal</b>	<b>41</b>	<b>8.99</b>
<b>Total</b>	<b>456</b>	<b>100</b>

\* 7 participants have 2 different rare diseases. Multiple diseases in the group of metabolic diseases are: Phenylketonuria + DHPR deficiency and Cystic fibrosis + Familial Mediterranean Fever (FMF); multiple diseases in the group of muscular and nervous system diseases are: DMD + Becker muscular dystrophy and Ataxia telangiectasia + Hodgkin lymphoma; multiple diseases in the other group are: Cohen syndrome + NCL Type II and Pulmonary arterial hypertension + Atrial septal defect.

## Findings About the Expenditures

After obtaining data on the treatment services, doctor's examinations, medications, medical supplies and access to treatment of individuals with rare diseases; out-of-pocket expenditures were determined in relation to the disease. Analysis of the expenditures of individuals with rare diseases was carried out of 452 households. These expenditures are determined on the basis of expenditure items according to the usage and payment status of the individual with rare diseases. When the expenditures for the entire group of participants were examined, it was determined that special nutrition expenditures were the highest expenditure group and emergency department expenditures were the lowest expenditure group. Transportation, food and accommodation expenses for access to healthcare services are second in total expenditures after special nutrition (Table 4).

Following the general analyses of all participants, out-of-pocket expenditures were examined on the basis of disease group. For 233 people in the metabolic diseases group, the average out-of-pocket expenditure in the last year was lower than the general average. Special nutrition expenditures constitute the highest expenditure group for metabolic diseases (Table 5).

Neuromuscular system diseases group is the disease group with the highest average out-of-pocket expenditure. Special nutrition, medicine and transportation-food-accommodation expenditures are the items that are spent at similar rates after medical and non-medical devices and supplies. (Table 6).

In the others group, the average out-of-pocket expenditures are close to the neuromuscular system diseases group and are higher than the general average. Other diseases include transportation-food-accommodation, laboratory and imaging tests, and high expenditure items for medical and non-medical devices and materials (Table 7).

Table 4  
Out-of-pocket Expenditures by Participants in the Last 1 Year

<b>Spending Item</b>	<b>Total Expenditure (₺)</b>	<b>Average Expenditure (₺)</b>	<b>Total Expenditure (€)</b>	<b>Average Expenditure (€)</b>	<b>Percentage in Total Expenditure</b>
Special Nutrition	1,284,866.00	3,303.00	162,535.55	417.83	%25.86
Medicine	601,790.00	1,657.82	76,126.44	209.71	%12.11
Laboratory and Imaging Tests	344,740.00	993.40	43,609.61	125.66	%6.94
Medical and Non-Medical Devices and Supplies	738,915.00	1,771.35	93,472,75	224.08	%14.88
Traditional / Complementary Medicine	222,965.00	501.04	28,205.07	63.38	%4.49
Emergency	22,405.00	56.29	2,834.23	7.12	%0.45
Hospitalization	279,190.00	697.98	35,317.54	88.29	%5.62
Transportation-Food-Accommodation	839,970.00	2,074.00	106,256.21	262.36	%16.91
Patient care	380,000.00	840.71	48,070.00	106.35	%7.65
Specialist Physician Visit	253,007.00	614.09	32,005.39	77.68	%5.09
<b>Total</b>	<b>4,967,848.00</b>	<b>12,509.68</b>	<b>628,432.77</b>	<b>1,582.47</b>	<b>%100</b>

\*1 TL= € 0.13

Table 5  
Out-of-pocket Expenditures Regarding Metabolic Diseases Group

Spending Item	Total Expenditure (₺)	Average Expenditure (₺)	Total Expenditure (€)	Average Expenditure (€)	Percentage in Total Expenditure
Special Nutrition	847,100.00	4,172.91	107,158.15	527.87	%38.79
Medicine	218,900.00	1,189.67	27,690.85	150.49	%10.02
Laboratory and Imaging Tests	143,550.00	792.05	18,159.08	100.19	%6.57
Medical and Non-Medical Devices and Supplies	154,055.00	682.40	19,487.96	86.32	%7.05
Traditional / Complementary Medicine	22,250.00	95.91	2,814.63	12.13	%1.02
Emergency	8,900.00	43.84	1,125.85	5.55	%0.41
Hospitalization	75,405.00	369.63	9,538.73	46.76	%3.45
Transportation-Food-Accommodation	444,750.00	2,127.99	56,260.88	269.19	%20.37
Patient care	181,500.00	778.97	22,959.75	98.54	%8.31
Specialist Physician Visit	87,387.00	408,35	11,054,46	51,66	%4.00
<b>Total</b>	<b>2.183.797,00</b>	<b>10.661,73</b>	<b>276.250,32</b>	<b>1.348,71</b>	<b>%100</b>

\*1 TL= € 0.13

Table 6  
Out-of-pocket Expenditures Regarding Muscular and Nervous System Diseases Group

<b>Spending Item</b>	<b>Total Expenditure (₺)</b>	<b>Average Expenditure (₺)</b>	<b>Total Expenditure (€)</b>	<b>Average Expenditure (€)</b>	<b>Percentage in Total Expenditure</b>
Special Nutrition	374,900.00	2,533.11	47,424.85	320.44	%16.52
Medicine	348,490.00	2,370.68	44,083.99	299.89	%15.35
Laboratory and Imaging Tests	106,390.00	795.79	13,458.34	100.67	%4.69
Medical and Non-Medical Devices and Supplies	503,790.00	3,263.10	63,729.44	412.78	%22.20
Traditional / Complementary Medicine	194,515.00	1,117.90	24,606.15	141.41	%8.57
Emergency	12,835.00	80.22	1,623.63	10.15	%0.57
Hospitalization	137,435.00	848.36	17,385.53	107.32	%6.06
Transportation-Food-Accommodation	298,920.00	1,868.25	37,813.38	236.33	%13.17
Patient care	169,000.00	949.44	21,378.50	120.10	%7.45
Specialist Physician Visit	123,470.00	776.54	15,618.96	98.23	%5.44
<b>Total</b>	<b>2,269,745.00</b>	<b>14,603.39</b>	<b>287,122.74</b>	<b>1,847.33</b>	<b>%100</b>

\*1 TL= € 0.13

Table 7  
Out-of-pocket Expenditures Related to Other Diseases Group

Spending Item	Total Expenditure (₺)	Average Expenditure (₺)	Total Expenditure (€)	Average Expenditure (€)	Percentage in Total Expenditure
Special Nutrition	62,866.00	1,654.37	7,952.55	209.28	%12.22
Medicine	34,400.00	1,075.00	4,351.60	135.99	%6.69
Laboratory and Imaging Tests	94,800.00	2,943.56	11,992.20	372.36	%18.43
Medical and Non-Medical Devices and Supplies	81,070.00	2,184.54	10,255.36	276.34	%15.76
Traditional / Complementary Medicine	6,200.00	158.97	784.30	20.11	%1.21
Emergency	670.00	19.14	84.76	2.42	%0.13
Hospitalization	66,350.00	1,951.47	8,393.28	246.86	%12.90
Transportation-Food-Accommodation	96,300.00	2,675.00	12,181.95	338.39	%18.72
Patient care	29,500.00	719.51	3,731.75	91.02	%5.74
Specialist Physician Visit	42,150.00	1,080.77	5,331.98	136.72	%8.20
<b>Total</b>	<b>514,306.00</b>	<b>14,462.33</b>	<b>65,059.71</b>	<b>1,829.49</b>	<b>%100</b>

\*1 TL= € 0.13

In addition to the analysis carried out on the basis of disease groups, average out-of-pocket expenses were compared according to average annual income. When examined for all participants; it is possible to say that out-of-pocket expenses related to the disease makes up of 30% of the average annual income of the household of the individual with the rare disease. When examined on the basis of disease group, the average amount of out-of-pocket expense according to average annual income shows similar results in neuromuscular system diseases and other diseases groups. The average out-of-pocket expenditures based on their average annual income is the lowest in the group of metabolic diseases (Graph 1).

The average annual household income for individuals with rare diseases is ₺41,489 (€5,248), while the average household income across Turkey is ₺59,873 (€7,573) for 2019, according to data published by the Turkish Statistical Institute (TURKSTAT). According to the analysis, 80.31% (363 people) of all participants had incomes below the average household income announced by TURKSTAT. 79.40% (185 people) of the metabolic diseases group, 82.02% (146 people) of the neuromuscular system diseases group and 78.05% (32 people) of the other diseases group have a household income lower than the

average household income announced by TURKSTAT. When evaluated for all participants; the average household income in individuals with rare diseases was 30.70% below the average household income for Turkey (Graph 2). This ratio is similar for all disease groups.

When a household member quits their job to care for the patient, it creates a loss of income. Adding the total loss of income to the total out-of-pocket expenditures makes up the cost of the disease. When evaluated for all participants, the average cost of rare diseases was found to be ₺22,796 (€2,883). The costs of the diseases were found to be ₺20,283 (€2,565) for the metabolic diseases group, ₺25,720 (€3,253) for the neuromuscular system diseases group, and ₺25,629 (€3,242) for the other diseases group.

When all participants' out-of-pocket expenses are evaluated; 72.26% of the total expenses were allocated to medical, and 27.74% to non-medical expenses. When the reimbursed amount is subtracted from medical expenses; it has been observed that 47.35% of all participants allocate more than 10% of the annual average household income and 4.65% more than 100% of the annual average household income for medical expenses. This rate shows similar results for all disease groups. When the amount reimbursed from non-medical expenses is removed; it was observed that 22.79% of all participants allocated more than 10% of their average annual household income and 1.11% allocated more than 100% of the average annual household income to non-medical expenses. This rate was found to be higher in the others group (4.88%) than the rest of the disease groups (Table 8).

Table 8  
Ratio of Out-of-pocket Medical and Non-Medical Expenditures to Average Household Income

Expenditure Rate	Households Expenditures More Than 10%				Households Expenditures More Than 100%			
	Medical Expenditures		Non-Medical Expenditures		Medical Expenditures		Non-Medical Expenditures	
	n	%	n	%	n	%	n	%
Overall	214	47.35	103	22.79	21	4.65	5	1.11
Metabolic Diseases	109	46.78	55	23.61	9	3.86	1	0.43
Muscular and Nervous System Diseases	85	47.75	40	22.47	11	6.18	2	1.12
Other	20	48.78	8	19.51	1	2.44	2	4.88

In addition to general analyses involving all participants and analysis according to the disease group, out-of-pocket expenses were analyzed on the basis of disease. This analysis included the rare diseases that more than 10 people had among all the rare diseases that the participants had. Accordingly, it was observed that the average out-of-pocket expense was in the lowest in albinism disease and the highest in extrophy vesica disease. In addition, it is seen that the average out-of-pocket expenses in DMD, SMA, cystinosis and cystic fibrosis diseases are close to each other (Table 9).

Table 9  
Out-of-pocket Expenditures Based on Disease

Disease	Total Expenditure (₺)	Average Expenditure (₺)	Total Expenditure (€)	Average Expenditure (€)
Albinism	117,770.00	5,145.56	14,897.91	650.91
DMD	1,622,405.00	14,127.78	205,234.23	1,787.16
Ekstrophy Vesika	169,190.00	15,348.94	21,402.54	1,941.64
Phenylketonuria	843,400.00	10,282.51	106,690.10	1,300.74
SMA	217,600.00	14,635.73	27,526.40	1,851.42
Cystinosis	290,664.00	14,510.24	36,769.00	1,835.55
Cystic fibrosis	788,413.00	13,882.11	99,734.24	1,756.09

\*1 TL= € 0.13

## Discussion

Compared to other diseases, rare diseases show very different characteristics on diagnosis and treatment stages, and disease processes. However, due to the low prevalence in the general population, rare diseases are often an area that is not emphasized, and the policies are inadequate. For this reason, it is of great importance to determine the economic burden that individuals with rare diseases and their families are subjected to, and to organize development policies. In this study carried out with this specific purpose, out-of-pocket expenditure of individuals with rare diseases and their families were analyzed.

According to the analyses, the average age of the participants was found to be quite low. Considering that the rare diseases mostly affect children; it is an expected result that the average age of the participants is 12. The fact that 95% of the participants are single, 40% are illiterate, the rate of primary school graduates is very low, and the working population is only 7% can be explained by the low average age. In addition, the vast majority of individuals with rare diseases have difficulty participating in education and work life due to their diseases. This situation is caused by the physical limitations they experience, those limitations making it difficult to continue their education and business life, the difficulties in participating in social life due to the lack of awareness and consciousness in the society, the difficulties they experience in finding a job and the treatment processes making it difficult to participate in education and business life.

92% of participants are covered by general health insurance, almost 3% are covered by private health insurance, and 5% have both types of insurance. Although all participants are covered by insurance, enormous out-of-pocket expenses indicate that there are unmet needs in rare diseases.

When the total out-of-pocket expenditures related to rare diseases are examined, from highest to lowest; special nutrition expenditures (25.86%), transportation/accommodation/food (16.91%), medical and non-medical devices and supplies (14.87%), medicine (12.11%), patient care (7.65%), laboratory and imaging tests (6.94%), hospitalization (5.62%), specialist visits (5.09%), traditional and complementary medicine (4.49%) and emergency department services (0.45%). The fact that special nutrition expenditures account for a quarter of all expenditures shows how big food expenditures are in these diseases and that there is no improvement in this field since there is no awareness in our country about this issue. According to a 2019 study with rare disease sufferers, it was determined that 28% of the difficulties encountered in the treatment process in rare diseases were caused by management/system and policy, 23% from access and 19% from finance. These challenges are; the lack of coverage of treatment services and medicines, the low coverage of medical devices, the expensiveness of low protein products, the lack of reimbursement due to the high costs of genetic therapies to correct the mutation seen in rare diseases, and the failure to cover certain disease-specific foods [18]. The study found that many of the difficulties experienced in rare diseases are due to economic problems related to treatment and medicines, food and medical supplies needed.

According to the results of the analysis, it was observed that the participants had an average income of 30.70% lower than the average household income announced by TURKSTAT. This rate shows similar results for all disease groups. It is thought that this is due to the fact that when there is a rare disease sufferer in the household, one of the households usually quits for care or can only work in part-time jobs for short periods. Although the average household income is low, according to the data released by TURKSTAT, per capita expenditure on health in 2019 is ₺2,434 (€307), while according to this study, almost 6 times more health expenditures are made out-of-pocket in individuals with rare diseases.

When evaluated according to the disease groups, it was observed that the average annual out-of-pocket expenditure in diseases in the neuromuscular system and the other diseases groups were very close to each other and higher than the general average. The average annual out-of-pocket expenditure rate of the metabolic diseases group is lower than the other diseases groups and the general average. Similarly, when evaluated according to the average annual income; while out-of-pocket expenditures made for diseases in the neuromuscular system and other diseases groups cover 35% of the average income, this rate is around 26% in the metabolic diseases group. When examined on the basis of expenditure for each group; it was observed that the area that was paid the most is special nutrition expenditures (39%) in the metabolic diseases group, medical and non-medical devices and materials expenditures (22%) in the neuromuscular system diseases group, and laboratory and medical imaging tests expenditures (18%) in the others group.

Of the studies on the subject, the study by Lopez-Bastida and his colleagues (2016) analyzed the quality of life and annual expenditures of individuals with rare diseases and their caregivers for specific countries [19]. In the study, the difference of the areas spent according to the type of disease and the costs varying in different countries are noted. This is due to the difference in the use of medicines and healthcare that are approved and covered by reimbursement in each country. Similarly, the study

conducted by Gong and his colleagues (2016) examined the availability and affordability of orphan drugs in China. The average cost of 23 orphan drugs analyzed in the study was found to be \$4,843.5, which equates to the 505.6-day net income of a middle-income individual. The study results show that the availability of orphan drugs in China is not only very low (20.8%), but also the drug costs are unaffordable for most patients [20].

The economic cost of the disease includes similar results in neuromuscular system diseases and other diseases groups, while it is lower in the metabolic diseases group. It is thought that this is due to the fact that participants with neuromuscular system diseases and other diseases groups with rare diseases are more difficult to care for, therefore the total loss of income is also higher because one of the households quits their job. When evaluated for all participants; It was observed that the economic cost of the disease was above 10% of their average annual income of 70.13% of the participants and above their average income of 26.11%.

Considering the out-of-pocket expenditures of all participants based on their average annual income, it is seen that the participants allocated 30% of their average annual income to expenditures associated with their rare diseases. It was observed that 7.74% of the participants allocated more than all of their average annual income and 59.51% did more than 10% of their average annual income to out-of-pocket expenses associated with rare disease. It is understood that households experiencing this situation maintain their lives through financial support provided from non-governmental organizations, municipalities, patient associations or by friends, relatives, neighbors and through bank loans and/or borrowing. Excessive out-of-pocket expenses can result in catastrophic expenditures. The catastrophic effect occurs when health expenditures exceed a certain threshold and often has an impoverishing effect on households. Although there are two different threshold definitions in the literature, expenditures above 10% of household total income and 40% of non-food expenditures (payment capacity) are considered catastrophic [21]. When evaluated in accordance with this explanation, it can be said that almost 60% of participants with rare diseases are exposed to catastrophic health expenditure.

Among all diseases, rare diseases of more than 10 people were specially analyzed, and it was seen that the highest average out-of-pocket expenditure among these diseases was in extrophy vesica disease. In addition, the average out-of-pocket expenditure in DMD, cystic fibrosis, cystinosis and SMA disease are similar. The disease with the lowest out-of-pocket expenditure was determined as albinism. The area of expenditure according to the type of disease also varies. Although out-of-pocket expenditure amounts are similar, when evaluated on expenditure group basis; Medical and non-medical devices and supplies in albinism (32%) and SMA (41%), special nutrition in DMD (20%) and phenylketonuria (71%), and transportation/accommodation/food expenses in patients with extrophy vesica (47%), cystic fibrosis (24%) and cystinosis (32%) were found to be the highest expenditure groups. In the research conducted by TURKSTAT, out-of-pocket expenditure per capita for 2019 was found to be ₺407 [22]. Statistics on out-of-pocket health expenditures, including TURKSTAT data, omit the costs in accessing the healthcare. According to the general average, approximately 31 times the expenditure is made in households where

individuals with rare diseases live. This, in addition to being economically destructive, also brings about health inequalities.

## Conclusion

This study is of great importance in order to ensure a clear picture of the economic difficulties experienced by individuals with rare diseases. Since individuals with rare diseases are often unable to work, out-of-pocket expenditures related to the disease lead to financial difficulties and even impoverishment. Their already difficult lives get even more difficult by the financial sacrifices made for treatment. Treatments for rare diseases need to go beyond special exclusivity for patient access and reimbursement.

For this purpose, it is necessary to ensure that patients have complete and unrestricted access to treatments, that access to treatment not only in big cities but also in every patient's own city, that insurance coverages related to treatment and medicine are expanded and regulated according to current market figures, that special needs related to the disease are not dependent on the patient's ability to pay, and that the national plan for the rare diseases missing in our country should be prepared as soon as possible. The cooperation and support of all responsible stakeholders such as patients, patient relatives, associations, physicians, political actors and sector representatives will make significant contributions to the solution of the problems experienced by patients.

## Abbreviations

### **ALS**

Amyotrophic Lateral Sclerosis

### **DMD**

Duchenne Muscular Dystrophy

### **FMF**

Familial Mediterranean Fever

### **LGMD**

Limb-Girdle Muscular Dystrophies

### **MSUD**

Maple Syrup Urine Disease

### **OTC**

Ornithine Transcarbamylase

### **PKAN**

Pantothenate Kinase Associated Neurodegeneration

### **PNH**

Paroxysmal Nocturnal Hemoglobinuria

### **SMA**

Spinal Muscular Atrophy

TL

Turkish Liras

TURKSTAT

Turkish Statistical Institute

WHO

World Health Organization

## Declarations

**Ethics approval and consent to participate:** The necessary Ethics approval have been obtained from the Social and Human Sciences Research Ethics Committee of Ondokuz Mayıs University. Consent have been obtained from the participants.

**Consent for publication:** Informed consent to participate in the study was obtained from participants or their parent or legal guardian in the case of child or baby.

**Availability of data and materials:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Authors' contributions:** Data collection, literature review and writing: Selin Ökçün, Mustafa Kurnaz, Ekin Begüm Karahan. Data analysis: Guvenc Kockaya, Zafer Çalışkan. Idea, interpretation, revision: Gulpembe Oguzhan, Deniz Atalay. All authors read and approved the final manuscript.

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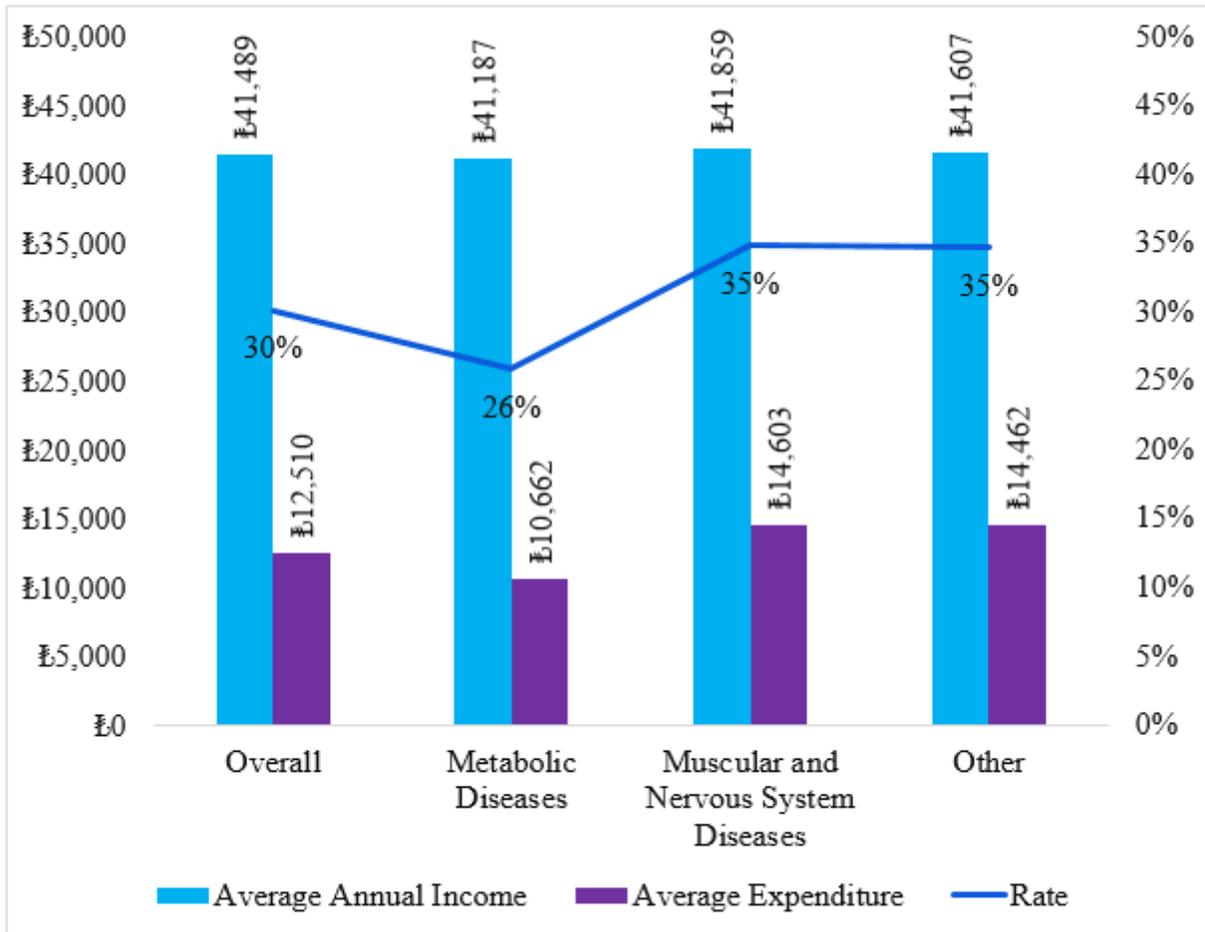
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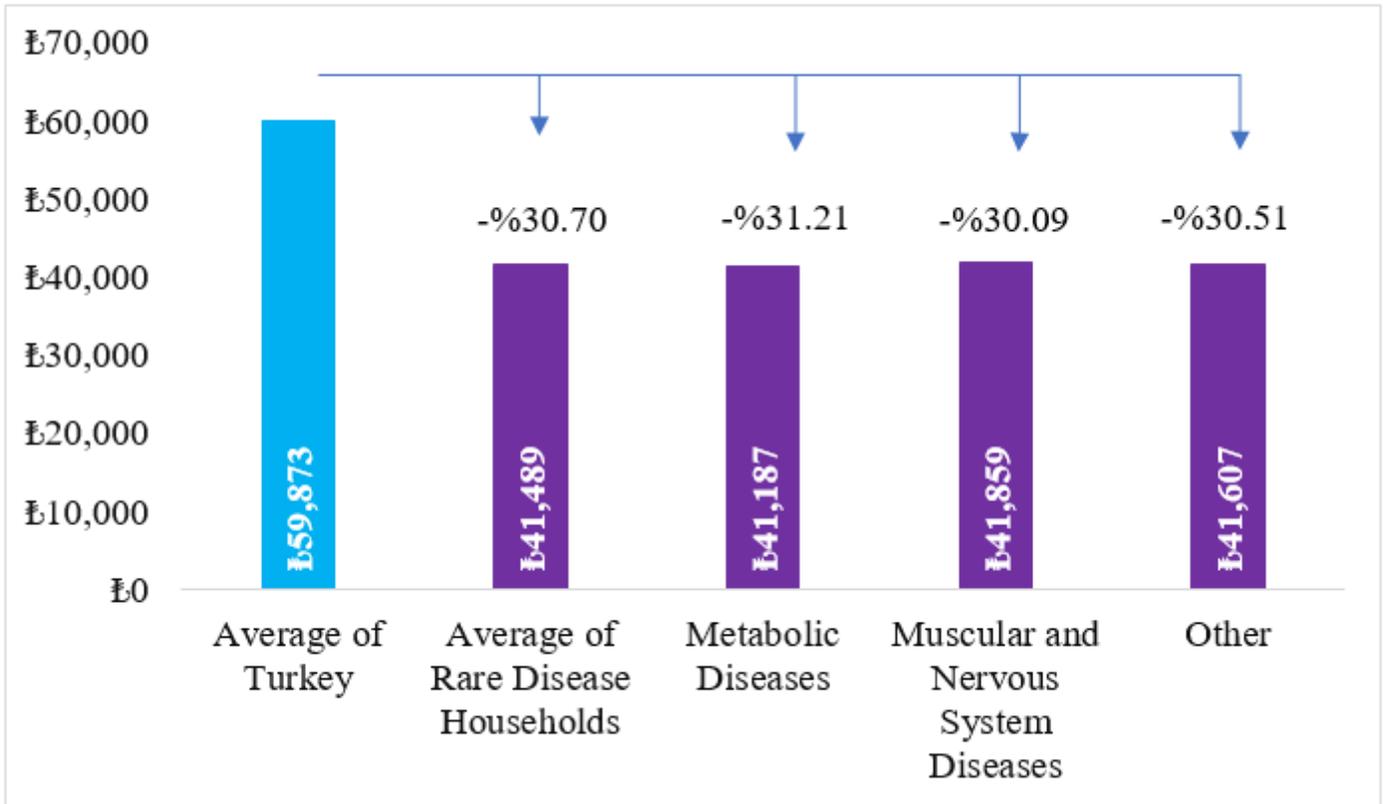
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23. **Graph 1.** Average Annual Income and Average Out-of-Pocket Expense.

## Figures



**Figure 1**

Average Annual Income and Average Out-of-Pocket Expense



**Figure 2**

Comparison of the Annual Average Income of Households with Rare Diseases