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ORIGINAL ARTICLES AND REVIEWS

# Gender and burden differences in family caregivers of patients affected by ten rare diseases

**Flavia Chiarotti[1], Yllka Kodra[2], Marta De Santis[2], Maria Bellenghi[3], Domenica Taruscio[2], Alessandra Carè[3*] and Marina Petrini[3*]**

[1]*Centro di Riferimento Scienze Comportamentali e Salute Mentale, Istituto Superiore di Sanità, Rome, Italy*
[2]*Centro Nazionale Malattie Rare, Istituto Superiore di Sanità, Rome, Italy*
[3]*Centro di Riferimento Medicina di Genere, Istituto Superiore di Sanità, Rome, Italy*
[*]*equal senior contributors*

**Abstract**

***Objectives.*** Gender differences in caregiving may determine social and/or health inequalities among family caregivers (FCs). This study aimed to analyse gender specific differences of burden and quality of life (QoL) in FCs belonging to ten different rare diseases (RD).

***Methods.*** Burden levels and QoL data, derived from a sample of 210 FCs of RD patients, were analysed by student t-test, Anova and Kruskal-Wallis followed by multiple comparisons and evaluation of factors, including sex, by correlation and multiple regression analyses.

***Results.*** FCs caring for Prader Willi, X-fragile, mucopolysaccharidosis and epidermolysis bullosa patients showed significant higher levels of burden as compared to other RDs. Burden is related to FC's QoL and can be down modulated by the reduction of the number of hours/week devoted to care and by the improvement of patient's QoL. No gender-specific burden differences were observed among all FCs. However, female FCs devoted to care significant more numerous hours/week than men and perceived more emotional/physical burden and poorer psychological health than males. Women, who are more frequently early retired from work, not occupied or homemakers than men, suffered more burden as compared to men in the same conditions.

***Conclusions.*** This study showed gender specific differences in RD caregiving, which are important for planning personalized health prevention policies.

**Key words**

- family caregivers
- burden, rare diseases
- gender differences

## INTRODUCTION

Family caregivers (FCs) typically are the unpaid care providers for a not self-sufficient family member. In Italy, it is estimated that the number of FCs is about three million people (Italian National Institute of Statistics, Istituto Nazionale di Statistica, 2018). Most FCs are women, 45-55 aged, 60% of which have given up their job to devote themselves full time to the care.

The Italian Orphanet website has estimated two million of rare disease (RD) patients, 70% of which are pediatric. Based on the National Rare Disease Registry (NRDR) of the Italian National Health Institute (Istituto Superiore di Sanità, ISS), 20 cases per 10,000 inhabitants are estimated and about 19,000 new cases are reported each year by more than 200 health care centers (www.malattierare.gov.it).

The number of RDs fluctuates between 7,000 and 8,000, but this is a number that grows with the progress of genetic research (https://globalgenes.org/rare-list).

In the last two decades, many studies have shown a relation between FCs' mental and physical health and caregiving activity, being health negatively influenced by high levels of chronic stress [1-4]. Accordingly, it has been reported that FCs may develop depression, anxiety, worse sleep quality and poor physical health, more frequently than the general population [5-7]. However, few studies exist on FCs of RD patients, probably due to the low number of recruitable FCs as compared to other conditions.

RDs may contribute to enhance caregiver burden as compared to more common disorders, likely because of the additional challenges involved in the RD condition, such as complexity of clinical management, emotional impact on patients, long lasting wait to receive an accurate diagnosis, lack of information, uncertainty of the

*Address for correspondence:* Marina Petrini, Centro di Riferimento Medicina di Genere, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. Email: marina.petrini@iss.it.

future and tension in the hope of a cure not yet available [8, 9].

Although no curative treatments are available for approximately 95% of the identified RDs, much can be done to improve patients' QoL, alleviation of physical suffering, preservation of individual autonomy, dignity, and support for caregivers [10].

Few studies to date have addressed gender focus among FCs, even if this should be a main research question for planning targeted interventions for a population, which is itself exposed to socio-cultural influences. Some studies have shown that gender differences in depression and physical health are indeed larger than those found in the general adult population, being in part explained by gender differences in facing caregiving stressors [11]. In particular, high levels of stressors and low levels of social resources accounted for elevated gender differences in burden [12]. Recently, the Health Related Quality of Life (HRQoL) score was reported useful for explaining health gender specific differences in population studies [13] and HRQoL resulted inversely correlated with burden in RDs caregivers [14]. Moreover, mothers of RDs' patients, as compared to fathers, were significantly more impaired in their QoL and mental health [15]. At the best of our knowledge, this study is the first looking for gender specific burden and HRQoL differences in FCs of patients with ten different RDs.

## METHODS

This study analyses data from a cross-sectional study carried out in 2012 [16] coordinated by the Italian National Center for Rare Diseases in collaboration with Italian rare disease federations and patients' organizations in the framework of BURQoL-RD project, funded by the European Commission. The survey was fully anonymous. Data were collected via on-line questionnaires completed by FCs and included socio demographic characteristics (sex and age of the patients, sex and age of FCs, relationship with the care recipient, marital and occupational status), HRQoL of both patients and FCs, burden, number of hours/week devoted to care by the principal FC and by a secondary caregiver where present.

*Rare diseases*: we selected FCs of individuals with the following 10 RDs: 1. Prader Willi syndrome (PWS); 2. hemophilia (Hem); 3. Duchenne muscular dystrophy (DMD); 4. scleroderma (Scl); 5. cystic fibrosis (CF); 6. fragile X syndrome (FXS); 7. histiocytosis (His); 8. mucopolysaccharidosis (MPS); 9. juvenile idiopathic arthritis (JIA); 10. epidermolysis bullosa (EB). The RDs selected differ in terms of genetic origin, age at onset during adulthood or childhood, physical impairment and/or mental impairment, availability of effective therapies, and represent a wide range of effective examples of RDs for our analysis.

*Study's instruments/tools*: the HRQoL was measured with the EuroQoL 5-domain questionnaire (EQ-5D) for both patients and FCs. The EQ-5D includes six items and measures generic HRQoL with regards to 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [17]. It also includes a Visual Analogue Scale (VAS) that patients and their caregivers use to rate their health status between 0 ("worst health") and 100 ("best health"). *Subjective burden* was measured with the 22-items version of the Zarit [18]. Each item is a statement which the caregiver is asked to respond to, using a five-point scale with options ranging from 0 (never) to 4 (nearly always) (burden scores: <21, little or no burden; 21-40, mild to moderate burden; 41-60, moderate to severe burden; >61, severe burden). *Barthel index* measures the patient's ability to perform ten basic activities of daily living, providing a quantitative estimate of the dependence degree [19]; it is recommended for measuring physical disability (scores: 90-99, mild dependence; 61-89, moderate dependence. 21-60, severe dependence; <20, complete dependence).

*Statistical analysis*: the analyses were performed on data from the FCs of the survey (n=210). Qualitative data are summarised by absolute and percent frequencies, while quantitative data by mean ± standard deviation (SD), median, range (minimum-maximum).

Patients and FCs were grouped according to patients' characteristics (rare diseases: 10 groups; age group: child *vs* adult) and FCs' characteristics (sex: male *vs* female; age class: up to 39, 40-54, 55 years and over; work condition: occupied *vs* retired *vs* homemaker *vs* other). Differences among subgroups with respect to categorical variables were analysed by chi-square test, or Fisher's exact probability test when appropriate. For the analysis of the quantitative variables, that is Zarit index, Barthel index, EQ-5D-VAS for both patients and FCs and the number of hours/week devoted to care, we used parametric analysis of variance (ANOVA) or non-parametric Kruskal-Wallis test. Multiple comparisons were performed by Tukey test. Since results were in accordance, only nonparametric analyses are reported.

Association between quantitative variables was assessed by Pearson linear correlation coefficient. Multiple linear regression analysis was performed to assess the effect of selected quantitative and/or categorical variables on the quantitative outcomes burden and FCs' HRQoL. Two regression models were applied, including different sets of potential explanatory variables. Model A included FCs' sex, patient's HRQoL, Barthel index, principal and support caregiver's number of hours/week devoted to care, and burden (the latter when assessing the effect of variables on FCs' HRQoL). Model B included Barthel index, patient's age, kind of pathology. For the latter, DMD was chosen as the reference level being the pathology with the more numerous FCs. The variance inflation factor (VIF) was calculated to test for multicollinearity among the independent variables, which was excluded for VIF values lower than 5. All VIF values were actually lower than 1.5.

The statistical analyses were then repeated on the subsample of FCs who were parents of the patients (n=182).

In particular, to assess the hypothesis that FCs are more frequently females than males we analyzed data on the subset of RDs patients living with both parents, using the Binomial test to assess if the proportion of female FCs in the parental couples was significantly different from the chance level of 50%.

All the analyses were performed using STATA release 16.0.

Limits of this study were: convenience samples, low number of caregivers and too few male FCs; no data on disease severity or phenotypic classification was collected by the questionnaire.

## RESULTS

### *Family caregivers' characteristics and sex/gender differences*

As reported in *Table 1a*, FCs showed significant sex/gender specific differences of the number of hours/week devoted to care with women dedicating a higher number of hours (53.7±34.1) as compared to men (41.8±32.7). Differently, no significant sex/gender-specific differences were detected for burden or HRQoL.

However, on regard to burden, we detected significant differences between males and females in the answers to Zarit single items. Specifically, to the question "do you feel fear for the future" 68.5% of women *vs* 43.4% of men answered "always" or "very often". Similarly, 54.7% of men *vs* 31.5% of women answered "never" to the question "do you believe that taking care of your family member has adversely affected your health" (*Tables 1aS* and *1bS* available online as *Supplementary Material*).

Since the significant sex/gender specific differences in the caregiver's age and employment status, we analysed burden in FCs grouped by sex (males *vs* females), age groups (up to 39 years, 40-54 years, over 55 years), and working condition (occupied *vs* retired *vs* homemaker *vs* others) (see *Table 2S* available online as *Supplementary Material*). Our results indicate that: a) in the 40-54 age

**Table 1a**
Socio-demographic characteristics of family caregivers by sex

| Characteristics | Males | Females | Total | Significance level p |
|---|---|---|---|---|
| | n<br>mean (SD)<br>median (min-max) | n<br>mean (SD)<br>median (min-max) | n<br>mean (SD)<br>median (min-max) | Mann-Whitney U test |
| Age | 56<br>51.2 (11.2)<br>50 (28-78) | 152<br>44.0 (9.1)<br>43 (25-82) | 208<br>45.7 (10.2)<br>45 (25-82) | **<0.001*** ** |
| Zarit tot | 53<br>25.6 (12.6)<br>22 (0-60) | 146<br>28.1 (12.6)<br>27 (6-59) | 199<br>27.4 (12.5)<br>25 (0-60) | 0.185 |
| EQ5D-VAS | 49<br>78.9 (17.5)<br>80 (30-100) | 144<br>78.7 (14.5)<br>80 (30-100) | 193<br>78.7 (15.3)<br>80 (30-100) | 0.563 |
| FC n hours/week | 57<br>41.8 (32.7)<br>36.8 (0-112) | 153<br>53.7 (34.1)<br>47.7 (0-112) | 210<br>50.5 (34.1)<br>46.7 (0-112) | **0.023*** |
| | ***n (%)*** | ***n (%)*** | ***n (%)*** | ***Fisher's exact probability test*** |
| Marital status | 56 | 150 | 206 | 0.600 |
| Single + widow | 4 (7.1%) | 17 (11.3%) | 21 (10.2%) | |
| Divorced + Separated | 2 (3.6%) | 9 (6.0%) | 11 (5.3%) | |
| Married | 50 (89.3%) | 124 (83.7%) | 174 (84.5%) | |
| Occupational status | 57 | 153 | 210 | **<0.001*** ** |
| Employed | 42 (73.7%) | 76 (49.6%) | 118 (56.2%) | |
| Retired | 9 (15.8%) | 16 (10.5%) | 25 (11.9%) | |
| Homemakers | 3 (5.3%) | 45 (29.4%) | 48 (22.9%) | |
| Other | 3 (5.3%) | 16 (10.5%) | 19 (9.0%) | |

FC: family caregiver; Other: never occupied or forced to leave job.
SD: standard deviation; min-max: minimum-maximum; p: significance levels of the Fisher's exact probability test or of the Mann-Whitney U test: * p≤0.05; *** p≤0.001.

**Table 1b**
Married/cohabiting family caregivers grouped by sex and age

| Married/cohabiting FCs | <39 age n (%) | 40-54 age n (%) | >55 age n (%) | Total n (%) |
|---|---|---|---|---|
| | **p<0.001*** ** | **p<0.001*** ** | p=0.315 | |
| Males | 5 (11.1%) | 25 (27.5%) | 7 (41.0%) | 37 (24.1%) |
| Females | 40 (88.9%) | 66 (72.5%) | 10 (59.0%) | 116 (75.8%) |
| Total | 45 (100.0%) | 91 (100.0%) | 17 (100.0%) | 153 (100.0%) |

FC: family caregiver.
p: significance level with binomial test: *** p≤0.001.

group, commonly representing the working age, 9% of women were already retired and reported moderate levels of burden, whereas no man was retired in the same age group. The occupied women were less numerous than men and female homemakers were more numerous than males with burden levels double than men; b) not considering age, women never occupied or forced to leave work (named as others), suffered higher levels of burden as compared to men; c) female FCs, under 39 years of age and occupied, reported more burden than males of the same age group, likely for the presence of additional stressors, such as reconciling time for family care with work outside home. Despite the not significant differences found between the different groups, due to the small sample size, the above data suggest that gender specific burden differences can be associated with FCs' age and working status conditions.

Among the 179 FCs respondents to the marital status item, we selected the 153 cohabiting/married FCs, assuming that they are one of the two members of a parental couple with a rare disease patient in a home care context. We stratified them by sex and age in order to investigate if an equal sex/gender distribution of the care activity might exist between the two members of a parental couple. Results, shown in *Table 1b*, indicate that there is a significant sex/gender difference of the care activity in the age groups under 39 and 40-54 years of age with women representing 88.9 and 72.5% respectively ($p<0.001$ in both groups when compared to the 50% expected in case of parity). Only in the over 55 years age group, the percentage of females dropped, being only slightly over the 50% expected parity frequency ($p=0.31$).

We also stratified FCs by patient's age, child *vs* adult. We did not observe significant differences in burden, HRQoL or number of hours/week between FCs who care for children or adults patients. We indeed observed a significant difference in the answers to the EQ-5D item, asking caregivers to refer their actual pain and discomfort. FCs caring for adults showed pain and discomfort more frequently (63% *vs* 37%; *Table 3S* available online as *Supplementary Material*) and with high intensity as compared to those caring for child patients. Specifically for those caring children the median was positioned in the answer "no pain and discomfort", while for those caring adults the median was positioned in the answer "mild pain and discomfort".

### *Family caregivers grouped by the 10 RDs*

*Table 2* reports the characteristics of FCs grouped according to the 10 RDs. Sex distribution of FCs among RDs was not so much different, being females more than 62% in all RDs, except for Scl with 58.8% males. This exception can be explained by the fact that Scl patients are mainly adult females and their FCs are primarily their partners. FCs age was significantly different among 10 RDs with a mean value of 45.9±10.2. Multiple paired comparisons showed that FCs of Scl patients were significantly older than FCs of PWS, DMD, CF and FXS patients, due to the fact that Scl arises in adulthood, while other pathologies mostly arise in pediatric age (although can also occur in adolescence/adulthood).

Burden levels, as measured by the total Zarit score, showed large significant differences among RDs with an overall mean value of 27.4±12.5. We classified RDs in two subgroups, based on the mean FCs' burden level, above or below the overall mean: FCs of PWS, FXS, EB and MPS patients reported moderate levels of burden, while FCs of Hem, JIA, CF, DMD and Scl patients reported light/mild levels of burden. Due to the presence of only 6 FCs of His patients, the statistical power of the comparisons involving His is too low to make results of such comparisons reliable. Multiple paired comparisons stated that PWS specific burden is significantly heavier than that of Hem, JIA, CF and DMD; FXS heavier than that of Hem and JIA, while EB and MPS higher than that of Hem.

No HRQoL significant differences were observed among the 10 selected RDs.

The overall mean number of hours/week devoted to care was 50.5±34.1, with significant differences among 10 RDs. We distinguished three different FCs groups: MPS, EB and PWS requiring the highest number of hours/week devoted by FCs, DMD, FXS and CF the intermediate number and Hem, Scl and JIA the lowest number. The quite large SDs, within any disease group, suggest that the kind of pathology is only one of the factors determining the number of hours/week that are necessary to patient's care. As consequence of this high variability, no paired comparison was statistically significant.

### *Patients' characteristics*

Out of the 683 RD patients of the BURQoL survey, we selected the 210 of them that reported to be assisted by a FC. About the rest, the information was lacking or patients were cared by a formal caregiver [16].

A description of the 210 RD patients' characteristics is shown in *Table 3a*. Patients were 67.6% males *vs* 32.4% females, being sex distribution significant different among RDs: all males in Hem and DMD; mostly males in CF, FXS, MPS and JIA; mostly females in PWS and Scl and the same percentage of males and females in His and EB.

The mean value of patient's age was 17.3±16.5 and Scl patients were significantly older than all the other RD patients.

Patients showed a Barthel index mean value of 66.9±32.4, which is in the range of moderate dependence. DMD and MPS patients reported severe dependence while PWS, Scl, FXS and EB moderate dependence and Hem, CF and JIA mild dependence.

Patient's HRQoL mean value was 60.7±20.6. Better HRQoL was observed in JIA, CF and Hem patients, in agreement with their good levels of self-sufficiency. FXS patients reported a similar better HRQoL, even if they are more dependent than JIA, CF or Hem patients. PWS and DMD patients showed an intermediate HRQoL score. The worst scores were reported by EB, MPS and Scl patients.

Interestingly, we observed a very large HRQoL difference between child and adult patients, with adults showing a worse HRQoL than children, and a smaller Barthel difference between the two groups (*Table 3b*).

**Table 2**
Characteristics of family caregivers grouped by 10 rare diseases

| Rare diseases | Family caregivers | | | | | |
|---|---|---|---|---|---|---|
| | Subjects n | Sex n (%) | Age n mean (SD) median (min-max) | Zarit n mean (SD) median (min-max) | EQ5D-VAS n mean (SD) median (min-max) | n hours/week n mean (SD) median (min-max) |
| | | p=0.061 | **p=0.005**** | **p<0.001***** | p=0.826 | **p=0.020*** |
| 1. PWS | 24 | M: 4 (16.7)<br>F: 20 (83.3) | 24<br>44.3 (9.7)<br>43 (28-66) | 23<br>36.7 (12.9)<br>37 (16-60) | 22<br>76.8 (16.0)<br>80 (50-95) | 24<br>58.2 (36.4)<br>61.5 (0.0-112.0) |
| 2. Hem | 14 | M: 2 (14.3)<br>F: 12 (85.7) | 14<br>45.3 (11.0)<br>42 (33-70) | 14<br>16.4 (5.7)<br>16 (9-28) | 14<br>82.1 (15.3)<br>85 (60-100) | 14<br>36.0 (41.2)<br>16.3 (0.0-112.0) |
| 3. DMD | 51 | M: 18 (35.3)<br>F: 33 (64.7) | 51<br>46.8 (8.8)<br>46 (28-66) | 50<br>25.4 (10.3)<br>26 (0-50) | 49<br>79.4 (14.2)<br>80 (50-100) | 51<br>52.3 (29.6)<br>46.7 (6.4-112.0) |
| 4. Scl | 17 | M: 10 (58.8)<br>F: 7 (41.2) | 16<br>56.5 (12.6)<br>57 (31-78) | 16<br>26.1 (10.8)<br>23.5 (11-46) | 14<br>71.4 (20.6)<br>75 (40-100) | 17<br>34.9 (26.6)<br>26.5 (0.0-102.0) |
| 5. CF | 43 | M: 11 (25.6)<br>F: 32 (74.4) | 43<br>42.7 (8.0)<br>43 (25-57) | 40<br>24.6 (9.8)<br>24 (6-53) | 39<br>82.4 (12.1)<br>85 (50-100) | 43<br>46.7 (33.7)<br>38.5 (0.6-112.0) |
| 6. FXS | 12 | M: 2 (16.7)<br>F: 10 (83.3) | 12<br>44.6 (13.5)<br>40 (31-76) | 12<br>34.6 (12.7)<br>36 (15-59) | 12<br>76.7 (11.3)<br>77.5 (60-95) | 12<br>49.9 (27.1)<br>44.2 (22.0-102.1) |
| 7. His | 6 | M: 0 (0.0)<br>F: 6 (100.0) | 6<br>38.7 (3.5)<br>37.5 (35-43) | 6<br>33.0 (20.9)<br>33.5 (6-56) | 6<br>77.5 (17.3)<br>80 (50-95) | 6<br>54.1 (27.7)<br>64.3 (0.0-76.0) |
| 8. MPS | 19 | M: 3 (15.8)<br>F: 16 (84.2) | 18<br>48.3 (11.0)<br>46 (36-82) | 16<br>32.1 (12.3)<br>29.5 (17-56) | 16<br>76.1 (19.5)<br>77.5 (30-100) | 19<br>66.0 (41.8)<br>56.0 (0.0-112.0) |
| 9. JIA | 8 | M: 3 (37.5)<br>F: 5 (62.5) | 8<br>44.8 (7.0)<br>42 (38-58) | 8<br>16.9 (7.0)<br>14 (11-32) | 8<br>79.4 (18.0)<br>87.5 (45-100) | 8<br>27.8 (28.3)<br>21.9 (0.0-63.5) |
| 10. EB | 16 | M: 4 (25.0)<br>F: 12 (75.0) | 16<br>46.3 (10.0)<br>45 (29-64) | 14<br>32.4 (14.7)<br>30 (11-52) | 13<br>78.1 (16.7)<br>80 (30-95) | 16<br>64.2 (33.6)<br>61.6 (0.0-112.0) |
| Total | 210 | M: 57 (27.1)<br>F: 153 (72.9) | 208<br>45.9 (10.2)<br>45 (25-82) | 199<br>27.4 (12.5)<br>25 (0-60) | 193<br>78.7 (15.3)<br>80 (30-100) | 210<br>50.5 (34.1)<br>46.7 (0.0-112.0) |

1. PWS: Prader Willi syndrome; 2. Hem: hemophilia; 3. DMD: Duchenne muscular dystrophy; 4. Scl: scleroderma; 5. CF: cystic fibrosis; 6. FXS: fragile X syndrome; 7. His: histiocytosis; 8. MPS: mucopolysaccharidosis; 9. JIA: juvenile idiopathic arthritis; 10. EB: epidermolysis bullosa.
M: males; F: females.
SD: standard deviation; min-max: minimum-maximum; p: significance level of the Chi-squared test comparing ten rare diseases with respect to sex distribution and of the Kruskal-Wallis test comparing ten rare diseases with respect to age, Zarit, EQ5D-VAS and n of hours/week values:
* p≤0.05; ** p≤0.01; *** p≤0.001. n: number of respondent subjects, when n is lower it means that not all subjects answered to that item.

The worst HRQoL of the Scl patients is in agreement with their older age as compared to other RDs. However, older age is not the only variable playing a role in worsening patient's HRQoL because MPS and EB patients are younger and more dependent than Scl patients and yet they have similar bad HRQoL.

### *Factors influencing family caregivers' burden*

Correlation analyses between the quantitative variables, patients' HRQoL and Barthel index, Zarit, FCs' HRQoL, principal or support FCs' number of hours/week, are shown in *Table 4*. Our results indicate that burden is inversely associated with FCs' HRQoL and, at lesser extent, with patient's HRQoL, while directly to the number of hours/week devoted to care by the principal FC. FCs' HRQoL is directly associated with patient's HRQoL. Finally, the number of hours/week devoted to care by the principal FC are inversely associated with the Barthel index and directly with the number of hours/week devoted to care by a support FC. As for the principal FC, also the number of hours/week devoted to care by a support FC is inversely associated with the Barthel index.

Multiple linear regression analyses are reported in *Table 5*. Considering Model A, burden resulted negatively affected by patient's HRQoL and positively by the number of hours/week devoted to care by the principal FC. Considering Model B, burden levels were affected by the kind of pathology, and not by patient' age or dependence level, with significantly higher levels in PWS,

**Table 3a**
Characteristics of patients grouped by 10 rare diseases

| Rare diseases | Patients | | | | |
|---|---|---|---|---|---|
| | Subjects n | Sex n (%) | Age n mean (SD) median (min-max) | Barthel index n mean (SD) median (min-max) | EQ5D -VAS n mean (SD) median (min-max) |
| | | p<0.001*** | p<0.001*** | p<0.001*** | p<0.001*** |
| 1. PWS | 24 | M:11 (45.8)<br>F:13 (54.2) | 24<br>11.4 (8.0)<br>10 (1-29) | 19<br>70.5 (25.2)<br>75 (10-100) | 19<br>60.0 (15.3)<br>55 (35-90) |
| 2. Hem | 14 | M:14 (100.0)<br>F:0 (0.0) | 14<br>23.2 (22.4)<br>9 (2-64) | 10<br>89.5 (14.0)<br>95 (65-100) | 10<br>65.5 (26.5)<br>65 (30-100) |
| 3. DMD | 51 | M:51 (100.0)<br>F:0 (0.0) | 51<br>14.0 (8.0)<br>12 (1-35) | 46<br>43.2 (30.2)<br>40 (0-100) | 46<br>60.7 (21.5)<br>60 (10-100) |
| 4. Scl | 17 | M:3 (17.6)<br>F:14 (82.4) | 17<br>56.5 (14.0)<br>59 (20-75) | 17<br>75.9 (19.0)<br>80 (20-95) | 16<br>43.4 (18.5)<br>42.5 (5-80) |
| 5. CF | 43 | M:26 (60.5)<br>F:17 (39.5) | 43<br>10.9 (9.0)<br>10 (0-41) | 28<br>90.5 (25.8)<br>100 (0-100) | 28<br>69.8 (17.9)<br>70 (20-100) |
| 6. FXS | 12 | M:9 (75.0)<br>F:3(25.0) | 12<br>14.7 (11.3)<br>12 (5-46) | 11<br>70.9 (29.7)<br>80 (5-95) | 11<br>71.4 (16.6)<br>70 (30-95) |
| 7. His | 6 | M:3 (50.0)<br>F:3 (50.0) | 6<br>4.2 (2.9)<br>3 (3-10) | 1<br>90<br>90 | 1<br>50<br>50 |
| 8. MPS | 19 | M:12 (63.2)<br>F:7 (36.8) | 19<br>18.6 (14.9)<br>13 (1-55) | 16<br>45.6 (37.9)<br>47.5 (0-100) | 15<br>50.7 (20.5)<br>50 (10-90) |
| 9. JIA | 8 | M:5 (62.5)<br>F:3 (37.5) | 8<br>8.3 (4.0)<br>8 (2-13) | 6<br>97.5 (6.1)<br>100 (85-100) | 6<br>75.0 (8.9)<br>72.5 (65-90) |
| 10. EB | 16 | M:8 (50.0)<br>F:8 (50.0) | 16<br>16.3 (12.5)<br>14.5 (0-42) | 12<br>72.9 (13.6)<br>70 (55-90) | 12<br>55.4 (16.8)<br>52.5 (30-90) |
| Total | 210 | M:142 (67.6%)<br>F:68 (32.4%) | 210<br>17.3 (16.5)<br>12 (0-75) | 166<br>66.9 (32.4)<br>75 (0-100) | 164<br>60.7 (20.6)<br>60 (5-100) |

1. PWS: Prader Willi syndrome; 2. Hem: hemophilia; 3. DMD: Duchenne muscular dystrophy; 4. Scl: scleroderma; 5. CF: cystic fibrosis; 6. FXS: fragile X syndrome; 7. His: histiocytosis; 8. MPS: mucopolysaccharidosis; 9. JIA: juvenile idiopathic arthritis; 10. EB: epidermolysis bullosa.
M: males; F: females.
SD: standard deviation; min-max: minimum-maximum; p: significance level of the Chi-squared test comparing ten rare diseases with respect to sex distribution and of the Kruskal-Wallis test comparing ten rare diseases with respect to age, Barthel index and EQ5D-VAS values: *** p≤0.001.
n: number of respondent subjects, when n is lower it means that not all subjects answered to that item.

FXS and MPS compared to DMD, and lower levels in Hem. On the contrary, the kind of pathology did not affect FC's HRQoL.

## DISCUSSION

The study of sex/gender-specific health differences in FCs is of considerable importance in order to address precision medicine. FC population may present some health risk factors associated to home care activity, impacting males and females differently [1]. A recent study on RD patients reported that female FCs perceived the condition of their child to be highly symptomatic and requiring disease control, with negative consequences. By contrast, male FCs had stronger perceptions regarding the negative effects of the disease on the child's QoL. This sex/gender discrepancy of illness perception may contribute to female higher levels of stress and depressive symptoms than males [20]. In addition, mothers of RD patients were significantly more impaired in their QoL and mental health, as compared to fathers [15].

Indeed, not only the care activity itself but also the socio-cultural influencing factors may impact FCs' health in a gender specific way. At this regard, a recent study, about caregiving experiences of fathers and mothers of RD children in Italy, showed that gender differences emerged in the social support experienced, in the different challenges to be faced and in the narratives about the specific experience of the caregiving impact on job and, more in general, on worries [21]. Moreover, the enhanced cost of informal care, other than resulting in

**Table 3b**
Characteristics of patients with rare diseases grouped by age: children *vs* adults

| Group | Patients | | | |
|---|---|---|---|---|
| | Subjects n | Sex n (%) | Barthel index n mean (SD) median (min-max) | EQ5D -VAS n mean (SD) median (min-max) |
| | | p=0.038* | p=0.025* | p<0.00*** |
| Child | 145 | M: 105 (72.4)<br>F: 40 (27.6) | 101<br>71.0 (30.3)<br>80 (0-100) | 100<br>66.8 (19.2)<br>70 (10-100) |
| Adult | 65 | M: 37 (56.9)<br>F: 28 (43.1) | 65<br>60.5 (34.6)<br>70 (0-100) | 64<br>51.0 (19.0)<br>50 (5-90) |
| Total | 210 | M: 142 (67.6)<br>F: 68 (32.4) | 166<br>66.9 (32.4)<br>75 (0-100) | 164<br>60.7 (20.6)<br>60 (5-100) |

EQ5D-VAS: EuroQoL-5 dimensions Visual Analogue Scale.
SD: standard deviation; min-max: minimum-maximum; p: significance level of the Chi-squared test comparing child versus adult patients with respect to sex distribution and of the Kruskal-Wallis test comparing child *vs* adult patients with respect to Barthel index and EQ5D-VAS: * p≤0.05; *** p≤0.001.
M: males; F: females. n: number of respondent subjects, when n is lower it means that not all subjects answered to that item.

**Table 4**
Pearson's pairwise correlation coefficients

| | Patients EQ5D-VAS | Barthel | Zarit | FCs' EQ5D-VAS | Principal FCs' n hours/week | Support care n hours/week |
|---|---|---|---|---|---|---|
| Patients' EQ5D-VAS | | 0.290*** | -0.236** | 0.347*** | -0.188* | -0.138 |
| Barthel | 0.290*** | | -0.074 | 0.010 | -0.318*** | -0.391*** |
| Zarit | -0.236** | -0.074 | | -0.282*** | 0.229*** | 0.115 |
| FCs' EQ5D-VAS | 0.347*** | 0.010 | -0.282*** | | -0.105 | -0.090 |
| Principal FCs' n hours/week | -0.188* | -0.318*** | 0.229*** | -0.105 | | 0.468*** |
| Support care n hours/week | -0.138 | -0.391*** | 0.115 | -0.090 | 0.468*** | |

FC: family caregiver.
The significance levels of the Pearson correlation coefficients r reported in the table are denoted as:: * p≤0.05; ** p≤0.01; *** p≤0.001. The number of subjects was ranging from 144 to 203.

a better patient's QoL, involves a loss of the productivity, as reported in FCs who care for child patients with haemophilia, because of early retirement or loss of working days [22]. Nazco and coauthors recently published an article on burden and HRQoL from FCs of RD patients from six European countries based on the 2012 BURQoL survey. They showed that higher levels of burden are associated with lower caregiver's HRQoL. However, their study did not look at gender-specific differences [13].

Our study showed a significant difference in the number of hours/week devoted to care by women as compared to men FCs. This data is important for the prevention of women's health, considering that a high number of weekly hours of informal caregiving, as opposed to few weekly hours, is associated with a higher risk of cardiovascular disease [23]. Indeed, as the number of hours/week devoted to care resulted directly associated with burden, we suggest that women are at higher risk for burden than men. At this regard, we showed significant gender differences in two Zarit single item answers, reported more frequently by women and consisting in "a strong feeling of fear for the future" and "the belief that the care activity has harmed their own health". It is possible that larger sex/gender associated differences may exist but could be hidden due to the numerical limit of our sample with few male FCs. The higher numerosity of men, mostly husbands, taking care of Scl patients, due to the prevalence of female adult patients (Scl F/M ratio 3:1) [24], makes Scl a useful model for future studies with the aim to verify the true nature of burden and/or HRQoL differences between men and women.

Interestingly, we also detected some sex/gender-specific burden differences according to FCs' socio demographic characteristics, albeit not statistically significant due to the small number of caregivers stratified by sex/gender and occupation: women that have difficulty in keeping their occupation outside home or in reconciling the time necessary for family care with work outside home, showed higher burden levels than men, suggesting that burden levels of female FCs can be influenced by their occupation status. In addition, we observed that care activities are not equally distributed

**Table 5**
Regression analysis

Model A - Zarit

| Independent variables | coeff | 95% CI lower; upper | p |
|---|---|---|---|
| FCs' sex | 1.352 | -3.083; 5.786 | 0.548 |
| **patient' QoL** | **-0.121** | **-0.221; -0.021** | **0.018*** |
| Barthel index | 0.032 | -0.035; 0.098 | 0.349 |
| **FCs' n hours/week** | **0.082** | **0.009; 0.154** | **0.028*** |
| Support care n hours/ week | 0.031 | -0.045; 0.107 | 0.426 |

Model A - FC's EQ5D-VAS

| Independent variables | coeff | 95% CI lower; upper | p |
|---|---|---|---|
| FCs' sex | -1.643 | -7.080; 3.794 | 0.551 |
| **Zarit** | **-0.296** | **-0.494; -0.098** | **0.004**** |
| **patient' EQ5DVAS** | **0.214** | **0.091; 0.336** | **<0.001***** |
| Barthel index | -0.072 | -0.154; 0.009 | 0.081 |
| FCs' n hours/week | -0.063 | -0.153; 0.027 | 0.170 |
| Support care n hours/ week | -0.030 | -0.123; 0.063 | 0.522 |

FC: family caregiver; coeff: regression coefficient; 95% CI: 95% Confidence Interval;
p: significance levels: * p≤0.05; ** p≤0.01; *** p≤0.001.

Model B - Zarit

| Independent variables | coeff | 95% CI lower; upper | p |
|---|---|---|---|
| Barthel index | -0.004 | -0.076; 0.068 | 0.906 |
| Patient's age | -0.042 | -0.220; 0.136 | 0.643 |
| Rare disease *(vs DMD)* | | | |
| **PWS** | **11.624** | **5.029; 18.219** | **<0.001***** |
| Hem | -8.425 | -17.706; 0.857 | 0.075 |
| Scl | 2.435 | -8.082; 12.953 | 0.648 |
| CF | 0.259 | -6.236; 6.754 | 0.937 |
| **FXS** | **10.559** | **2.680; 18.438** | **0.009**** |
| His | -11.500 | -34.644; 11.644 | 0.328 |
| **MPS** | **7.755** | **0.544; 14.966** | **0.035*** |
| JIA | -7.134 | -17.685; 3.416 | 0.183 |
| EB | 2.974 | -5.333; 11.280 | 0.480 |

PWS: Prader Willi syndrome; Hem: hemophilia; DMD: Duchenne muscular dystrophy;
Scl: scleroderma; CF: cystic fibrosis; FXS: fragile X syndrome; His: histiocytosis; MPS: mucopolysaccharidosis; JIA: juvenile idiopathic arthritis; EB: epidermolysis bullosa;
Reference group: Duchenne muscular dystrophy. coeff: regression coefficient; 95% CI: 95% Confidence Interval; p: significance levels: * p≤0.05; ** p≤0.01; *** p≤0.001.

between mothers and fathers of the parental couples, with mothers being prevalent. As consequence, women may undergo to social and health inequality because of sex and gender differences [25, 26].

Moreover, our results showed that there are significant burden differences among FCs, depending on the kind of rare disease: FCs of patients with PWS, FXS, MPS and EB are those reporting the highest levels of burden. We suggest that PWS, FXS, MPS and EB patients may have specific challenges, independently from dependence, that can be more stressful for their FCs, as for example: hyperphagia and obesity in PWS; developmental delay and autism in FXS; progressive damage which affects patient's appearance, physical abilities, organ function and mental development in MPS patients; only palliative treatment available and reduced life expectancy in EB patients [27-30]. On the contrary, the good levels of self-sufficiency and better HRQoL, reported in Hem, JIA and CF patients, may be responsible for the lowest burden levels. The highest number of hours/week devoted to care by PWS, MPS and EB caregivers, suggests that this can be one of the factors enhancing their burden. In MPS and EB patients, it is possible that their reported worst HRQoL can contribute to increase burden too, while it is not in PWS and FXS patients that reported a better HRQoL. In addition, those FCs showing more burden than others could be at higher risk for their health. However, we need further research to identify the specific RD challenges involved in health risks, for example comparing burden with both patient's clinical diagnosis and mental and physical health data derived from their FCs. Surprisingly, the enhanced burden in PWS, FXS, MPS and EB was not accompanied by a poorer FC's HRQoL, as expected. We suggest that it may depend both on the peculiarities of our Italian sample compared to other European countries [14] and/or on the limit of the EQ-5D tool. In fact, the EQ-5D is a generic tool more suitable for patients with physical disability and dependency [17] than for the generally not dependent FCs. However, we observed a significant HRQoL difference in the answers to one of the five EQ-5D items, asking caregivers to refer their actual pain and discomfort: FCs caring for adults showed more frequently pain and discomfort and with higher intensity, as compared to those caring for child patients, suggesting that physical health is more frequently impaired in FCs of adult rather than child patients.

The UN Resolution "Addressing the challenges of persons living with a rare disease and their families" recently approved by the United Nations General Assembly [31] affirms the need to achieve gender equality, also taking into account "that women and girls undertake a disproportionate share of unpaid care and domestic work when a member of their household or family lives with a rare disease, and that women face more barriers in accessing decent work". Hence, the UN Resolution "Encourages Member States to adopt gender-sensitive national strategies, action plans and legislation, to contribute to the well-being of persons living with a RD and their families, including on the protection and enjoyment of their human rights, consistent with their obligations under international law" [32]. Notably this Resolution contributes to the UN Agenda 2030 Sustainable Development Goals (SDG) and it fits for persons living with a RD patient. Women are disproportionately discriminated in society, either as patients or as mothers of RD patients (SDG5 "Gender inequality"). Families

with a member living with a RD are at greater risk of impoverishment, as they have more expenses and less income (SDG1 "No poverty") [33]. The informal care is a major challenge and it is likely to become even more important in the field of RDs. Informal care is often seen as a cost-effective way of preventing institutionalization and enabling patients to remain at home. In Italy, the family had traditionally a strong role, probably due to largely underdeveloped formal care systems at national level. The findings suggest that formalising informal care through cash payments, legal rights, social security, and training opportunities can have important beneficial effects on informal careers and the patients that they care for.

In conclusion, the significant gender disparity of the number of hours/week devoted to care by female FCs, who have also a social disadvantage in the occupation status because of their traditional family role, suggests that women may be exposed to health risks more than men. These data, together with the identification of those RDs associated to higher burden and likely to worse caregiver's health, provide useful information for socio-health policies in order to improve accuracy and equity in health prevention interventions.

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## REFERENCES

1. Petrini M, Cirulli F, D'Amore A, Masella R, Venerosi A. and Carè, A. Health issues and informal caregiving in Europe and Italy. Ann Ist Super Sanità. 2019;55(1):41-50. doi: 10.4415/ANN_19_01_08
2. Pinquart M, Sörensen S. Differences between caregivers and non caregivers in psychological health and physical health: a meta-analysis. Psychol Aging. 2003;18(2):250-67. doi: 10.1037/0882-7974.18.2.250
3. Vitaliano PP, Zhang J, Scanlan JM. Is caregiving hazardous to one's physical health? A meta-analysis. Psychol Bull. 2003 129(6):946-72. doi: 10.1037/0033-2909.129.6.946
4. Vedhara K, Shanks N, Anderson S, Lightman S. The role of stressors and psychosocial variables in the stress process: a study of chronic caregiver stress. Psychosom Med. 2000;62(3):374-85. doi: 10.1097/00006842-200005000-00011
5. Pinquart M, Sörensen S. Correlates of physical health of informal caregivers: a meta-analysis. J Gerontol B. 2007;62(2):P126-37. doi: 10.1093/geronb/62.2. p126
6. Schulz R, Sherwood PR. Physical and mental health effects of family caregiving. Am J Nurs. 2008;108(9 Suppl):23-7; quiz 27. doi: 10.1097/01.NAJ.0000336406.45248.4c
7. Simón MA, Bueno AM, Otero P, Blanco V, Vázquez FL. Caregiver burden and sleep quality in dependent people's family caregivers. J Clin Med. 2019;8(7):1072. doi: 10.3390/jcm8071072
8. Adams LS, Miller JL, and Grady PA. The spectrum of caregiving in palliative care for serious, advanced, rare diseases: Key issues and research directions. J Palliat Med. 2016;19(7):698-705. doi: 10.1089/jpm.2015.0464
9. Lyon ME, Thompkins JD, Fratantoni K, Fraser JL, Schellinger SE, Briggs L, Friebert S, Aoun S, Cheng YI, Wang J. Family caregivers of children and adolescents with rare diseases: a novel palliative care intervention. BMJ Support Palliat Care. 2019;12(e5):e705-14. doi: 10.1136/bmjspcare-2019-001766
10. Currie G, Szabo J. It is like a jungle gym, and everything is under construction: The parent's perspective of caring for a child with a rare disease. Child Care Health Dev. 2019;45(1):96-103. doi: 10.1111/cch.12628
11. Pinquart M, Sörensen S. Gender differences in caregiver stressors, social resources, and health: an updated meta-analysis. J Gerontol B Psychol Sci Soc Sci. 2006;61(1):P33-45. doi: 10.1093/geronb/61.1.p33
12. Del Río Lozano M, García-Calvente MDM, Calle-Romero J, Machón-Sobrado M, Larrañaga-Padilla I. Health-related quality of life in Spanish informal caregivers: gender differences and support received. Qual Life Res. 2017;26(12):3227-38. doi: 10.1007/s11136-017-1678-2
13. Cherepanov D, Palta M, Fryback DG, Robert SA. Gender differences in health-related quality-of-life are partly explained by sociodemographic and socioeconomic variation between adult men and women in the US: evidence from four US nationally representative data sets. Qual Life Res. 2010;19(8):1115-24. doi: 10.1007/s11136-010-9673-x
14. Valcárcel-Nazco C, Ramallo-Fariña Y, Linertová R, Ramos-Goñi JM, García-Pérez L, Serrano-Aguilar P. Health-related quality of life and perceived burden of informal caregivers of patients with rare diseases in selected European Countries. Int J Environ Res Public Health. 2022;19(13):8208. doi: 10.3390/ijerph19138208
15. Boettcher J, Denecke J, Barkmann C, Wiegand-Grefe S. Quality of life and mental health in mothers and fathers caring for children and adolescents with rare diseases requiring long-term mechanical ventilation. Int J Environ Res Public Health. 2020:17(23):8975. doi:10.3390/ijerph17238975
16. Linertová R, Serrano-Aguilar P, Posada-de-la-Paz M, Hens-Pérez M, Kanavos P, Taruscio D, Schieppati A, Stefanov R, Péntek M, Delgado C, Graf von der Schulenburg JM, Persson U, Chevreul K, Fattore G, Worbes-Cerezo M, Sefton M, López-Bastida J. Delphi approach to select rare diseases for a European representative survey. The BURQOL-RD study. Health Policy. 2012;108(1):19-26. doi: 10.1016/j.healthpol.2012.08.001
17. Dolan P. Modeling valutations for EuroQol health states. Med Care. 1997;35(11):1095-108. doi: 10.1097/00005650-199711000-00002
18. Herbert R, Bravo G, Preville M. Reliability, validity, and reference values of the Zarit Burden Interview for assessing informal caregivers of community-dwelling older persons with dementia. Can J Aging. 2000;19(4):494-507. doi: 10.1017/S0714980800012484
19. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel index for stroke rehabilitation. J Clin Epidemiol. 1989;42(8):703-9. doi: 10.1016/0895-4356(89)90065-6

20. Chu SY, Wen CC, Weng CY. Gender differences in caring for children with genetic or rare diseases: A mixed-methods study. Children (Basel). 2022;9(5):627. doi:10.3390/children9050627
21. Cardinali P, Migliorini L, Rania N. The caregiving experiences of fathers and mothers of children with rare diseases in Italy: Challenges and social support perceptions. Front Psychol. 2019;10:1780. doi: 10.3389/fpsyg.2019.01780
22. Kodra Y, Cavazza M, Schieppati A, De Santis M, Armeni P, Arcieri R, Calizzani G, Fattore G, Manzoli L, Mantovani L, Taruscio D. The social burden and quality of life of patients with haemophilia in Italy. Blood Transfus. 2014;12(Suppl 3):s567-75. doi: 10.2450/2014.0042-14s
23. Mortensen J, Dich N, Lange T, Høst Ramlau-Hansen C, Head J, Kivimäki M, Leineweber C, Hulvej Rod N. Weekly hours of informal caregiving and paid work, and the risk of cardiovascular disease. Eur J Public Health. 2018:28(4):743-7. doi: 10.1093/eurpub/ckx227
24. Peoples C, Medsger Jr TA, Lucas M, Rosario BL, Feghali-Bostwick CA. Gender differences in systemic sclerosis: relationship to clinical features, serologic status and outcomes. J Scleroderma Relat Disord. 2016;1(2):177-240. doi: 10.5301/jsrd.5000209
25. Salvador-Piedrafita M, Malmusi D, Borrell C. Time trends in health inequalities due to care in the context of the Spanish Dependency Law. Gac Sanit. 2017;31(1):11-7. doi: 10.1016/j.gaceta.2016.06.006
26. Del-Pino-Casado R, Pastor-Bravo MD, Palomino-Moral PA, Frías-Osuna A. Gender differences in primary home caregivers of older relatives in a Mediterranean environment: A cross-sectional study. Arch Gerontol Geriatr. 2017;69:128-33. doi: 10.1016/j.archger.2016.11.012
27. Kayadjanian N, Schwartz L, Farrar E, Comtois KA, Strong TV. High levels of caregiver burden in Prader-Willi syndrome. PLoS One. 2018;13(3):e0194655. doi: 10.1371/journal.pone.0194655
28. Salcedo-Arellano MJ, Hagerman RJ, Martínez-Cerdeño V. Fragile X syndrome: clinical presentation, pathology and treatment. Gac Med Mex. 2020;156(1):60-6. doi: 10.24875/GMM.19005275
29. Grant N. Evaluating strategies to manage and endure challenging behaviors in mucopolysaccharidoses. Orphanet J Rare Dis. 2021;16(1):165. doi: 10.1186/s13023-021-01767-8
30. Bruckner AL, Losow M, Wisk J, Patel N, Reha A, Lagast H, Gault J, Gershkowitz J, Kopelan B, Hund M, Murrell DF. The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. Orphanet J Rare Dis. 2020;15(1):1. doi: 10.1186/s13023-019-1279-y
31. General Assembly, United Nations. Resolution adopted by the General Assembly on 16 December 2021. 76/132. Addressing the challenges of persons living with a rare disease and their families. 2021. Available from: https://digitallibrary.un.org/record/3953765?ln=en.
32. Taruscio D. The long journey of people with rare diseases: from darkness to the UN Resolution 2021. Ann Ist Super Sanità. 2022;58(2):79-80. doi: 10.4415/ANN_22_02_01
33. European Commission. Informal care in Europe: Exploring formalisation, availability and quality. Publications Office, 2018. Available from: https://op.europa.eu/en/publication-detail/-/publication/96d27995-6dee-11e8-9483-01aa75ed71a1/language-en (accessed on 1 June 2022).