

# Coping with Wolf-Hirschhorn Syndrome: quality of life and psychosocial features of family carers

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## Research

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# Abstract

**Background:** Wolf-Hirschhorn Syndrome (WHS) is a rare, congenital disease characterized by a distinctive facial phenotype, seizures, intellectual disability and developmental delay, and pre and postnatal growth requiring lifelong care. The psychosocial status of the family caregivers of children diagnosed with WHS is unknown. This study aims to characterize the sociodemographic and psychosocial profile of WHS caregivers and analyze how these variables impact their quality of life (QoL) and well-being.

**Results:** The sociodemographic and clinical profile of 22 Spanish caregivers of children with WHS and the characteristics of those affected have been described. Significant relationships were found between sociodemographic and psychosocial characteristics among caregivers. The impact on the parents' QoL and negative relationship with the symptomatology were assessed. The use of engagement strategies such as problem focused coping was associated with improved psychological QoL and social support.

**Conclusions:** WHS caregivers share similarities in their profile and needs with caregivers of children with other rare diseases. Psychosocial support groups involving parents caring for children with the same disease could improve caregivers' well-being and QoL by strengthening their social support network and using positive coping styles.

## Background

Wolf-Hirschhorn Syndrome (WHS; ONIM #194190, ORPHA #280) [1] is a congenital malformation disorder first described in 1961 [2]. It was later recognized in 1965 as the syndrome known today [3,4]. WHS is a rare genetic condition whose incidence is estimated at 1 in 50,000 births [5] and is predominantly female 2:1 [6]. Some authors suspect that incidence may be higher, about 1 per 20,000 births, since not all patients could gain access to accurate diagnostic evaluations or due to miscarriages [7,8].

This syndrome is caused by a variable size deletion of the distal region of the short arm of chromosome 4 (4p16.3) and is therefore also known as 4p-syndrome [9]. It has a phenotype core characterized by distinctive craniofacial features (Greek warrior helmet-shaped face), pre and postnatal growth and psychomotor development retardation, seizures and intellectual disability. Other non-nuclear clinical manifestations may also coexist such as cardiological, visual, auditory, genitourinary or hypotonia problems, among others [10].

WHS is a contiguous gene deletion syndrome whose clinical severity has, for a long time, been linked to deletion size. However, existing chromosomal duplications, variations in genetic sequencing and other aspects may contribute to phenotypic variation in patients [11].

At the neurocognitive level, these children are described as having a profile of intellectual disability and language disorders, with particular difficulty in the expressive type (only 6% of children could construct simple sentences) [12]. However, more current studies indicate that one-third of patients with cognitive

delay could be classified as mild or moderate [11,13], showing strong socialization skills, and whose level of communication may improve with time [14,15]. Furthermore, the most recent cohorts described, such as the Spanish cohort, apparently perform better than in previous descriptions of the syndrome [16].

Seizures are reported as the major source of concern for parents and professionals of children with WHS, with a high prevalence of around 90% of patients, with their first episode within the first 3 years [10]. It can arise regardless of deletion size, although a study by Zollino et al. [11] estimates its incidence in 96% of cases involving children with deletions equal to or greater than 22 Mb.

All the above-mentioned manifestations accompanying this syndrome, its co-morbidities with other diseases and increased vulnerability to immunological issues may worsen these children's quality of life (QoL) [17]. To date, there are no studies on WHS that carry out objective analysis of this significant variable, both for the children themselves and their parents [18].

QoL is described as a subjective and multidimensional process, whose most representative dimensions include an individual's physical health, psychological state, relationship to the environment and social relationships [19,20]. It has become a focus of research in recent decades in clinical trial studies, cost-utility analysis, evaluating the state of the general and clinical population, and as a variable of outcome/effectiveness of interventions involving both patients and caregivers. Its inclusion in studies of rare diseases such as genetic, metabolic and neuromuscular diseases should be noted [21–26], and in other chronic diseases such as epilepsy, respiratory disorders and cerebral palsy [27–31]. In all these cases, the child's condition negatively affected the parents' QoL to a greater or lesser extent.

Children's state of health, the task of caring for them over time, changes in family roles and uncertainty regarding the evolution of their children's illness also lead to stress and emotional issues for parents, such as burnout, anxiety and depression [32,33]. For all of the above reasons, there are an increasing number of studies on variables affecting the improvement of caregivers' well-being, such as coping strategies and social support. The way parents cope and adjust to their children's illness is not only important in order to improve their own physical and emotional well-being, but has also been linked to improving the child's well-being [34,35].

The focus on parents of children with rare diseases (RDs) and their situation was limited until recent years [33]. Increased knowledge and understanding of the impact of living with a RD is needed in order to improve good practice guidelines for the care and support of families and professionals [36].

This study aims to describe the characteristics of parents and children with WHS in a Spanish sample and explore caregivers' socioemotional status by assessing their QoL, burden, symptoms, spirituality, coping strategies and social network.

## **Methods**

### **Participants**

Study participants were contacted via the Spanish Wolf-Hirschhorn Syndrome Association (AESWH). A total of 22 caregivers (parents) of children and young people with confirmed WHS diagnosis were recruited. Participants were included in the sample if they met the following criteria: 1) had a child under the age of 21, with a professionally confirmed diagnosis of WHS; 2) were a family (mother or father) caregiver of a person with WHS and an “intensive carer”, defined as a person who provides a minimum of 20 hours of care per week [37]; 3) lived with the person with WHS or had frequent contact with him/her. Participants were excluded who: a) were not resident in Spain; b) were caregivers under the age of 18; c) had uncompensated sensory deficits preventing the assessment protocol from being administered; and d) were illiterate.

## **Instruments**

### **Sociodemographic characteristics**

A sociodemographic questionnaire was included that gathered information on caregivers such as age, gender, marital status, education, employment status, relationship with the patient, daily hours dedicated to care, population type and socioeconomic status. Questions relating to age, gender, time of diagnosis, type of communication, and the children's deletion size of the short arm of chromosome 4 were also included.

### **Caregivers' QoL**

WHOQOL-BREF [20] - Spanish version [38]. This is the World Health Organization's abridged QoL questionnaire, which consists of 24 items in the Likert 5-point response format and evaluates a total of four domains: physical, psychological, social relationships and the environment. It also includes two additional items reflecting the perception of overall QoL and satisfaction with regard to health. The score ranges from 4-20, which can be converted into a scale of 0-100 to match the WHOQOL-100 scores. Its adaptation in Spain reveals good psychometric properties except for the psychological domain, with Cronbach's Alpha values ranging from  $\alpha = 0.69$  to  $\alpha = 0.77$ .

WHOQOL-SRPB – Spanish Version [39]. This 32-item module evaluates eight facets of spirituality, religiousness and personal beliefs in their relationship to QoL and health: connectedness to a spiritual being or force, meaning of life, awe, wholeness and integration, spiritual strength, inner peace/serenity/harmony, hope and optimism, and faith. The response format is type 5-point Likert and the questionnaire design allows it to be administered to individuals with differing ranges of spiritual, religious and/or personal beliefs. This instrument's international psychometric properties indicate that internal consistency reliability is adequate despite presenting no concrete data.

### **Functional and symptomatic assessment of the caregiver**

Zarit Burden Interview - ZBI [40] – Spanish Version [41]. This is a self-report instrument that assesses the level of caregiver burden. It consists of 22 items that are assessed using a Likert-type scale, where higher scores indicate greater burnout. Its validation in Spain has good psychometric properties (Cronbach's  $\alpha = 0.91$ ).

The Symptom Checklist-90-R - SCL-90-R [42] – Spanish Version [43]. This is a self-report checklist for overall psychopathological evaluation. It consists of a total of 90 Likert-type items and contains 9 dimensions: Somatization, Obsessive Symptoms, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation and Psychoticism; in addition to three global indices: Global Severity Index, Positive Symptom Total and Positive Symptom Distress Index. It has adequate internal consistency (Cronbach's Alpha ranged from  $\alpha = 0.79$  to  $\alpha = 0.90$ ), good test-retest reliability and appropriate validity criteria due to its correlation with other scales such as the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI).

Coping Strategies Inventory - CSI [44] – Spanish Version [45]. This self-report instrument assesses coping strategies. It consists of a total of 40 Likert-type scale items divided into a hierarchical structure made up of eight primary subscales: problem solving, cognitive restructuring, social support, emotional expression, problem avoidance, wishful thinking, social withdrawal and self-criticism; four secondary subscales: problem or emotion focused engagement or disengagement; and two tertiary subscales: engagement or disengagement. The scale has adequate internal consistency indices (Cronbach's Alpha ranged from  $\alpha = 0.63$  to  $\alpha = 0.89$ ).

Social Network Questionnaire - SNQ [46] – Spanish Version [47]. This is a self-report questionnaire aimed at caregivers of chronic patients that assesses the quality and frequency of social contacts, as well as the subjective perception of support received by the social network. It contains a total of 15 items with four response options divided into four subscales: social contacts, affective support, instrumental support and supportive relationships. The full scale's reliability index was  $\alpha = 0.84$ , and ranged from  $\alpha = 0.62$  to  $\alpha = 0.93$  for the subscales.

## **Procedure**

After a face-to-face meeting with AESWH board members, families were contacted via e-mail. Participants completed an online form on the Google Forms platform in October and November 2017. The assessment protocol was estimated to take 45-60 minutes and contact details were provided in the event of any queries arising during completion of the questionnaire. All participants were informed of the study's goals and ethical conditions; participation in the study was voluntary and there was no remuneration. Ethical Approval and Informed Consent: All procedures performed in this study were developed in accordance with the ethical standards and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study. This study also complies with national laws and regulations (Act 41/2002, 14th November) and guarantees the confidentiality of participants and their data in accordance with the Organic Law on the Protection of Personal Data (15/1999, 13th December).

## Study design and data analysis

This was a descriptive cross-sectional and correlational study of caregivers for patients diagnosed with WHS.

Statistical Package for Social Sciences, version 25.0, was used for data analysis. Frequencies, percentages (%), mean (M), standard deviations (SD) and ranges were used to describe the sample. The Cronbach Alpha reliability index calculation was collected for all instruments and the Lilliefors corrected Kolmogorov-Smirnov test was used to check normal sample distribution across the study variables. In the bivariate analysis, Pearson's correlation coefficient was used between normal distributed and continuous variables. Spearman's coefficients were used for non-normal distributed and ordinal variables. The independent t-test was used to determine the existence of statistically significant differences with normative reference populations in two variables of importance to the study, using the SCL-90-R and WHOQOL-BREF instruments. Hedge's g was used to assess the effect size of these differences. The Mann Whitney U test was used to compare differences in psychosocial and clinical variables based on caregivers' employment status and duration of illness. The Kruskal-Wallis test was used for differences based on deletion size. The level of significance adopted was 5%, with a 95% confidence interval (95% CI).

## Results

A total of 22 caregivers participated in the study, whose main characteristics, along with those of the children with WHS, are shown in Tables 1 and 2. The average participant age was 39.73 years (SD = 7.19), of whom 86.4% were women. 84.21% of the main childcare duties are undertaken by mothers. Almost all participants, 90.9%, were married or with a partner and they all lived with the children. As for their education, the average number of years of education received was 14.45 (SD = 4.60) and 11 participants completed higher education. As regards their work situation, 36.4% of the caregivers were unemployed and 54.5% stated that they had completely or partially given up their job in order to provide care. Moreover, 63.6% of the caregivers reported that they were not the main breadwinner in the family. Most of the caregivers' family units, 95.5%, were made up of 3-4 people and 40.9% had other children. In relation to the caregiving situation, the average number of daily hours devoted to these duties was 13.19 (SD = 7.61), seven participants reported that they had more people in their care and only half of the total number of caregivers received support for this task. Finally, 86.4% of the caregivers acknowledged that they had been

through a stressful time in the last 3 months, but only 13.6% received some form of psychological or psychiatric support at the time.

In terms of the profile of children with WHS, 55% were girls (ratio: 1.2 to 1) and the mean age was  $6.82 \pm 4.73$  years. However, due to the syndrome's characteristics, all the children showed symptoms from pregnancy (15%) or at birth. The average waiting time for WHS diagnosis confirmation was 11.60 months (SD = 21.0), and diagnosis was received at 16.70 (SD = 30.39) months of age. Nonetheless, 35% of these were diagnosed in the first month of life, reaching 60% of cases diagnosed in the first half year. Regarding the type of communication used, half of the children (52.9%) did not use words to communicate and/or used pictograms to do so. As for the deletion size causing the syndrome, 30% of cases have an average deletion.

Finally, to evaluate the children's functional and language abilities, the profile of 2-year-olds or younger (8 children) was not taken into account for some items, as they had not reached the developmental age to acquire such skills. 69% of the children (9 out of 13) walked independently and 84.61% with some kind of assistance. 33% (4 out of 12) had mastered bowel and bladder control and 16.6% could feed themselves, although 40% (8 out of 20) were able to do so with some help. In terms of communication, 52.9% did not use words to communicate and/or used pictograms to do so, 17.6% used gestures and/or one-word utterances and 29.4% communicated verbally by means of 2 or 3-word utterances or elaborate speech.

**Table 1.** Sociodemographic characteristics of the caregiver sample

	M(SD)/n (%)
<b>Caregivers</b>	
Gender	
Female	19 (86.4%)
Male	3 (13.6%)
Age	39.73 (7.19)
Marital status	
Married	19 (86.4%)
Single	1 (4.5%)
Divorced	1 (4.5%)
Widowed	1 (4.5%)
Years of education	14.45 (4.60)
Primary or below	1 (4.55%)
Secondary	10 (45.5%)
University	11 (50%)
<sup>a</sup> Population	
Urban	3 (13.6%)
Intermediate	4 (18.2%)
Rural	15 (68.2%)
Employment status	
Employed	14 (63.6%)
Unemployed	8 (36.4%)
Left work for caregiving	
Completely	7 (31.8%)
Partially	5 (22.7%)
Adjustment to day for caregiving	4 (18.2%)
No	3 (13.6%)
Others	3 (13.6%)
Socioeconomic status	
Low	1 (4.5%)
Lower-middle	10 (45.5%)
Middle	7 (31.8%)
Higher-middle	3 (13.6%)
High	1 (4.5%)
Primary caregiver	
Yes	17 (77.3%)
No	5 (22.7%)
Hours of care	13.19 (7.61)
Care assistance	
No	11 (50%)
Family member	5 (22.7%)
External caregiver	3 (13.6%)
Benefits	2 (9.1%)
Center	1 (4.5%)

*SD*, standard deviation. <sup>a</sup>Number of inhabitants per population: urban (>50,000), intermediate (10,000-50,000), rural (<10,000).

**Table 2.** Sociodemographic and clinical characteristics of the patient sample

	M(SD)/n (%)	<sup>a</sup> Range
<b>Patients</b>		
<b>Gender</b>		
Female	11 (55%)	
Male	9 (45%)	
Age (months)	81.85 (56.70)	
<b>Birth order</b>		
Only child	10 (50%)	
Firstborn	4 (20%)	
Second child	4 (20%)	
Third or Subsequent child	2 (10%)	
<b>Length of illness</b>		
Mid-term illness	10 (50%)	
Long-term illness	10 (50%)	
<b>Deletion size</b>		
Small(<3Mb)	4 (30.8%)	
Medium (3-9Mb)	6 (46.2%)	
Large(>9Mb)	3 (23.1%)	
<b><sup>b</sup>Communication skill</b>		
1	9 (52.9%)	1.33-18.42
2	3 (17.6%)	1.83-10.25
3	3 (17.6%)	3.75-13.33
4	2 (11.8%).	11.08-11.15
Walking with no help	9 (69.2%)	3.75-18.42
Bowel and bladder control	4 (33.3%)	10.25-18.42
<b>Feeding autonomy</b>		
With no help	2 (16.6%)	4.08-4.42
With help	8 (40%)	1.5-18.42

SD, standard deviation;<sup>a</sup>Minimum and maximum age range of patients who have reached this milestone;

<sup>b</sup>Communication skill: 1 (does not use words to communicate and/or uses pictograms to do so), 2 (uses gestures and/or

one-word utterances, e.g., when asking for water, points to water or says "water"), 3 (uses 2 or 3-word utterances, e.g., "I want water"), 4 (sentences or speech).

Table 3 shows the mean scores, scale ranges and standard deviations for the different study instruments.

**Table 3.** Clinical characteristics of the caregivers

<b>Measures</b>	<b>Scale/item range</b>	<b>Mean(SD)</b>
<b>Subjective burnout (<i>Zarit</i>)</b>	0-88	30.18 (10.0)
<b>Coping strategies (<i>CSI</i>)</b>		
Problem solving (1)	0-20	13.68(5.86)
Cognitive restructuring (2)	0-20	9.41(6.15)
Social support (3)	0-20	10.73(6.39)
Emotional expression (4)	0-20	8.86(6.58)
Problem avoidance (5)	0-20	4.82(4.10)
Wishful thinking (6)	0-20	10.10(5.88)
Social withdrawal (7)	0-20	3.63(3.0)
Self-criticism (8)	0-20	6.09(6.59)
Problem focused engagement (1,2)	0-40	23.10(11.20)
Emotion focused engagement (3,4)	0-40	19.59(11.92)
Problem focused disengagement (5,6)	0-40	14.91(8.30)
Emotion focused disengagement (7,8)	0-40	9.73(8.69)
Engagement (1-4)	0-80	42.68(21.65)
Disengagement (5-8)	0-80	24.64(15.74)
<b>Quality of Life (<i>WHOQOL-BREF</i>)</b>		
Physical domain	0-100	65.58(15.61)
Psychological domain	0-100	61.17(16.93)
Social Relationships	0-100	53.03(17.55)
Environmental domain	0-100	60.31(11.52)
Individual's overall perception of quality of life	0-100	48.86(19.64)
Individual's overall perception of their health	0-100	60.23(19.91)
<b>Spirituality, religiousness and personal beliefs (<i>SRPB</i>)</b>	0-20	9.91(2.87)
Spiritual connection	0-5	1.80(1.11)
Meaning and purpose in life	0-5	3.17(1.09)
Experiences of awe and wonder	0-5	2.74(0.78)
Wholeness and integration	0-5	2.72(0.88)
Spiritual Strength	0-5	2.10(1.10)
Inner peace	0-5	2.64(0.93)
Hope	0-5	2.95(0.69)
Faith	0-5	1.69(1.09)
<b>Symptom Checklist 90R (<i>SCL-90R</i>)</b>		
Somatization (SOM)	0-4	1.0(0.69)
Obsessive-compulsive (OBS)	0-4	0.85(0.73)
Interpersonal sensitivity (INT)	0-4	0.75(0.71)
Depression (DEP)	0-4	1.15(0.63)
Anxiety (ANX)	0-4	0.65(0.65)
Hostility (HOS)	0-4	0.82(0.67)
Phobic anxiety (PHO)	0-4	0.27(0.40)
Paranoid ideation (PAR)	0-4	0.61(0.59)
Pyschoticism (PSY)	0-4	0.39(0.39)
Global Severity Index (GSI)	0-4	0.78(0.49)
Positive Symptom Total (PST)	0-90	39.36(21.25)
Positive Symptom Distress Index (PSDI)	0-4	1.73(0.43)
<b>Social Network (<i>SNQ</i>)</b>	1-4	2.96(0.59)
Social contact	1-4	2.57 (0.52)

Instrumental support	1-4	3.03 (0.90)
Affective support	1-4	2.95 (0.81)

SD, Standard deviation

## Quality of life

Respondents obtained the lowest scores in the questionnaire for the social relationships domain 53.03 (SD = 17.55) and for the individual's overall perception of quality of life 48.86 (SD = 19.65). QoL scores on the WHOQOL-BREF subscales were compared with the primary care patient sample [48] using the independent t-test. As shown in Table 3, the primary care sample obtained a higher score in the physical domain, which is statistically significant, showing no differences for the other domains. The WHOQOL-BREF subscales were also compared with published norms for the normative Spanish sample [38]. The mean scores for the physical, psychological, social relationships and environmental domains on the 4-20 range scale were 14.49 (SD =2.50), 13.79 (SD =2.71), 12.48 (SD =2.81) and 13.65 (SD =1.84), respectively. Our study shows that caregivers had lower scores in all domains.

Table 4. Comparisons between the caregivers and primary care sample for the WHOQOL-BREF

WHOQOL-BREF	Caregivers <sup>a</sup>		Primary care Sample <sup>b</sup>		Mean differences	Effect size (g) a vs. b
	Mean (n = 22)	SD	Mean (n = 1241)	SD		
Overall QoL	2.95	0.79	2.9	0.9	0.05	-
Physical domain	65.58	15.61	44.8	17.4	a>b***	1.20
Psychological domain	61.17	16.93	54.2	17.2	7.00	-
Social relationships	53.03	17.55	50.0	20.7	4.44	-
Environment	60.31	11.52	56.1	14.8	4.21	-

SD, standard deviation. Higher scores indicate higher QoL. \*\*\* $p < 0.001$ , \*\* $p < 0.01$ , \* $p < 0.05$ . Hedge'  $g$  are designated as small (0.20), medium (0.50), and large (0.80). <sup>a</sup>Caregiver sample of this current study <sup>b</sup>Primary care sample findings

With regard to the WHOQOL-SRPB module, 72.72% of the respondents did not consider themselves part of a religious community. Similarly, 45.45% expressed no spiritual beliefs and finally, 54.54% of the sample feels that they have strong personal beliefs with scores ranging from moderately to extremely. The subscales with the highest scores for this questionnaire were meaning and purpose in life 3.17 (SD = 1.09), hope 2.95 (SD = 0.69) and experiences of awe and wonder 2.74 (SD = 0.78).

### **Clinical characteristics**

In the SCL-90-R symptom checklist, the symptom dimensions with the highest score were Somatization, Obsessive-Compulsive, Depression and Hostility. 13.6% of caregivers are at risk on the Somatization subscale, while 9.1% are at risk with regard to Obsessive-Compulsive, Depression and Hostility. In the case of Obsessive-Compulsive and Hostility, 4.5% of the sample would meet clinical severity criteria according to this instrument.

Subsequently, analysis of the item responses was carried out, quantifying only those that were endorsed "quite a bit" or "extremely". These were only taken into account when the percentage of responses was equal to or greater than 20%. 40.9% of caregivers reported headaches, 31.8% expressed concern about uncleanliness, neglect or disorganization, 27.2% admitted feeling inwardly nervous or restless and/or easily upset, annoyed or angry; and 22.7% felt lonely. As regards the clinical significance items on the SCL-90-R, 45.5% of caregivers reported restless or disturbed sleep, 49.9% overeating and 23.8% feelings of guilt.

Finally, the caregivers' responses to SCL-90-R were evaluated against the scores obtained from a normative sample of healthy population [49] and a sample categorized as code Z, made up of people with issues relating to distress or feelings deriving from day-to-day life issues, but do not constitute a diagnosable mental disorder [50]. A code Z sample was selected to draw a comparison with a related population that has already shown significant clinical distress. The independent t-test was used to determine whether there were any statistically significant differences within a broad range of caregivers' psychological

problems and psychopathological symptoms in comparison to the normative and code Z groups. As shown in Table 4, parents show no differences with the code Z group in Positive Symptom Total (PST), Somatization (SOM), Interpersonal Sensitivity (INT) and Hostility (HOS) but reported significantly higher scores for the sample from the normative group. However, group Z obtained a higher score, which is statistically significant, than parents in the Global Severity Index (GSI), Obsessive-Compulsive (OBS), Depression (DEP) and Psychoticism (PSY) but, at the same time, the group of parents recorded a higher average than the normative population. Finally, in the case of Anxiety (ANX), Phobic Anxiety (PHO) and Paranoid Ideation (PAR), group Z obtained a higher score than the group of caregivers, and the latter displayed no differences in relation to the normative population.

**Table 4.** Comparisons between caregivers, normative and code Z samples for the SCL-90-R

SCL-90-R	Caregivers <sup>a</sup>		Normative Sample <sup>b</sup>		Code Z Sample <sup>c</sup>		Mean differences	Effect size (g) a vs.b	Effect size (g) a vs.c
	Mean	SD	Mean	SD	Mean	SD			
	(n = 22)		(n = 530)		(n = 188)				
GSI	0.78	0.49	0.51	0.36	1.20	0.69	a>b** a<c**	0.74	0.62
PST	39.36	21.25	25.30	14.30	38.81	29.03	a>b***	0.96	-
PSDI	1.73	0.43	1.75	0.48	2.13	0.67	-	-	-
SOM	1.00	0.69	0.55	0.55	1.35	0.86	a>b***	0.81	-
OBS	0.85	0.73	0.60	0.51	1.43	0.86	a>b* a<c**	0.48	0.68
INT	0.75	0.71	0.45	0.44	1.13	0.88	a>b*	0.66	-
DEP	1.15	0.63	0.72	0.45	1.70	0.96	a>b*** a<c**	0.94	0.59
ANX	0.65	0.65	0.52	0.49	1.35	0.81	a<c***	-	0.88
HOS	0.82	0.67	0.45	0.53	1.07	0.95	a>b*	0.69	-
PHO	0.27	0.40	0.25	0.36	0.60	0.72	a<c*	-	0.48
PAR	0.61	0.59	0.47	0.50	1.10	0.89	a<c*	-	0.57
PSY	0.39	0.39	0.21	0.30	0.74	0.70	a>b** a<c*	0.59	0.52

SD, standard deviation. Higher scores indicate worse functioning on a scale of 1-4. \*\*\* $p < 0.001$ , \*\* $p < 0.01$ , \* $p < 0.05$ . Hedge'  $g$  are designated as small (0.20), medium (0.50), and large (0.80). GSI= Global Severity Index; PST= Positive Symptom Total; PSDI= Positive Symptom Distress Index; SOM= Somatization; OBS= Obsessive-Compulsive; INT= Interpersonal Sensitivity; DEP= Depression; ANX= Anxiety; HOS= Hostility; PHO= Phobic Anxiety; PAR= Paranoid Ideation; PSY= Psychoticism. <sup>a</sup>Caregiver sample of this current study <sup>b</sup> Normative sample findings as published by González de Rivera et al., (2002). <sup>c</sup>Z code sample findings as published by Lozano, Ortiz & González (2011).

## Burnout

The mean score for the ZBI was 30.18 (SD = 10). The frequency of response was recorded for some items considered of importance for this group. In item 7, "Are afraid of what the future holds for the relative", 77.3% of the caregivers expressed notable concern (quite often or almost always). While for item 18, "Wish you could leave the care of the relative to someone else", 86.2% of the caregivers expressed their disapproval in this respect (never or rarely).

## Sociodemographic characteristics related to psychosocial and clinical variables

In accordance with the cutoff points established by Cohen's strength of association for correlations ( $r$ ) or ( $r_s$ ) [51], the psychological and environmental domains in the WHOQOL-BREF revealed a high and medium strength relationship with the years of education received by the caregivers ( $r_s = 0.49, p = 0.020$ ) and ( $r = 0.60, p = 0.003$ ), respectively. The experiences of awe and wonder subscale also revealed a relationship with years of education. ( $r = 0.46, p = 0.032$ ). Statistically significant differences were observed in some of the WHOQOL-BREF domain scores and SRPB was based on the caregiver's town of residence and size of genetic deletion. A Man-Whitney test indicated that the environment domain was significantly greater for caregivers residing in rural areas (Mdn = 65.63) than those in urban or intermediate areas (Mdn = 53.13), ( $U = 82.5, p = 0.032$ ). A Kruskal-Wallis Test was conducted to examine the differences in deletion size. A statistically significant difference ( $H = 8.34, p = 0.015$ ) exists between little and high deletions, (Mdn little = 2.25; Mdn high = 3.50) in wholeness and integration. The same applies to the peace scale ( $H = 6.49, p = 0.39$ ), (Mdn little = 2.13; Mdn high = 3.88).

In terms of clinical symptomatology, Interpersonal Sensitivity ( $r_s = 0.61, p = 0.004$ ), Depression ( $r = 0.45, p = 0.045$ ), the GSI ( $r = 0.54, p = 0.013$ ) and PST ( $r = 0.54, p = 0.015$ ) showed an average positive association with the child's age. A statistically significant difference ( $H = 6.21, p = 0.045$ ) exists between little and medium deletions in the PSDI score, (Mdn little = 1.30; Mdn medium = 2.04).

With regard to coping strategies, a positive association was observed with the child's age for self-criticism ( $r_s = 0.49, p = 0.003$ ) and social withdrawal strategies ( $r = 0.45, p = 0.005$ ); likewise, a strong relationship was also observed with emotion focused disengagement strategies ( $r_s = 0.52, p = 0.016$ ).

Furthermore, time devoted to caregiving revealed a negative relationship with engagement and disengagement strategies ( $r = -0.60, p = 0.004$ ;  $r = -0.52, p = 0.016$ ); problem and emotion focused engagement ( $r = -0.57, p = 0.007$ ;  $r = -0.58, p = 0.006$ ); and problem focused disengagement ( $r = -0.53, p = 0.013$ ). Likewise, with the following specific

strategies, such as emotional expression ( $r_s = -0.44, p = 0.044$ ), problem solving ( $r = -0.63, p = 0.002$ ), desiderative thinking ( $r = -0.49, p = 0.023$ ), social support ( $r = -0.61, p = 0.003$ ) and cognitive restructuring ( $r = -0.44, p = 0.044$ ). A Man-Whitney test indicated statistically significant differences for caregivers place of residence in problem avoidance ( $U = 19.5, p = 0.017, \text{Mdn rural} = 2, \text{Mdn urban} = 8$ ), social withdrawal ( $U = 24.5, p = 0.039, \text{Mdn rural} = 2, \text{Mdn urban} = 6$ ) and problem focused disengagement strategies ( $U = 23.5, p = 0.039, \text{Mdn rural} = 14, \text{Mdn urban} = 19$ ). Statistically significant differences were also found for problem solving and social support strategies between employed or unemployed caregivers ( $U = 23.5, p = 0.024, \text{Mdn employed} = 16, \text{Mdn unemployed} = 10$ ) and ( $U = 26.5, p = 0.042, \text{Mdn employed} = 15, \text{Mdn unemployed} = 7.5$ ). In relation to social support networks, statistically significant relationships were found according to the place of residence for the instrumental and affective support scales ( $U = 83.0, p = 0.032, \text{Mdn rural} = 3.67, \text{Mdn urban} = 2.33$ ) and ( $U = 81.5, p = 0.039, \text{Mdn rural} = 3.4, \text{Mdn urban} = 2.4$ ), respectively. A statistically significant difference was also found ( $H = 6.61, p = 0.037$ ) between caregivers' social contacts and size of small ( $\text{Mdn} = 2.5$ ) and large ( $\text{Mdn} = 3.25$ ) deletion.

Burnout showed no significant relationship with sociodemographic variables, and in relation to the length of illness (mid term or long term), it revealed no significant difference between the study variables.

### **Association between psychosocial and clinical variables**

The caregivers' burnout level revealed a relationship with a variety of SCL-90-R symptoms such as Interpersonal Sensitivity, Depression, Hostility, Obsessive-Compulsive, and the GSI ranged from 0.48 to 0.74 with a  $p$  mean value of 0.024. A positive correlation with coping strategies has also been obtained for disengagement, problem and emotion focused disengagement, and desiderative thinking, with an effect size ( $r$  or  $r_s$  values) ranging from 0.47 to 0.57 with a  $p$  mean value of 0.019. It also reveals a negative relationship with the WHOQOL-BREF social relationships domain ( $r = -0.54, p = .009$ ).

Numerous relationships have been found with the different QoL domains. The magnitude of the depression level correlation with the QoL domains ranged from -0.45 to -0.58 with a  $p$  mean value of 0.015. The GSI, Obsession and Interpersonal Sensitivity were shown to have a negative relationship with the physical and environment domains ranged from -0.52 to -0.80 with  $p$  mean value of 0.005. For their part, Obsession and Interpersonal Sensitivity were also shown to have a negative relationship with individual caregiver's perception of their health ( $r_s = -0.44, p = .042$ ;  $r_s = 0.53, p = .012$ ). It is worth noting the positive relationship of different adaptive coping strategies with the QoL psychological domain, such as social support and problem solving ( $r_s = 0.54, p = .010$ ;  $r_s = 0.4, p = .045$ ); Furthermore, this domain also displayed a positive relationship with hope and feelings of awe and wholeness ( $r_s = 0.058, p = .0004$ ;  $r_s = 0.49, p = .020$ ).

Finally, in terms of coping strategies, those classified as engagement strategies displayed a positive association with the psychological social support subscale ( $r = 0.90, p = .000$ ) and the facets of experiences of awe and wonder, wholeness and integration, inner peace and hope in the WHOQOL-SRPB, which ranged from 0.52 to 0.69 with a  $p$  mean value of 0.003. Whereas in disengagement, a relationship was seen with symptom dimensions such as Somatization, Anger-Hostility, Anxiety and indices such as the GSI, which ranged from 0.44 to 0.66 and a  $p$  mean value of 0.001.

## Discussion

### Sociodemographic and psychosocial profile of caregivers

The purpose of analyzing the variables presented in this study was to further our knowledge regarding the sociodemographic and clinical profile of caregivers of children and young people with WHS in Spain. Moreover, to characterize their psychosocial status by analyzing the relationships between quality of life and clinical symptomatology with variables such as burnout, coping strategies and social support networks. Since there is no prior knowledge in this area, the results obtained from this study will be compared with research involving caregivers from related groups, such as chronic illnesses and other rare diseases.

Regarding the first aim of the study, determining the sociodemographic profile of WHS caregivers, the results showed that the caregiver profile was characterized by being a woman who had completed

secondary or higher education, completely or partially given up their job to care for someone, saw their socioeconomic level as low to middle, and lived in a rural area.

This profile coincides with previous research on caregivers with children with rare and/or chronic diseases (32,52–57). For example, in the last two US and European reports on caregivers of people with RDs [52,57], data similar to that obtained in our study is shown. Firstly, 87% and 67% of those surveyed were mothers of children with RDs. Secondly, the mean caregiver age was similar to the US report, placing our caregivers in the Millennial (18 to 36 years) and Gen X (37 to 52 years) generations. Thirdly, in relation to this very report, similar results were reached with regard to caregivers' academic background; this sociodemographic variable revealed a significant relationship with different QoL domains, which will be explained later. Finally, 68.2% of the caregivers in this study lived in a rural area. Previous research highlights that caregivers living in rural areas experience difficulties accessing formal and informal support, such as access to medical services or certain health professionals and/or difficulty contacting social support networks [58]. This geographical constraint has been associated with increased caregiver burnout [54], as well as poorer QoL compared to caregivers living in urban areas. Nonetheless, rural caregivers actively adopt problem focused engagement strategies [59]. No differences were found in this study in the use of problem focused engagement between urban and rural caregivers. However, differences were found in problem focused disengagement strategies such as social withdrawal and problem avoidance. In this case, caregivers living in urban areas obtained higher scores. Caregivers in rural areas perceived more practical and psychological support than caregivers in urban areas, along with a better perception of their environment. Different authors indicate that limited access to support may encourage caregivers to seek out other means to make up for the shortcomings of their environment, such as in our case; greater support in social networks [59,60].

Our study coincides with others carried out on rare and/or chronic diseases. The average number of hours per day devoted to caregiving in our study was 13.19, which classifies our caregivers as "Intense carers" [37]. The European and US guidelines provide inferior or similar data to our study [52,57]. More than six hours of caregiving per day takes up a large part of the caregiver's "active" day. Such dedication has been associated with a greater risk of physical and psychological distress, as well as depleting socioeconomic resources in the family unit [23,61]. The time devoted to caregiving in our study revealed a negative relationship with other variables such as coping strategies for problem solving, social support, emotional expression and cognitive restructuring. Greater dedication to caregiving duties may be impacting on the use of engagement strategies by caregivers, but it has also reduced the use of disengagement strategies such as desiderative thinking and problem avoidance.

Finally, one of the most representative impacts of the caregiver's profile is the impact it has on their work situation. 36.4% of caregivers are unemployed and 72.7% have adapted their job or given it up completely or partially as a result of caregiving. These data have been replicated in other studies with representative samples, where the impact on working life was more prevalent among mothers [52]. In our study, working caregivers used more problem solving and sought social support, as in other research, where working caregivers made more functional use of coping strategies [62].

# Clinical and developmental profile of children with WHS

The children with WHS in this study presented a level of functional, psychomotor and language skills development similar to previous research on the Spanish cohort [16]. In general, the results obtained in this area are in line with the contributions of authors who point out that motor function and expressive communication in WHS may have a better outcome than the outcome represented in classical studies [63].

With regard to genetic characterization, cases with small or medium-sized deletions were highlighted in this study. Deletion size and/or associated genetic alterations have been linked to the level of development, severity of epilepsy and other phenotypic expressions [10,11]. This study conducted a preliminary analysis of the relationship between genetic characterization and psychosocial aspects of caregivers. An increased perception of the social network of parents with children with larger deletions was identified; contrary to other studies, where greater symptom severity of children was predictive of less social support perceived by parents [64]. However, when children had larger (mean) deletions, parents reported greater symptomatic distress. Thus, when faced with a larger deletion size, the parents reported more distress but perceived a stronger social support network and used more coping strategies such as problem solving. Moreover, they experienced a greater sense of gratitude, peace and serenity in their lives; these indicators have been seen as a useful resource for coping strategies and improving caregivers' well-being [65].

Finally, the children in our study were diagnosed at an average age of 17 months, with the average waiting time estimated at approximately one year. Few WHS studies have yielded more data on mean age of diagnosis [6,16–18]. Diagnostic delay is one of the characteristics common to many RDs, with European estimates ranging from a 5 to 30-year waiting time [66]. The results obtained in this study are similar to those of Zurynski et al. [67], where most children were diagnosed during their first year of life. Even though waiting time was shorter in this study, we need to keep in mind that diagnostic delay has a negative impact on caregivers, the child and the family, thereby increasing levels of uncertainty, anxiety and stress. It also hinders access to required medical treatment and social care; and reduces opportunities for family members to access socioeconomic resources [32,68].

## Caregivers' psychosocial and clinical status

As for the psychosocial and clinical characteristics of WHS caregivers, according to the cutoff points determined by Zarit et al., [40], 95.5% of our caregivers would not be overburdened, as they scored less than or equal to 46 points. However, an average was obtained that is similar to the average of studies involving caregivers of children with other RDs such as Prader Willi and Duchenne Muscular Dystrophy [23,69,70]. The ZBI results were analyzed taking into account the analysis of certain clinically relevant items [71]. Caregivers of children with WHS obtained similar or even higher scores for fear for their relatives' future than other studies of caregivers with children suffering from other RDs, such as

Duchenne Muscular Dystrophy [23]. This feeling of uncertainty may be associated with certain WHS characteristics. On the one hand, despite the fact that the prognosis of children with WHS seems to be more promising than it was decades ago, mean life expectancy is unknown [72]. On the other hand, the difficulty in dealing with seizures and their impact could be another factor contributing to this uncertainty, as is the case of caregivers of children suffering from Dravet Syndrome [73]. Sustained uncertainty over time can produce significant emotional distress for the caregiver [71]

In the ZBI responses, 86.2% of caregivers expressed no desire to leave their family member's care to somebody else. This data is similar to other studies involving infant patients [23] and has been associated as an indicator of parental burnout. Caregivers in these groups may experience feelings of guilt when delegating caregiving to other family members and/or professionals. Some authors have described this as a feeling of omnipotence on the part of the main caregiver, seeing themselves as the most suitable and qualified person to care for their children. Hence, handing this role over to someone else would make them feel guilty [71]. However, other authors have interpreted it as an indicator of parents' devotion to their caregiving responsibilities despite the high levels of stress and demand involved [23]. A higher burnout score among our caregivers has been associated with a lower perception of social relationships and, in turn, higher levels of symptoms such as Depression, Hostility, Interpersonal Sensitivity and Obsession. We could thus conclude that the caregivers in this study may be experiencing difficulties delegating caregiving to other family members or support persons, which may distance them from their social networks and add to their emotional distress [54,61,74,75].

Since there is no background data on the emotional and clinical aspects experienced by caregivers of children with WHS, we sought to investigate its nature and analyze whether its impact was similar to or greater than the impact in normative reference populations. The most frequent symptom dimensions arising were Depression, Somatization, Obsessive-Compulsive (including unwanted or unavoidable recurrent thoughts or actions), and Hostility (thoughts, feelings, and actions characterizing the negative effects of anger), only 13.6%, however, met clinical risk or severity criteria. The results of the caregivers in our study were compared with a sample of healthy population [49] and a code Z population of people with no diagnosis but who were suffering from significant clinical distress [50]. The caregivers obtained a symptom score equivalent to the Z code population in two of the highest scoring variables in the study; Somatization and Hostility. Moreover, they scored higher than healthy populations for many of the scale dimensions, among which Somatization, Depression and the Positive Symptom Total with large effect sizes were again prominent. The illness' impact and caregiving situation often leads to psychological distress among caregivers, which often manifests itself in higher levels of depression. These results are in line with numerous studies involving parents of children with other rare or chronic diseases [30,61,75–79], and use data obtained in a study involving parents of children with Dravet Syndrome, [80] where, as in our study, despite the distress experienced, caregivers made little use of psychological or psychiatric support.

The symptom dimensions revealed a positive relationship with child age. The longer the illness lasted, the greater the increase experienced by parents in Depression, Interpersonal Sensitivity, the Global Severity

Index and Positive Symptom Total. Several studies have associated children's age or illness duration with the negative psychosocial adjustment of caregivers [34,54,77]. Furthermore, research involving family carers indicates that sleep deprivation, feelings of guilt, loneliness and isolation are closely linked to well-being and QoL [70,81–85]. The caregivers in this study experienced this range of emotions, which are acknowledged as stressors that impact caregivers and can, at the same time, also affect a child's QoL.

Understanding the impact of rare diseases on caregivers' QoL is important in order to improve socio-healthcare and implement policies for patient and family support and care. In this research, WHS caregivers showed greater deterioration in the WHOQOL-BREF environment and social relationships domains. When comparing their scores with the normative reference population, caregivers obtained lower QoL in all domains. However, they showed no differences, with the exception of the physical domain, when compared to a primary care population [48]. On the basis of results from other studies involving parents with chronically ill children, we found similar results were obtained from the parents of children with congenital metabolic disorders [21]. WHS carers presented a lower QoL than other studies of children with epilepsy, attention deficit hyperactivity disorder and cerebral palsy [86,87]. All QoL domains in our study were negatively associated with Depression. Other indices such as burnout were only for the social relationships domain; and Obsession and Interpersonal Sensitivity obtained a negative relationship with the physical and environment domains. The psychological domain, however, related positively to engagement strategies such as social support and problem solving and increased feelings of hope. This data can be linked to one of the most recent studies conducted on caregivers of children suffering from rare diseases (RDs) [56]. Finally, the parents with higher levels of education displayed a better QoL in the psychological and environment domains. Associating sociodemographic variables with QoL has become increasingly important in recent years, which also reflects the impact of the level of education on the total QoL perceived by the individual [48,88].

Finally, in terms of coping strategies, emotion-focused coping was the most commonly used in our study and involves the use of direct approach strategies on the stressful event. This coping style is related to improved caregiver status [89]. Moreover, emotion-focused strategies, aimed at relieving the tension created by the stressful event, and which tend to be used when the health condition is perceived as uncontrollable or threatening [90], were the second most widely used by parents in our study. In general, emotion-focused strategies, including disengagement strategies such as social withdrawal and self-criticism, have been associated with an increase in the caregiver's depressive symptoms, anxiety, burden and distress, as they have in our study [91–93]. Furthermore, emotion-focused disengagement strategies were more visible when the illness lasted longer and, thus, the time devoted to caregiving. This coincides with previous empirical findings [62]. Finally, with regard to coping, religious type has not been evaluated in this study. However, dimensions of spirituality and religiousness linked to QoL that have been shown to be related to some engagement strategies have been evaluated. Such is the case of the awe and wonder, wholeness and integration, and peace and hope variables. Hope was seen as a protective factor in situations faced by parents [94]. Indeed, some studies indicate that in the face of uncertainty, parents of children with RDs make greater use of religious coping [33].

These strategies have been effective in seeking social support, positive reinterpretation and growth [95]. In fact, some authors, such as Chivukula [65], suggest that spirituality taken as a multidimensional construct could be a valuable resource for improving caregiver coping and well-being.

## Conclusions

The profile of parents caring for children with WHS was characterized by being a woman, with secondary or higher education, completely or partially giving up their job, lower-middle socioeconomic status, and residing in a rural area. The sociodemographic variables included in the study revealed significant relationships with different psychosocial and clinical variables.

The caregivers presented a lower QoL than family carers with other rare, chronic diseases and normative reference populations. The different domains representing the caregiver's total QoL displayed negative relationships with burnout, Depression, Obsession and Interpersonal Sensitivity, which were the most representative symptom dimensions of the group in this research. Moreover, the caregivers' QoL was more favorable toward the use of adaptive coping strategies and a greater feeling of hope.

As far as coping strategies are concerned, problem focused engagement was the most commonly used by caregivers. The strategies encompassing engagement were more dominant and reinforced by a greater perception of affective support in their environment. Disengagement strategies displayed a strong link to caregivers' psychological distress.

Having analyzed the situation of caregivers of children with WHS, we have been able to prove that, despite the disease's particularities and evolution, there are similarities in the characteristics and needs experienced by caregivers in various rare pediatric disorders or related diseases. According to the results of this study, these parents experience emotional distress when coping with the day-to-day care of children with such diseases. This relates to a drop in their perceived QoL. We propose that the implementation of interventions, such as psychosocial support groups with other parents, could encourage the improvement of caregivers' well-being and quality of life by improving their social support network, using positive coping strategies and creating new resources [96]. Further research should consider the use of longitudinal studies and larger samples in order to examine the effect of the associations found in this study.

## Limitations and future lines

Some of the strengths of our study are that: firstly, to our knowledge, this is the first study focusing on the psychosocial status of parents of children with WHS; secondly, standardized and validated tools have been used, enabling the comparison of our results with other studies, either with normative reference samples or other RDs.

However, the sample size evaluated is small and may not be representative of the entire WHS population. The use of small sample sizes is a limitation often found in the RD population. There is bias toward the use of certain statistical analysis methods, meaning that the interpretation of the significance of results has to be taken with caution and cross-checked with future studies. Nonetheless, all the caregivers are members of a National Association for the Syndrome. This support can have an impact on our results, especially on the coping strategies used and on their QoL.

Finally, the use of a cross-sectional design provides us with a still image of a given moment but gives us no information on its evolution throughout the course of time. A longitudinal follow-up study would be of particular interest to this research topic, which, in turn, would increase the sample size so that the results would be more representative of the group of caregivers of children and young people with WHS in Spain.

## List Of Abbreviations

SWH: Wolf-Hirschhorn Syndrome; QoL: Quality of Life; RDs: Rare Diseases.

## Declarations

### Ethics approval and consent to participate

All procedures performed in this study were developed in accordance with the ethical standards and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study. They were also informed about the data privacy and that only the researcher will have access to the data. This study also complies with national laws and regulations (Act 41/2002, 14th November) and guarantees the confidentiality of participants and their data in accordance with the Organic Law on the Protection of Personal Data (15/1999, 13th December).

### Consent for publication

Informed consents for publication were obtained from all caregivers.

### Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because they belong to the University of Deusto, but are available from the corresponding author (Sarah Berrocoso Cascallana) on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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### **Authors' contribution**

SB designed the project, performed the literature searches and wrote the manuscript. IA and EL participated in supervision. MG and AAR performed some of the statistical analysis. MAR, PML and PPN helped to establish the participant assessment tools. SB collected the data with the help from OM, JFL, MP, RB and JN. All authors have read and approved the final manuscript.

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