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### ► To cite this version:

Pascal Amedro, Nabil Tahhan, H  lena Bertet, Claire Jeandel, Sophie Guillaumont, et al.. Health-related quality of life among children with Turner syndrome: controlled cross-sectional study. Journal of Pediatric Endocrinology and Metabolism, 2017, 30 (8), pp.863-868. 10.1515/jpem-2017-0026 . hal-01757618

**HAL Id: hal-01757618**

**<https://hal.science/hal-01757618>**

Submitted on 11 Dec 2019

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# Health-related quality of life among children with Turner syndrome: controlled cross-sectional study

## Abstract

**Background:** The aim of the study was to assess health-related quality of life (HR-QoL) in children with Turner syndrome in comparison with controls.

**Methods:** We prospectively recruited 16 female girls with Turner syndrome (mean age  $15.2 \pm 2.6$  years) and 78 female controls (mean age  $12.7 \pm 2.8$  years) in randomly selected schools. We used the PedsQL, a generic HR-QoL questionnaire (self and parents' versions).

**Results:** Global HR-QoL scores in Turner syndrome were lower than controls for self-reports (respectively,  $74.3 \pm 3.0$  vs.  $82.8 \pm 1.3$ ,  $p=0.01$ ) and parents' reports ( $62.7 \pm 3.8$  vs.  $80.1 \pm 1.7$ ,  $p<0.0001$ ). In Turner syndrome, self-reported HR-QoL was impaired in school functioning ( $70.6 \pm 4.0$  vs.  $80.71 \pm 1.7$ ,  $p=0.02$ ), social functioning ( $78.2 \pm 4.0$  vs.  $90.4 \pm 1.8$ ,  $p<0.01$ ) and physical functioning ( $78.5 \pm 3.2$  vs.  $87.1 \pm 1.4$ ,  $p=0.02$ ), but not in emotional functioning. Parents' reported HR-QoL was impaired in all four dimensions.

**Conclusions:** HR-QoL was impaired in this cohort of young females with Turner syndrome, as in previously reported adult studies. In addition to medical treatment and routine clinical follow-up, female girls and teenagers with Turner syndrome should also be supported psychologically by social, educational and psychotherapeutic interventions that aim to address their self-esteem and emotional difficulties.

**Keywords:** health-related quality of life; pediatrics; PedsQL; Turner syndrome.

## Introduction

Turner syndrome is a rare genetic disorder caused by a complete or partial absence of the X chromosome. In all cases, there is a short stature. Ovarian failure is common but the degree of infertility depends on the chromosomal abnormality. Bone anomalies, lymphedema, deafness, cardiovascular lesions, thyroid and digestive abnormalities are less frequent.

One out of 2500 female neonates are affected. Epidemiological studies carried out in adult populations refer to a diminished overall life expectancy mostly related to cardio-vascular and metabolic disorders [1].

Quality of life (QoL) assessment in chronic diseases is now considered as a major "patient-related outcome". It has been defined as "the overall life satisfaction" [2] but healthcare professionals need a more operational definition, and most clinical trials refer to "health-related quality of life (HR-QoL)". Therefore, HR-QoL questionnaires are built with a multidimensional approach embracing at least physical, social, psychological, mental and functional aspects. The validation of HR-QoL questionnaires requires consistent psychometric properties such as validity, reproducibility and sensitivity to change [2–4]. HR-QoL assessment is more often used as a secondary endpoint, especially in cardiovascular clinical trials [5].

On a large cohort of 568 women with Turner syndrome treated by growth hormone during childhood, Carel et al. [6] showed that patients' self-esteem and social adjustment were impacted by comorbidities such as hearing loss and/

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or heart diseases. When Turner syndrome is diagnosed during childhood, these young patients must cope with this “rare disease” label, impacting their physical appearance, puberty and sexuality. Besides, some of them have to endure significant cardio-vascular lesions such as bicuspid aortic valve, aortic dilatation, coarctation of aorta and arterial hypertension. This leads to additional burdens such as medical therapy and/or heart surgery [7].

In pediatrics, we recently reported that the impact of a cardio-vascular disease on HR-QoL is crucial when physical activity becomes important, usually at the end of elementary school and throughout adolescence [8]. Besides, we have recently pointed out the link between HR-QoL and the actual physical performances among children with congenital heart diseases aged 8–18 years old [9]. However, no such analogy can be made today among children and teenagers with Turner syndrome, with or without cardio-vascular lesion, as HR-QoL data are lacking in this pediatric population.

Our study aimed at assessing the HR-QoL of girls with Turner syndrome aged 8–18 years old in comparison with a contemporary control population using a generic pediatric health-related QoL questionnaire.

## Materials and methods

### Study design

This comparative cross-sectional study was carried out between May 2014 and October 2014 (6 months) in a tertiary care pediatric department (Montpellier University Hospital, France) and in 10 school classes selected in the Languedoc-Roussillon Region, Southern France.

### Patients’ population

Girls with Turner syndrome, as defined by the guidelines of the Turner syndrome study group [10], aged 8–18 years were prospectively recruited during their annual pediatric endocrinology or cardiology outpatient visit. Children with recent surgical or catheter cardiac intervention (6 months delay) and hospitalized children were temporarily excluded but could be recruited during their following annual outpatient visit.

### Control population

From the Education Ministry database, 10 school classes (one per level from 3rd grade [elementary school] to 12th grade [high school]) were randomly selected in the same region as patients’ population

(Languedoc-Roussillon, Southern France). In the 10 selected school classes, the study was proposed to all children from 8 to 18 years and their parents. The recruitment procedure was the same for each class and common to the one at the hospital.

### HR-QoL questionnaires

Children filled in the PedsQL 4.0 questionnaire, a generic HR-QoL pediatric instrument developed by Varni et al. [11] and reported by Uzark et al. in a large similar comparative HR-QoL study among cardiac children [12]. In both groups, questionnaires were administered under trained study nurse supervision. Depending on the age of the child, we used one of the two versions available: 8–12 years old and 13–18 years old. At the same time, in a separate room, parents filled in the proxy version of the PedsQL, adapted to the age of their child.

The PedsQL generic QoL questionnaire is dedicated to healthy and ill children and adolescents. The 23-item PedsQL generic questionnaire was designed to measure the core dimensions of health as defined by the World Health Organization, as well as role (school) functioning. The four multidimensional scales are: physical functioning (eight items), emotional functioning (five items), social functioning (five items), school functioning (five items). The three summary scores are: total scale score (23 items), physical health summary score (eight items), psychosocial health summary score (15 items). Each item uses a 5-point Likert scale from 0 (never) to 4 (almost always). Items are reversed scored and linearly transformed to a 0–100 scale, higher scores indicating a better QoL. Psychometric properties showed reliability, validity and responsiveness to clinical change over time [13]. The translation and cultural adaptation into French was performed by MAPI Research Institute following the international guidelines [14]. The psychometric properties of the French version of the PedsQL appeared to be acceptable [15].

### Formal aspects

This study complies with the Declaration of Helsinki. It was approved by our Institutional Ethics Committee (South Mediterranean IV) and was registered on ClinicalTrials.gov (number NCT01202916). The Ministry of Education Regional Authority authorized schools’ participation. Informed consent was obtained from all parents.

### Statistical analysis

The study population was described with means and standard deviations (SD) or standard errors of the mean (SEM) for quantitative variables and with frequencies and percentage for qualitative variables. Quantitative variables were compared with the parametric Student’s t-test when the distribution was Gaussian and with the Mann-Whitney test otherwise. Qualitative variables were compared with the  $\chi^2$ -test or Fisher’s exact test.

To compare HR-QoL scores of patients with Turner syndrome and controls, we compared the age-adjusted means ( $\pm$ standard error of the mean, SEM) with an analysis of covariance (ANCOVA).

The two-sided significance level was 0.05. SAS version 9 (SAS Institute, Cary, NC, USA) was used.



Results

Populations’ characteristics

Our institution’s database identified 22 children with Turner syndrome aged 8–18 followed by the Department of Pediatric Endocrinology. Three were boys with chromosomal mosaicism. During the study period, 19 girls with Turner syndrome had their annual follow-up, and three families refused to participate in the HR-QoL study. In the control group, 166 girls were selected in the 10 classes, 75 families refused to participate and 13 girls were excluded because they did not have both self and proxy reports.

A total of 16 girls (and their parents) with Turner syndrome and 78 girls (and their parents) from the control group filled in the PedsQL questionnaire (self and proxy versions) (Figure 1).

Females with Turner syndrome who participated in the study were mostly teenagers with few significant cardio-vascular lesions. Growth hormone was the most predominant treatment. We found no difference in terms of school levels between both groups (Table 1).

HR-QoL results

Self-reported HR-QoL scores among teenagers with Turner syndrome were significantly impaired, globally and for the three following dimensions: social, school and physical functioning. The emotional functioning was not significantly affected (Table 2).

Proxy reported HR-QoL scores among parents of teenagers with Turner syndrome were significantly impaired,

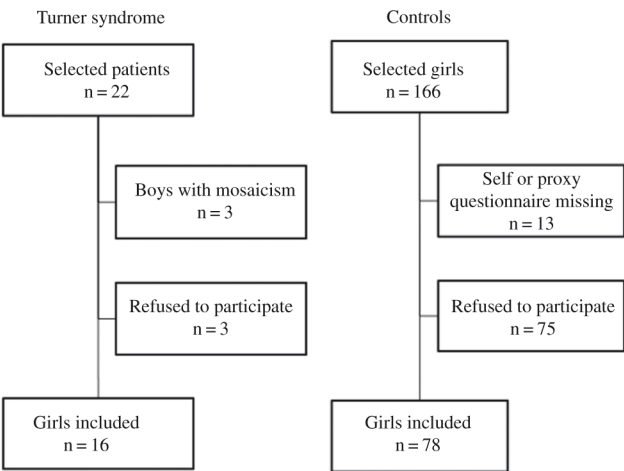


Figure 1: Flow chart.

Table 1: Population characteristics.

Variable	Turner syndrome (n = 16)	Controls (n = 78)	p-Value
Age, mean (SD)	15.2 ± 2.6	12.7 ± 2.8	<0.01
Cardio-vascular lesion, n (%)			
Bicuspid aortic valve/ aortic dilatation	3 (19%)	NA	NA
Repaired aortic coarctation	1 (6%)	NA	
Arterial hypertension	1 (6%)	NA	
Medical treatment, n (%)			
Growth hormone	12 (75%)	NA	NA
β blocker	4 (25%)	NA	
Genotype, n (%)			
Monosome	3 (19%)	NA	NA
Isochromosome	3 (19%)	NA	
Mosaicism	10 (62%)	NA	
School class, n (%)			
Elementary school	0 (0%)	25 (32%)	0.01
Middle school	6 (46%)	28 (36%)	
High school	6 (46%)	25 (32%)	
Specialized education	1 (8%)	0 (0%)	
School level, n (%)			
Normal	12 (80%)	69 (88%)	0.18
Advanced	2 (13%)	2 (3%)	
Repeated	1 (7%)	7 (9%)	

Table 2: Self-reported PedsQL scores: comparisons between Turner syndrome and controls.

Dimension	Turner syndrome Mean (SEM) (n = 16)	Controls Mean (SEM) (n = 73)	p-Value
School	70.6 ± 4.0	80.7 ± 1.7	<b>0.02</b>
Social	78.2 ± 4.0	90.4 ± 1.8	<b>&lt;0.01</b>
Emotion	67.5 ± 5.1	70.5 ± 2.3	0.59
Physical	78.5 ± 3.2	87.1 ± 1.4	<b>0.02</b>
Total score	74.3 ± 3.0	82.8 ± 1.3	<b>0.01</b>

Mean (±SEM) adjusted on continuous age. Significant p-Values <0.05 are marked in bold.

globally and in all four dimensions (school, social, emotion, physical) (Table 3).

Discussion

HR-QoL global scores were significantly lower in this cohort of teenagers with Turner syndrome than in the control population, as reported by patients themselves and by their parents. When focusing on the level of impairment, two dimensions were particularly affected in both self and parents reports: school functioning and social functioning. The impairment in these two specific dimensions



**Table 3:** Parents-reported PedsQL scores: comparisons between Turner syndrome and controls.

Dimension	Turner syndrome Mean (SEM) (n = 16)	Controls Mean (SEM) (n = 73)	p-Value
School	58.5 ± 4.8	76.6 ± 2.1	<b>&lt;0.01</b>
Social	58.4 ± 4.8	86.9 ± 2.1	<b>&lt;0.0001</b>
Emotion	54.6 ± 5.0	70.6 ± 2.2	<b>&lt;0.01</b>
Physical	73.2 ± 4.6	83.9 ± 2.0	<b>0.04</b>
Total score	62.7 ± 3.8	80.1 ± 1.7	<b>&lt;0.0001</b>

Mean (±SEM) adjusted on continuous age. Significant p-Values <0.05 are marked in bold.

is probably multifactorial. Peers and/or teachers might stigmatize children with a chronic disease; parents’ over-protection could prevent children from developing some autonomy. Sustained hospital follow-up in the most severe situations (heart surgery, medical treatment) often result in school absenteeism. At school, girls with Turner syndrome might struggle with inhibitory control, being distracted easily, planning and short-term recall as well as working memory [16]. Some of them have an increased likelihood of attention deficit hyperactivity disorder [17]. In a large comparative study, McCauley et al. [16] found that girls with Turner syndrome were less mature than control girls, with weaker social relationships, school performance and self-esteem. This study also described a decline in self-esteem for the girls with Turner syndrome, but not the comparison group, as they moved into early adolescence. School performances are also probably impacted by specific deficits in visual-spatial/perceptual abilities, nonverbal memory function, motor function, executive function that often occur in Turner syndrome [18, 19]. In line with our results, Boman et al. stated that problems in school accounted for 25% of the variance in well-being among adult women with Turner syndrome [20]. In Turner syndrome, the non verbal learning disorder usually includes difficulties in adapting to new situations, which could result in inappropriate behavior and lead to some issues with social skills (how to make new friends, how to act in a social environment, etc.). In that context, anxiety and depression may easily develop. Hearing loss in patients with Turner syndrome is another example of situation that might impact both school and social functioning. Conductive and sensorineural hearing losses are frequent in Turner syndrome, representing up to 39% and 16%, respectively, in a large pediatric cohort [21]. Therefore regular audiological follow-up is extremely important and needs to be performed during childhood. By identifying early stage hearing loss, we might prevent middle

ear anatomic sequel and limit HR-QoL impairment among these children.

A third dimension was impaired in our cohort of Turner syndrome patients, but only in the parents’ reports: the emotional functioning. Parents usually identify more impact of a chronic disease on their child than the child themselves [8]. Many pediatric studies reported that parents tend to underscore HR-QoL in comparison with the child’s own estimation [12, 22–26]. We recently showed in a large cohort of cardiac children that parents were actually more accurate in correlating their child’s HR-QoL to the actual severity of the disease [9]. Among teenagers with Turner syndrome, depression, anxiety and shyness are frequent, partly in relation with the premature ovarian failure and the fertility issues [27, 28]. Some authors tried to evaluate the impact of growth hormone during childhood on HR-QoL in females with Turner syndrome, but results are controversial. Some studies found low HR-QoL scores [29] or high anxiety and depression levels [30]. Others found no difference between patients treated and patients not treated [31]. One study stated that patients’ satisfaction with height and breast growth resulted in good HR-QoL scores in social and emotional functioning [32]. According to the recent guidelines, all women with Turner syndrome should be evaluated by an expert as soon as possible in childhood as the vast majority will have their ovarian reserve depleted before adulthood [33]. For the experts, the present challenge is to identify these women as early in life as is possible, so as to allow them to benefit from a variety of existing fertility preservation options. This “challenge” is certainly in the patient’s interest, but in the mean time is likely to add more pressure on these children and their family. Therefore, in addition to medical treatment and routine clinical follow-up, girls with Turner syndrome should also be supported psychologically by social, educational and psychotherapeutic interventions that aim to address their self-esteem and emotional difficulties [34].

The physical well-being was also significantly impaired in our cohort of girls with Turner syndrome when compared with the control population, as in a recently reported study [35]. The physical dimension of HR-QoL is usually impaired in children with chronic diseases including motor disabilities, respiratory insufficiency or heart diseases [8]. In our study, one child with Turner syndrome underwent heart surgery for aortic coarctation and four were prescribed cardiac medical drugs but none had a significant hemodynamic impairment. Therefore, once stabilized or healed, the cardiac condition might have taken second place after Turner syndrome itself in terms of HR-QoL. In our recently reported controlled HR-QoL study among a large cohort of 282 children with congenital heart diseases (CHD) vs.

180 controls, the physical well-being was not impaired for the least severe CHD such as aortic coarctation or bicuspid aortic valve; besides, multivariate analysis showed no impact of any drugs on HR-QoL [8]. In the absence of aortic dilatation, significant aortic valve disease or re-coarctation of aorta after treatment, physical activity and sports are authorized under individual pediatric cardiologist's prescription [36]. High intensity static exercises are however, usually avoided in Turner syndrome. However, studies about physical performance in Turner syndrome remain controversial. Some authors reported a "relatively high level of physical activity" [37], others mentioned "normal force but decreased power" [38], or "limited endurance" [39]. Tancredi et al. [40] showed that the maximal oxygen uptake was lower in adult patients with Turner syndrome than in the controls ( $28.4 \pm 4.0$  vs.  $35.6 \pm 6.2$  mL/min/kg;  $p < 0.0001$ ). We have recently shown that HR-QoL was well correlated to maximal oxygen uptake and anaerobic threshold in pediatric cardiac patients [9]. However, no pediatric data is available in terms of a cardio-pulmonary exercise test in Turner syndrome.

Some patients might suffer from low oxygen uptake, deconditioning or hypertension during effort, which might impact their HR-QoL. Therefore, we plan to perform a complete cardio-pulmonary exercise test in our patients with Turner syndrome in order to evaluate the actual physical performances of these teenagers, before transition to adulthood.

## Study limitation

Most of our patients consented to participate to this HR-QoL study, however, the results are primarily limited by the small size of patients with Turner syndrome. With a larger cohort, a multivariate analysis could help identify explanatory variables (growth hormone, height, fertility, heart lesion, etc.). A multicenter HR-QoL study in Turner syndrome would therefore be very useful.

## Conclusions

HR-QoL was significantly impaired in this cohort of young females with Turner syndrome in comparison to a contemporary control population. School, social and physical functioning were significantly altered for both self and parents' reported HR-QoL, and emotional functioning for parents' reports. In addition to medical treatment and routine clinical follow-up, female children and teenagers with Turner syndrome should also be supported

psychologically by social, educational and psychotherapeutic interventions that aim to address their self-esteem and emotional difficulties.

**Acknowledgments:** We thank Jean-Christophe Azorin, National Ministry of Education, for his collaboration to perform the study in schools. We also thank Cristel Gerl (study nurse), Annie Auer (pediatric specialist nurse), Amandine Marquina (pediatric specialist nurse), Anne Requirand (laboratory technician) and Valerie Macioce (medical writer).

**Author contributions:** All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

**Research funding:** Montpellier University Hospital Clinical Research Program funded this work (grant's reference: UF8422).

**Employment or leadership:** None declared.

**Honorarium:** None declared.

**Competing interests:** The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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