Health-Related Quality of Life in Youth with Hypercholesterolemia

Nicole Jamieson, BS, MS4

Mentor: Don P Wilson, MD

Additional Author: Luke Hamilton, MS

Burnett School of Medicine, Texas Christian University

Abstract

Research Question:

Is the perceived quality of life different in youth <18 years-of-age with familial hypercholesterolemia (FH) compared to healthy peers?

Background:

In the U.S. and developed countries, cardiovascular disease (CVD) is the [#]1 cause of death in adults. Children with FH, a genetic disorder of dysregulated low-density lipoprotein cholesterol (LDL-C) metabolism, have the highest risk of developing premature CVD.

Over the past 25 years, there has been an increased awareness of the need to assess and, whenever possible, optimize an individual's quality of life. This is particularly compelling in children, who encounter medical conditions during a vulnerable time of cognitive and emotional development. The Pediatric Quality of Life Inventory (PedsQL®) has been shown to reliably measure Health Related Quality of Life (HRQOL) in healthy youth, and in youth with a wide variety of medical conditions, such as obesity, congenital heart and kidney disease. The PedsQL® questionnaire is a comprehensive and multidimensional instrument capable of quantitating physical, emotional and social well-being, as well as school functioning. Completion of the PedsQL® is validated in both written and electronic formats, and several languages, including English and Spanish. While previous research has shown that youth with medical conditions often score significantly lower on the PedsQL® than their healthy peers, no prior studies have evaluated HRQOL in youth with FH.

Materials and Methods:

The PedsQL® 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL® Disease-Specific Modules. The PedsQL® 4.0 Generic Core Scales consist of 23 items applicable for healthy school and community populations, as well as pediatric populations with acute and chronic health conditions. The scales measure physical, emotional, social, and school functioning.

The R.E.A.C.H. (Risk Evaluation to Assess Cardiovascular Health) Clinic was established by Cook Children's Medical Center to better understand the cause(s) of premature CVD, including genetic and acquired forms of abnormal blood fats, elevated blood pressure, and weight-related health risks; developing effective means of prevention through health education, early detection of those at risk and timely treatment. The REACH clinic has a robust screening program, which has identified youth with FH. We compared the child self-report questionnaires of this population to published data of healthy peers.

Results:

Children with hypercholesterolemia demonstrated a significant difference in their perceived HRQOL compared healthy peers; and similar to children with chronic illness. Additionally, the average parent-proxy scores in children with hypercholesterolemia were lower when compared to a healthy population.

Conclusion:

Because the HRQOL assesses multidimensional well-being, an evaluation of these scores provide a comprehensive assessment of this vulnerable population. Although data are limited, an impaired HRQOL may be a risk factor for co-morbid conditions. Furthermore, these data will help identify unmet needs beyond current recommendations for clinical care of youth with FH.

Research Question:

Is the perceived quality of life different in youth <18 years of age with hypercholesterolemia compared to healthy peers?

Introduction and Significance:

In the U.S. and developed countries, cardiovascular disease (CVD) is the leading cause of death in adults[1]. Over the past three decades, it has become evident that atherosclerosis, the major cause of CVD, has its origins in childhood. Familial Hypercholesterolemia (FH), a genetic disorder of dysregulated low-density lipoprotein cholesterol (LDL-C) metabolism, leads to a chronic exposure to LDL-C over the lifetime[2]. These children have the highest risk of developing premature CVD, putting them at risk for fatal complications like stroke and myocardial infarction. 50% of men and 30% of women with FH have a heart attack by age 50. This makes identifying and treating this disorder early in life crucial[3]. Understanding how this early diagnosis can impact all aspects of a child's life can help us reach our goal of primary prevention.

Medicine has historically focused on longevity. Over the past 25 years, there has been an increased awareness of the need to assess and, whenever possible, optimize an individual's quality of life. This is particularly compelling in children, who encounter medical conditions during a vulnerable time of cognitive and emotional development. Important interventions, such as resilience training, have been shown to improve HRQOL. Children with dyslipidemia may require preventive healthcare, health education, and ongoing medical care. Understanding their quality of life can help tailor interventions to provide optimal benefits.

The Pediatric Quality of Life Inventory (PedsQL®) has been shown to reliably measure Health Related Quality of Life (HRQOL) in healthy youth, and in youth with a wide variety of medical conditions, such as obesity, congenital heart and kidney disease[4]. The PedsQL® questionnaire is a comprehensive and multidimensional instrument capable of quantitating physical, emotional and social well-being, as well as school functioning. Completion of the PedsQL® is validated in both written and electronic formats, and several languages, including English and Spanish. While previous research has shown that youth with medical conditions often score significantly lower on the PedsQL® than their healthy peers, no prior studies have evaluated HRQOL in youth with hypercholesterolemia. This study evaluates the HRQOL in this group in individual domains and total HRQOL.

Preliminary Data:

The R.E.A.C.H. (Risk Evaluation to Assess Cardiovascular Health) Clinic was established by Cook Children's Medical Center to better understand the causes of premature CVD, including genetic and acquired forms of abnormal blood fats, elevated blood pressure, and weight-related health risks; developing effective means of prevention through health education, early detection of those at risk, and timely treatment. The REACH clinic has a robust screening program, which has identified youth with hypercholesterolemia. This population was used for the analysis.

Hypothesis and Specific Aims:

Our primary research goal was to critically evaluate the impact of FH on the quality of life in children. The experimental hypothesis which will drive this research is as follows: "Children with FH will generally report a quality of life that is lower than that reported from children of a similar age who do not have FH."

Specific Aim: Using research data from IRB approved studies, we will analyze child self-report questionnaires from the REACH clinic and compare those to published data of healthy peers. Completion of this aim will enable us to evaluate the impact of hypercholesterolemia in children on quality of life.

Materials and Methods

Materials:

This study used the PedsQL® 4.0 (Pediatric Quality of Life Inventory Version 4.0). The PedsQL® 4.0 Generic Core Scales encompass 4 broad categories with a total of 23 items: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items). The Child self-report includes ages 5 to 7, 8 to 12, and 13 to 18 years. The items for each of the forms differ in developmentally appropriate language or tense but are essentially identical. The instructions ask: how much of a problem each item has been during the past 1 month?

A 5-point response scale is utilized across child self-report for ages 8 to 18 (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). The young child self-report (ages 5-7), is made more appropriate for the age the response scale is reworded and simplified to a 3-point scale (0 = not at all a problem; 2 = sometimes a problem; 4 = a lot of a problem), with each response choice anchored to a happy to sad faces scale. Items are reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100,1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQOL[2].

Subjects:

The study participants were recruited from the REACH clinic at Cook Children's Hospital (Fort Worth, TX). The children (both male and female) range from 5-18 years of age who have met the qualifications for hypercholesterolemia. Familial hypercholesterolemia is considered to be present in a child who, despite compliance with a proper diet, has a persistently elevated level of LDL-C and/or the presence of a confirmed pathologic gene variant for LDLR, APOB, PCSK9 or LDLRAD1[7]. This will include children that have been screened in the clinic and have completed the PedsQL®. While all the population studied with meet criteria for hypercholesterolemia, some subjects may not have the FH diagnosis.

Comparison Groups:

The subjects identified in the REACH clinic were compared to the published healthy population. The data on healthy children will be derived from the PedsQL® 4.0 field test[4]. Healthy children were those assessed either in physicians' offices during well-child checks or by telephone and whose parents did not report the presence of a chronic health condition. For child self-report, the average age of the sample was 10.78 years (SD = 3.61 years). The number of child participants was 401, with 389 parent proxies. The sample was heterogeneous with respect to race/ethnicity and socioeconomic status[4]. The participants from the REACH clinic were also compared to a chronically ill population[5]. The number of child participants was 106, with 104

parent proxies. The average age was 11 (SD=4.3 years). The sample was heterogeneous with respect to race/ethnicity and socioeconomic status.

Methods:

Data of patients seen in the REACH clinic was collected from an internal registry, previously approved by the Cook Children's Institutional Review Board. Basic descriptive analyses were conducted to describe the patient population. Various statistical methods will be employed to compare and analyze patient and parent scores against one another and to healthy populations in which PedsQL® data has previously been reported.

Results:

There were 243 parents and 231 patients from the REACH clinic who completed the PedsQL®. The average age of children was 11.3 years. The reported ethnicity of the respondents was 77.8% White/Caucasian, 12.8% Black/African American, 3.7% Asian, 3.3% Other, and 2.5% not reported. Of the subjects who completed the survey, 50.2% were female, 50.8% male. The average BIM was in the 77th percentile. The average Total Cholesterol 220md/dL. The average HDL-C was 47mg/dL. The LDL-C was 146mg/dL. The average Lipoprotein(a) was 85 nmol/L. Children with hypercholesterolemia demonstrated a significant difference in their perceived HRQOL compared to healthy peers; and similar to children with chronic illness. When comparing the average child report PedsQL® scores of children with hypocholesteremia to the chronically ill population, the results demonstrate the populations are similar in the Total PedsQL® score. Children with hypercholesterolemia are 2.7% less in the Psychosocial PedsQL® when compared to the chronically ill population. Children with hypercholesterolemia reported a higher score in the Physical PedsQL® when compared to the chronically ill population. Additionally, the average child report PedsQL® in children with hypercholesterolemia is less than the healthy child report in the Total, Physical, and Psychosocial PedsQL® scores. When assessing the average parent-proxy scores in those with a child with hypercholesterolemia, the scores were similar to that of the chronically ill population in Total and Psychological PedsQL® scores, and higher in the Physical PedsQL® score. The average parent-proxy scores in children with hypercholesterolemia were lower in Total, Psychosocial, and Physical PedsQL® scores when compared to a healthy population. The percentage difference between groups in each domain of the PedsQL® was calculated and described in *Table 1.*
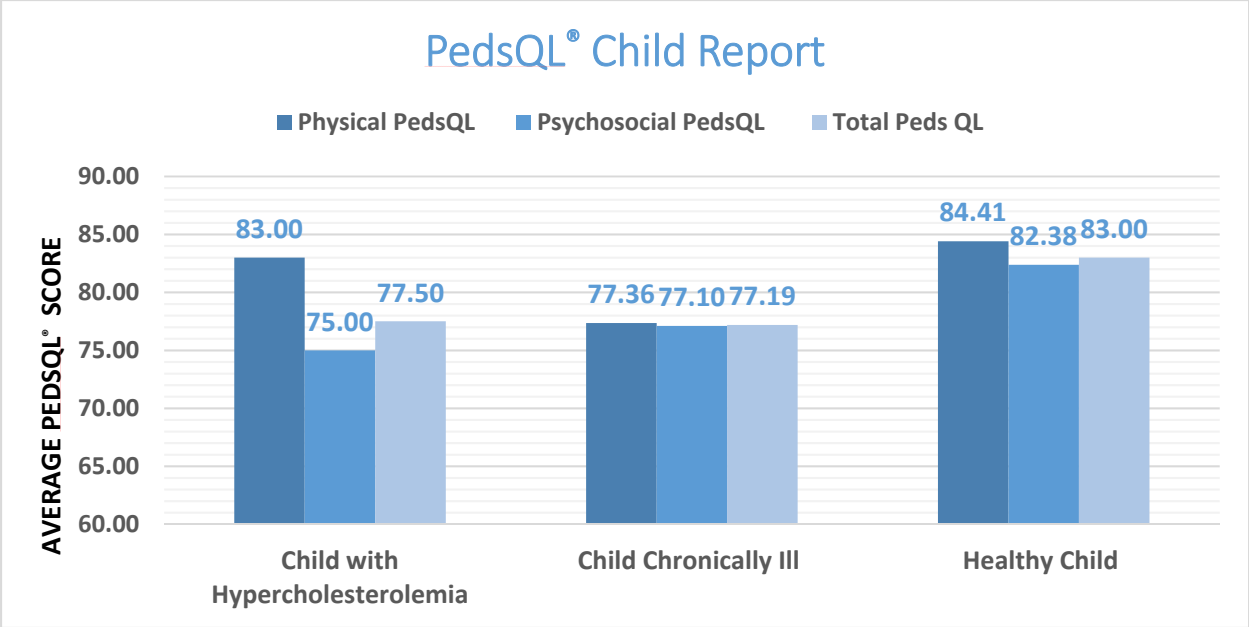
Figure 1: Results of the PedsQL® child report comparing Child with Hypercholesterolemia, Child Chronically Ill, and Healthy Child in Physical, Psychosocial, and Total PedsQL® scores.
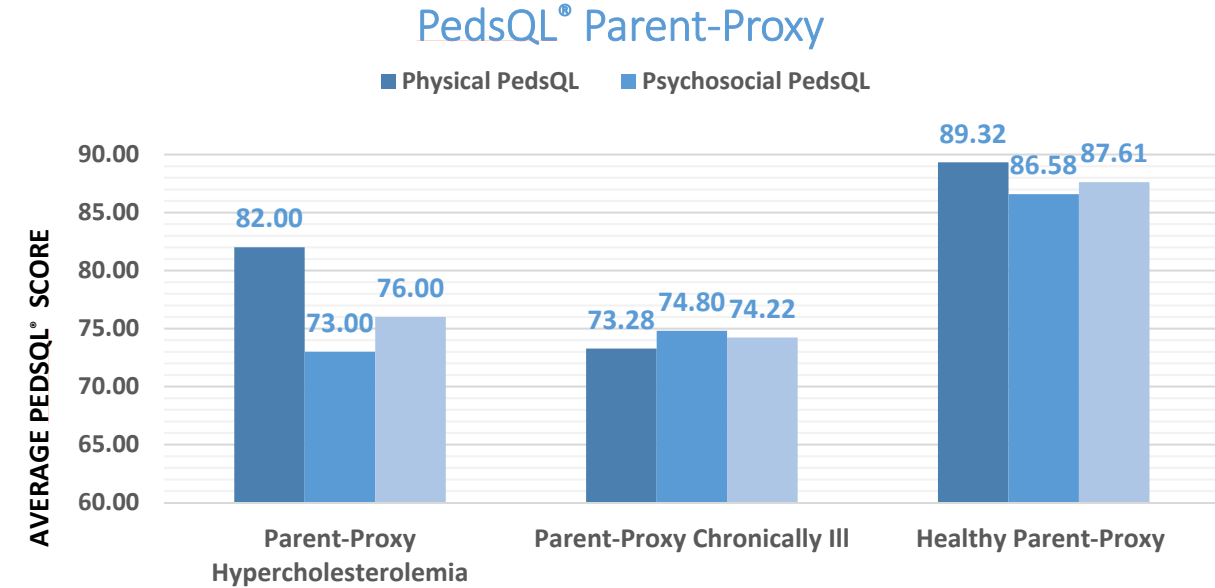

Figure 2: Results of the PedsQL® parent-proxy report comparing Parent-Proxy with Hypercholesterolemia, Parent-Proxy Chronically Ill, and Parent-Proxy in Physical, Psychosocial, and Total PedsQL® scores.

Percentage Difference in Average Scores				
	Child Hypercholesterolemia vs Chronically Ill Child	Child Hypercholesterolemia vs Healthy Child	Parent-Proxy Hypercholesterolemia vs Parent-Proxy Chronically Ill	Parent-Proxy Hypercholesterolemia vs Healthy Parent-Proxy
Physical PedsQL®	7.3	-1.7	11.9	-8.2
Psychosocial PedsQL®	-2.7	-9.0	-2.4	-15.7
Total PedsQL®	0.4	-6.6	2.4	-13.3

Table 1: The percentage difference between groups in each domain of the PedsQL®

Mean Anthropometric and Laboratory Measurements	
BMI Percentile	77%
Total Cholesterol	220 md/dL
HDL-C	47 mg/dL
LDL-C	146 mg/dL
Lipoprotein(a)	85 nmol/L

Table 2: Mean Anthropometric and Laboratory Measurements of children with hypercholesterolemia who completed the PedsQL®.

Discussion:

The data demonstrate a significant relationship between hypercholesterolemia and health-related QOL, indicating that children with hypercholesterolemia have a lower HRQOL than their healthy cohorts. This should be considered in moving forward in caring for children with hypercholesterolemia. Of specific note, the youth with hypercholesterolemia reported a lower total and psychosocial HRQOL. This is consistent with the idea that hypercholesterolemia is not a physically debilitating disease. However, the lower scores in Psychosocial and Total HRQOL indicate that the knowledge of the disease is a significant stressor in the lives of the children studied.

One important aspect of the PedsQL® is child-report is it emphasizes the self-perception of the child in their everyday life. Meaning that this is impacting the relationships they make, their ability to learn, develop, and grow in more than just their physical health. Their care may benefit from being further targeted to not only treat their medical condition, and control their lipid numbers, but address the functioning in all domains of their life.

Impairment in the domains of physical, psychosocial, emotional, social, and school functioning may all have downstream impacts on the child's well-being later down the line. Each of these domains may be addressed by different professionals, especially if one domain is more significantly affected. It would be important for the primary physician to understand the meanings of these scores and the potential impacts each has. This may help them better understand the emotional state the patient is coming from and the degree to which their illness is impacting their life. While the relationship among comorbidities and quality of life can be cyclic, it is important to note that some factors associated with poor quality of life have associations with health risks such as smoking and obesity. These could further potentiate their underlying condition and lead to an overall decline in health[6].

Furthermore, knowing that children with hypercholesterolemia tend to have a significantly lower HRQOL compared to the healthy population, further emphasizes the importance of early screening for the disease. The earlier it is identified, the more resources the children can be offered not just for their physical well-being, but all to add protective measures to safeguard their overall functioning.

Future Directions:

Knowing that youth with hypercholesterolemia report a lower psychosocial and total health-related quality of life provides support for various interventions and follow-ups. It would be important to follow these subjects over the years of their treatment whilst receiving social support and have them again complete the survey to determine if certain interventions may be beneficial to their overall well-being.

Conclusion:

The data demonstrate a significant relationship between hypercholesterolemia and HRQOL, indicating that children with hypercholesterolemia have a lower HRQOL than their healthy cohorts. Specifically, the youth with hypercholesterolemia reported a lower total and psychosocial HRQOL. This may indicate that the knowledge of the disease is a significant stressor in the lives of the children studied. It is important for healthcare providers, and caregivers to be aware of this to best care for these children and help them succeed. It may be beneficial to have these children complete the PedsQL® after treatments, intervention, and support have been provided in order to gauge the effectiveness of these interventions in improving the HRQOL.

Compliance Plan:

The IRB was submitted and completed through the Cook Children's IRB system. All patient data was in REDCAP and deidentified.

References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020 Mar 3;141(9):e139-

2. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Borén J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgözoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017 Aug 21;38(32):2459-2472. doi: 10.1093/eurheartj/ehx144. PMID: 28444290; PMCID: PMC5837225.

3. Ambika P Ashraf, Brenda Kohn, Don P Wilson, Improving Long-Term Outcomes of Youth With Lipid Abnormalities—Expanding the Role of Pediatric Endocrinologists, *The Journal of Clinical Endocrinology & Metabolism*, Volume 104, Issue 10, October 2019, Pages 4421–4426

4. Varni JW, Seid M, Kurtin PS: The PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 39: 800–812, 2001

5. Schwimmer JB, Burwinkle TM, Varni JW. Health-Related Quality of Life of Severely Obese Children and Adolescents. *JAMA.* 2003;289(14):1813–1819. doi:10.1001/jama.289.14.1813

6. Centers for Disease Control and Prevention. Measuring Healthy Days. Atlanta, Georgia: CDC, November 2000

7. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004 Sep 1;160(5):407-20.