Exercise Performance and 22q11.2 Deletion Status Affect Quality of Life in Tetralogy of Fallot

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Objective To identify mediators of health status and quality of life (QOL) in children and adolescents aged 8-18 years old following surgical repair for tetralogy of Fallot (TOF), including resource use, exercise performance, and 22q11.2 deletion status.

Study design We performed a corollary study to a cross-sectional analysis of subjects following repair for TOF that completed cardiac magnetic resonance imaging, cardiopulmonary exercise tests, and instruments assessing health status and QOL. General linear models were used to test for mediation.

Results A total of 29 of 151 (19%) patients carried a 22q11.2 deletion. Parents of children with a deletion compared with those without a deletion reported worse physical and psychosocial functioning on the Child Health Questionnaire. The patients with a 22q11.2 deletion and their parents reported lower total and Disease Impact scores compared with the group without a deletion on the Pediatric Cardiac Quality of Life Inventory. Medical care use negatively correlated with measures of health status/QOL. Greater maximum work correlated with better patient health status and QOL, regardless of deletion status. Exercise performance mediated the association between deletion status and parent-reported outcomes (unstandardized effects ranging from 2.4 to 4.2) and patient-reported Disease Impact (0.99; 95% CI 0.02-2.70).

Conclusion Children and adolescents following repair for TOF seem to suffer significant challenges to their health status and QOL, which is amplified markedly in the context of the 22q11.2 deletion syndrome, and related to exercise performance. *(J Pediatr 2017;189:162-8).*

Patients with tetralogy of Fallot (TOF) now survive well into adulthood given the marked improvement in medical and surgical therapies.[1-3] Concern has therefore turned from questions of early mortality to associated long-term morbidities. Numerous studies have detailed the cardiovascular status of survivors of TOF, but only recently have studies begun to investigate patient and parent proxy-reported quality of life (QOL).[4-7] Although health and functional status describes the physical health and well-being of an individual and their ability to perform activities of daily living, health-related QOL describes the ability of the patient to both function and derive personal satisfaction from various physical, psychological, and social life contexts.[8] Most series assessing QOL in TOF have focused on adult survivors,[9-16] with few delineating QOL in children.[4,17-20] The impact of genotype in general and 22q11.2 deletion status in particular on QOL in the survivor of TOF also has not been examined, yet 25% of TOF cases have an associated genetic syndrome or additional congenital anomaly and approximately 15% of all TOF cases have a 22q11.2 deletion.[21,22] Given the prevalence of 22q11.2 deletion in the TOF population, defining the impact of genotype on health status and QOL is critical to maximizing outcomes in this high-risk population.

We previously found that cardiac function was relatively well preserved and not influenced by 22q11.2 deletion status.[23] However, compared with normal controls, exercise performance was significantly decreased for those with TOF without a 22q11.2 deletion and even more so in those carrying a 22q11.2 deletion. In addition, medical care use, measured by number of hospitalizations and medications, was increased substantially in those with a 22q11.2 deletion compared with the TOF subgroup without a deletion. To what extent deletion status, exercise performance, and medical care use impacted their health status and QOL is the focus of this study.

CHQ	Child Health Questionnaire
CPET	Cardiopulmonary exercise test
DI	Disease Impact
PCQLI	Pediatric Cardiac Quality of Life Inventory
QOL	Quality of life
TOF	Tetralogy of Fallot

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Methods

The current analysis was a corollary study to a cross-sectional analysis of subjects aged 8-18 years following repair for TOF with and without a 22q11.2 deletion at the Children's Hospital of Philadelphia, described previously.[23] Subjects who provided consent underwent cardiac magnetic resonance imaging and a cardiopulmonary exercise test (CPET), most often on the same day, but otherwise within 6 months. Patients were excluded if cardiac procedures were performed in between research-based tests. Study subjects and their parent/guardian completed the Child Health Questionnaire (CHQ) and Pediatric Cardiac Quality of Life Inventory (PCQLI) if not at the time of testing, then within the same 6-month period. Only those parent/guardian-child pairs that completed the PCQLI were included in the analysis. The study protocol was approved by the institutional review board for the Protection of Human Subjects at the Children's Hospital of Philadelphia.

For the present study, two analyses were conducted: (1) a test to determine whether the effect of deletion status on health status/QOL was moderated by cardiac function (moderation analysis determines whether there is an interaction between the predictor [ie, deletion status] and moderator variable [ie, cardiac function] on the outcome [ie, health status/QOL]. The moderator analysis seeks to examine whether the direction of the association between predictor and outcome changes due to the presence of the moderator variable. In these tests, the predictor variable is not causing the moderator, just interacting with the moderator). (2) A mediation analysis to determine whether there is an indirect affect between deletion status and health status/QOL through exercise performance and medical care use. (In mediation analysis, the predictor variable directly affects the mediator variable[s] and the mediator variable has a direct effect on the outcome[s].) A conceptual model is presented in the **Figure**.

The predictor variable for the analysis was 22q11.2 deletion status. Study outcome variables were health status/QOL, measured as follows: (1) Health status was measured with the CHQ Parent Form,[24] Psychosocial Health Status and Physical Health Status summary scores, and the Child Form Global Health questionnaire; and (2) the PCQLI was used to assess QOL (patient and parent-proxy).[25,26] Both the total score and subscale scores (Disease Impact [DI] and Psychosocial Impact) were obtained. The sample for this study was not contingent on patient/parent pairs.

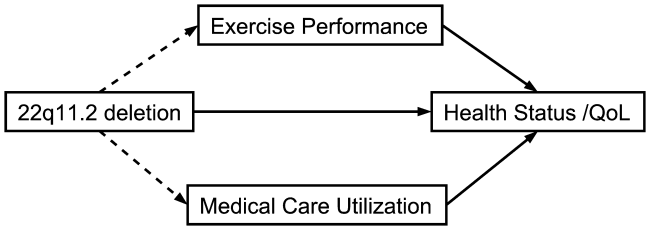

Figure. Conceptual model depicting proposed mediators of association between deletion status and health status/QOL in TOF. The model proposes possible direct effects of deletion status, exercise performance, and resource use on health status/QOL in TOF (*solid arrows*), as well as possible indirect effects of 22q11.2 deletion via exercise performance and resource use (ie, proposed mediators of 22q11.2 deletion status) on health status/QOL in TOF.

For the first analysis, moderator variables of cardiac function were analyzed to determine whether they impacted the association between deletion status and health status/QOL. Cardiac function variables obtained by cardiac magnetic resonance included pulmonary regurgitant fraction, right ventricular end-diastolic volume, right ventricular ejection fraction, left ventricular ejection fraction, and left ventricular cardiac index.

The final analysis assessed whether the association between deletion status and health status/QOL was mediated by exercise performance on CPET and/or medical care use. Exercise performance variables included forced vital capacity (% predicted value), maximum oxygen consumption (% predicted value), oxygen consumption at anaerobic threshold (% predicted value), maximum work (watts/kg) (% predicted value), and indexed O_2 pulse ($mLO_2/beats/m^2$). Medical care use variables included number of medications at enrollment, cardiac catheterizations, cardiac surgeries, total cardiac-related procedures (surgeries and cardiac catheterizations), and total hospitalizations (cardiac and noncardiac).

Potential model covariates included age, sex, race, parental education, use of a transannular patch for TOF repair, type of surgical repair (a single procedure to accomplish a complete repair vs placement of a Blalock-Taussig shunt before complete repair), and age at enrollment as an approximation of time from the first surgery.

Statistical Analyses

Descriptive statistics were used to examine the distribution of the data, to test for skewness and kurtosis, with variables transformed where necessary. Summary statistics (frequencies, means [SDs], and medians [ranges]) were reported. The relationship between the predictor variable and mediators, moderators, covariates, and study outcomes was tested with either the Student *t* test for normally distributed data or a Wilcoxon rank sum test for the medical use variables, which are count-level data. Pearson (for continuous variables), Spearman (for count variables), and point biserial (for dichotomous variables) correlations were used to examine the relationships among mediators, moderators, covariates, and outcomes.

The first set of analyses, the moderation models, tested for interactions between deletion status and cardiac function on health status and QOL. General linear modeling with an interaction statement (deletion status by specific cardiac functioning variable) was used to test for moderation, in the presence of significant covariates. Interactions were considered statistically significant if the P value was $< .05$.

The second set of analyses tested whether medical care use and exercise performance variables mediated the association between deletion status and health status/QOL. For these