Behavioral Functioning and Quality of Life in South African Children Living with HIV on Antiretroviral Therapy

Stephanie Shiau, PhD, MPH[1], Henry Evans, MD[2], Renate Strehlau, MBBch[3], Yanhan Shen, MS[4], Megan Burke, MBBch[3], Afaaf Liberty, MBBch[5], Ashraf Coovadia, MBBch[3], Elaine J. Abrams, MD[6,7,8], Michael T. Yin, MD, MS[2], Avy Violari, MD[5], Louise Kuhn, PhD, MPH[4,7], and Stephen M. Arpadi, MD, MS[4,7,8]

This study examined behavioral functioning and quality of life in South African children living with perinatally acquired HIV. Compared with controls, children living with perinatally acquired HIV had a higher mean total difficulties score assessed by the Strengths and Difficulties Questionnaire and lower mean quality of life scores assessed by the Pediatric Quality of Life Inventory. *(J Pediatr 2020;227:308-13).*

In addition to multiple infectious diseases, children living with perinatally acquired HIV (CLWH) are at increased risk for a number of other morbidities that affect their quality of life and mental health, including developmental delays, motor and cognitive impairment, and behavioral problems.[1-6] CLWH are also more likely to experience illness or death of a parent, stigma, and discrimination that are harmful to emotional and social well-being during childhood.[7]

The use of combination antiretroviral therapy (ART) has resulted in substantial decreases in mortality and prevents or mitigates many of the more severe manifestations of perinatally acquired HIV.[8] In addition, many but not all studies conducted in both well- and less-resourced settings find better neurodevelopmental outcomes associated with ART.[9-13] These studies vary with respect to therapeutic agents, duration of observations, and consistency of viral suppression, as well as age, immune status, and stage of disease at time of treatment initiation. More recent reports from clinical trials involving children started on ART at early ages with less advanced disease find even greater benefit; however, neurocognitive deficits and behavior problems persist.[10,12,13]

Data on the overall impact of HIV infection, HIV-associated conditions, and quality of life—that is, the physical, psychological, school-related, and social well-being—among CLWH who initiate ART early in life and maintain viral suppression are limited. Prior studies report lower quality of life with significant deficits in physical as well as social, emotional, and school functioning.[14-17] Few of these studies, however, are able to account for age of ART initiation and degree of viral suppression.

ART	Antiretroviral therapy
CHANGES	Childhood HAART Alterations in Normal Growth, Genes, and aGing Evaluation Study
CLWH	Children living with perinatally acquired HIV
ESRU	Empilweni Services and Research Unit
LPV/r	Ritonavir-boosted lopinavir-based
PedsQL	Pediatric Quality of Life Inventory
PHRU	Perinatal HIV Research Unit
SDQ	Strengths and Difficulties Questionnaire

The aim of this study was to assess behavioral functioning and quality of life of South African school-aged CLWH who initiated ART early in life (mean, 6 months of age) and are clinically stable on ART, and compare these outcomes with a group of children without HIV. In addition, we compared these outcomes among CLWH by age at ART initiation (≤6 months vs >6 months) and by ART regimen (efavirenz-based vs ritonavir-boosted lopinavir-based [LPV/r]).

Methods

Study Population

The Childhood HAART Alterations in Normal Growth, Genes, and aGing Evaluation Study (CHANGES) is a longitudinal cohort study of CLWH and controls without HIV conducted at 2 research sites in Johannesburg, South Africa: the Empilweni Services and Research Unit (ESRU) at Rahima Moosa Mother and Child Hospital and the Perinatal HIV Research Unit (PHRU) at Chris Hani Baragwanath Hospital.[18-25] CHANGES was designed to study the chronic effects of growing up with HIV, including the role of host epigenetics and mitochondrial function in HIV disease progression. Enrollment began in December 2014 and the study was completed in February 2018. A total of 553 CLWH were recruited from earlier trials and achieved early virologic suppression with commonly prescribed ART.[8,26-28] Control participants were recruited from among eligible siblings or household members of CLWH in the study as well as from those attending the study site for routine outpatient health

From the [1]Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, NJ; [2]Division of Infectious Diseases, Department of Medicine, Vagelos College of Physicians & Surgeons, Columbia University Irving Medical Center, New York, NY; [3]Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, Department of Pediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [4]ICAP at Columbia University, Mailman School of Public Health; [5]Department of Epidemiology, Mailman School of Public Health; [6]Department of Pediatrics, Vagelos College of Physicians and Surgeons; [7]G.H. Sergievsky Center, Vagelos College of Physicians & Surgeons, Columbia University Irving Medical Center, New York, NY; and [8]Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, University of the Witwatersrand, Johannesburg, South Africa

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services. Controls were frequency matched in age bands to the CLWH, but no matching by sex was attempted. Controls were interviewed at the same time as the cases.

Written informed consent was obtained from parents or guardians. In addition, children 7 years of age or older were asked for assent. The study was approved by the Institutional Review Boards of Columbia University (New York, New York) and the University of the Witwatersrand (Johannesburg, South Africa). This analysis uses data collected from the exit visit of CHANGES.

Measurements

Data were collected on participants' age, sex, education, anthropometry, and caregiver and household characteristics. For CLWH, information on their ART regimen was obtained and plasma HIV-RNA levels (lower limit of detection 40 copies/mL) were measured by the Abbott RealTime HIV-1 Assay (Abbott Laboratories, Abbott Park, Illinois). Cluster of differential 4 (CD4) T-cell counts and percentage were measured by the TruCount Method (BD Biosciences, Heidelberg, Germany).

At the exit visit from CHANGES after approximately 4 years of follow-up, we assessed behavioral functioning using the Strengths and Difficulties Questionnaire (SDQ), a brief, validated behavioral health screening tool that has been translated and adapted into multiple languages and has been applied in prior studies of children with HIV.[29-32] Briefly, 25 items related to behavioral and emotional health were rated on a 3-point Likert scale. Five subscale scores were calculated from these items, including emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. A total difficulties score was calculated based on the first 4 subscales and scoring was performed using published algorithms (https://www.sdqinfo.org/). Surveys were completed once by the primary caregiver (parent rated). Only surveys completed using official versions of the SDQ in English, Afrikaans, isiXhosa, and isiZulu were included in analysis.

The Pediatric Quality of Life Inventory (PedsQL version 4.0) was used to measure health-related quality of life. The PedsQL Measurement model is a brief, reliable, and valid modular approach with 23 items rated on a 5-point Likert scale. PedsQL items were scored following standardized methods (www.pedsql.org/about_pedsql.html) and 3 summary scores were created: a total scale score (23 items), a physical health summary score (8 items), and a psychosocial health summary score (15 items). In addition, 3 subscale scores were created for emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Surveys were completed once by children (self-rated). Only surveys completed using official versions of the PedsQL in English, Afrikaans, isiXhosa, Sesotho, and isiZulu as per participant preference were included in the analysis.

Statistical Analyses

Comparisons of demographics between groups were conducted using Pearson χ^2 test (or Fisher exact test), Student t test, or Wilcoxon signed rank-sum test, as appropriate. Multivariable linear regression models were used to assess the association between HIV status and all individual scales and summary scales of SDQ and PedsQL questionnaires. We assessed if the following covariates were associated with scores on the SDQ and PedsQL: age, sex, study site (ESRU vs PHRU), primary caregiver (mother vs other), caregiver education (no completion of grade 9 vs completion of grade 9), caregiver marital status (married vs not married), caregiver age, and number of children in the family. Variables with P values of less than .05 in univariate analysis were included in the multivariable model with HIV status.

Among CLWH only, we assessed the association between age at ART initiation and the SDQ and PedsQL scales, adjusted for age, sex, and study site. We adjusted for study site because CLWH at PHRU had participated in an early treatment study that led to earlier age at ART initiation.[8,28] Finally, we assessed the association between ART regimen (LPV/r vs efavirenz) and the SDQ scales scores and PedsQL among CLWH at ESRU. It was only at this site, that appreciable numbers of children were on an efavirenz-containing regimen.[33] At PHRU, more than 90% of children were on LPV/r-containing regimens.[8,28] All P values are 2-tailed and P values of less than .05 were considered statistically significant. All statistical calculations were performed using SAS version 9.4 (SAS institute, Cary, North Carolina).

Results

A total of 463 CLWH and 122 controls without HIV were included in this analysis. They were recruited beginning in December 2014 and evaluated through the study's completion in February 2018. Their characteristics are shown in **Table I**. A greater proportion of CLWH were female compared with controls (54% vs 40.2%; P = .008). The mean age at behavioral health and quality of life analysis was similar between groups (10.9 ± 1.3 years vs 10.8 ± 1.8 years; P = .57). Almost all (99.5%) children attended school. More controls had their mother as their primary caregiver than CLWH (96.7% vs 84.7%; P < .001) and a greater proportion of caregivers of controls completed lower secondary school (grade 9) compared with CLWH (91.8% vs 81.0%; P = .004). Household characteristics (access to inside tap, toilet, electricity, television, radio, computer, and refrigerator) were similar in the 2 groups.

At the time of the study visit, all CLWH were on ART initiated at a mean age of 6.6 ± 5.9 months (range, 0.8-32.4 months), with 60.9% on a LPV/r-based regimen and 36.5% on an efavirenz-based ART regimen. Twelve children were on other regimens, including nevirapine, atazanavir, bictegravir, and dolutegravir-based regimens. Most children (90.2%) had viral suppression with an HIV RNA of less than 40 copies/mL. The mean $CD4^+$ T-cell count was 931 ± 308 cells/μL and $CD4^+$ T-cell percentage was 36.2 ± 6.6%. About two-thirds (63.3%) of CLWH initiated ART 6 months of age or younger and 36.7% initiated ART at more than 6 months of age.

Table I. Characteristics of CLWH and controls without HIV

Characteristics	CLWH (n = 463)	Controls (n = 122)	*P* value
Age (years)			
Range	8.0-14.0	7.5-14.2	NA
Mean ± SD	10.9 ± 1.3	10.8 ± 1.8	.57
Median (IQR)	11.1 (9.8-11.9)	10.5 (9.3-12.5)	.53
Sex			
Male	213 (46.0)	73 (59.8)	**.008**
Female	250 (54.0)	49 (40.2)	
Child attends school			
Yes	461 (99.6)	121 (99.2)	.50
No	2 (0.4)	1 (0.8)	
Caregiver education			
Grade 0-9	88 (19.0)	10 (8.2)	**.004**
Grade ≥10	375 (81.0)	112 (91.8)	
Caregiver is biological mother	392 (84.7)	118 (96.7)	**<.001**
Housing type			
House	313 (67.6)	78 (63.9)	**.03**
Flat	23 (5.0)	15 (12.3)	
Shack	83 (17.9)	16 (13.1)	
Outbuilding	18 (3.9)	8 (6.6)	
Other	26 (5.6)	5 (4.1)	
Inside tap in household	300 (64.8)	79 (64.8)	>.99
Toilet in household	257 (55.5)	66 (54.1)	.84
Electricity in household	447 (96.5)	119 (97.5)	.78
Television in household	451 (97.4)	115 (94.3)	.09
Radio in household	370 (79.9)	96 (78.7)	.80
Computer in household	141 (30.5)	44 (36.1)	.27
Fridge in household	434 (93.7)	109 (89.3)	.11
Children's physical anthropometry characteristics			
Height-for-age Z-score	−1.05 (0.98)	−0.46 (0.95)	**<.001**
Stunted	68 (14.8)	7 (5.7)	**.006**
BMI (kg/m^2)	16.7 (2.4)	17.5 (3.4)	**.01**
BMI-for-age Z-score	−0.38 (1.00)	−0.07 (1.28)	**.02**
Tanner stage			
I	239 (51.6)	62 (50.8)	.92
II-V	224 (48.4)	60 (49.2)	
HIV characteristics			
Time since ART initiation (years)	10.3 ± 1.3		
Current HIV RNA viral load (copies/mL)			
<40	416 (90.2)		
41-1000	21 (4.6)		
>1000	24 (5.2)		
Current CD4 count (cells/mm^3)	931 ± 308		
Current CD4 percentage (%)	36.2 ± 6.6		
Age at ART initiation (months)			
Mean ± SD	6.6 ± 5.9		
Range	0.8-32.4		
Age at ART initiation (months)			
≤6	293 (63.3)		
>6	170 (36.7)		
ART regimen			
LPVR based*	282 (60.9)		
Efavirenz based	169 (36.5)		
Other†	12 (2.6)		

BMI, body mass index.
Values are range, mean ± SD, or number (%) unless otherwise indicated.
*Ninety-three percent of CLWH at PHRU vs 26% of CLWH at ESRU were on LPVR-based regimens, as described in the Methods.
†Twelve CLWH were on other regimens, including nevirapine (n = 2), atazanavir (n = 2), bictegravir (n = 5), and dolutegravir (n = 3)-based regimens.

As shown in the **Figure**, on the SDQ CLWH had a higher mean total difficulties score (9.6 ± 5.3 vs 6.7 ± 3.9; P <.0001), emotional symptoms score (2.2 ± 2.1 vs 1.1 ± 1.3; P < .0001), and hyperactivity/inattention score (3.0 ± 2.4 vs 1.6 ± 1.8; P < .0001) than controls. On the PedsQL, compared with controls, CLWH had a lower mean total quality of life score (85 ± 10 vs 94 ± 5; P < .0001), physical health summary score (88 ± 11 vs 93 ± 7; P < .0001), and psychosocial health summary score (85 ± 11 vs 94 ± 6; P < .0001). In addition, CLWH had lower mean scores on the emotional functioning (89 ± 15 vs 99 ± 5; P < .0001), social functioning (89 ± 13 vs 99 ± 5; P < .0001), and school functioning (75 ± 15 vs 84 ± 12; P < .0001) scores that comprised the psychosocial health summary score. Findings were similar when stratified by sex (**Table II**; available at www.jpeds.com). Male CLWH had a higher mean total difficulties score, emotional symptoms score, and hyperactivity/inattention score than male controls. Female CLWH also had a higher mean total difficulties score, emotional symptoms score, and hyperactivity/inattention score than female controls. The prosocial behavior scores did not differ between female CLWH and female controls and was higher in female CLWH than male CLWH. All quality of life scores were lower in male CLWH compared with male controls and in female CLWH compared with female controls.

Study site, caregiver education, and caregiver age were associated with SDQ scores, whereas whether the mother was the primary caregiver, the caregiver's marital status, and number of children in the family were not. Study site, caregiver education, caregiver age, and whether the mother was the primary caregiver were associated with PedsQL scores, whereas caregiver marital status and number of children in the family, were not. In a multivariable analysis of SDQ adjusted for age, sex, study site, caregiver education, and caregiver age, CLWH had a higher total difficulties score (1.1; 95% CI, 0.0-2.3), and hyperactivity/inattention (0.8; 95% CI, 0.3-1.3) subscale score compared with controls (**Table III**; available at www.jpeds.com). On the PedsQL, CLWH had lower mean scores on the total quality of life score (−4.6; 95% CI, −6.4 to −2.7) and psychosocial health score (−5.6; 95% CI, −7.6 to −3.5), adjusted for age, sex, study site, caregiver education, caregiver age, and whether the mother was the primary caregiver (**Table III**).

In CLWH, we evaluated the association between age at ART initiation (≤6 months, >6 months) and the SDQ and PedsQL scores, adjusted for sex, age, and site. Scores on the SDQ and PedsQL did not differ between CLWH starting ART 6 months or younger and CLWH starting more than 6 months of age. In an analysis of CLWH limited to the ESRU site, we evaluated the association between ART regimen and the SDQ scales scores and PedsQL. No significant differences were observed between those on LPV/r and those on efavirenz.

Discussion

CLWH with well-controlled infection who started ART early in life are at increased risk for behavioral and mental health problems and poorer quality of life compared with healthy children from the same community and similar socioeconomic status. The SDQ has been widely used as a screening tool in African contexts, and specifically in South Africa to identify children at high risk for mental health and behavioral

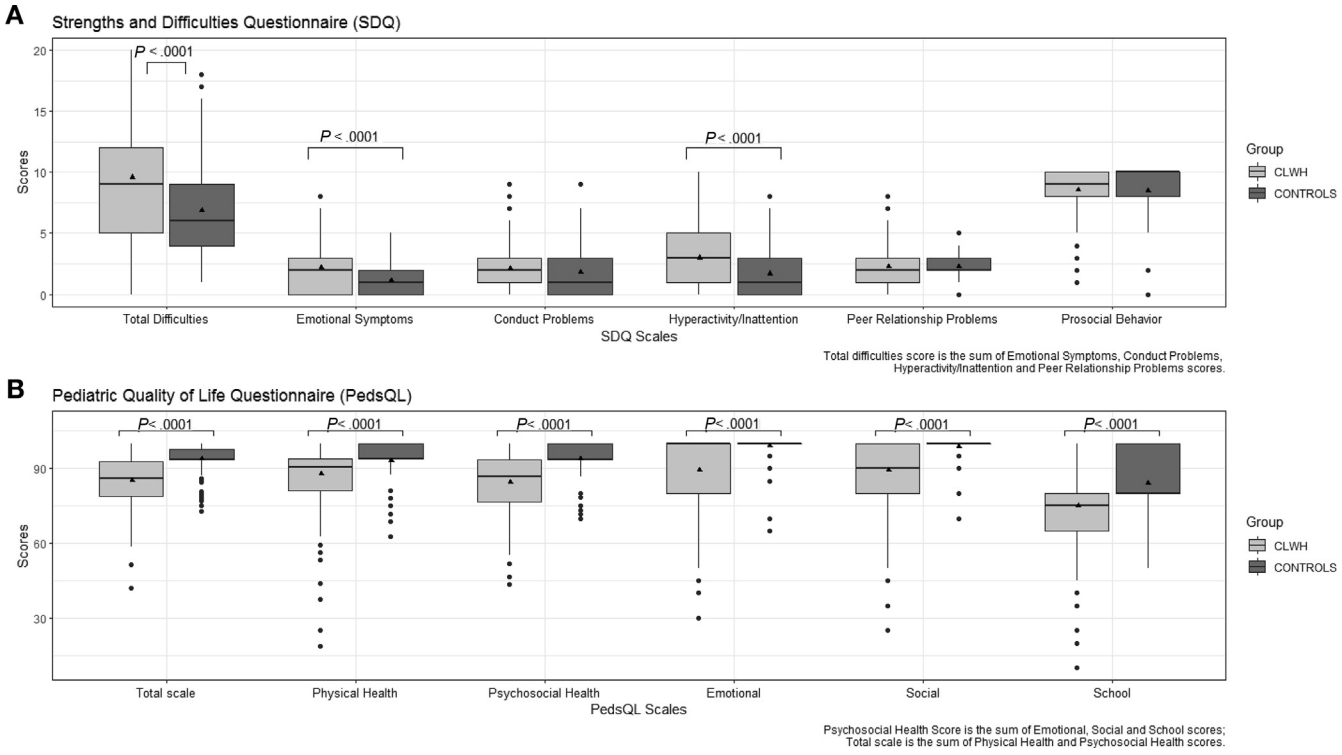

Figure. Box plots of scores from the SDQ and PedsQL for CLWH (n = 463) and control children (n = 122). • Represents the values greater than first quartile (Q1) + 1.5 × IQR, or values lower than third quartile (Q3) – 1.5 × IQR. Δ represents the mean values. All analyses are unadjusted.

problems.[29,31] Our findings signal a risk of mental health problems and additional diagnostic assessments may be warranted to aid early intervention.

The greater difficulties reported by SDQ among CLWH compared with controls is consistent with prior research. The increased hyperactivity and inattention among CLWH in our study is similar to reports conducted in the US, Europe, and Cameroon.[32,34,35] Although it is possible that these findings stem from HIV infection and associated neurocognitive deficits or antiretroviral agents used for treatment, social and other contextual factors that were not adequately measured in our study might also contribute to the findings. These factors include the death of a parent, frequent parental illness and hospitalizations, membership in a family with a highly stigmatized disease, disclosure status of the CLWH, parental mental health diagnoses, or adverse in utero exposures. In addition, caregiver internalized stigma related to their own or their child's HIV status may have influenced their perceptions of the child's strengths and difficulties.[36] Other studies reporting mental health problems among CLWH have also suggested that some of these factors may play an important role and warrant further study.[37,38] Of note, female CLWH did not differ from controls on prosocial behavior scores and had higher prosocial behavior scores than male CLWH. Although studies historically have focused on the negative consequences associated with perinatal HIV infection, increasing attention is being paid to the factors associated with resilience, positive development and successful transition through adolescence in youth with HIV.[39-41]

Although studies conducted on the quality of life of CLWH especially in resource-constrained settings are few, the lower quality of life seen in our cohort is consistent with prior research.[14-17] Our cohort of CLWH reported lower physical health and psychosocial health on all 3 subdomains. The higher total difficulty scores and lower prosocial scores found in our cohort are likely to contribute to reduced quality of life and interventions targeting these areas could be beneficial.

Behavioral functioning and quality of life did not seem to be related to age at ART initiation (≤6 months vs > 6 months) or ART regimen (LPV/r-based vs efavirenz based) among CLWH. Efavirenz has been associated with neuropsychiatric symptoms in adults and previously was shown to cause transient sleep difficulties in this study population.[27,42] Given that nearly all children in this study started ART by 2 years of age, there is limited heterogeneity in age at ART start. In addition, the study instruments that are intended as screening tools may have missed outcomes that could be detectable with more in-depth psychometric assessments.

Our study has a number of limitations. The cross-sectional design prevents ascertaining temporal changes in behavioral function and quality of life. Participants for this study were recruited from 2 research centers in a single urban area in a middle-income country with a high HIV prevalence, which limits the generalizability of our findings. Nonetheless, this

study provides important information regarding mental health risk and quality of life of CLWH in endemic communities. We did not have information on parental mental health diagnoses that may be related to our findings on hyperactivity and inattention.[43,44] Finally, our comparison population was composed of a mix of children living in families with and without an HIV-infected family member. These contextual factors may play a larger role in negative quality health and mental health outcomes than perinatal HIV itself.

CLWH demonstrate persistent difficulties in behavioral and emotional functioning and quality of life despite excellent virologic control with effective ART regimens. Although the causes of these deficits are not fully understood, the evidence suggests that the ART regimens these children have received from a reasonably early age have not been sufficient to ameliorate these negative behavioral impacts. As recommendations about optimal regimens change and ART is started at even earlier ages, it will be important to consider whether improvements in these behavioral and social outcomes can be achieved. Our findings suggest that behavioral and social interventions may be needed in concert with ART to optimize mental health and quality of life for this vulnerable population throughout the life course. ■

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Reprint requests: Stephen M. Arpadi, MD, MS, Gertrude H. Sergievsky Center, Columbia University, 630 W. 168th Street, PH 19-114, New York, NY 10032. E-mail: sma2@columbia.edu

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Table II. SDQ and PedsQL by HIV group, stratified by sex

	Sex						CLWH	Controls
	Male			Female			Male vs female	Male vs female
Scales	CLWH (n = 189)	Controls (n = 68)	*P* value	CLWH (n = 228)	Controls (n = 45)	*P* value	*P* value	*P* value
SDQ								
Total difficulties score								
Mean ± SD	10.4 ± 5.5	7.4 ± 4.1	**<.001**	8.9 ± 5.1	6.1 ± 3.5	**<.001**	**.007**	.08
Median (IQR)	9.0 (7.0-14.0)	6.0 (4.0-10.0)	**<.001**	8.0 (5.0-12.0)	5.0 (4.0-7.0)	**<.001**	**.006**	.11
Emotional symptoms								
Mean ± SD	2.1 ± 2.0	1.1 ± 1.2	**<.001**	2.3 ± 2.2	1.1 ± 1.3	**<.001**	.25	.88
Median (IQR)	2.0 (0-3.0)	1.0 (0-2.0)	**<.001**	2.0 (0-4.0)	1.0 (0-2.0)	**<.001**	.39	.80
Conduct problems								
Mean ± SD	2.5 ± 2.0	2.0 ± 2.0	.10	1.8 ± 1.6	1.4 ± 1.6	.22	**<.001**	.09
Median (IQR)	2.0 (1.0-4.0)	1.5 (0.5-3.0)	.06	2.0 (0-3.0)	1.0 (0-2.0)	.16	**<.001**	.12
Hyperactivity/inattention								
Mean ± SD	3.4 ± 2.5	2.0 ± 1.9	**<.001**	2.7 ± 2.3	1.1 ± 1.6	**<.001**	**.001**	**.01**
Median (IQR)	3.0 (1.0-5.0)	2.0 (0-3.0)	**<.001**	2.0 (1.0-4.0)	0 (0-2.0)	**<.001**	**.001**	**.007**
Peer relationship problems								
Mean ± SD	2.3 ± 1.5	2.2 ± 1.3	.66	2.2 ± 1.5	2.5 ± 1.1	.15	.37	.32
Median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	.84	2.0 (1.0-3.0)	2.0 (2.0-3.0)	.11	.35	.26
Strength: Prosocial behavior								
Mean ± SD	8.2 ± 1.9	8.7 ± 1.7	**.05**	8.9 ± 1.4	8.2 ± 2.2	.06	**<.001**	.19
Median (IQR)	9.0 (7.0-10.0)	10.0 (8.0-10.0)	**.03**	9.0 (8.0-10.0)	10.0 (6.0-10.0)	.19	**<.001**	.33
PedsQL								
Total scale score								
Mean ± SD	84.7 ± 10.1	93.4 ± 5.5	**<.001**	85.9 ± 9.0	94.3 ± 5.3	**<.001**	.20	.36
Median (IQR)	85.9 (77.8-92.7)	93.4 (93.4-95.9)	**<.001**	86.7 (80.0-92.8)	93.4 (93.4-100.0)	**<.001**	.31	.38
Physical health summary score								
Mean ± SD	88.6 ± 9.9	92.6 ± 7.2	**.002**	87.0 ± 12.0	94.0 ± 7.9	**<.001**	.12	.32
Median (IQR)	93.8 (81.3-93.8)	93.8 (93.8-93.8)	**.002**	90.6 (81.3-93.8)	93.8 (93.8-100.0)	**<.001**	.18	**.04**
Psychosocial health summary score								
Mean ± SD	83.4 ± 11.4	93.7 ± 5.9	**<.001**	85.5 ± 9.6	94.4 ± 5.7	**<.001**	**.04**	.48
Median (IQR)	83.3 (76.7-93.3)	93.3 (93.3-98.3)	**<.001**	86.7 (78.3-93.3)	93.3 (93.3-100.0)	**<.001**	.09	.31
Emotional functioning								
Mean ± SD	89.9 ± 14.5	99.2 ± 4.4	**<.001**	88.6 ± 14.8	99.1 ± 4.8	**<.001**	.36	.90
Median (IQR)	100.0 (80.0-100.0)	100.0 (100.0-100.0)	**<.001**	100.0 (80.0-100.0)	100.0 (100.0-100.0)	**<.001**	.29	.76
Social functioning								
Mean ± SD	88.0 ± 13.9	98.5 ± 5.7	**<.001**	90.6 ± 11.9	99.0 ± 3.6	**<.001**	**.03**	.57
Median (IQR)	90.0 (80.0-100.0)	100.0 (100.0-100.0)	**<.001**	95.0 (85.0-100.0)	100.0 (100.0-100.0)	**<.001**	.07	.77
School functioning								
Mean ± SD	72.4 ± 16.9	83.4 ± 12.2	**<.001**	77.3 ± 12.7	85.3 ± 12.9	**<.001**	**<.001**	.41
Median (IQR)	70.0 (60.0-80.0)	80.0 (80.0-100.0)	**<.001**	80.0 (70.0-85.0)	80.0 (80.0-100.0)	**<.001**	**<.001**	.26

Table III. Adjusted mean difference and 95% CI from multivariable models of SDQ and PedsQL scores for CLWH (n = 463) compared with control children (n = 122)

Scales	Unadjusted mean difference and 95% CI	Adjusted* mean difference and 95% CI
SDQ		
Total difficulties score	**2.7 (1.6 to 3.7)**	**1.1 (0 to 2.3)**
Emotional symptoms	**1.1 (0.7 to 1.5)**	−0.1 (−0.3 to 0.3)
Conduct problems	0.3 (−0.1 to 0.7)	0.3 (−0.1 to 0.8)
Hyperactivity/Inattention	**1.3 (0.9 to 1.8)**	**0.8 (0.3 to 1.3)**
Peer relationship problems	−0.1 (−0.4 to 0.2)	0.1 (−0.2 to 0.4)
Strength: Prosocial behavior	0.1 (−0.3 to 0.4)	−0.1 (−0.5 to 0.3)
PedsQL		
Total scale score	**−8.5 (−10.2 to −6.7)**	**−4.6 (−6.4 to −2.7)**
Physical health summary score	**−5.5 (−7.6 to −3.4)**	−1.3 (−3.6 to 0.9)
Psychosocial health summary score	**−9.4 (−11.4 to −7.5)**	**−5.6 (−7.6 to −3.5)**
Emotional functioning	**−9.9 (−12.6 to −7.2)**	−0.7 (−3.1 to 1.7)
Social functioning	**−9.3 (−11.6 to −6.9)**	**−6.9 (−9.5 to −4.4)**
School functioning	**−9.1 (−12.0 to −6.2)**	**−9.3 (−12.5 to −6.1)**

*The SDQ is adjusted for age, sex, study site, and caregiver education and caregiver age. The PedsQL adjusted for age, sex, study site, and caregiver education, caregiver age, and primary caregiver.