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Quality of life among perinatally HIV-affected and HIV-unaffected school-aged and adolescent Ugandan children: a multi-dimensional assessment of wellbeing in the post-HAART era

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Abstract
Objective To examine quality of life (QOL) in perinatally HIV-infected (PHIV) or HIV-exposed uninfected (PHEU) vs. healthy HIV-unexposed uninfected (HUU) children during school-age/adolescence.
Methods PHIV infection was diagnosed via DNA PCR. Current HIV status was confirmed by HIV rapid diagnostic test. Three HIV groups were defined: PHIV, PHEU, and HUU. QOL was assessed with proxy and self-report versions of the PedsQL^{TM} 4.0 instrument at 6–18 years of age. QOL scores ranged from zero (least QOL) to 100 (highest QOL) in the following dimensions: combined QOL inventory (CQOLI), multi-dimensional vigor (MDV), general wellbeing (GWB), present functioning, and general cognitive functioning (CF). Multivariable linear regression models estimated HIV-related percent differences (β) in QOL scores and 95% confidence intervals (CI).
Findings Compared to HUU CQOLI deficits ranged from 6.5 to 9.2% (95% CI −15.4, −1.6), GWB deficit ranged from 6.5 to 10.5% (95% CI −16.0, −1.3), MDV deficit ranged from 6.8 to 11.6% (95% CI −14.5, 0.9), and CF deficit ranged from 9.7 to 13.1% for PHIV children. QOL deficits of similar magnitude and direction in most domains were observed for PHIV compared to PHEU. However, self-reported indicators of GWB ($\beta = -3.5$; 95% CI −9.0, 2.0) and present functioning ($\beta = 4.0$; 95% CI −4.6, 12.5) were similar for PHIV compared to PHEU. QOL scores were generally similar for PHEU compared to HUU.
Conclusion PHEU and HUU had similar QOL profile but PHIV predicted sustained deficits in multiple QOL domains. PHIV and PHEU children were similar with respect to general wellbeing and present functioning. Psychosocial and scholastic interventions in combination with HIV care are likely to improve QOL in PHIV.

Keywords Quality of life · Perinatally acquired HIV infection · Perinatally HIV-exposed uninfected · Healthy unexposed uninfected controls · School-age · Adolescence

Introduction

An estimated 2.6 million children and adolescents live with vertically acquired HIV infection [1, 2]. Prompt and reliable access to highly active antiretroviral therapy (HAART) allows the vast majority to survive into school-age, adolescence, and adulthood with chronic HIV infection. Survival with chronic HIV-related morbidity [3, 4]

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demands that HIV care and treatment goals be broadened beyond reduction of premature mortality [5–10] to include maintenance of sufficiently high quality of life (QOL) for human potential to be realized [11].

QOL is a measure of overall wellbeing which by definition is multi-dimensional and subjectively evaluated by respondents [12, 13]. It integrates the respondent's level of physical, psychological, and social function compared to peers of similar developmental stage [14]. The HAART-facilitated transition in the HIV epidemic to a chronic disease state resulted in a sizeable population of HIV-affected school-age and adolescent children in sub-Saharan Africa. More information on their health-related-QOL (HR-QOL) is needed to understand the long-term survival experience of these children living in the most severely HIV-affected region of the world [15].

A handful of epidemiologic studies in school-aged children implemented during the post-HAART era have found HIV-associated deficits in overall QOL. [4, 11, 16, 17]. Compared to HIV-uninfected children, HIV-infected children had a higher prevalence of behavioral problems [4] and they performed consistently worse in the physical and psychosocial functioning domains of QOL [4, 11, 17]. However, available evidence does not reliably distinguish between the adverse impact of HIV infection [4] and the possible negative QOL impact of growing up within an HIV-affected context [11, 17]. Recent studies of long-term functional survival—with emphasis on cognitive function and psychosocial adjustment, in HIV-affected and -unaffected school-aged African children have emerged [18, 19]. However, there are still few specific investigations of long-term QOL in this group. Hence, we inform existing knowledge gaps by evaluating the extent to which perinatal HIV infection/exposure exerts a sustained adverse effect on QOL during school-age and adolescence among perinatal HIV-infected/exposed and community control children without HIV infection or exposure. We hypothesize that perinatally HIV-infected/exposed children will experience lower QOL compared to perinatally HIV-unexposed children in school-age and adolescence. Our results provide empirical justification for combining psychosocial and scholastic interventions with HIV care to improve QOL in HIV-affected children.

Methods

Study design and participants

We implemented a retrospective cohort study of children with and without perinatal HIV infection in the Kawaala Health Center, Kampala, Uganda between March 20 and July 26, 2014. Children were recruited upon presentation for either HIV-disease management or a non-HIV-related cause at health center. Children were eligible for the study if they had documented records of birth in a hospital/health care setting, were between 6 and 18 years old, and had available health records from which data regarding their general health, HIV status of index child at birth, and the HIV status of birth mother were objectively confirmed. All HIV-infected children had access to HIV care and management, which may include HAART.

We excluded children born in non-clinic settings and children of caregivers without official birth records and/or missing antenatal register/delivery medical records as the HIV status of the birth mother and HIV status of the index child at birth could not be reliably ascertained. Current HIV status of HIV-negative children was ascertained via HIV rapid diagnostic test at QOL testing. Additional study design details—including HAART duration, current regimen, and immunologic status of HIV-infected children, have been reported elsewhere [18, 19].

Ethical approval

The study protocol was approved by the ethics review committees at the University of Georgia, Makerere University School of Public Health, and the Uganda National Council for Science and Technology. All caregivers gave written informed consent and children provided assent at enrolment.

QOL measures

QOL in children was assessed from child and caregiver perspectives using the self- and proxy-reported versions of the Pediatric Quality of Life Inventory (PedsQL^{TM} 4.0) [20, 21]. We evaluated child QOL in five domains, including overall QOL using the combined quality-of-life inventory (CQOLI), the degree of fatigue using the multidimensional vigor (MDV) scale, general wellbeing (GWB) over the past 30 days, present functioning impairment (PF), and general cognitive functioning (CF). Care givers provided proxy reports of QOL using structured instruments by QOL domain/scale. A parallel age-specific set of questionnaires, including developmentally appropriate language and rating scales,were used for child self-reports [20]. Scores were computed by domain per published instructions and standardized on a scale of 0–100. Within domains, reverse coding was used per instructions published in the PedsQL^{TM} 4.0 Users' Manual to ensure that higher scores indicated better health/functioning with the exception of PF where higher scores implied greater current functional deficit.

Three of the five QOL domains included distinct subscales that were summed to derive QOL scores for that

domain. Overall QOL as measured by CQOLI included four subscales, namely physical, emotional, social, and school functioning. The MDV domain assessed body weakness (i.e., lack of vigor) and included three subscales: general, sleep, and cognitive vigor subscales. The GWB domain comprised two measures: a wellbeing index and self-rated health (SRH). Except for SRH which was assessed as a single questionnaire item, all subscales within respective domains consisted of an index of six questions. Questions in the general CF domain assessed problems with short-term memory. The six questions included in the PF impairment domain used a visual analogue scale to rank a child's current feeling of fear, sadness, anger, worry, tiredness, and pain.

Prior to the start of the study, QOL instruments were translated into Luganda and culturally adapted to the study setting as described in detail elsewhere [22]. Briefly translation involved forward translation by into Luganda by two graduate students proficient in Luganda and English. Each worked independently and any discrepancies were resolved by consensus between the students and the principal investigator (AEE) to ensure that the empirical intent of respective questionnaire items was preserved. The forward translated documents were then back translated to English from Luganda by a second team of Luganda and English proficient individuals who were not familiar with the source documents. Lastly, the study instruments were tested in the field on research assistants to finalize their adaptation, before being administered to study subjects.

To determine their psychometric properties, the translated questionnaires were tested in a pilot study on 15 children along with their caregivers. The questionnaires were administered by two research assistants that alternated between visits on study enrolment (both child and caregiver pair) and repeated 14–21 days later in caregivers only because subjects were enrolled upon child presentation for care at the study clinic. Thus for child-reported QOL measures, we had limited ability to informatively distinguish the impact of child ill state at enrolment from that of the instrument reliability as measured via test–retest and inter-rater reliabilities. Using the %INTRACC macro, we estimated measures of internal consistency, test–retest, and inter-rater reliabilities for proxy-reported measures of QOL [23]. For child self-reported measures, only measures of internal consistency were estimated. Revisions suggested in pilot testing based on proxy reports were incorporated and final instruments were administered once to an additional 153 child-caregiver pairs.

Primary exposure

The primary exposure in the study was perinatal child HIV exposure or infection. HIV infection was restricted to perinatal mother-to-child transmission that had occurred by the end of breast-feeding. Perinatal HIV status confirmed objectively using DNA PCR and defined in 3 groups, PHIV, PHEU, and HUU children. PHIV included HIV-positive children of HIV-infected women. PHEU included perinatally HIV-exposed but uninfected children of HIV-positive women. HUU controls consisted of HIV-negative and perinatally HIV-unexposed children of HIV-negative women.

Other measures

Medical history, physical examination, and laboratory evaluations were performed on all children at study enrolment. Medical history included review of the child's medical records to ascertain birth weight and date of birth and to verify maternal HIV status in pregnancy. Physical examinations were performed by clinicians to establish current health status. Laboratory investigations included rapid diagnostic malaria testing, complete blood counts, and stool tests for helminth infections, protozoa, and other intestinal parasites. Additional information collected included body mass index as surrogate indicator of caregiver's health and caregiver socio-demographic factors such as age, sex, and household income and educational attainment.

Statistical analyses

Descriptive analyses estimated means, standard deviations (SD), frequencies, and percentages by perinatal HIV infection status. Hypothesis testing for descriptive analyses were implemented using t tests for continuous variables and X^2 tests for categorical variables. Tests of reliability on each QOL scale assessed internal consistency using Cronbach's alpha coefficients [24], and intra-class correlations for test–retest and inter-rater reliability [23].

We conducted univariate analyses to derive means and standard deviations for QOL measures in the entire sample and by HIV status. Next bivariate analyses examined associations between QOL scores and each potential confounder. Those associated with perinatal HIV status at a p value of ≤ 0.20 were considered potential confounders and were further evaluated in multivariable analyses using a linear regression model [25]. Our goal was to derive the most de-confounded measures of effect by adjusting for confounders in light of subject matter knowledge and using a conservative threshold for inclusion of variables into multivariable models. We retained covariates such as child's age, sex and caregivers' age, sex, and socio-economic status in light of the extant literature establishing their confounding effects on QOL measures. Crude and

multivariable linear regression models estimated HIV-related risk differences (β) in QOL scores and 95% confidence intervals (CI). Social/demographic characteristics controlled for included child's relationship with primary caregiver (parent vs. non-parent), education level, and income status of primary caregiver. Because multiple children from the same households were enrolled in some cases, all analyses were clustered by household to accommodate the potential lack of independence in QOL for children with a shared caregiver. Missing data for potential confounders were analytically addressed using the missing indicator method [26]. All analyses were performed with SAS version 9.3 (SAS Institute, Inc. Cary, NC) and p values of less than 0.05 were considered to be statistically significant in multivariable analyses. Associations between perinatal HIV status and QOL are presented using the proxy-reported measures as main results because the psychometric properties, specifically the inter-rater and test–retest reliabilities, were higher for parent proxy—than child—self-reports. Results for child self-reported measures are presented as secondary outcomes to evaluate result consistency.

Results

We enrolled 168 school-aged children of 108 unique caregivers including 58 PHIV, 54 PHEU, and 56 HUU from Kawaala Health Center in Kampala between March 20, 2014 and July 26, 2014. Their mean age was 10.8 (SD 3.5; range 5.0–18.3) years. Across perinatal HIV groups, the children were similar with regard to age, sex, and short-term nutritional status. However, PHIV children showed greater deficits in long-term growth (height-for-age z-score) and were more likely to have a non-parent caregiver. Most caregiver characteristics were similar by HIV status although caregivers of HIV-affected children (infected or exposed) were more likely to have lower educational level compared to caregivers of HIV-unexposed children (Table 1). Of the 58 PHIV, average CD4 value at assessment was 772 (minimum = 63, maximum = 2521) cells/μL, 22.4% ($n = 13$) were HAART naïve and 77.6% ($n = 45$) were HAART experienced. At QOL assessment, PHIV were more likely than PHEU and HUU children to be anemic and current health assessment revealed greater abnormality of the lymphatic, respiratory, and neurologic systems compared to both PHEU and HUU children (data not shown). The health status of the enrolled children—including HIV treatment duration, HAART regimen, and immune details for PHIV, has been extensively described elsewhere [18].

Validation and psychometric property of QOL questionnaires

The QOL instrument validation sample included 15 caregivers of 10 boys and 5 girls between 6 and 18 years, among whom were five PHIV, six PHEU, and four HUU control children. For child self-reported QOL measures, internal consistency was at least acceptable (Cronbach's-α: 0.65–0.89) for all questionnaires (Table 2). Per proxy assessments of QOL, questions in the combined MDV and CQOLI, GWB and PF scales all demonstrated good internal consistency (Cronbach's-α: 0.71–0.87). Over 14- to 21-day interval, test–retest reliability was determined to be fair to excellent for all MDV subscales and for combined MDV scale (intra-class correlation (ICC) ≥ 0.43) and GWB (ICC = 0.66). Test–retest reliability was fair to good for CQOLI (ICC = 0.61) with the highest test–retest reliability values observed for physical (ICC = 0.92) and emotional functioning (ICC = 0.66). The test–retest reliability was poor in the social and school functioning subscales of combined quality of life and for assessment of present functioning impairment (both ICCs < 0.40). The inter-rater reliability of measures across raters was fair for PF (ICC = 0.21) and moderate for combined MDV, CQOLI, and GWB (ICC = 0.45–0.53). For child self-reported QOL measures, internal consistency was at least acceptable (Cronbach's-α: 0.65–0.89) for all questionnaires (Table 2).

Comparison of QOL scores across perinatal HIV groups

Mean QOL scores were generally lower for PHIV compared with PHEU and HUU children, whereas average scores were similar in magnitude for PHEU and HUU children (Fig. 1, Table S1–S2). On average, proxy-reported CQOLI, MDV, and -CF scores were, respectively, 10, 8, and 14% lower for PHIV relative to PHEU after adjusting for child's age, sex, nutritional status, relationship to caregiver, and caregiver's age, sex, BMI, and educational level (Fig. 2a, Table S3). Within CQOLI subscales, the largest QOL deficits were observed in school functioning (−16%) and general vigor (−12%) for PHIV compared to PHEU, whereas these groups were statistically equivalent in terms of social functioning, sleep vigor, and general wellbeing (Fig. 2a, Table S3). Likewise, average scores on CQOLI, GWB, and CF were, respectively, 9, 11, and 13% lower for PHIV compared to HUU children with the largest deficits were observed in school functioning (−17%) and general vigor (−13%) (Fig. 2b, Table S3). Proxy-reported QOL scores were statistically equivalent for HIV-uninfected groups (PHEU and HUU) with the exception of caregiver rating of superior self-rated health (6.5%) for

Table 1 Socio-demographic and basic health characteristics of school-aged Ugandan children and their caregivers involved in this study

	Overall	Perinatally HIV-infected	Perinatally HIV-exposed uninfected	Healthy unexposed uninfected	*P* value
Child characteristics	168 (100)	58 (34.5)	56 (33.3)	54 (32.1)	
Age (in years, mean (SD); range)	10.8 (3.5; 5.0–18.3)	11.2 (3.0; 6.3–17.2)	10.6 (3.7; 6.0–17.8)	10.6 (3.8; 5.0–18.3)	0.6117
Sex; male (%)	91 (54.2)	32 (55.2)	33 (58.9)	26 (48.2)	0.5161
Child education					
Nursery and below	19 (11.5)	06(10.9)	08 (14.2)	05 (09.3)	0.0211
Primary	121 (73.3)	46 (83.6)	38 (67.9)	37 (68.5)	
Secondary	25 (15.2)	03 (05.5)	10 (17.9)	12 (22.2)	
Relationship with caregiver					
Mother	117 (70.5)	33 (58.9)	45 (80.4)	39 (72.2)	0.0219
Father	16 (09.6)	05 (08.9)	07 (12.5)	04 (07.4)	
Other relative	33 (19.9)	18 (32.2)	04 (07.1)	11 (20.4)	
Child's nutrition					
HAZ [*N*, mean (SD)]	152, −0.81 (1.7)	54, −1.43 (1.7)	50, −0.35 (1.7)	48, −0.58 (1.70)	0.0114
BMIZ [*N*, mean (SD)]	152, −0.97 (1.6)	54, −0.88 (1.8)	50, −1.29 (1.7)	48, −0.72 (1.14)	0.6660
On HAART (*n*, %)				45 (83.3%)	
CD4 cell count (cells/μL)					
Median (min–max)				772 (63–2521)	
Caregiver characteristics	154 (100)	56	50	48	
Age (in years, mean (SD))	38.8 (10.4)	39.3 (13.3)	39.8 (8.4)	37.3 (8.2)	0.4446
Sex; female (%)	129 (83.8)	50 (89.3)	39 (78)	40 (83.3)	0.2888
BMI (kg/m^2); mean (SD)	24.3 (4.3)	24.4 (4.6)	22.8 (3.2)	25.9 (4.5)	0.07
Married (%)	95 (57.6)	30 (53.6)	28 (50.9)	37 (68.5)	0.1343
Education					
Primary and below	98 (59.4)	38 (67.9)	39 (70.9)	21 (38.9)	0.0009
Secondary and beyond	67 (40.6)	18 (32.1)	16 (29.1)	33 (61.1)	
Has own income n (%)	117 (70.9)	35 (62.5)	43 (78.2)	39 (70.9)	0.1850
Wealth score: mean (SD)	2.73 (2.1)	2.14 (1.8)	1.98 (1.9)	4.17 (2.0)	0.2179

HAZ height-for-age *z*-score, *BMIZ* body mass index for age *z*-score, *SD* standard deviation

PHEU compared to HUU (Fig. 2c, Table S3). Child self-reported QOL measures confirmed significant deficits for PHIV compared to PHEU in CQOLI scores, MDV, and GCF (Fig. 3a, Table S4). Similarly, statistically significant QOL deficit was observed for PHIV compared to HUU in all but social functioning and present functioning impairment (Fig. 3b, Table S4).

Of note, the most striking QOL differences were evident for perinatally HIV-infected children compared to HIV-uninfected children (whether PHEU or HUU) regardless of respondent. Specifically, in our sample caregivers of PHEU and HUU tended to report similar QOL for their HIV-negative children (Fig. 2, Table S3). Likewise, HIV-negative children (PHEU or HUU) tended to self-report statistically similar QOL scores (Fig. 3c, Table S4) across QOL domains.

Discussion

We evaluated perinatal HIV status-related differences in five dimensions of child wellbeing—combined quality-of-life inventory (CQOLI), multi-dimensional vigor (MDV), general wellbeing (GWB), present functioning impairment (PF), and general cognitive performance (CF), in school-aged and adolescent Ugandan children. We found consistent and generally lower QOL, wellbeing, vigor/vitality scores for PHIV compared to either PHEU or HUU regardless of respondent. Our data confirm previously reported HIV-related deficits in physical functioning [27–30] and demonstrate additional significant deficits in emotional and school functioning QOL subscales. These observed QOL deficits are consistent with our hypothesis that QOL will be most impaired in PHIV and prior

Table 2 Psychometric property of pediatric quality-of-life questionnaires as evaluated in 15 school-aged children enrolled for instrument validation and refinement

Quality-of-life dimension	Inter-rater reliability[a]	Test–retest reliability[b]	Internal consistency[c]	
	ICC	ICC	Cronbach's α	
	Proxy report	Proxy report	Proxy report	Child self-report
Multi-dimensional vigor				
General vigor subscale	0.70	0.83	0.90	0.73
Sleep vigor subscale	0.27	0.43	0.53	0.85
Cognitive vigor subscale	0.60	0.75	0.89	0.88
Multi-dimensional vigor scale	0.53	0.70	0.87	0.87
Quality-of-life inventory				
Physical functioning subscale	0.85	0.92	0.55	0.79
Emotional functioning subscale	0.50	0.66	0.75	0.69
Social functioning subscale	0.22	0.37	0.83	0.65
School functioning subscale	0.16	0.28	0.78	0.68
Combined quality-of-life score	0.44	0.61	0.87	0.89
General wellbeing index	0.49	0.66	0.85	0.66
Present functioning impairment	0.21	0.35	0.71	0.70

ICC intra-class correlation

[a] ICC $\geq$ 0.81 (Very good); 0.61 $\leq$ ICC $\leq$ 0.8 (Good); 0.41 $\leq$ ICC $\leq$ 0.6 (Moderate); 0.21 $\leq$ ICC $\leq$ 0.4 (Fair); ICC $\leq$ 0.2 (Poor)

[b] ICC $>$ 0.75 (Excellent); 0.40 $\leq$ ICC $\leq$ 0.75 (Fair to Good); ICC $<$ 0.4 (poor)

[c] $\alpha \geq 0.9$ (Excellent); $0.7 \leq \alpha < 0.9$ (Good); $0.6 \leq \alpha < 0.7$ (Acceptable); $0.5 \leq \alpha < 0.6$ (Poor); $\alpha < 0.5$ (unacceptable)

investigations [4, 11, 16, 17, 31]. Widespread deficits in multiple dimensions of vigor/vitality were observed, suggesting that overall deficit in QOL and general wellbeing may in part be mediated by vulnerability of PHIV children to fatigue.

In our study, the general and cognitive vigor scales—which reflected general physical fatigue and lower ability to pay attention, multi-task, remember or think quickly, were strongly adversely affected in PHIV. Self-reported QOL measures suggest the additional importance of problems with sleep. Previous research has found a high prevalence of sleep impairment [32], as well as shorter duration and lower quality sleep for HIV-infected children compared to healthy controls [33]. Also in line with our study hypothesis and in support of prior report among PHIV-infected children [4], we found significant HIV-related deficits in the school functioning domain of CQOLI. This finding is in agreement with our recent findings that significant PHIV-related deficits persist in school esteem, positive outlook, and distress in this sample [19]. Additional contributors to lower quality of life in the school functioning domain for HIV-infected children described in another study include learning disabilities and a greater propensity to avoid school attendance altogether [34]. Hence, we speculate that the deficits in school functioning for PHIV and overall QOL are likely explained by the combination of greater general fatigue, greater school absenteeism due to HIV-related severe illness requiring hospitalization, and/or the need for frequent medical consultations with or without hospitalization. Further, the presence of high pill burden, rigorous pill schedules, caring for ill caregivers or siblings, and changes in key relationships due to caregiver death as illness progresses have also been identified as factors that contribute to low esteem while reinforcing the perception of low wellbeing in PHIV-infected children [34].

Despite an overall lower QOL score in many domains, there were no caregiver-reported differences in sleep vigor subscale of the MDV scale by HIV status. This observation was contrary to our study hypothesis and was contradicted by self-report findings where HIV infection was associated with lower sleep vigor relative to HIV-uninfected children. Additionally, all HIV groups were similar with respect to self-reported PF score. Given low psychometric values for both reliability and internal consistency across these subscales, we are unable to rule out respondent difficulty in comprehending or interpreting component questions as alternative explanations for these observations despite acceptable to high internal consistency for child-reported measures.

The observation that social functioning subscale of the CQOLI did not vary by HIV status regardless of

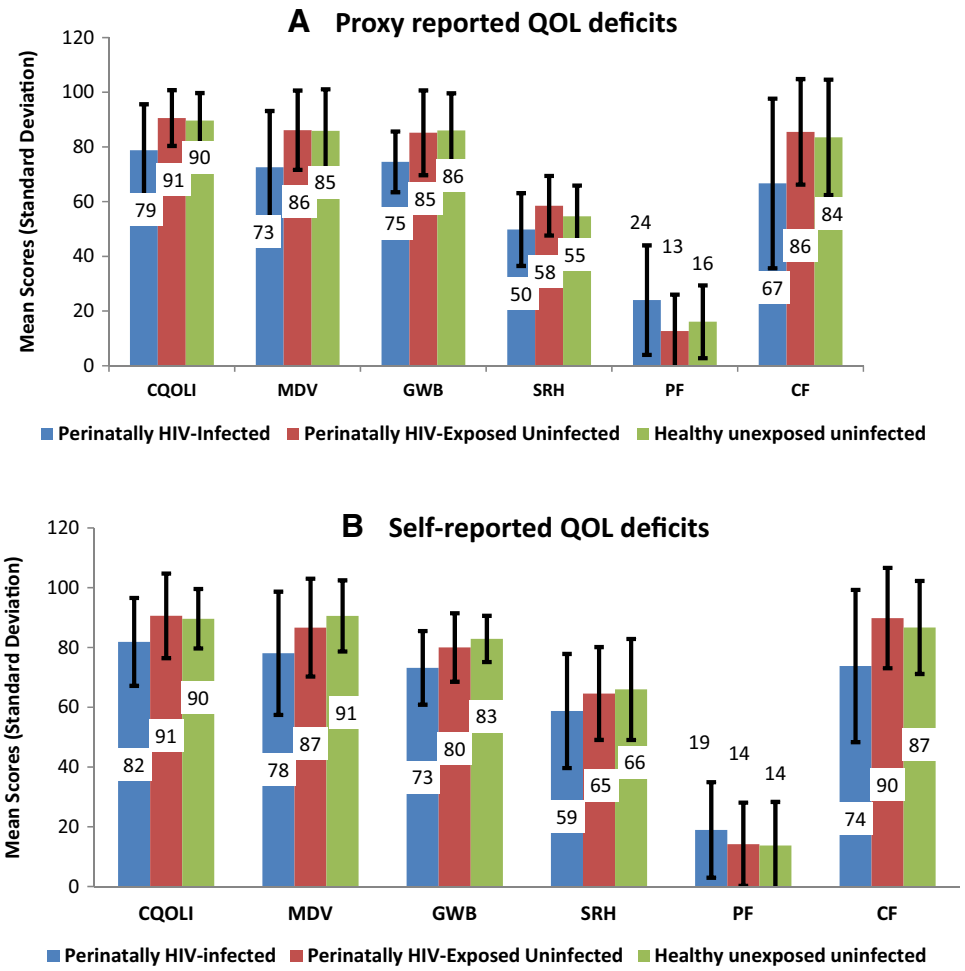

Fig. 1 Mean scores by quality-of-life domains and perinatal HIV status school-aged ugandan children. *QOL* quality of life, *CQOLI* combined quality-of-life inventory, *MDV* multi-dimensional vigor, *GWB* general wellbeing Index, *SRH* self-rated health, *PF* present functioning impairment, *CF* general cognitive function

respondent, if true, suggests that the ability of children to get along with other children, make friends, play, and engage in child appropriate activities is not adversely impacted by HIV infection/exposure. This finding is consistent with the absence of HIV-related differences in social functioning QOL dimension among Italian children [4] but does not align with HIV-related deficits in the same domain reported in other contexts [11, 16, 17]. Of note, two questions included in the social functioning domain could potentially differ by HIV status; however, our study design, which included clinic-based enrolment, may have systematically impacted responses. The first "In the past month, has your child had problems with being teased by other children?" captures stigma. The second "In the past month, has your child had problems keeping up when playing with other children?" captures elements of physical fatigue. All children in this study had access to basic health care. HIV-infected children have been cared for at the current clinic for a median of 5.9 (range 0.6–16.6) years and had little obvious physical symptoms of HIV/AIDS. The generally healthy appearance of PHIV may lower stigmatization as found in other settings [35]. HAART, particularly, if provided early is likely to improve QOL deficits mediated via the physical and functional impairment domains. However, deficits in emotional and educational outcomes may persist as HIV-related stigma may continue to adversely affect QOL despite HAART. Given our design, we are unable to rule out the possibility that using a clinic rather than community control and the presence of some morbidity at interview affected children and proxy respondents' perception of child's capacity to keep up with others during play.

Additionally, PHEU were no different from PHIV children with respect to cognitive vigor and general well-being index regardless of respondent. From self-reported QOL measures, PHEU were similar to PHIV children in terms of emotional functioning and both general and sleep vigor subscales. The many areas of QOL similarity for PHEU and PHIV children suggest that perinatal HIV exposure may be associated with enduring deficits in QOL even in the absence of HIV infection. The extent to which

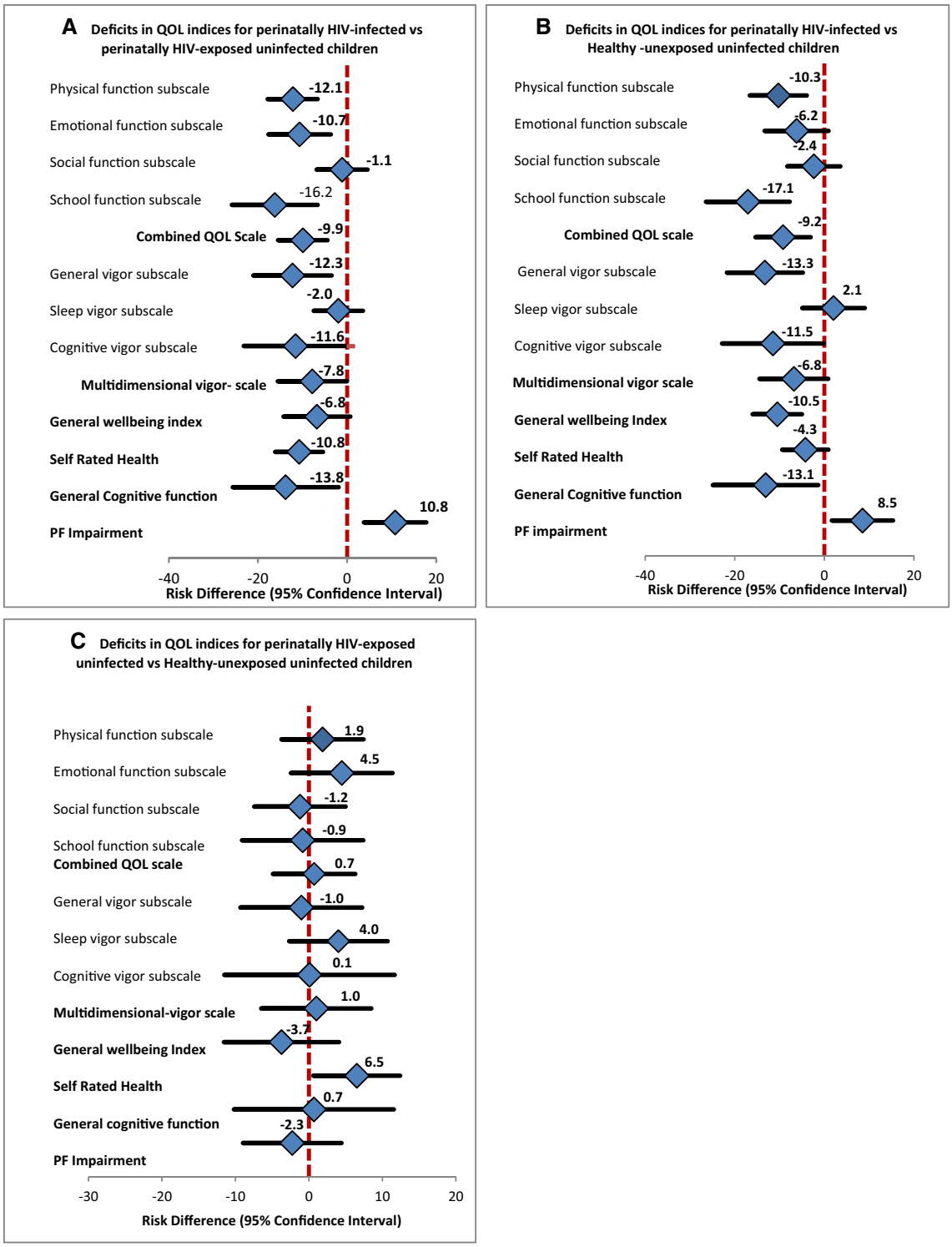

Fig. 2 Proxy-reported associations between perinatal HIV status and quality-of-life (QOL) deficits during school-age and adolescence. Shown estimates are mean differences derived from multivariable linear regression models with respective QOL dimensions as outcome variable. Adjusted covariates include child's age, sex, child's relationship to caregiver, child nutritional status, caregiver's BMI, caregiver's age, and caregiver's education level. *PF* present functioning

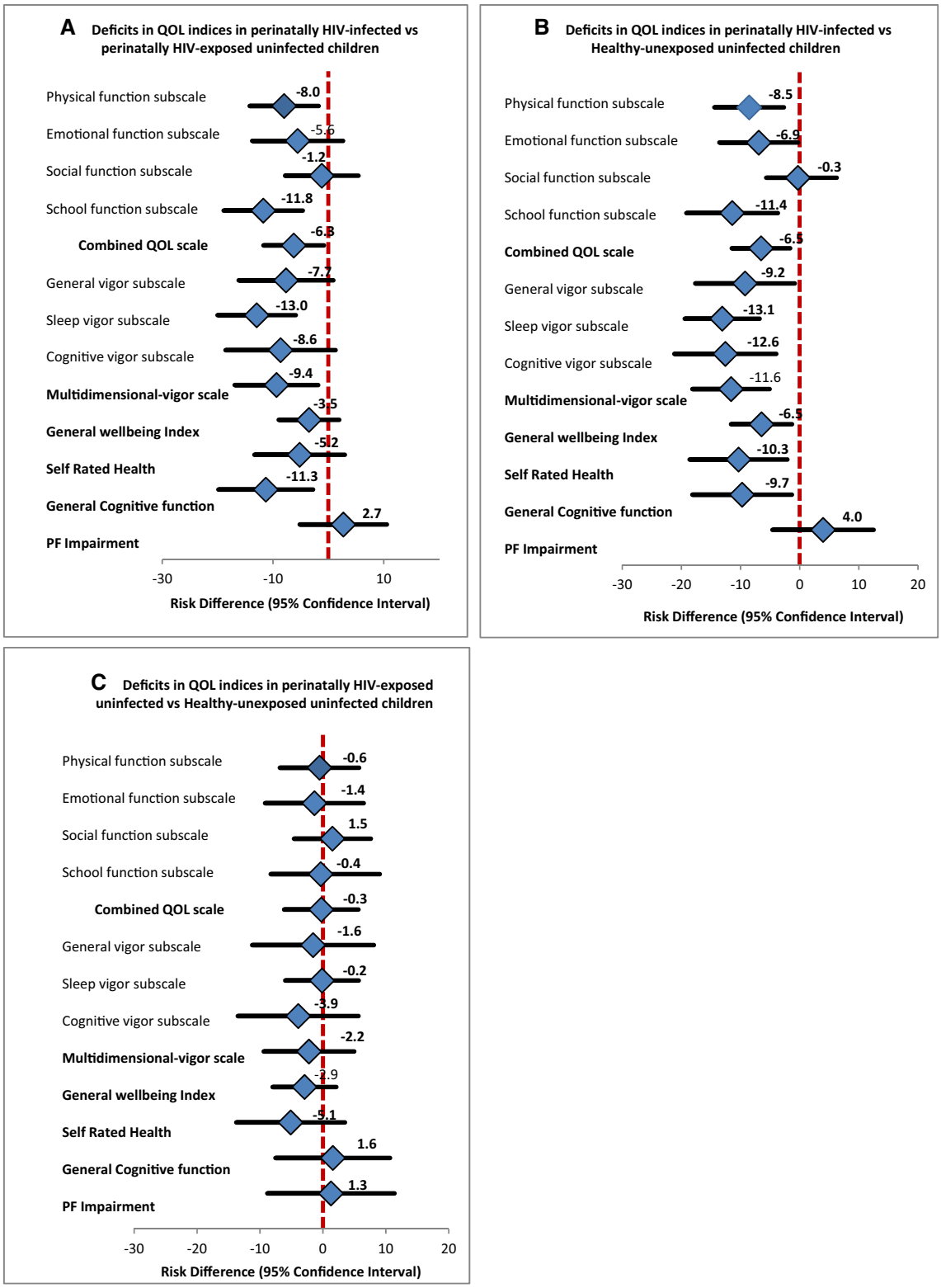

Fig. 3 Self-reported associations between perinatal HIV status and quality-of-life (QOL) deficits during school-age and adolescence. Shown estimates are mean differences derived from multivariable linear regression models with respective QOL dimensions as outcome variable. Adjusted covariates include child's age, sex, child's relationship to caregiver, child nutritional status, caregiver's BMI, caregiver's age, and caregiver's education level. *PF* present functioning

these deficits persists during school-age, adolescence, and young adulthood deserves further elucidation in a larger sample of well-characterized perinatally HIV-affected and -unaffected children.

The finding that caregivers of PHEU compared with caregivers of HUU reported significantly higher wellbeing and lower average PF for PHEU compared to HUU children. This was particularly surprising. With the exception of proxy-reported child general health, all QOL were statistically similar for PHEU and HUU community controls in this study. This contradictory finding may be partly related to our study design as "community controls" were recruited upon seeking health care at study clinics for any reason. Hence, the HUU children in this study may be less healthy than HUU children recruited from a non-hospital setting. Of note, the non-statistically significant trend of lower average QOL scores CQLI, MDV, and GWB scales for PHEU compared to HUU children provides contrary evidence from that derived from proxy report of child QOL. Hence, it remains unclear whether PHEU experience lower overall wellbeing than HUU children. Furthermore, the age-range in this study is wide and it could also be argued that at least some children—supposedly the younger ones—are unreliable evaluators of their own wellbeing [36]. Hence, future larger prospective studies of HIV-affected and -unaffected children with a narrower age-range are needed to clarify the impact of living in HIV-affected contexts for PHEU.

Limitations and strengths

Our study is subject to certain limitations that must be considered in the interpretation of our findings. Firstly, we found lower reliability values in three of eight component subscales of questionnaires used to define respective QOL domains. By QOL domain, reliability and internal consistency values were at least moderate for three of the four composite QOL scales but the findings with respect to present functioning in particular are to be interpreted with caution as reliability values for these was low. Secondly, although multiple confounders were controlled for in multivariable analyses, residual confounding by unmeasured covariates cannot be excluded due to the observational design of this study. Thirdly, by design our study excluded children without birth records and those born outside of the healthcare system because of the need to objectively determine HIV status of the child and their birth mother during pregnancy and early childhood. Of note, a relatively high proportion of births—as much as 43%, in some Ugandan settings may occur outside the healthcare system [37]. Our findings are not generalizable to children of caregivers that delivered outside the healthcare system. There is no evidence to suggest that children born outside the healthcare setting in Uganda are more likely to be HIV-infected. However, if the realized QOL and the prevalence of perinatal HIV infection for excluded children are substantially different from those included in the present study, then selection bias may have occurred. In spite of these limitations, our study had the important strengths as follows: (1) given perinatal HIV status defined at birth or prior to age two for enrolled children, we had the ability to tease out temporal sequence for the relation of perinatal HIV infection/exposure to QOL, (2) we used translated and culturally adapted questionnaire instruments of known psychometric property in the study sample, and (3) we conducted a comprehensive multi-dimensional assessment of QOL. These strengths enhance the empirical and inferential value of this investigation.

Two prior studies evaluated the specific impact of HIV infection by comparing QOL among HIV-affected (i.e., infected children vs. HIV-exposed but uninfected) [11, 17] children. Another compared QOL in HIV-infected compared to HIV-unexposed community control [4] children and the authors found QOL deficits due to HIV infection and residence in an HIV-affected context. The inclusion of three perinatal HIV-exposure groups is a distinct strength of this investigation that allows for comprehensive comparative evaluation of QOL during school-age. By including two perinatally HIV-exposed groups—i.e., infected and exposed uninfected (PHIV and PHEU) children, we are able to isolate the effect of HIV infection on QOL in children affected by HIV. The presence of HUU children as community controls, allowed us to quantify the impact of living in an HIV-affected context that may independently adversely affect QOL or compound QOL deficits for infected children. This understanding is important for informing appropriate interventions as residence within an HIV-affected context (even if HIV-uninfected) may confer QOL disadvantage through poverty, illness-compromised caregiving quality, low levels of caregiver stimulation, and psychosocial stress. Our findings confirm the detrimental QOL effects of perinatal HIV infection while suggesting no adverse QOL impact of PHEU status. Of note, this study represents an initial effort to understand the HR-QOL experience of HIV-uninfected community controls and HIV-exposed uninfected children. The impact of perinatal exposure to the HIV virus on QOL indices deserves specific investigation as PHEU as a group are likely to increase in the Ugandan population and QOL deficits be mediated through compromised caregiving, emotional, and other environment pathways. Adequately powered future studies will be necessary to clarify this relationship.

Conclusions

Perinatal HIV infection is associated with sustained deficits in QOL in school-age and adolescence relative to HIV-uninfected children with or without HIV exposure. Higher levels of fatigue, poor school performance, and sub-optimal levels of wellbeing are among the major contributors to poor QOL during school-age and adolescence in HIV-infected children. In most QOL domains assessed, QOL scores were comparable for HIV-exposed uninfected children and HIV-unexposed uninfected community controls. QOL equivalence was noted for HIV-infected and HIV-exposed and uninfected children with respect to key QOL domains and subscales including among others general wellbeing index, present functioning, emotional functioning, and social functioning suggesting that interventions to increase QOL will benefit all HIV-affected children regardless of infection status. The persistence of low QOL among PHIV in spite of access to HIV care suggests that medical management of HIV alone is insufficient to maintain wellbeing in HIV-infected children. Of note, PHEU are strongly affected by HIV-related stigma and other HIV-associated hardships and may benefit from specific interventions to improve overall wellbeing. Therefore, usual medical interventions that enhance physical health and sleep quality should be combined with psychosocial interventions to facilitate social inclusion, counseling programs for emotional health, and cognitive remediation programs to minimize HIV-related disadvantages and support wellbeing in children living with or affected by chronic HIV infection.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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