



ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/vhri

Patient-Reported Outcomes

Cerebral Malaria in Childhood Is Associated With Decreased Long-Term Health-Related Quality of Life



Perez N. Ochanda, MA, Paul Bangirana, PhD, Carol Kamya, MPH, Arild Aakvik, PhD, Dibyadyuti Datta, MS, PhD, Chandy C. John, MD, MS, Bjarne Robberstad, PhD, Kagan A. Mellencamp, PhD

ABSTRACT

Objectives: Severe malaria in childhood causes long-term cognitive and behavioral problems; however, its impact on health-related quality of life (HRQoL) remains understudied. We assessed HRQoL 4 to 20 years after cerebral malaria (CM), severe malarial anemia (SMA), or other severe malaria (OSM) in Uganda.

Methods: Participants from 3 longitudinal cohorts with CM, SMA, or OSM were included. Asymptomatic community children (CC) served as the reference group. HRQoL was assessed with a mean (SD) duration of 10.0 (3.3) years after enrollment using the EuroQol 5-Dimension 3-Level instrument (EQ-5D-3L) (age ≥ 12 years) and EQ-5D-Y-3L (age 8 to 11 years). Model-predicted EQ-5D-3L index and visual analog scale (VAS) scores (children ≥ 12 years) and EQ-5D-Y-3L VAS scores (children 8 to 11 years) were compared across groups using adjusted 2-part models with log transformation.

Results: Among the 479 study participants aged ≥ 12 years (187 CM, 133 SMA, and 159 CC), model-predicted EQ-5D-3L index and VAS scores were significantly lower in children with CM than SMA or CC, and VAS scores were higher in children with SMA than CC. Among the 313 children aged 8 to 11 years (39 CM, 76 SMA, 130 OSM, and 68 CC), model-predicted EQ-5D-Y-3L VAS scores were significantly lower in children with CM than in those with SMA, OSM, or CC and also lower in children with SMA than OSM or CC.

Conclusions: CM and, to a lesser extent, SMA in childhood are associated with long-term reduction in HRQoL. The chronic effects extend beyond cognition and behavior to affect overall HRQoL.

Keywords: cerebral malaria, health-related quality of life, long-term outcomes, severe malarial anemia.

Cite this article as: Ochanda PN, Bangirana P, Kamya C, et al. Cerebral malaria in childhood is associated with decreased long-term health-related quality of life. *Value Health Reg Issues*. 2026;58-101677. <https://doi.org/10.1016/j.vhri.2026.101677>

Introduction

The global technical strategy to eradicate malaria by 2030 calls for improving the quality of life for the approximately 200 million individuals infected with malaria each year, the majority of whom live in Africa.¹ Malaria remains a leading cause of mortality in high-burden countries such as Uganda.² Without timely and effective treatment, uncomplicated malaria can progress to severe malaria, which presents in several clinical forms. Among these, cerebral malaria (CM) represents the most severe manifestation, often resulting in coma and neurologic complications, whereas severe malarial anemia (SMA) is the most common severe form, particularly among young children.³ Previous studies in Africa have established associations between CM and SMA and long-term impairments in cognition, behavior, and academic achievement in children.⁴⁻¹⁰ In addition, survivors of CM can develop persistent neurologic deficits, such as vision and hearing impairments, loss of speech, and movement disorders.¹¹⁻¹⁴

Given these long-term consequences, understanding the broader impact of severe malaria requires measures beyond traditional clinical outcomes. Health-related quality of life (HRQoL) is a valuable outcome for assessing the lasting effects of illness and the effectiveness of health interventions, particularly in chronic and postacute conditions.¹⁵ HRQoL focuses on nonclinical aspects of well-being, including physical, psychological, and social functioning, which are often affected in survivors of severe illness.¹⁶⁻¹⁸ Self-reported outcomes such as HRQoL provide insights that complement clinical data and are critical for informing policy decisions and designing interventions that address the lived experiences of affected individuals. Additionally, HRQoL offers a broader perspective on health impacts, offering policy makers, especially in resource-limited settings, valuable evidence to guide efficient resource allocation and targeted support strategies. Furthermore, HRQoL is a valuable measure of healthcare interventions.¹⁹

Research on the impact of severe malaria in childhood on long-term HRQoL is limited. Some short-term studies have found that uncomplicated malaria reduces HRQoL,^{20–22} whereas other patient-reported outcome studies have focused on perceptions of malaria disease and its causes.^{23–25} However, uncomplicated and severe malaria differ in clinical severity and long-term consequences, limiting the relevance of these findings for survivors of severe malaria. Moreover, existing studies primarily examine quality of life cross-sectionally among small samples, often without a comparison group. Given the well-established long-term cognitive, behavioral, and mental health sequelae of severe malaria, long-term HRQoL data with a clear comparator are essential for understanding its broader effects on well-being. This study aimed to assess HRQoL in survivors of CM or SMA relative to asymptomatic community peers 4 to 20 years after severe acute illness.

Methods

Study Design and Participants

This study used data from a follow-up study conducted between 2020 and 2023 in Kampala and Jinja, Uganda, assessing long-term neurobehavioral, functional, and socioeconomic outcomes following childhood severe malaria. Kampala is a peri-urban site with low malaria transmission, whereas Jinja is a rural site with moderate malaria transmission. Participants were children previously enrolled in 3 prospective cohort studies investigating neurocognitive impairments after severe *P. falciparum* malaria.^{4,8,10,26} In the parent studies, participants were recruited from Mulago National Referral and Teaching Hospital (Kampala) or the Pediatric Emergency Ward at Jinja Regional Referral Hospital. The first study (2003–2006) enrolled children aged 4 to 12 years with CM or uncomplicated malaria and followed them for 24 months.^{4,10} The second study (2008–2015) enrolled children aged 18 months to 12 years with CM or SMA, with 24 months of follow-up.⁸ The third study (2014–2018) enrolled children aged 6 months to 4 years with at least 1 of 5 common manifestations of severe malaria: CM, SMA, respiratory distress syndrome, malaria with complicated seizures, and prostration, with 12 months of follow-up.²⁶ In each parent study, asymptomatic community children (CC) of similar ages and from the extended families or neighborhoods of the children with severe malaria were enrolled as a comparison group. Full details of the parent studies have been published previously.^{4,8,10,26} Between 2020 and 2023, 4 to 20 years after initial enrollment with severe malaria, eligible participants were traced and recruited for a single follow-up study visit, during which HRQoL data were collected. A flowchart according to the 3 parent studies is presented in Figure 1.

Ethical Considerations

The study received ethical approval from the institutional review boards for human studies at Makerere University School of Medicine and Indiana University School of Medicine. The study was also approved by the Uganda National Council of Science and Technology and the Regional Ethics Committee of Western Norway.

Health-Related Quality-of-Life Measurement

For participants ≥ 12 years of age, HRQoL was assessed using the 5-dimension, 3-level instrument (EQ-5D-3L).^{27–29} Although the adult version is generally recommended for individuals aged ≥ 16 years, EuroQol permits its use from age 12 in mixed adolescent-adult samples. At follow-up, cohort 1 consisted

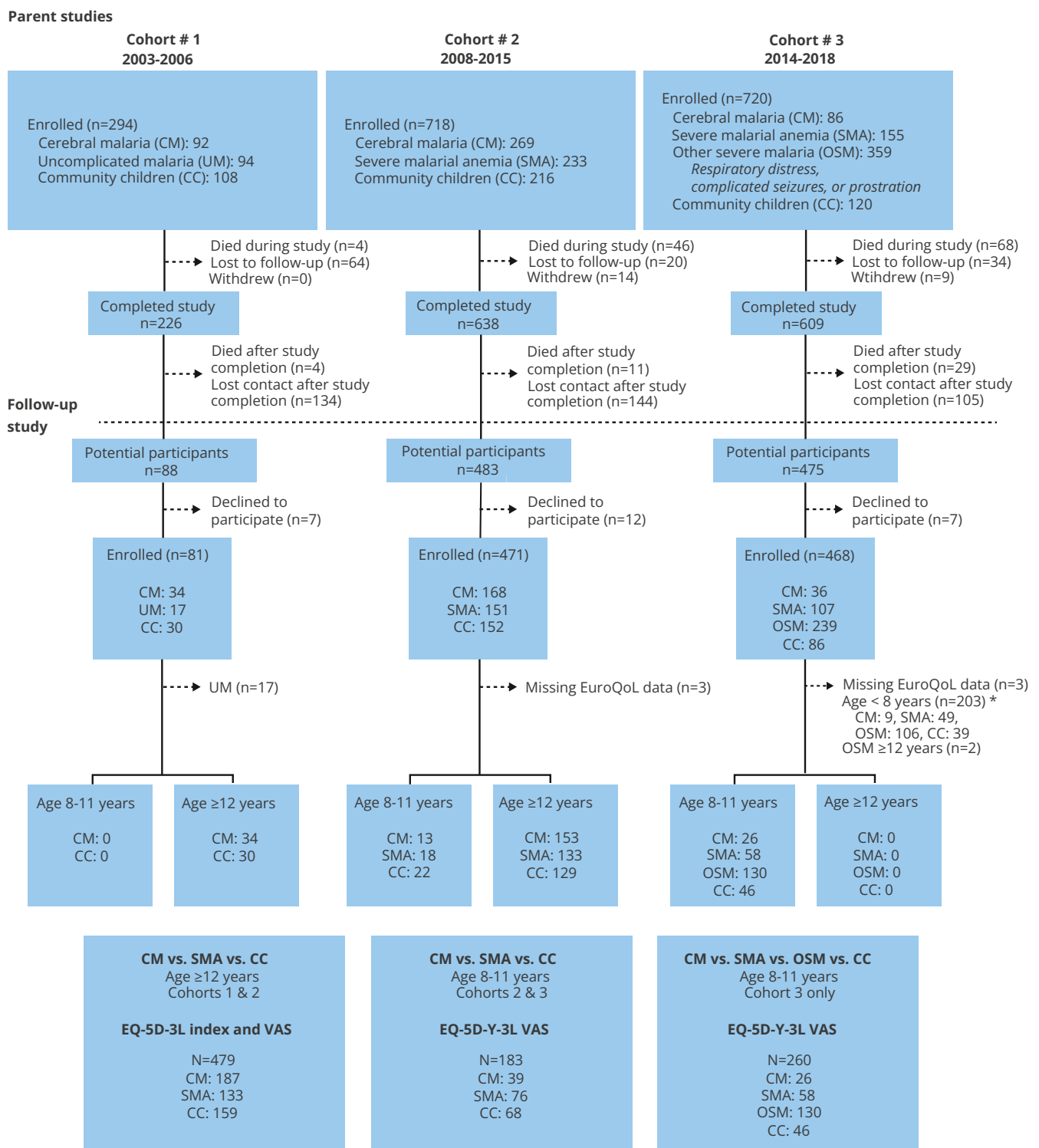
entirely of adults and cohort 2 primarily included adolescents aged 12 to 15 years and young adults. Therefore, to maintain overall consistency in testing within cohorts 1 and 2, we used the adult instrument beginning at age 12. In addition, no African value sets were available for child version of the EQ-5D, which further limited its use in this age range. The EQ-5D-3L is a standardized, generic, preference-based measure of self-reported health widely used in clinical and economic evaluations.³⁰ It captures health status across 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with 3 response levels: (1) no problems, (2) some problems, and (3) extreme problems. For each dimension, respondents selected the level that best described their current health, resulting in a 5-digit health profile (eg, 12132). Profiles were converted to a single summary EQ-5D-3L index using a Zimbabwean value set, chosen as the closest available for this population.³¹ Index scores have an ideal range from 0 (equivalent to death) to 1 (perfect health), but can in empirical situations be negative depending on the value set applied.^{29,32} Although a score of 1 is officially referred to as “perfect health,” we use the term “full health” hereafter to acknowledge that this reflects the absence of reported problems in the 5 EQ-5D dimensions rather than a literal state of perfect health. Additionally, participants completed the EQ-5D visual analog scale (VAS), rating their overall health from 0 (worst imaginable health) to 100 (best imaginable health).^{29,30} The primary outcome was the EQ-5D-3L index score, with the EQ-VAS analyzed as a secondary outcome.

For participants aged <12 years, we used the child-friendly EQ-5D-Y-3L instrument.²⁷ It retains the same 5 dimensions and 3-level response structure as the adult version but uses simplified wording appropriate for younger respondents. The application of the EQ-5D-Y-3L in this study setting has limitations because available value sets for this tool are mostly restricted to high-income countries, with no African country represented.^{33–35} In addition, a South African study found that the EQ-5D-Y-3L demonstrated weaker psychometric properties in children without health conditions or with chronic illnesses, compared with acutely ill children.³⁶ We did not calculate EQ-5D-Y-3L index scores and instead summarized dimension responses descriptively. In contrast, VAS scores, which are self-reported and do not rely on value sets, were also analyzed. Analyses in this age range were limited to children aged 8 to 11 years, consistent with EuroQol guidance recommending self-completion of the EQ-5D-Y-3L starting at age 8 due to concerns about younger children's capacity to reliably self-report health status.³⁵ Children younger than 8 years were excluded from analyses. Paper versions of study instruments were administered in Luganda, the predominant local language of Uganda, using an official, validated translation provided by the EuroQol Group, as in previous research in Uganda.³⁷ Pilot testing was completed in an earlier phase of the study, confirming that the instrument was appropriate.

Sociodemographic Data

Sociodemographic data collected at follow-up included participant age, sex, and individual and socioeconomic indicators. Individual measures covered paid and unpaid work in the past 12 months and current school attendance. Household data included asset ownership, living conditions, and dwelling characteristics. Economic data were gathered using a questionnaire adapted from the Demographic and Health Surveys and the Living Standards Measurement Study, internationally recognized tools designed to improve socioeconomic data collection for policy making at the national and global level.^{38,39} A household socioeconomic index (SEI) score was calculated using multiple correspondence

Figure 1. Flowchart of study enrollment and description of analysis. *Per EuroQoL guidelines, EQ-5D-Y-3L testing has not been verified as accurate for children younger than 8 years.



VAS indicates visual analog scale.

analysis.⁴⁰ The multiple correspondence analysis dimension that accounted for the largest variation in the household-level data was used to estimate a continuous household SEI score for each participant, wherein higher scores reflected better socioeconomic conditions.⁴¹

Analytic Approach

We hypothesized that children exposed to severe malaria would report lower HRQoL during follow-up compared with asymptomatic CC. The analysis was 2-fold: first, in individuals

aged ≥ 12 years from cohorts 1 and 2, we compared the EQ-5D-3L between those with a history of CM or SMA and CC; second, for children aged 8 to 11 years from cohorts 2 and 3, we compared the EQ-5D-Y-3L between those with a history of CM or SMA and CC. Children with other forms of severe malaria, including respiratory distress syndrome, malaria with complicated seizures, or prostration, were only present in a single cohort (cohort 3) and were exclusively aged < 12 years. Therefore, they were grouped as “other severe malaria” and compared with the other groups in cohort 3 only for secondary analysis. Additionally, children aged 8 to 11 years were enrolled in both Kampala and Jinja, whereas those aged ≥ 12 years were enrolled in Kampala exclusively.

Statistical Analysis

Continuous descriptive data were presented as mean (SD) or median (IQR), where appropriate, and analyzed across groups using Kruskal-Wallis tests with Dunn's post hoc tests for pairwise comparisons. Categorical data were presented with frequencies and percentages and analyzed across groups using Pearson's chi-squared tests or Fisher's exact tests, where appropriate.

Given the bounded nature and skew characteristic of EQ-5D-3L and EQ-5D-Y-3L outcomes,^{29,35,42,43} we used 2-part models with log transformation (TPM-L) to assess HRQoL across severe malaria groups. TPM-L allows separate estimation of the probability of reporting full health (part 1) and the extent of health deficits among those with less than full health (part 2), providing a more appropriate and interpretable analysis of EQ-5D data.^{44,45} Part 1 uses logistic regression to model the odds of full health (index = 1 or VAS = 100), adjusting for covariates. Part 2 uses a proportional deficit model, regressing the log-transformed complement of full health [(1 – index) or (100 – VAS)] on severe malaria group and covariates. Coefficients from part 2 reflect the severity of health deficits, with positive values indicating greater deficits. Model-predicted index and VAS scores were derived by combining part 1 and part 2 estimates following the approach by Huang et al.⁴⁴ The predicted scores for each participant were calculated using the following formula:

$$\text{Predicted score} = 1 - \frac{\exp(\hat{x}\hat{\beta} + 0.5\hat{\sigma}^2)}{1 + \exp(\hat{x}\hat{\alpha})}$$

where $\hat{x}\hat{\beta}$ is the predicted value and $\hat{\sigma}^2$ is the residual variance from the linear model with log transformation among sub-maximal values (part 2), and $\hat{x}\hat{\alpha}$ is the predicted log-odds from the logistic regression of full health (part 1). Model-predicted scores were approximately normally distributed, and the resulting predicted mean scores were compared across severe malaria groups using linear regression.

Covariates included parent study cohort, severe malaria group, age at enrollment, current age, sex, household SEI, school attendance, and recent paid or unpaid work. In analysis of children aged 8 to 11 years, parent study site was included as a covariate, but paid and unpaid work were excluded as covariates because of low reporting, and school attendance was omitted given its near-universal participation. Marginal mean differences in predicted EQ-5D scores across sociodemographic covariates were derived from the TPM-L models following the same approach as the primary analysis. To assess differences by study site in children aged 8 to 11 years, predicted EQ-VAS scores were estimated using TPM-L, incorporating an interaction between severe malaria group and site. Model diagnostics were performed for both parts of the TPM-L; the logistic models demonstrated adequate fit, and residual plots for part 2 did not indicate substantial violations of homoscedasticity or normality on the log

scale. Bonferroni correction addressed multiple testing, as noted in figure and table legends. All analyses were conducted using Stata v18.0 (StataCorp LLC, College Station, TX).

Results

Participant Characteristics

A total of 792 participants with complete EQ-5D data were included in this study. Among the 479 participants aged ≥ 12 years from cohorts 1 and 2 (187 CM, 133 SMA, and 159 CC), the mean (SD) time from enrollment in the parent study with severe malaria (CM, SMA) or as a CC to follow-up study enrollment was 12.2 (2.5) years. Group differences were observed in age at parent study enrollment, age at follow-up, cohort membership, household SEI, and participation in paid or unpaid work within the past 12 months (Table 1).

In pairwise comparisons with Bonferroni correction (adjusted $\alpha = 0.0167$), participants with SMA were younger at parent study enrollment (mean [SD] years: 3.6 [1.8]) than those with CM (4.4 [2.1]) and CC (4.9 [2.5]). This difference persisted at follow-up, with participants with SMA younger (15.1 [2.0]) than those with CM (16.8 [3.8]) and CC (17.3 [4.5]). Household SEI scores were lower among participants with SMA (mean [SD]: 0.06 [1.0]) compared with those with CC (0.39 [0.95]). Participation in paid work was less common among those with SMA (16.7%) compared with CM (36.6%), and unpaid work participation was also lower in participants with SMA (12.9%) compared with both CM (26.9%) and CC (28.0%).

Among the 183 children aged 8 to 11 years from cohorts 2 and 3 (39 CM, 76 SMA, and 68 CC), the mean (SD) time from parent study to follow-up study enrollment was 7.0 (1.1) years. Among the 260 children from cohort 3 included in the analysis of children with OSM (26 CM, 58 SMA, 130 OSM, and 46 CC), the average time to follow-up was 6.6 (1.0) years. In children aged 8 to 11 years, most of the characteristics assessed were similar across study groups, except children from cohort 3 with OSM who were younger than CC and had higher household SEI scores than children with SMA (Appendix Table 1).

Adjusted EQ-5D Health Profiles

Histograms of the EQ-5D-3L index score (individuals aged ≥ 12 years) and EQ-5D-3L and EQ-5D-Y-3L VAS scores (individuals aged ≥ 12 years and 8–11 years, respectively) demonstrated a large proportion of participants reporting the maximum possible score (index = 1 or EQ-VAS = 100) and substantial negative skew (Appendix Figs. 1 and 2). These qualities violate the assumptions of standard linear regression and undermine the interpretation of unadjusted differences.^{42–45} To address these issues, TPM-L were used and model-predicted index (individuals aged ≥ 12 years) and EQ-VAS (individuals aged 8–11 and ≥ 12 years) scores were calculated by pooling the estimates from both parts into an overall predicted mean score for each group.⁴⁴

Individuals ≥ 12 years old: Adjusted EQ-5D-3L index and EQ-VAS scores

Model-predicted mean EQ-5D-3L index scores, adjusted for sociodemographic factors, were significantly lower among participants with CM (mean [95% CI] 0.852 [0.847, 0.858]) compared with SMA (0.881 [0.874, 0.887]) and CC (0.877 [0.871, 0.883]; Bonferroni-corrected $P < .001$) (Fig. 2). Two individuals with CM aged ≥ 12 years had a negative EQ-5D-3L index score (–0.145 for both) before estimating the TPM-L, indicating health states

Table 1. Characteristics of participants aged ≥ 12 years by severe malaria group.

Characteristic	CM (n = 187)	SMA (n = 133)	CC (n = 159)	P value
Age at parent study, years	4.4 (2.1)	3.6 (1.8)	4.9 (2.5)	<.001* [†]
Age at follow-up study, years	16.8 (3.8)	15.1 (2.0)	17.3 (4.5)	<.001* [†]
Sex, n (%)				.15
Female	79 (42.3)	56 (42.1)	82 (51.6)	
Male	108 (57.8)	77 (57.9)	77 (48.4)	
Parent study, n (%)				<.001* [†]
Cohort 1	34 (18.2)	0 (0)	30 (18.9)	
Cohort 2	153 (81.8)	133 (100)	129 (81.1)	
Current household socioeconomic index	0.21 (0.92) (186)	0.06 (1.0) (132)	0.39 (0.95) (157)	.006*
Currently attending school, n (%)	136 (73.1)	110 (83.3)	114 (72.6)	.06
Paid work in past 12 months, n (%)	68 (36.6)	22 (16.7)	44 (28.0)	.001 [†]
Unpaid work in past 12 months, n (%)	50 (26.9)	17 (12.9)	44 (28.0)	.004* [†]

Note. Data are presented as mean (SD) or n (%) among participants included in primary analysis. P values reflect comparisons across groups using Kruskal-Wallis tests with post hoc Dunn's tests for pairwise comparisons for continuous outcomes, and Pearson's chi-squared tests or Fisher's exact tests for categorical outcomes. Nonmissing N are listed in final parentheses. Among characteristics significantly different across groups, the following groups differed after Bonferroni correction for 3 comparisons ($P < .01667$):

CC indicates community children; CM, cerebral malaria; SMA, severe malarial anemia.

*SMA vs CC.

[†]CM vs SMA.

valued as worse than death (Appendix Fig. 1), and results were robust to their exclusion. Model-predicted mean VAS scores were significantly lower in individuals with CM (mean [95% CI] 85.9 [85.5, 86.4]) compared with SMA (88.3 [87.8, 88.9]) and CC (87.2 [86.7, 87.8]; corrected $P < .001$ and $P = .001$, respectively), whereas participants with prior SMA showed slightly higher adjusted scores than CC (corrected $P = .02$) (Fig. 3). As a sensitivity for this primary analysis, we used a lower cutoff as for "best imaginable health" of $VAS \geq 95$; results were unchanged (Appendix Table 2).

Individuals 8 to 11 years old: Adjusted EQ-5D-Y-3L VAS scores

The overall pattern of model-predicted mean VAS scores for children with CM mirrored that of the older age group, with lower adjusted scores (mean [95% CI]: 76.6 [74.2, 79.0]) than SMA (84.3 [82.6, 86.0]) and CC (88.3 [86.5, 90.2]; corrected $P < .001$ for both). In contrast to older participants, children with SMA also reported lower adjusted VAS scores than CC (corrected $P = .03$) (Appendix Fig. 3).

When including children with OSM and limiting the analysis to cohort 3, mean VAS scores were lower in children with CM (mean [95% CI]: 71.7 [68.2, 75.1]) than in those with SMA (80.9 [78.6, 83.2]) or OSM (87.7 [86.1, 89.2]) and CC (86.9 [84.3, 89.5]; corrected $P < .001$ for all comparisons). Children with SMA also reported lower mean VAS scores than those with OSM and CC (corrected $P < .001$ and $P = .005$, respectively), who did not differ (Appendix Fig. 3).

EQ-5D-3L (≥ 12 years old) and EQ-5D-Y-3L (8 to 11 years old) dimensions

Among participants aged ≥ 12 years, the distribution of reported problems across the 5 EQ-5D-3L dimensions did not differ significantly by severe malaria group (Appendix Table 3). Problems with "pain/discomfort" were the most common, followed by "anxiety/depression" and "usual activities," although most participants reported no problems in all dimensions.

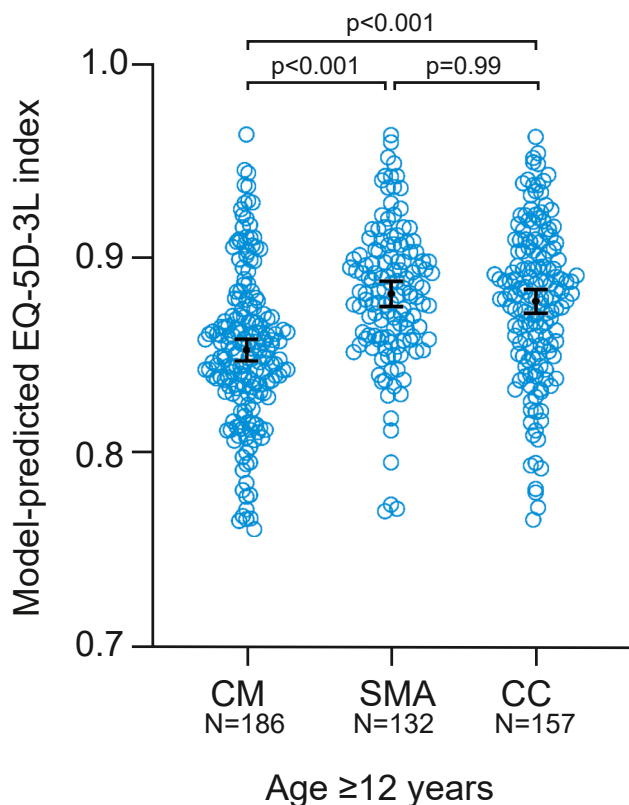
Among participants aged 8 to 11 years, problems with "pain/discomfort," "anxiety/depression," and "mobility" were most common, but again, most participants reported fewer problems across all dimensions. The distribution of reported problems across the 5 EQ-5D-Y-3L dimensions did not differ significantly by severe malaria group (Appendix Table 4), except when including children with OSM and limiting the analysis to cohort 3, in which children with OSM reported fewer severe problems with self-care compared with children with CM and CC (Appendix Table 4). When examining health dimensions by severe malaria group and parent study sites, children in Jinja more often reported some or extreme problems across most health dimensions compared with children in Kampala (Appendix Table 5).

EQ-5D-Y-3L VAS scores (8 to 11 years old) by parent study site

Site-specific model-predicted means for EQ-VAS scores among children aged 8 to 11 years showed significant differences between severe malaria groups in each study site. In Kampala (cohort 2 and 3), adjusted EQ-VAS scores were significantly lower for children with CM (mean [95% CI]: 84.3 [82.0, 86.7]) or SMA (mean [95% CI]: 87.1 [85.5, 88.7]) compared with those with CC (mean [95% CI]: 91.4 [89.5, 93.3]; corrected $P < .001$ for all comparisons). Similarly, in Jinja, children with CM had significantly lower scores than those with SMA and CC. After including OSM individuals in cohort 3 only, EQ-VAS scores for CM remained significantly lower than all other severe malaria groups in both Kampala and Jinja (Appendix Table 6).

When comparing model-predicted EQ-VAS scores within severe malaria group by study site, children aged 8 to 11 years (cohort 2 and 3) with CM in Kampala had higher scores (mean [95% CI]: 84.3 [82.0, 86.7]) compared with those in Jinja (mean [95% CI]: 50.5 [46.5, 54.4]; corrected $P < .001$). The pattern of predicted EQ-VAS scores in cohort 3 was similar to that observed in cohort 2 and 3 after including OSM group, with scores consistently higher in Kampala than in Jinja across all severe malaria categories (Appendix Table 7).

Figure 2. Model-predicted EQ-5D-3L index scores by severe malaria group among participants aged ≥ 12 years. Estimates reflect model-predicted index scores derived from a 2-part model with log transformation (TPM-L), adjusted for age at parent study enrollment, current age, sex, parent study cohort, household socioeconomic index, school attendance, and participation in paid and/or unpaid work over the past 12 months. Estimates were computed using the equation described by Huang et al⁴⁴ and reflect the expected score for each participant after adjustment for covariates. Group mean and 95% CIs are shown with error bars, and Bonferroni-corrected P values are presented.

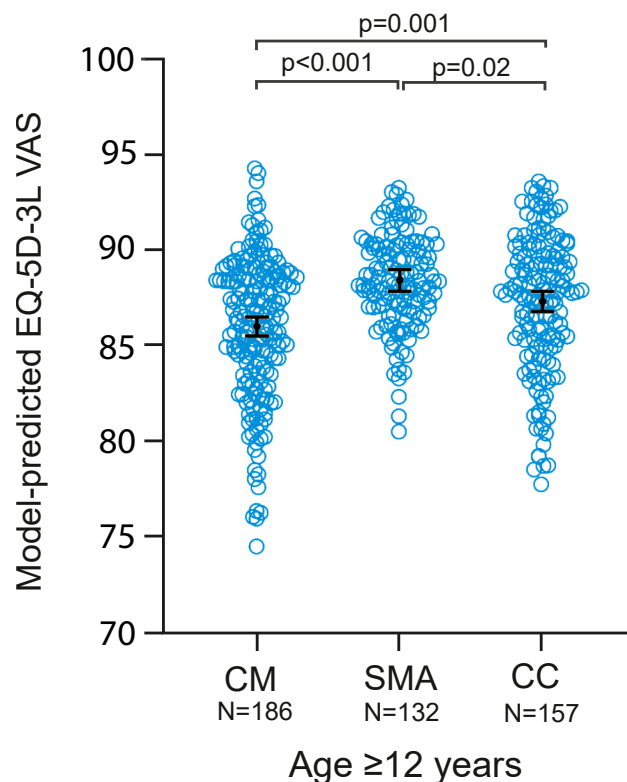


CC indicates community children; CM, cerebral malaria; SMA, severe malarial anemia.

Sociodemographic associations with EQ-5D outcomes

In addition to severe malaria status, several sociodemographic factors were associated with HRQoL outcomes. Among participants aged ≥ 12 years, older age at follow-up and prior enrollment in cohort 1 were associated with lower mean EQ-5D-3L index scores, whereas school attendance and recent participation in paid work were associated with higher scores (Appendix Table 8). In addition, in this age group, older age at the parent study and follow-up, being female, prior enrollment in cohort 1, and recently participating in unpaid work were all significantly associated with lower mean EQ-5D-3L VAS scores, whereas school attendance and higher household SEI were associated with higher scores (Appendix Table 9). Among children aged 8 to 11 years who participated in cohorts 2 and 3, being female, prior enrollment in cohort 2, and higher household SEI were associated with better EQ-5D-Y-3L VAS scores (Appendix Table 10). In cohort 3, older age at follow-up was also associated with higher scores (Appendix Table 10).

Figure 3. Model-predicted EQ-5D-3L visual analog scale (VAS) scores by severe malaria group among participants aged ≥ 12 years. Estimates reflect model-predicted VAS scores derived from a 2-part model with log transformation (TPM-L), adjusted for age at parent study enrollment, current age, sex, parent study cohort, household socioeconomic index, school attendance, and participation in paid and/or unpaid work over the past 12 months. Estimates were computed using the equation described by Huang et al⁴⁴ and reflect the expected score for each participant after adjustment for covariates. Group mean and 95% CIs are shown with error bars, and Bonferroni-corrected P values are presented.



CC indicates community children; CM, cerebral malaria; SMA, severe malarial anemia.

Discussion

To our knowledge, this study is the first to assess long-term HRQoL among survivors of childhood CM or SMA. In both 8–11 and ≥ 12 years age groups, children with prior CM had consistently lower adjusted EQ-5D index and VAS score than those with SMA or CC. For those aged ≥ 12 years, SMA was associated with slightly higher VAS scores than CC. In the 8–11 age group, adjusted EQ-5D-Y VAS scores were lowest in CM, with children with SMA reporting lower scores than those with other severe malaria (OSM) and CC. Overall, children with CM experienced significantly worse long-term HRQoL than those with SMA or CC, underscoring the lasting impact of CM and the need for targeted interventions to improve outcomes.

Although no prior studies have examined long-term HRQoL in children after CM or SMA, our findings align with previous research on severe malaria and short-term retrospective studies of malaria-exposed individuals. An Indonesian study found that the EQ-5D index was lower in severe malaria cases compared with mild cases.²⁰ Another study of Brazilians aged ≥ 12 years

exposed to malaria (primarily *Plasmodium vivax*) reported significantly lower EQ-5D-3L scores.²² In this study, CM was notably associated with long-term HRQoL reductions across all age groups, with SMA also affecting younger children to a lesser extent. Other forms of severe malaria did not show HRQoL deficits compared with CC. The larger differences between HRQoL outcomes in children with CM compared with other forms of severe malaria highlight the long-term harm associated with CM particularly. Our results indicate a need for further research to identify factors specific to these forms of severe malaria that contribute to worse long-term HRQoL, enabling targeted prevention efforts.

The greater burden of sequelae after CM than other forms of severe malaria likely contribute to the consistently lower HRQoL scores observed in participants with prior CM. Although both CM and SMA can lead to long-term neurocognitive, behavioral, and academic challenges in childhood survivors,^{4-10,46} CM more commonly results in a direct neurological insult because of brain swelling, seizures, and coma during the acute illness, which can result in persistent impairments in physical and psychological functioning. Compared with those with other forms of severe malaria, children with CM take on a higher burden of neurological sequelae, such as ataxia, loss of speech, blindness, deafness, and epilepsy,¹¹⁻¹⁴ and mental health disorders.⁴⁶ These challenges in CM survivors closely align with EQ-5D domains, particularly mobility, pain/discomfort, and anxiety/depression, for which our study participants with CM more frequently reported problems than their peers. Although SMA can affect neurodevelopment, direct evidence of neurologic and mental health consequences remains limited. However, younger children with prior SMA reported lower VAS scores than those with OSM and CC, indicating that the impact of SMA on perceived health and well-being may be more pronounced early in recovery and diminish over time. Further research is needed to investigate how severe malaria sequelae influence long-term HRQoL outcomes across the spectrum of severe malaria.

Our findings revealed significant regional differences in HRQoL among children aged 8 to 11 years previously exposed to severe malaria, with those in Jinja consistently reporting lower EQ-VAS scores. Children in Jinja also showed worse health states compared with those in Kampala, likely due to poorer clinical health evidenced by more malaria-related hospital visits and admissions and lower household socioeconomic status. These disparities suggest unequal healthcare access and socioeconomic inequalities between the sites. Supporting this, a Kenyan study found higher malaria prevalence among the poorest, with no decline over time, and that the poorest were less likely to use effective antimalarials and insecticide-treated bednets.⁴⁷ A systematic review of studies examining socioeconomic status and malaria burden, identified poor housing, low education, low income, and farming occupations as key risk factors for malaria in sub-Saharan Africa.⁴⁸ Furthermore, these regional differences may stem from disparities in malaria transmission or intervention coverage, which is mostly higher in periurban areas compared with rural regions, as shown in Malawi,⁴⁹ highlighting how socioeconomic and regional factors influence malaria burden and subsequent quality of life.

Our data also provide insights into various sociodemographic and economic factors associated with long-term HRQoL, including age, sex, household SEI, school attendance, and participation in paid and/or unpaid work. Notably, among participants aged ≥ 12 years, engagement in paid work and school

attendance were associated with better HRQoL. This finding could be indicative of the mental, psychosocial, and financial benefits that gainful activity confers⁵⁰ or alternatively could simply be that those with better self-perceived health are more likely to seek or maintain employment or school attendance.⁵¹ Among children 8 to 11 years of age, higher household SEI was associated with better VAS scores, emphasizing the importance of household-level resources in shaping perceived health. Together, these findings underscore that long-term quality of life after severe malaria is shaped not only by illness but also by broader socioeconomic contexts.

Our study has limitations. First, the skewed and upper-bounded nature of the EQ-5D-3L and EQ-5D-Y-3L instruments, often called a ceiling effect, may reduce their sensitivity to more subtle impairments.³⁶ We addressed these distributional features by applying TPM-L to generate adjusted HRQoL estimates that appropriately accounted for the nature of the data.⁴²⁻⁴⁵ This study was not designed as a validation study, and future research should consider using the 5-level EQ-5D instruments, which may provide greater granularity and may improve discrimination at higher levels of HRQoL. These versions were not available in the appropriate validated languages when this research was initiated. Second, the absence of a Ugandan value set for EQ-5D-3L scores meant we relied on a Zimbabwean value set, which provided the closest available preference weights for our setting,²⁹ and the absence of any African EQ-5D-Y values sets for children aged 8 to 11 years led us to omit index score calculations for this group. Third, only the Luganda version of the EQ-5D instruments was used for data collection. Although this version had been previously used in Uganda,³⁷ reliance on a single language may limit generalizability and could have affected comprehension among participants more fluent in other local languages, such as Lusoga. Fourth, differences in enrollment characteristics across the 3 parent cohorts may have introduced heterogeneity in long-term HRQoL, most notably in the analysis of participants aged ≥ 12 years (Appendix Tables 11 and 12). We addressed this by incorporating parent study, study site, and severe malaria group as covariates in all models, allowing the estimation of adjusted HRQoL scores while accounting for cohort- and site-level differences. Nevertheless, residual heterogeneity could still have affected results. Although we adjusted for various sociodemographic factors, unmeasured confounders, such as current health status or family functioning, may also influence HRQoL.⁵² Fifth, participants from Jinja and those with CM were underrepresented in the final sample (Appendix Table 13). Attrition and mortality over prolonged follow-up may have led to underrepresentation of individuals with more severe long-term impairments or socioeconomic disadvantage, potentially biasing results toward higher observed HRQoL. Finally, assessing HRQoL at a single follow-up time point precluded evaluation of individual health changes over time, and reliance on self-reported data may have introduced reporting bias, especially among younger children. Study strengths include a large prospective cohort with community controls, rigorous outcome evaluation using validated HRQoL instruments across 5 severe malaria forms, extended follow-up, and adjustment for multiple potential confounders.

The study provides new evidence that long-term impacts of childhood severe malaria, especially CM, may extend beyond neurocognitive and academic effects to include broader impairments in physical, emotional, and functional well-being. Survivors of CM across all ages reported lower HRQoL compared with

peers, whereas younger SMA survivors also experienced worse health than CC, suggesting an early but potentially reversible effect. These findings can guide policy makers and researchers in malaria-endemic countries to develop targeted rehabilitative interventions aimed at improving long-term HRQoL.

Author Disclosures

Author disclosure forms can be accessed below in the [Supplemental Material](#) section.

Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.vhri.2026.101677>.

Article and Author Information

Accepted for Publication: May 5, 2026

Published Online: xxxx

doi: <https://doi.org/10.1016/j.vhri.2026.101677>

Author Affiliations: Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway (Ochanda, Kanya, Robberstad); Department of Psychiatry, Makerere University College of Health Sciences, Kampala, Uganda (Bangirana); Department of Economics, University of Bergen, Bergen, Norway (Aakvik); Ryan White Center for Pediatric Infectious Disease and Global Health, Indiana University, Indiana, USA (Datta, John, Mellencamp); Global Health Uganda, Kampala, Uganda (Ochanda, Bangirana, Kanya).

Correspondence: Bjarne Robberstad, PhD, Department of Global Public Health and Primary Care, University of Bergen, Årstadveien 21, Bergen, Hordaland 5020, Norway. Email: bjarne.robberstad@uib.no

Authorship Confirmation: All authors certify that they meet the ICMJE criteria for authorship.

Funding/Support: This study was supported by the National Institute of Neurological Disorders and Stroke (grant number 2R01NS055349).

Role of the Funder/Sponsor: The content is solely the responsibility of the authors and does not represent the views of the National Institutes of Health (NIH). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgment: The authors thank the participants and their caregivers who took part in the study; the site project coordinator, Julius Caesar Ojuka; the study data managers, Michael J. Goings and Gloria Kyarisiima; and the entire study team who supported data collection.

REFERENCES

- World Health Organization (WHO). *Global Technical Strategy for Malaria 2016–2030*. Geneva: World Health Organization (WHO); 2015:9241564997.
- World Health Organization (WHO). *World Malaria Report 2023*. Geneva: World Health Organization (WHO); 2023.
- White NJ. Severe malaria. *Malar J*. 2022;21(1):284.
- John CC, Bangirana P, Byarugaba J, et al. Cerebral malaria in children is associated with long-term cognitive impairment. *Pediatrics*. 2008;122(1):e92–e99.
- Bangirana P, Musisi S, Boivin MJ, et al. Malaria with neurological involvement in Ugandan children: effect on cognitive ability, academic achievement and behaviour. *Malar J*. 2011;10:1–7.
- Ssenkusu JM, Hodges JS, Opoka RO, et al. Long-term behavioral problems in children with severe malaria. *Pediatrics*. 2016;138(5):e20161965.
- Bangirana P, Opoka RO, Boivin MJ, Idro R, Hodges JS, John CC. Neurocognitive domains affected by cerebral malaria and severe malarial anemia in children. *Learn Individ Differ*. 2016;46:38–44.
- Bangirana P, Opoka RO, Boivin MJ, et al. Severe malarial anemia is associated with long-term neurocognitive impairment. *Clin Infect Dis*. 2014;59(3):336–344.
- Nakitende AJ, Bangirana P, Nakasujja N, et al. Severe malaria and academic achievement. *Pediatrics*. 2023;151(4):e2022058310.
- Boivin MJ, Bangirana P, Byarugaba J, et al. Cognitive impairment after cerebral malaria in children: a prospective study. *Pediatrics*. 2007;119(2):e360–e366.
- Okullo AE, John CC, Idro R, et al. Prevalence and risk factors of gross neurologic deficits in children after severe malaria: a systematic review protocol. *Syst Rev*. 2025;14:76.
- Opoka RO, Bangirana P, Boivin MJ, John CC, Byarugaba J. Seizure activity and neurological sequelae in Ugandan children who have survived an episode of cerebral malaria. *Afr Health Sci*. 2009;9(2):75–81.
- Idro R, Kakooza-Mwesige A, Balyejussa S, et al. Severe neurological sequelae and behaviour problems after cerebral malaria in Ugandan children. *BMC Res Notes*. 2010;3:1–6.
- Idro R, Carter JA, Fegan G, Neville BG, Newton CR. Risk factors for persisting neurological and cognitive impairments following cerebral malaria. *Arch Dis Child*. 2006;91(2):142–148.
- Karimi M, Brazier J. Health, health-related quality of life, and quality of life: what is the difference? *Pharmacoeconomics*. 2016;34(7):645–649.
- Revicki DA. Health-related quality of life in the evaluation of medical therapy for chronic illness. *J Fam Pract*. 1989;29(4):377–380.
- Hahn EA, Cella D, Chassany O, et al. Precision of health-related quality-of-life data compared with other clinical measures. *Mayo Clin Proc*. 2007;82(10):1244–1254.
- Haslam A, Herrera-Perez D, Gill J, Prasad V. Patient experience captured by quality-of-life measurement in oncology clinical trials. *JAMA Netw Open*. 2020;3(3):e200363.
- Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press; 2015.
- Makatita DA, Nur Hasanah Haris RE, Endarti D, Wiedyaningsih C, Andayani TM. Measurement of health related quality of life in malaria patients in Indonesia using EQ-5D-5L. *J Clin Diagn Res*. 2019;13(7):13010.
- Kayiba NK, Yobi DM, Devleeschauwer B, et al. Care-seeking behaviour and socio-economic burden associated with uncomplicated malaria in the Democratic Republic of Congo. *Malar J*. 2021;20(1):260.
- Andrade MV, de Souza Noronha KVM, Guedes GR, et al. Health-Related Quality of Life due to malaria in the Brazilian Amazon using EQ-5D-3L. *PLOS Negl Trop Dis*. 2024;18(12):e0012739.
- Nuwaha F. People's perception of malaria in Mbarara, Uganda. *Trop Med Int Health*. 2002;7(5):462–470.
- Kengeya-Kayondo JF, Seeley JA, Kajura-Bajanja E, et al. Recognition, treatment seeking behaviour and perception of cause of malaria among rural women in Uganda. *Acta Trop*. 1994;58(3–4):267–273.
- Van Damme-Ostapowicz K, Krajewska-Kulak E, Rozwadowska E, Nahorski WL, Olszański R. Quality of life and satisfaction with life of malaria patients in context of acceptance of the disease: quantitative studies. *Malar J*. 2012;11(1):171.
- Namazzi R, Opoka R, Datta D, et al. Acute kidney injury interacts with coma, acidosis, and impaired perfusion to significantly increase risk of death in children with severe malaria. *Clin Infect Dis*. 2022;75(9):1511–1519.
- Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: past, present and future. *Appl Health Econ Health Policy*. 2017;15(2):127–137.
- Thompson AJ, Turner AJ. A comparison of the EQ-5D-3L and EQ-5D-5L. *Pharmacoeconomics*. 2020;38(6):575–591.
- EQ-5D-3L User Guide. Rotterdam, The Netherlands; 2018. <https://euroqol.org/information-and-support/documentation/user-guides/>. Accessed February 6, 2024.
- Devlin N, Parkin D, Janssen B. *Methods for Analysing and Reporting EQ-5D Data*. Cham: Springer Nature; 2020.
- Jelsma J, Hansen K, De Weertdt W, De Cock P, Kind P. How do Zimbabweans value health states? *Popul Health Metr*. 2003;1(1):1–10.
- Devlin NJ, Parkin D, Browne J. Patient-reported outcome measures in the NHS: new methods for analysing and reporting EQ-5D data. *Health Econ*. 2010;19(8):886–905. EQ-5D.
- Ravens-Sieberer U, Wille N, Badia X, et al. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. *Qual Life Res*. 2010;19(6):887–897.
- Devlin N, Roudijk B, Viney R, Stolk E. EQ-5D-Y-3L value sets, valuation methods and conceptual questions. *Pharmacoeconomics*. 2022;40(Suppl 2):123–127.
- EQ-5D-Y-3L User Guide. Rotterdam, The Netherlands; 2024. <https://euroqol-domain.ams3.digitaloceanspaces.com/wp-content/uploads/2025/01/23153947/Userguide-EQ-5D-Y-3L-0525-02-1.pdf>; 2024. Accessed February 4, 2024.
- Scott D, Ferguson GD, Jelsma J. The use of the EQ-5D-Y health related quality of life outcome measure in children in the Western Cape, South Africa: psychometric properties, feasibility and usefulness—a longitudinal, analytical study. *Health Qual Life Outcomes*. 2017;15(1):12.
- Wennemann S, Mudarshiru B, Zawedde-Muyanja S, Siddharthan T, Jackson PD. The effect of biomass smoke exposure on quality-of-life among Ugandan patients treated for tuberculosis: a cross-sectional analysis. *PLOS Glob Public Health*. 2024;4(2):e0002892.
- Rutstein SOS, H Iqbal. Infecundity, Infertility, and Childlessness in Developing Countries. Calverton, MD: ORC Macro and Geneva: World Health Organization (WHO); 2004.

39. Ministry of Health. *Uganda Bureau of Statistics: Kampala, Uganda and Calverton*; 2016. <https://library.health.go.ug/sites/default/files/resources/UBOS%20Statistical%20Abstract%202016%20.pdf>. Accessed August 15, 2025.
40. Abdi H, Valentin D. Multiple correspondence analysis. *Encyclopedia of measurement and statistics*. 2007;2(4):651–657.
41. Wittenberg M, Leibbrandt M. Measuring inequality by asset indices: a general approach with application to South Africa. *Rev Income Wealth*. 2017;63(4):706–730.
42. Cheng LJ, Pan T, Chen LA, et al. The ceiling effects of EQ-5D-3L and 5L in general population health surveys: a systematic review and meta-analysis. *Value Health*. 2024;27(7):986–997.
43. Hernández Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. *Value Health*. 2012;15(3):550–561.
44. Huang IC, Frangakis C, Atkinson MJ, et al. Addressing ceiling effects in health status measures: a comparison of techniques applied to measures for people with HIV disease. *Health Serv Res*. 2008;43(1 Pt 1):327–339.
45. Pullenayegum EM, Tarride J-E, Xie F, Goeree R, Gerstein HC, O'Reilly D. Analysis of health utility data when some subjects attain the upper bound of 1: are Tobit and CLAD models appropriate? *Value Health*. 2010;13(4):487–494.
46. Idro R, Kakooza-Mwesige A, Asea B, et al. Cerebral malaria is associated with long-term mental health disorders: a cross sectional survey of a long-term cohort. *Malar J*. 2016;15:1–11.
47. Were V, Buff AM, Desai M, et al. Trends in malaria prevalence and health related socioeconomic inequality in rural western Kenya: results from repeated household malaria cross-sectional surveys from 2006 to 2013. *BMJ Open*. 2019;9(9):e033883.
48. Degarege A, Fennie K, Degarege D, Chennupati S, Madhivanan P. Improving socioeconomic status may reduce the burden of malaria in sub Saharan Africa: a systematic review and meta-analysis. *PLOS One*. 2019;14(1):e0211205.
49. Kazembe LN, Appleton CC, Kleinschmidt I. Geographical disparities in core population coverage indicators for roll back malaria in Malawi. *Int J Equity Health*. 2007;6(1):5.
50. Modini M, Joyce S, Mykletun A, et al. The mental health benefits of employment: results of a systematic meta-review. *Australas Psychiatry*. 2016;24(4):331–336.
51. Jack W, Lewis M. *Health Investments and Economic Growth: Macroeconomic Evidence and Microeconomic Foundations*. Washington, DC: World Bank; 2009.
52. Imoebé FE, Orhé OG, Uniamikogbo EI, Oshobugie BN, et al. Family functioning and quality of life among HIV positive patients attending a clinic in South-South Nigeria. *Solov'evskie issledovaniya*. 2025;73(3):79.