Investigating Differences in Nutritional Parameters in Ugandan Children with *Plasmodium falciparum* Severe Malaria

Lucy D. Brown[1], Katrina Co[2], Robert O. Opoka[3], Caitlin Bond[2], Dibyadyuti Datta[2], Chandy C. John[2]

[1]Indiana University School of Medicine, Indianapolis, Indiana, [2]Ryan White Center for Pediatric Infectious Disease and Global Health, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, [3]Department of Paediatrics and Child Health, Makerere University, Kampala, Uganda
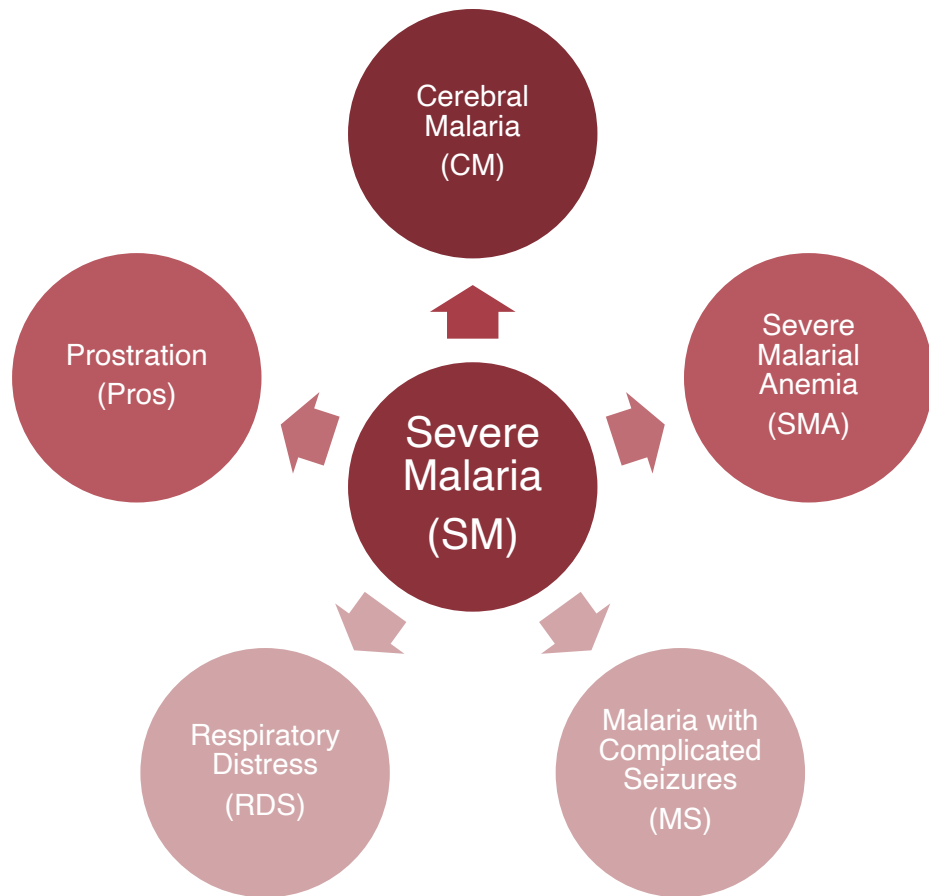
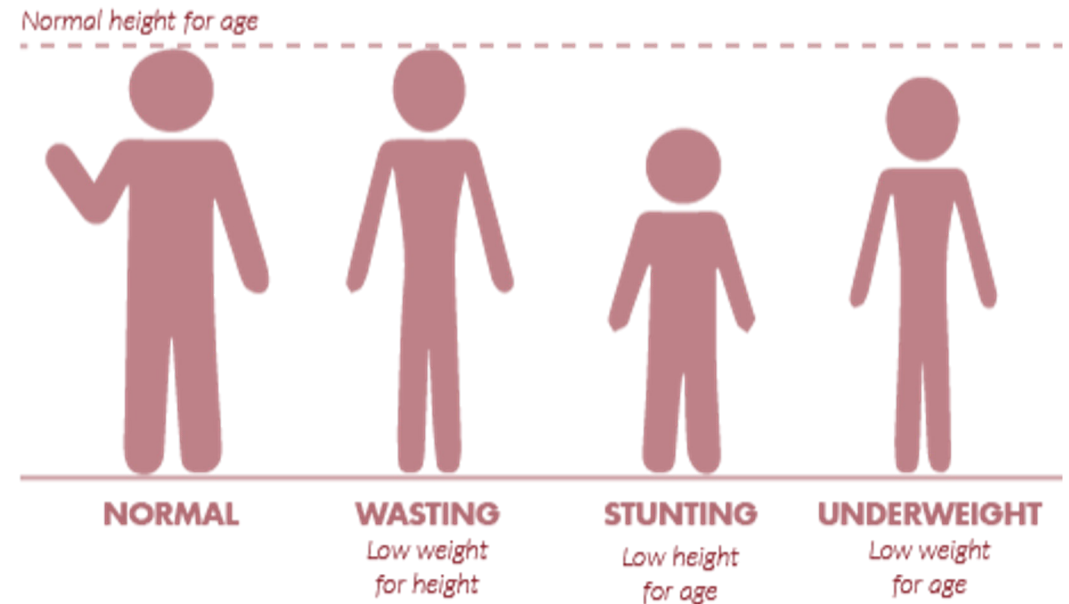INDIANA UNIVERSITY
SCHOOL OF MEDICINE
INDIANA MEDICAL STUDENT PROGRAM FOR RESEARCH AND SCHOLARSHIP

➢ **24 million children** are infected with *P. falciparum* each year in Sub-Saharan Africa.[1]

➢ In 2018, malaria produced an estimated **272,000 deaths** in children <5 years.[1]

➢ Worldwide, **67% of all malarial deaths** are among children <5 years.[1]

➢ Uganda carries **5%** of the global malaria burden.[1]

➢ **Undernutrition** is one of the most important risk factors associated with malaria.

BACKGROUND

Severe Malaria (SM):
- Cerebral Malaria (CM)
- Severe Malarial Anemia (SMA)
- Prostration (Pros)
- Respiratory Distress (RDS)
- Malaria with Complicated Seizures (MS)

DIFFERENT TYPES OF UNDERNUTRITION

Normal height for age

NORMAL

WASTING
Low weight for height

STUNTING
Low height for age

UNDERWEIGHT
Low weight for age

Source: World Vision (2015), "Definitions of hunger"

OBJECTIVES

➢ **AIM 1**: Establish whether Weight-for-Age, Height-for-Age, and Weight-for-Height Z-scores at enrollment and 12-month follow-up differ in Severe Malaria (SM) groups (CM, RDS, MS, SMA, and Pros) versus Community Controls (CC)

➢ **AIM 2**: Determine if nutritional markers differ in manifestations of malaria associated with Higher Mortality (CM and RDS) compared to groups with Lower Mortality (SMA, MS, and Pros)

➢ **AIM 3**: Compare nutritional markers by Mortality Status

Neurodevelopmental Outcomes in Children with Severe Malaria (NDI) Study Overview

- **Design:** Prospective longitudinal cohort study to assess neurodevelopmental outcomes in children with severe malaria

- **Location:** Mulago and Jinja, Uganda

- **Time points for nutritional markers:** Admission and 12-month follow-up

Cerebral Malaria (CM)

Coma (Blantyre coma score ≤2)
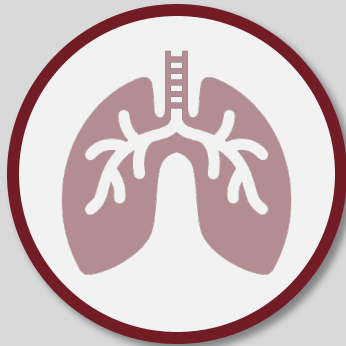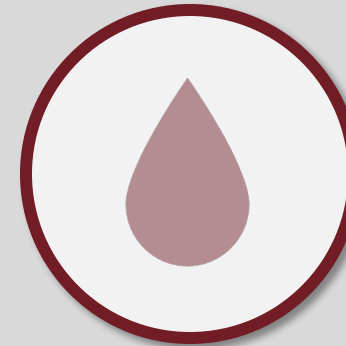
Respiratory Distress (RDS)

Deep acidotic breathing or lower chest wall retractions

No crepitations on pulmonary examination

Malaria w/ complicated seizures (MS)

Two or more generalized seizures in 24 hours, or seizure lasting >30 minutes in duration

Severe Malarial Anemia (SMA)

Serum hemoglobin ≤5 g/dL

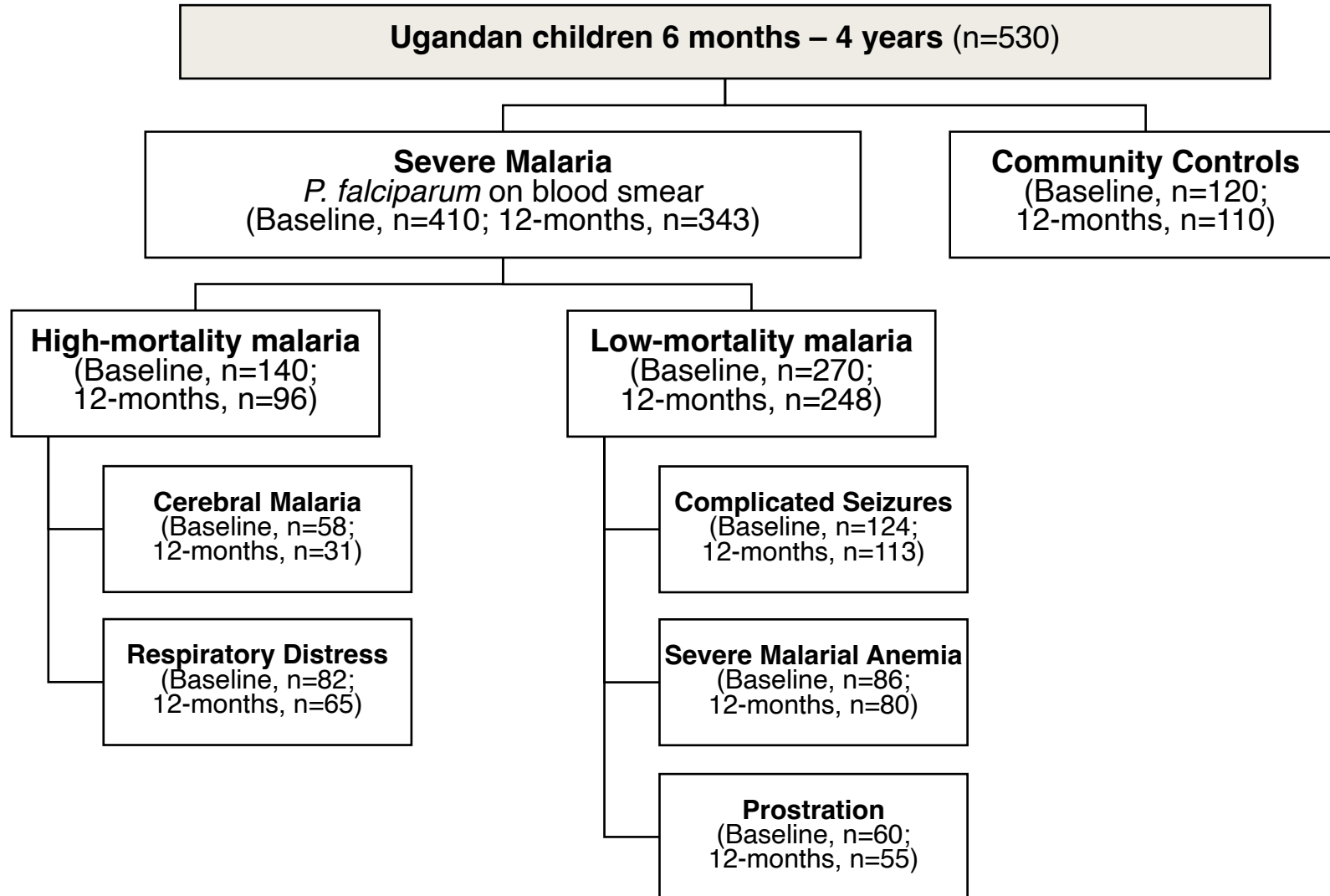**Prostration (Pros)**

In children ≥1 year-old, lost ability to sit unsupported or stand

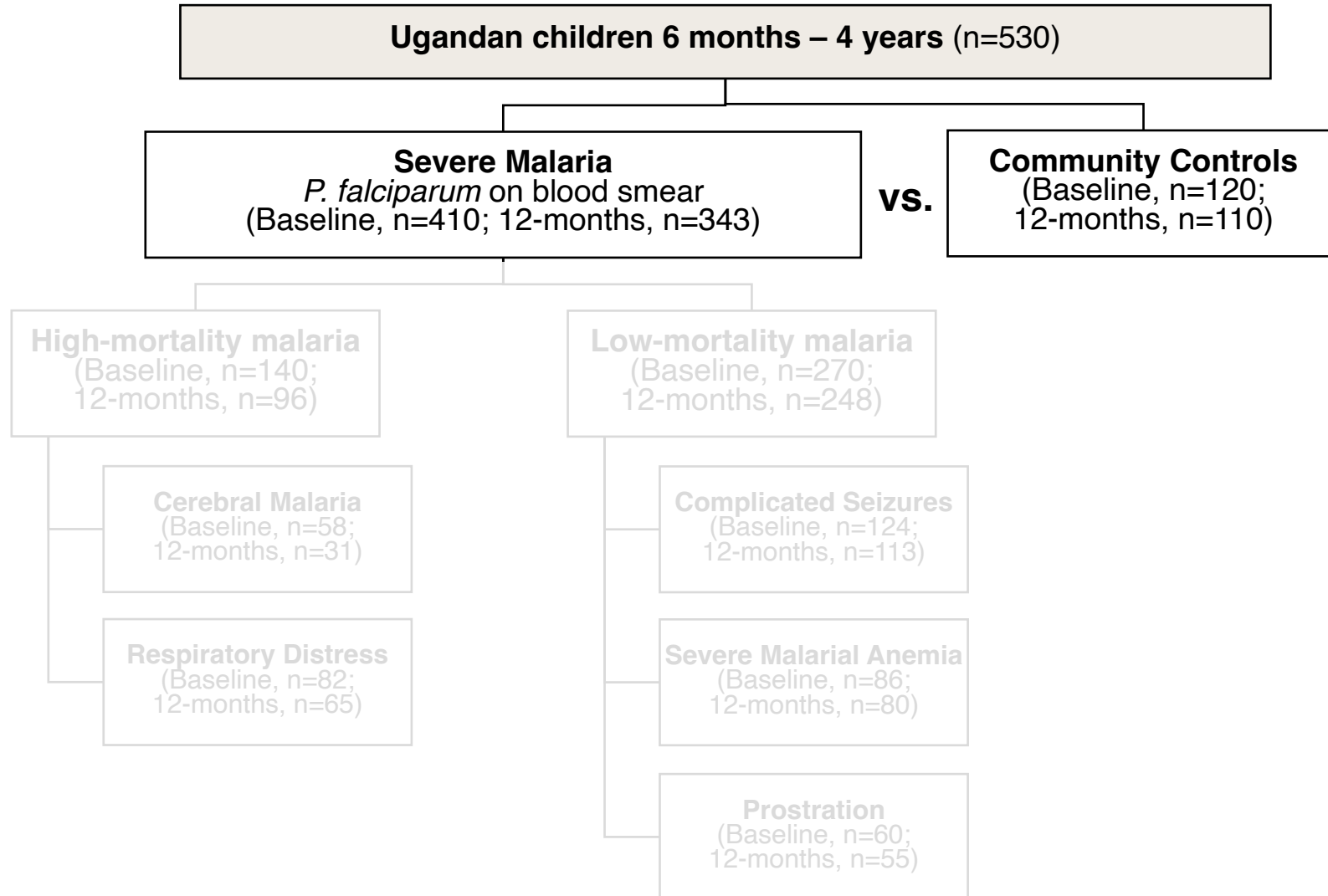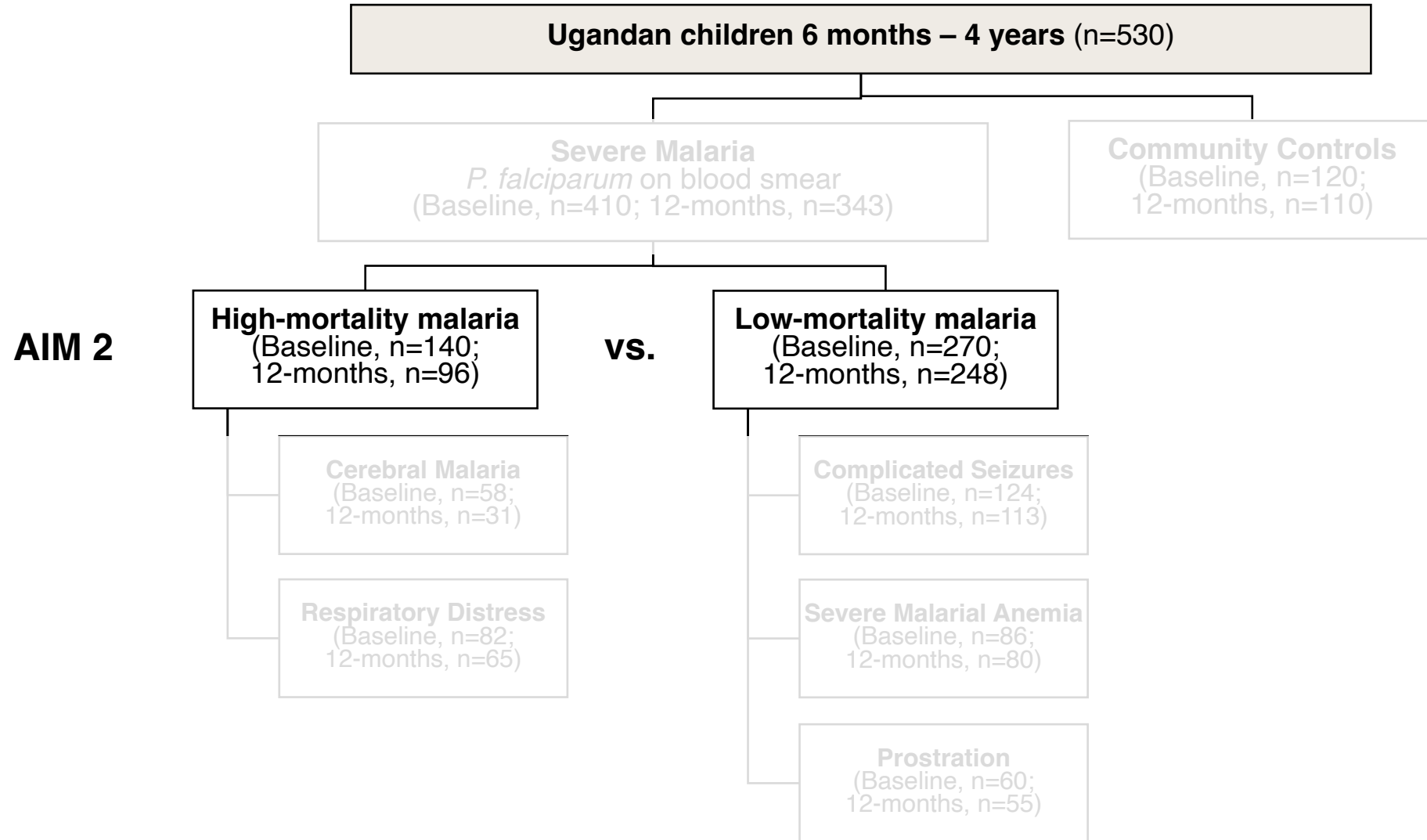In children <1 year-old, lost ability to drink or breastfeed

METHODS

METHODS

Ugandan children 6 months – 4 years (n=530)

Severe Malaria
P. falciparum on blood smear
(Baseline, n=410; 12-months, n=343)

AIM 1

vs.

Community Controls
(Baseline, n=120;
12-months, n=110)

High-mortality malaria
(Baseline, n=140;
12-months, n=96)

Low-mortality malaria
(Baseline, n=270;
12-months, n=248)

Cerebral Malaria
(Baseline, n=58;
12-months, n=31)

Respiratory Distress
(Baseline, n=82;
12-months, n=65)

Complicated Seizures
(Baseline, n=124;
12-months, n=113)

Severe Malarial Anemia
(Baseline, n=86;
12-months, n=80)

Prostration
(Baseline, n=60;
12-months, n=55)

STATISTICAL ANALYSIS

$$z^a = \frac{score - mean\ in\ CC}{SD\ in\ CC}$$

[a] Z-score is widely recognized as the most important descriptor for analysis and presentation of malnutrition data in children.

Nutritional Markers of Interest:
- *WAZ0* and *WAZ12*, Weight-for-Age Z-score at 0 and 12 months, <2SD is *underweight*
- *HAZ0* and *HAZ12*, Height-for-Age Z-score at 0 and 12 months, <2SD is *stunting*
- *WHZ0* and *WHZ12*, Weight-for-Height Z-score at 0 and 12 months, <2SD is *wasting*
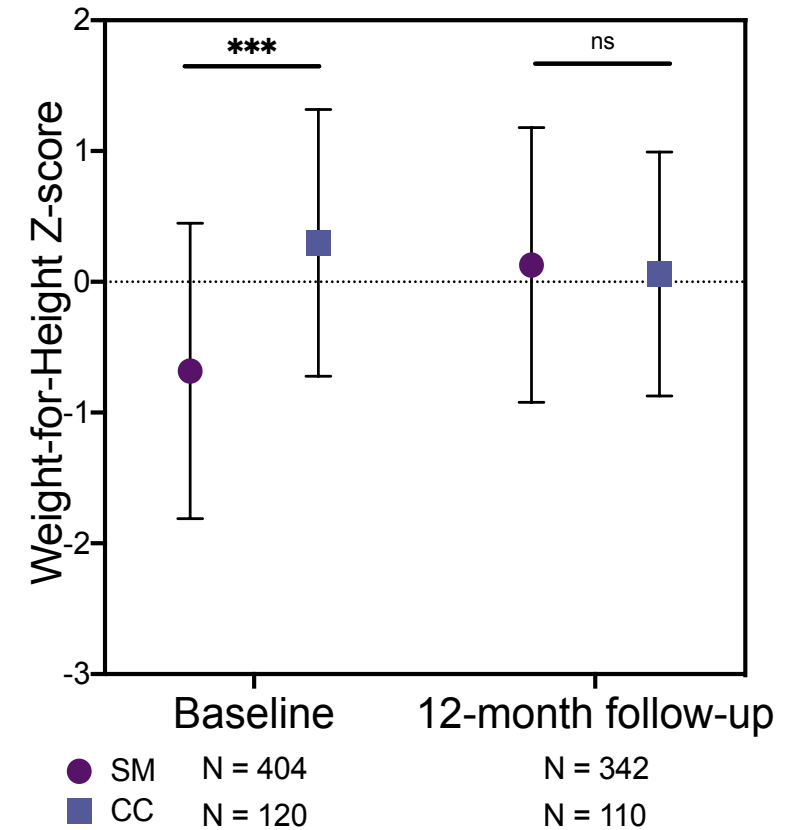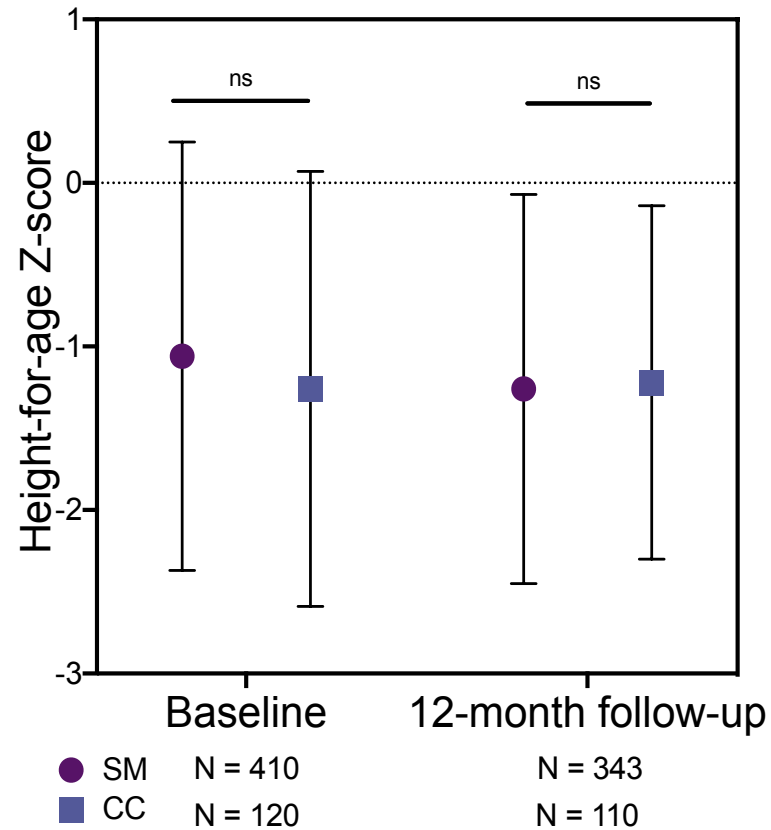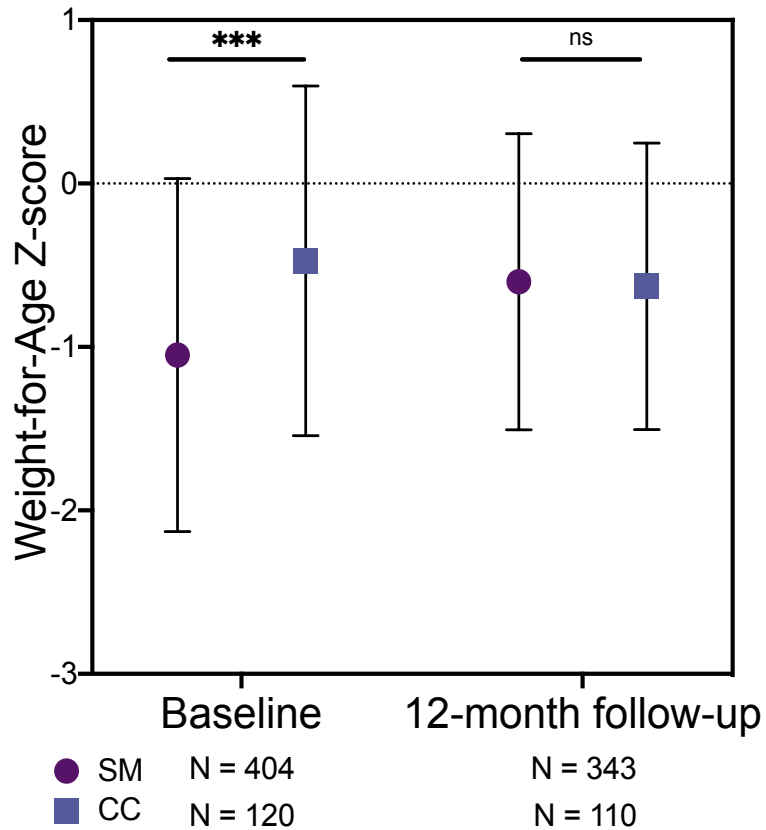
RESULTS

Table 1. Demographic characteristics of study children (N=530)

Characteristic	CM	RDS	MS	SMA	Pros	CC	Total
Sex, N (% female)	23 (40)	32 (39)	54 (44)	40 (47)	26 (43)	56 (47)	231 (44)
Age, Mean Years (SD)	2.33 (0.97)	1.77 (0.87)	2.16 (0.92)	2.00 (0.84)	2.20 (0.90)	2.20 (1.02)	2.11 (0.94)

DEMOGRAPHICS

WAZ and WHZ at baseline were significantly lower (p<0.001) among SM groups than in community controls (CC).

*p < .05, **p < .01, ***p < .001, ns not significant

WAZ and HAZ at baseline were significantly lower (p<0.01) among high mortality (HM) groups than in low mortality (LM) groups.
At 12-month follow-up, HAZ remained significantly lower (p<0.01) in HM vs. LM.
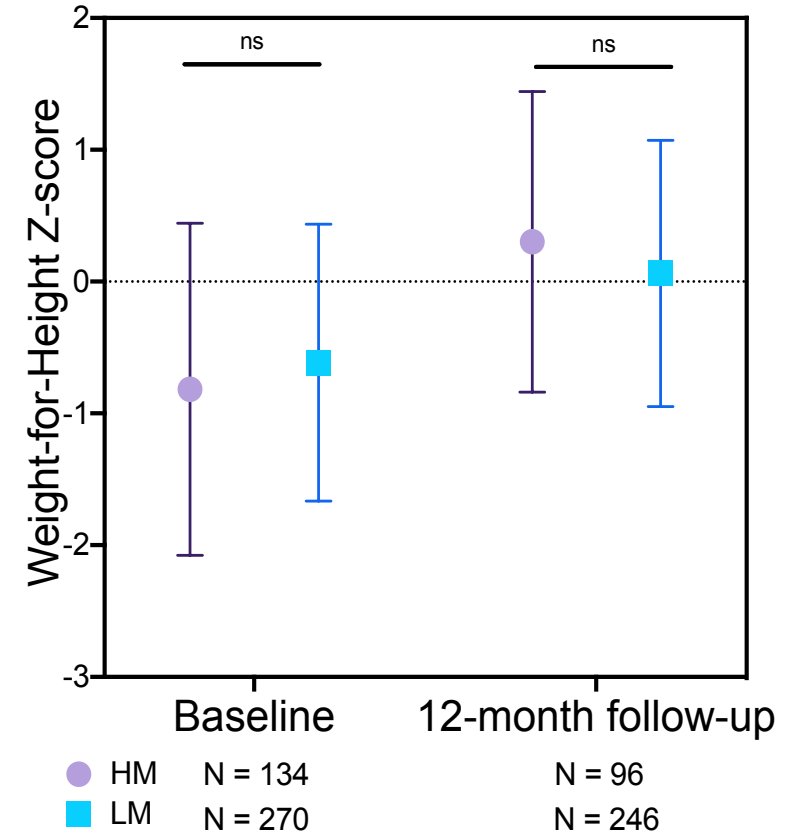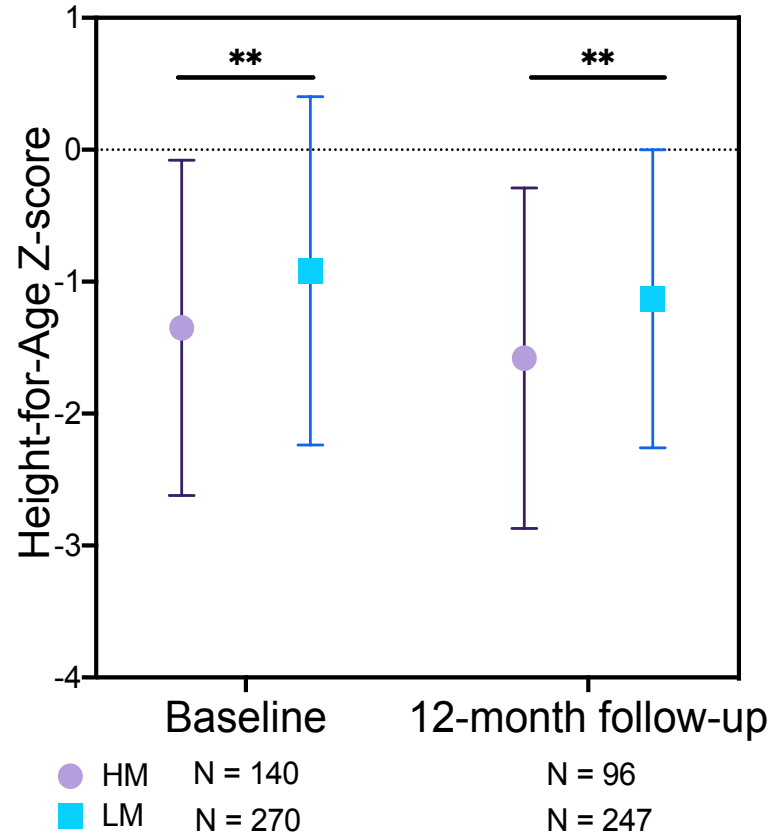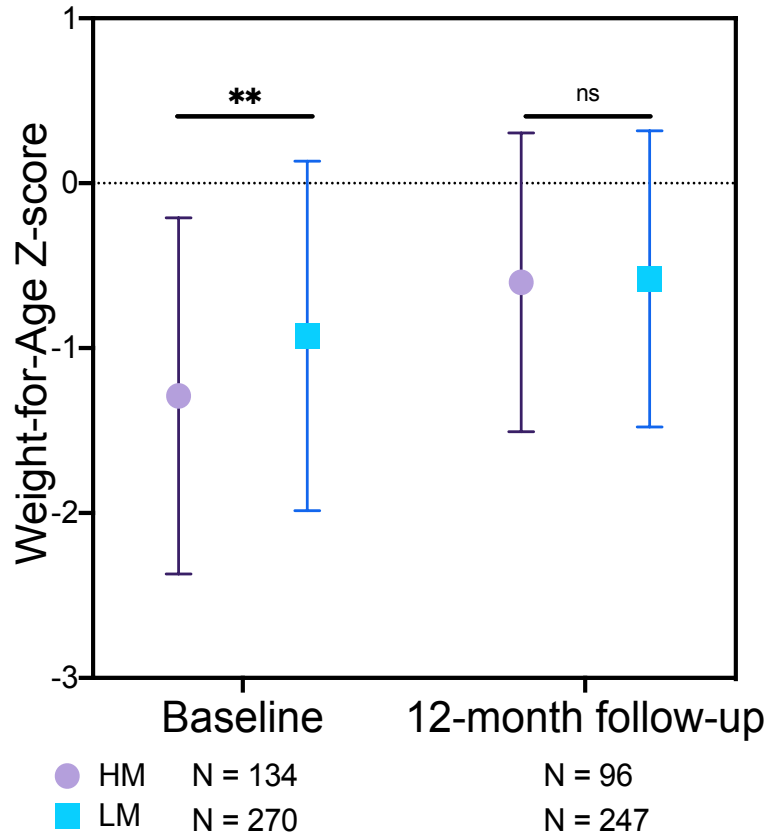
*p < .05, **p < .01, ***p < .001, ns not significant

Children who died at admission or following discharge (CM, N=20; RDS, N=7). had significantly lower WAZ (p<0.05) compared to those who survived.
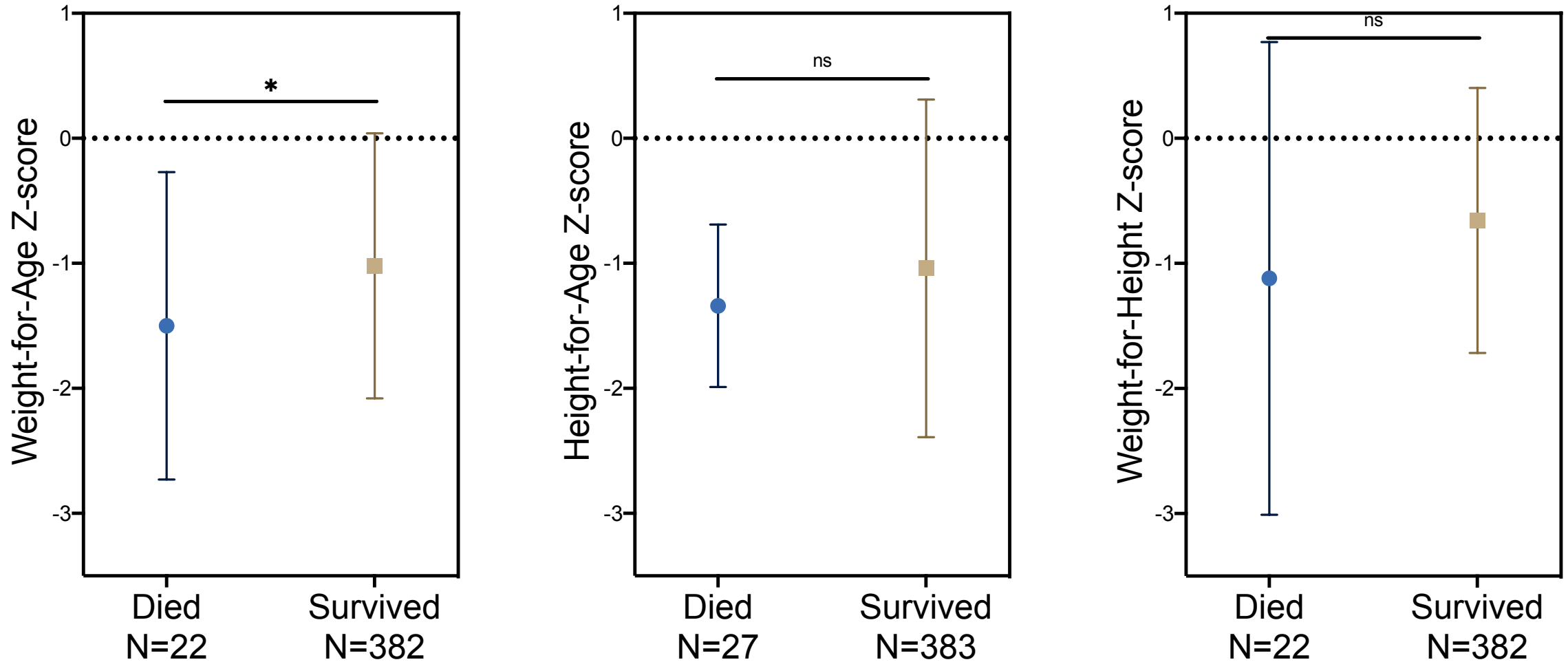
*p < .05, **p < .01, ***p < .001, ns not significant

DISCUSSION

WASTING
Low weight for height

STUNTING
Low height for age

UNDERWEIGHT
Low weight for age

↓ *WHZ*
(suggesting wasting)

At baseline, associated with **SM groups** (vs CC)

↓ *HAZ*
(suggesting stunting)

At baseline & follow-up, associated with **HM groups** (vs LM)

↓ *WAZ*
(suggesting underweight)

At baseline, associated with **SM groups** (vs CC), **HM groups** (vs LM), and **children who died**

These findings are substantiated by other studies on malnutrition and malaria:

Malaria as a Causal Agent for Malnutrition:

In Ethiopia, previous exposure to *P. falciparum* infection was a predictor for the manifestation of malnutrition in children <5, and children previously exposed to malaria were **1.87 times more likely to be malnourished** than children unexposed to malaria (Gone et al., 2017).

A study of *P. vivax* in the Brazilian Amazon suggested that children who had previously suffered malaria episodes presented **worse anthropometric parameters**, notably **reduced linear velocity** (Alexandre et al., 2015).

In Niger, children with malaria infection at admission and subsequently treated with an artemisinin-based combination therapy had reduced height gain, at -0.002 mm/day. **Malaria infection may impair height gain** (Oldenberg et al., 2018).

Malnutrition as a Causal Agent for Malaria:

Stunting, but not wasting, has been shown to be significantly associated with **down-regulation of the anti-*P. falciparum* antibodies** in pre-school children in Senegal, thereby modulating the overall immune response and increasing risk of infection (Fillol et al., 2009).

# These findings conflict with older studies on malaria and stunting:

Stunting as a Protective Agent Against Malaria:

A study from Papua New Guinea found that **stunting decreased susceptibility to malaria-related morbidity in children**. They proposed that parasites cannot proliferate in a host that is protein-deprived; therefore, there may be potentially beneficial effects of micronutrient deficiencies, particularly vitamin E and riboflavin (Genton et al., 1998).

However, we have shown that **stunting was the only nutritional parameter that remained significantly lower in HM groups at the 12-month follow-up**.

There exists a complex relationship between malnutrition and severe malaria (Schiable et al., 2007)
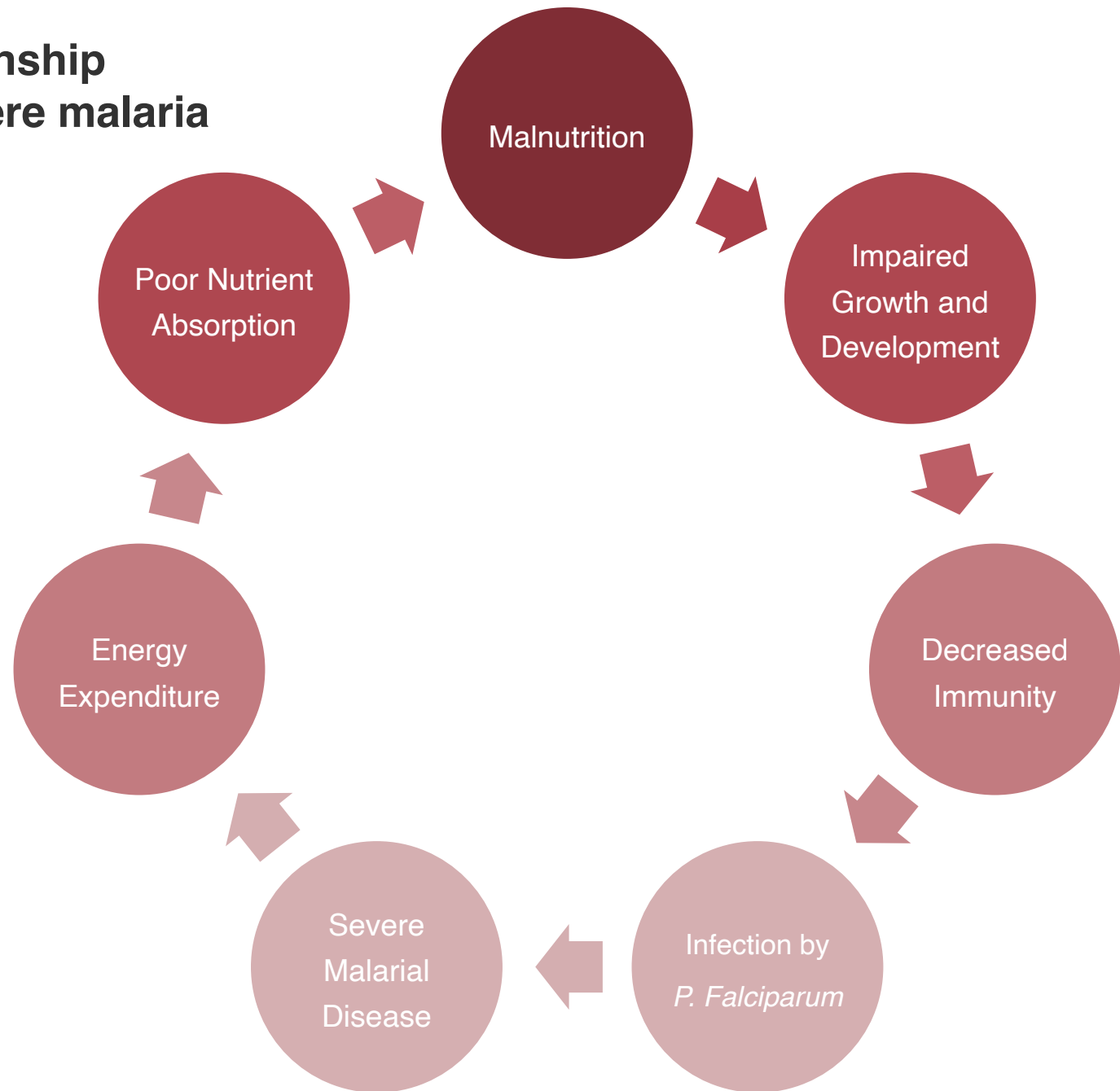
CONCLUSIONS

➢ Underweight, stunting, and wasting may be risk factors for severe malaria.

➢ Overall, improving nutritional status among children in Uganda is necessary to prevent malnutrition, to combat child mortality, and to reduce the global disease burden caused by severe malaria.

➢ Future directions include studying undernutrition as a causative risk factor for development of severe malaria by isolating children who acquired malaria during the study.

ACKNOWLEDGEMENTS

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APPENDIX

Blantyre coma score

|	Score
Eye movement	
Watches or follows	1
Fails to watch or follow	0
Best motor response	
Localizes painful stimulus	2
Withdraws limb from painful stimulus	1
No response or inappropriate response	0
Best verbal response	
Cries appropriately with pain, or, if verbal, speaks	2
Moan or abnormal cry with pain	1
No vocal response to pain	0
Total	

Fully conscious children score 5; children who do not respond to painful stimuli score 0. Response to pain should be assessed via firm nailbed pressure, sternal pressure, and pressure over the supraorbital ridge. Blantyre coma score ≤2 is associated with mortality.

Molyneux, ME, Taylor, TE, Wirima, JJ, Borgstein, A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. Q J Med 1989; 71:441.

Figure 4a. Nutritional markers according to disease group at baseline
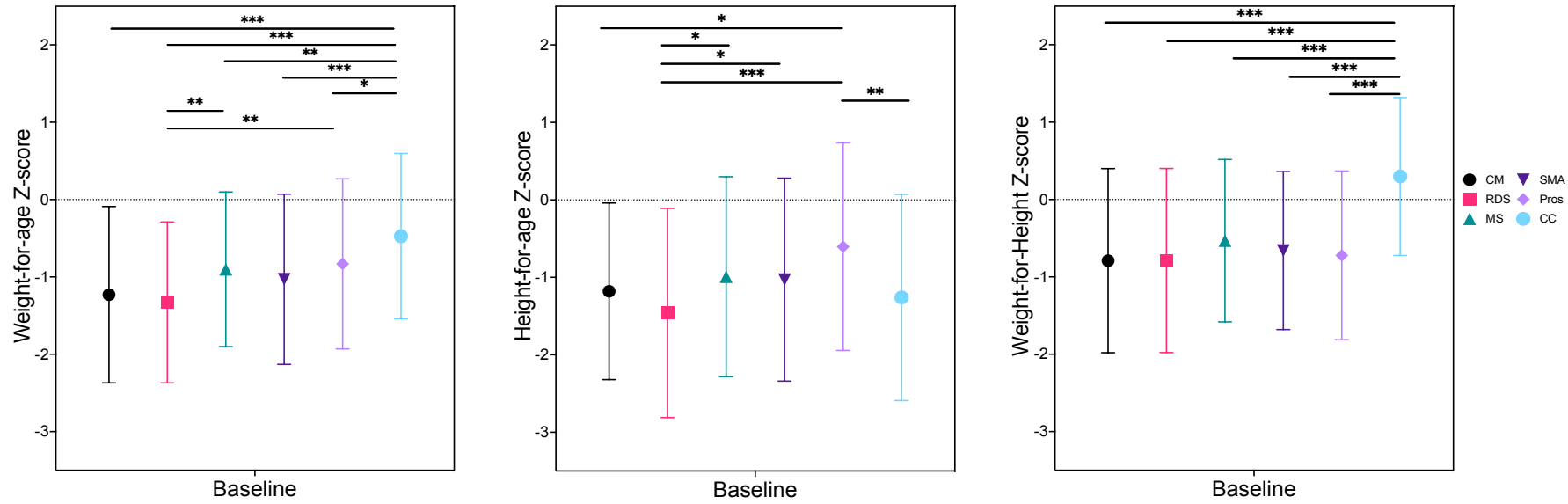
Figure 4b. Nutritional markers according to disease group at 12 months
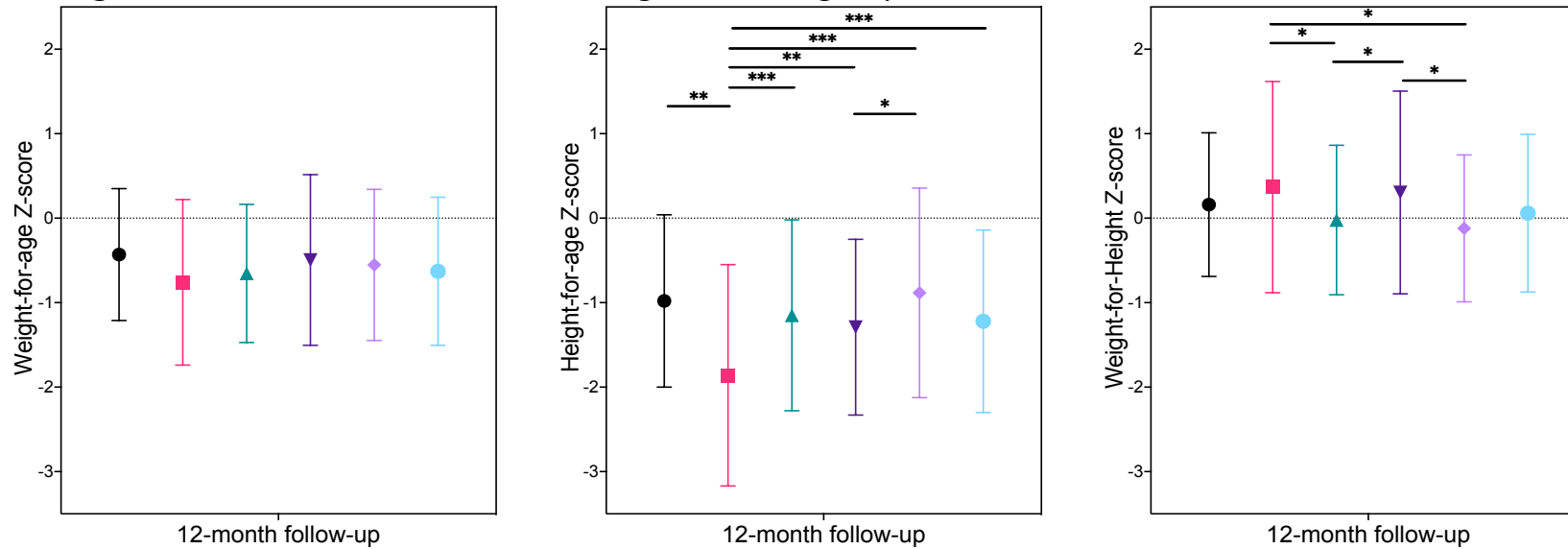
*p < .05, **p < .01, ***p < .001

Table 2a. Nutritional markers according to disease group at baseline

| Mean (SD) (N) | Severe malaria (SM) groups | | | | | CC N=120 |
| | Higher Mortality (HM) groups | | Lower Mortality (LM) groups | | | |
	CM N=58 [a]	RDS N=82 [a]	MS N=124	SMA N=86	Pros N=60	
Weight-for-age z-score, baseline	-1.23 (1.14) (54)	-1.33 (1.04) (80)	-0.901 (1.00)	-1.03 (1.10)	-0.831 (1.10)	-0.473 (1.07)
Height-for-age z-score, baseline	-1.18 (1.14) (58)	-1.46 (1.35) (82)	-0.992 (1.29)	-1.03 (1.31)	-0.604 (1.34)	-1.26 (1.33)
Weight-for-height z-score, baseline	-0.790 (1.19) (54)	-0.789 (1.19) (80)	-0.531 (1.05)	-0.660 (1.02)	-0.722 (1.09)	0.298 (1.02)

a For variables for which N is less than the total N listed for group, N's for that variable and group are noted in table

Table 2b. Nutritional markers according to disease group at 12 months

| Mean (SD) (N) | Severe malaria (SM) groups | | | | | CC N=110 |
| | Higher Mortality (HM) groups | | Lower Mortality (LM) groups | | | |
	CM N=31	RDS N=65	MS N=113 [a]	SMA N=80 [a]	Pros N=55	
Weight-for-age z-score, 12-months	-0.431 (0.781)	-0.76 (0.980)	-0.654 (0.818) (113)	-0.495 (1.01) (79)	-0.553 (0.894)	-0.629 (0.876)
Height-for-age z-score, 12-months	-0.98 (1.02)	-1.86 (1.31)	-1.15 (1.13) (112)	-1.29 (1.04) (80)	-0.884 (1.24)	-1.22 (1.08)
Weight-for-height z-score, 12-months	0.16 (0.85)	0.368 (1.25)	-0.022 (0.884) (112)	0.304 (1.20) (79)	-0.121 (0.870)	0.0592 (0.933)

a For variables for which N is less than the total N listed for group, N's for that variable and group are noted in table