

1 ***Schistosoma mansoni* infection as a Predictor of Low Aerobic**
2 **Capacity in Ugandan Children.**

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23 **ABSTRACT**

24 Using the 20-meter shuttle run test (20mSRT) as a morbidity metric, we assessed if
25 *Schistosoma mansoni* infection was associated with decreased aerobic capacity in Ugandan
26 children across a range of altitudes, either at low (~600m) or high (~1000m) altitudes. A total
27 of 305 children were recruited from six schools within the Buliisa district, Lake Albert,
28 Uganda. A subset (n=96) of these had been previously assessed and treated for
29 schistosomiasis +/- malaria two weeks prior. Fitness scores on the 20mSRT were translated
30 into VO₂max using a standardised equation. Unadjusted and multivariable-adjusted
31 analyses were performed using VO₂max as the primary outcome.

32 Analysis of fitness scores from 304 children, inclusive of the subset follow-up cohort,
33 revealed a median VO₂max of 45.4 mL kg⁻¹ min⁻¹ (IQR 42.9 - 48.0 mL kg⁻¹ min⁻¹). Children
34 residing at high altitudes demonstrated increased aerobic capacities (46.3 vs 44.8 mLkg⁻¹
35 min⁻¹, P = 0.031). The prevalence of stunting, wasting, *S. mansoni* egg patent infection,
36 malaria, giardiasis, anemia and fecal occult blood were 36.7%, 16.1%, 44.3%, 65.2%,
37 21.4%, 50.6%, and 41.2%, respectively. Median VO₂max was elevated in those previously
38 treated, compared with those newly recruited (46.3 mL kg⁻¹ min⁻¹ vs 44 mL kg⁻¹ min⁻¹, P <
39 0.001). Multivariable-adjusted analysis revealed a strong negative association between *S.*
40 *mansoni* egg patent infection and VO₂max at low altitude (beta coefficient -3.96, 95% CI -
41 6.56, -1.37, P = 0.004). This is the first study to document a negative association between *S.*
42 *mansoni* infection and aerobic capacity at low altitudes using the 20mSRT.

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50 INTRODUCTION

51 Intestinal schistosomiasis, as caused by infection with *Schistosoma mansoni*, is an
52 important contributor towards chronic morbidity in African children as measured by various
53 methodologies.^{1, 2, 3, 4, 5, 6, 7, 8, 9, 10} However, its impact upon diminished exercise tolerance is
54 not well explored. By contrast, the functional consequence of *Schistosoma haematobium*-
55 associated anemia has been assessed by the 20m shuttle run test (20mSRT) and validated
56 to provide an accurate correlate of aerobic capacity, the VO₂max (measured in mL kg⁻¹ min⁻
57 1).¹¹

58 The pathophysiological pathway underlying decreased physical fitness in children with
59 either form of schistosomiasis is complex, hinging upon immuno-pathological lesions and
60 generalised inflammatory responses.^{12, 13, 14} Anemia is a cause of decreased oxygen carrying
61 capacity and has been associated with both heavy and light *Schistosoma* infections in
62 childhood.^{1, 2, 4, 9, 15, 16, 17, 18, 19, 20, 21, 22} The predominant underlying mechanism seems to be
63 anemia of inflammation, involving pro-inflammatory cytokines including TNF-alpha and
64 Interleukin-6.^{23, 24, 25} Other mechanisms include ulcerative passage of eggs through the
65 intestinal wall causing extracorporeal blood loss, splenic sequestration and autoimmune
66 hemolysis.^{17, 26, 27}

67 Lake Albert in Western Uganda provides the optimum habitat for *Biomphalaria* snails,
68 the intermediate host for *S. mansoni*, making it a hub for *S. mansoni* transmission. Previous
69 studies have identified egg patent *S. mansoni* infection prevalences of up to 82% amongst
70 children aged 5-10 years living in the region.²⁸ Since 2004, the control of schistosomiasis-
71 related morbidity in Uganda has been centered upon the targeted, periodic distribution of
72 praziquantel therapy to school-aged children aged over 4 years and selected 'at risk' adult
73 populations.²⁹ Proxy markers of morbidity have since been evaluated, including faecal
74 occult blood, anemia, and faecal calprotectin testing, quality of life questionnaires, biometry,
75 clinical palpation and measurement, portable ultrasonography and fitness tests.^{12, 30, 31}

76 Previous studies investigating the relationship of *S. mansoni* infection with physical
77 fitness as measured by the 20mSRT have been inconclusive, limited by small sample sizes,

78 and have not compared or incorporated altitudinal effects.^{7, 8} Altitude acclimatization with an
79 associated increase in red blood cell volume may occur at altitudes as low as ~1000m.³²
80 This study aimed to determine whether *S. mansoni* infection was associated with decreased
81 aerobic capacity in Ugandan children living at low (~600m) or high (~1000m) altitudes. It was
82 hypothesised that *S. mansoni* infection would correlate with decreased aerobic capacity in
83 Ugandan children and that this association would be less pronounced in children living at
84 high altitude.

85

86 **METHODS**

87 **Ethics Statement & Eligibility Criteria**

88 Ethical approval was obtained from the London School of Hygiene & Tropical
89 Medicine (LSHTM) Ethics Committee (LSHTM number 12034), Liverpool School of Tropical
90 Medicine (LSTM) Masters Review Panel (M09-17), and the Vector Control Division, Ministry
91 of Health, Uganda (VCDREC-082). Children were considered eligible for enrolment if they
92 were aged 7-15 years, medically fit, had resided in a *S. mansoni*-endemic area for at least
93 two years, and could provide child assent.

94

95 **Study Setting & Population**

96 This study was carried out in six *S. mansoni*-endemic schools within the Buliisa
97 district of Lake Albert in Western Uganda: Biiso (latitude 41.4199, longitude 1.7606),
98 Busingiro (latitude 31.4475, longitude 1.7354), Bugoigo Islamic (latitude 31.4122, longitude
99 1.9000), Bugoigo Primary (latitude 31.4167, longitude 1.9089), Nyamukuta (latitude 31.4000,
100 longitude 1.8683), and Walukuba (latitude 31.3831, longitude 1.8425). Epidemiological data
101 previously collected within this region provided a useful foundation and thereby influenced
102 the selection of schools for our study.^{28, 33, 34} Buliisa is bordered by Nebbi (north), Masindi
103 (east), Hoima (south), and the Democratic Republic of Congo (west). Biiso and Busingiro lay
104 at altitudes of 1004m and 1062m respectively. The remainder of the schools lay adjacent to
105 Lake Albert with an altitude of 616m. The geographical proximities of the schools to the lake

106 shoreline are <1km for Bugoigo and Walukuba, and approximately 9km and 14km for Biiso,
107 and Busingiro, respectively. Egg patent *S. mansoni* infection prevalences among children
108 aged 5-10 years in the villages of Bugoigo, Walukuba, Biiso, and Busingiro have been
109 previously identified to be 36.7%, 82.0%, 19.7% and 8.0% respectively.²⁸ No transmission of
110 *Schistosoma haematobium* has been documented on parasitological surveys in the field of
111 study.^{28, 35}

112 The study involved 305 schoolchildren aged 7 to 15 years. Of the 305 schoolchildren,
113 a total of 96 children from Biiso, Busingiro, and Bugoigo Islamic schools were followed up
114 from two weeks prior. The team had performed an identical armory of parasitological
115 diagnostic tests, 20m-shuttle run testing, and had administered praziquantel, albendazole
116 and, if malaria-positive, artemether-lumefantrine therapy.

117 The study team was comprised of members from LSHTM, LSTM and the Vector
118 Control Division, Ministry of Health, Uganda. Subjects were enrolled following random
119 selection from the P2 to P6 class registers of each school over a 9-day period in June 2017.
120 For each village, community mobilisers assisted with community sensitisation prior to data
121 collection. Three of the six schools sampled had been recently sensitised by the preceding
122 LSTM team. Head teacher consent and written child assent were obtained. The information
123 sheets were translated into the local Alur dialect and distributed. The rationale for the study
124 was explained using a local translator.

125 Forty to sixty children were sampled per day. The principal investigator, a qualified
126 medical practitioner, assessed each child's general health prior to study participation. Each
127 child was assigned a unique study identification number which was written on a wristband to
128 be worn by the child during testing. They were asked a brief series of questions related to
129 their demographics, medical background, and previous praziquantel administration using
130 LSHTM Open Data Kit software on a tablet device (<http://opendatakit.lshtm.ac.uk/odk/>). The
131 frequency of mass drug administration with praziquantel at each school was recorded
132 following head teacher questioning.

133 Anthropometric Assessment

134 Assessment for stunting was performed using validated charts based on height-for-
135 age (HFA) Z-score: 'stunted' was defined as ≤ 2 to > 3 S.D. below the mean, and 'severely
136 stunted' was defined as ≤ 3 S.D. below the mean.³⁶ Calibrated measurements of weight and
137 height were obtained by trained field workers using standardised scales and a standardised
138 stadiometer, respectively. The height values obtained were for only a subset of the new
139 participants and were converted to HFA Z-scores according to a standardised reference.³⁷
140 Body mass index (BMI) was calculated for each child for whom height and weight were
141 obtained and converted to BMI-for-age (BFA) Z-scores according to a standardised
142 reference.³⁷ Results were recorded on the standardised data collection form.

143

144 20-meter Shuttle Run Test

145 Each participant undertook a 20-meter Shuttle Run Test (20mSRT).¹¹ The test was
146 performed in the school grounds on a clear and level playing field during school hours to
147 maximise convenience and minimise disruption to the school day program. Six to twelve
148 children were tested at any one time. For every four children, one observer was ascribed to
149 ensure adequate monitoring of their performance. Careful instructions were given using a
150 local translator and a brief demonstration of the test was performed by the principal
151 investigator prior to testing. All children were kept well hydrated, and water and sugary
152 snacks were made available.

153 Materials used included two pre-measured 20-meter ropes, markers, a microphone,
154 a portable speaker, and a tablet device with a relevant application for the 20mSRT (Bleep
155 Fitness Test, Aspectica Ltd). Coloured bibs were worn by the study participants for ease of
156 identification. Each fitness score was then translated into VO₂max (mL kg⁻¹ min⁻¹) using a
157 validated reference.¹¹

158 Field-Based Parasitological Diagnostic Testing & Treatment

159 A single urine specimen was obtained from each child and tested for the presence of
160 urine circulating cathodic antigen (urine-CCA; Rapid Medical Diagnostics, Pretoria, South
161 Africa). Urine-CCA has the advantage of detecting light intensity infections which may be
162 missed using the traditional Kato-Katz technique.³⁸ The test band reaction intensity was
163 semi-quantitatively graded as negative (-), trace positive (tr), single positive (+), double
164 positive (++) , and triple positive (+++).

165 The presence of *S. mansoni* infection was determined by duplicate Kato-Katz thick
166 fecal smears (each 41.7mg) prepared by trained field technicians in accordance with Katz et
167 al.³⁹ Kato-Katz examination indicates infection with mature, egg-shedding worms. The
168 technique was employed to provide further information into the level of egg excretion, which
169 is likely a proxy marker of bowel morbidity in addition to infection. Microscopy with a natural
170 light source was used for in-field interpretation on the day of testing. *S. mansoni* egg counts
171 and the number of eggs per gram (epg) of stool based upon the mean of the two specimens
172 were documented. Each fecal specimen was tested for the presence of *Giardia duodenalis*
173 infection using the Giardia/Cryptosporidium Quik Chek test (TECHLAB®, Inc.), and human
174 hemoglobin and transferrin using the Transferrin/FOB Combo Rapid Test Cassette
175 (Hangzhou AllTest Biotech co. Ltd.).

176 Capillary blood sampling was used to determine the total hemoglobin level
177 (HemoCue 201+, Angelholm, Sweden) and screen for malaria infection (Standard
178 Diagnostics BIOLINE Malaria Ag P.f./Pan, Alere, TM.). Follow-up children were not screened
179 for malaria, given the likelihood of persistent antigenemia following recent testing.

180 Of the new participants, those who tested positive for schistosomiasis on urine-CCA
181 and/or malaria were administered standardised therapy for schistosomiasis and/or malaria,
182 respectively in keeping with national guidelines. All participants were administered
183 albendazole therapy. Of the follow-up participants, only those who tested positive for urine-
184 CCA were administered praziquantel therapy, given their recent treatment by the preceding

185 team. No children were identified as being unwell or required referral to the local Level 2
186 health care facility.

187

188 [Data Management & Statistical Analysis](#)

189 All data collected was de-identified, entered into Microsoft Excel (Version 16.13.1) or
190 LSHTM Open Data Kit software, and stored on an encrypted USB device. Data analysis was
191 performed using STATA 14.2 on those for whom 20mSRT data was obtained. Separate
192 analyses of the entire cohort and of the follow-up participants were conducted. Descriptive
193 analyses with stratifications by school and altitude (low: ~600m, high: ~1000m) were
194 performed. Wilcoxon Rank Sum, Kruskal Wallis, Spearman's correlation, Chi-squared tests,
195 paired T test, and ANOVA were used to identify differences between schools and altitudes.
196 Linear regression was employed to determine the unadjusted associations between
197 independent covariates and the dependent variable, VO₂max (continuous). Independent
198 covariates of interest included egg patent *S. mansoni* infection (dichotomous), malaria
199 infection (dichotomous), fecal occult blood (ordinal), anemia (dichotomous), stunting based
200 on validated charts (dichotomous) and HFA Z-score ≤ 2 S.D. below the mean
201 (dichotomous), and wasting defined by BFA Z-score ≤ 2 S.D. below the mean
202 (dichotomous).^{29, 36, 37} Anemia was defined according to standardised cut-offs for age: <
203 11.5g dL⁻¹ (5 - 11y), < 12.0g dL⁻¹ (12 - 14y) and adjusted for altitude using the equation 'Hb
204 (g dL⁻¹) - 0.2g dL⁻¹' for an altitude approximating 1000m.⁴⁰ Logistic regression was used to
205 examine the unadjusted associations between the aforementioned covariates and
206 dependent variables of fecal occult blood, anemia and stunting (by validated charts).
207 Multivariable-adjusted linear regression was performed using VO₂max as the dependent
208 variable and multivariable-adjusted logistic regression analyses were undertaken using
209 anemia, fecal occult blood and stunting each as the dependent variable. Model selection
210 was performed using a stepwise procedure, followed by Akaike's Information Criterion (AIC)
211 as the model selection criterion. The model which minimised the AIC was selected. All
212 analyses were stratified by gender and altitude.

213

214 **RESULTS**215 **Participation**

216 Six schools within the Buliisa district were consecutively sampled: Biiso (n = 48),
217 Busingiro (n = 46), Bugoigo Islamic (n = 48), Bugoigo Primary (n = 61), Nyamukuta (n = 61),
218 and Walukuba (n = 40). Of the 305 children who participated, 304 completed the 20mSRT
219 and were included within the final analysis. Only one child did not complete the 20mSRT due
220 to a minor foot injury. Five children did not provide fecal samples and seven children did not
221 provide urine for testing. Malaria, capillary hemoglobin, and fecal occult blood were limited
222 by resource availability given the diversion of their use by the local clinic. Of 104 children
223 sampled at baseline, 96 children completed the 20mSRT at follow-up (92.3%) and were
224 included within the final analysis. The main reason for lack of follow-up was absence from
225 school on the day of testing (Table 1). The remaining 208 children included within the final
226 analysis were those newly recruited to the study.

227

228 **Descriptive Analyses**

229 The age, gender, and parasitology distributions were similar between schools, with
230 the exception of malaria (P = 0.003, Table 1, Figure 1). The prevalence of *S. mansoni* may
231 have been confounded by the variable distances of the schools from the lake. The
232 prevalence of *P. falciparum* malaria was significantly higher at 1000m compared with 600m
233 altitudes (P = 0.015, Table 2, Figure 1). Prevalence of *S. mansoni* by urine-CCA was highest
234 (80.5%), followed by *P. falciparum* (65.2%), *S. mansoni* by egg patency (44.3%), and
235 *Giardia duodenalis* infection (21.3%). All of the schools studied had received mass drug
236 administration with praziquantel within the preceding twelve months. Overall, 34.5% of
237 children were classified as anemic (n = 86/249) and 41.2% of children had fecal occult blood
238 in the stool. There were no differences in prevalence of anemia or fecal occult blood and
239 median hemoglobin between schools (Table 1).

240

241 **Anthropometrics & Nutritional Status**

242 Acute and chronic malnutrition were identified within all schools. Overall, 36.7% of
 243 children were stunted according to a height-for-age Z-score ≤ 2 S.D. below the mean (n =
 244 79/215) and 16.7% were stunted according to validated charts (n = 49/293). Of the latter, 1%
 245 were severely stunted based on a height-for-age score ≤ 3 S.D. below the mean (n = 3/293,
 246 Table 1).

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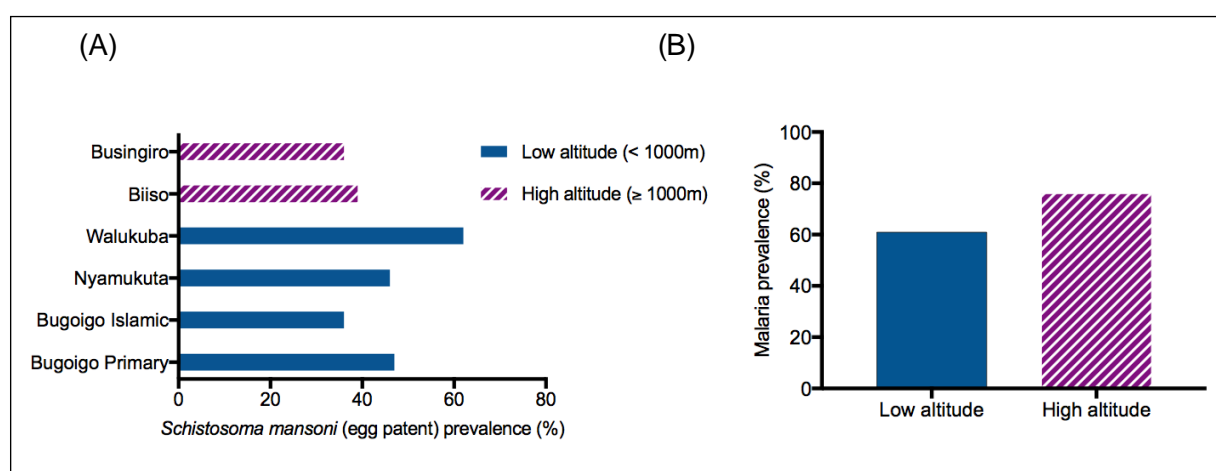
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255 *Figure 1: (A) Prevalence of egg patent S. mansoni infection according to school and altitude.*

256 *(B) Prevalence of malaria infection according to altitude.*

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258 **Performance in the 20mSRT**

259 Careful instructions and a test demonstration were provided prior to shuttle run
 260 testing. Overall, the 20mSRT was well understood with very few false starts and trips
 261 observed. If either occurred, a rest period was provided and testing was recommenced.
 262 Overall, median VO₂max was 45.4 mL kg⁻¹ min⁻¹ (IQR 42.9 – 48 mL kg⁻¹ min⁻¹) with higher
 263 values obtained by males compared with females (47.5 mL kg⁻¹ min⁻¹ vs 43.9 mL kg⁻¹ min⁻¹,
 264 P < 0.001, Table 1). Those children living at high altitude demonstrated a higher median
 265 VO₂max compared with those residing at low altitude (46.3 mL kg⁻¹ min⁻¹ vs 44.8 mL kg⁻¹
 266 min⁻¹, P = 0.031, S1 Table).

267 When compared with a Canadian cohort, males demonstrated lower VO₂max for all
268 ages.¹¹ Females demonstrated a lower VO₂max up until the age of 12 years, after which an
269 upward trend was observed. Figure 2 illustrates the differences between the Canadian and
270 study cohorts by age and gender, and incorporates data from a Kenyan cohort for
271 comparison.² Outliers at the ages of 7 years (n = 3) and 15 years (n = 3) were excluded (S3
272 Table).

TABLE 1: Demographic, Hematologic, Immunochemical, Parasitological & 20m-Shuttle Run Test Findings in Villages of the Buliisa District.

Parameter	Total (n = 304)	Biiso (n = 48)	Bugoigo Islamic (n = 48)	Bugoigo Primary (n = 61)	Busingiro (n = 46)	Nyamukuta (n = 61)	Walukuba (n = 40)	P Value*
DEMOGRAPHY								
Median age in years (interquartile range)	11 (10-12.5)	11.5 (10-12.5)	11 (9-12)	11 (10-13)	11 (9-12)	10 (10-12)	12 (10-13)	0.091
% Female (n)	49.7 (151/304)	50.0 (24/48)	50.0 (24/48)	49.2 (30/61)	47.8 (22/46)	50.8 (31/61)	50.0 (20/40)	1.000
ANTHROPOMETRY								
Median height in centimeters (interquartile range)	134 (128.5-140.5)	130.5 (126.4-137.5)	133.5 (127.7-142.2)	135.2 (127.6-141.7)	134 (129.6-139)	136 (131.0-139.5)	140.5 (131.1-145.2)	0.186
% Stunted by HFA Z- score (n)**	36.7 (79/215)	41.2 (14/34)	51.4 (19/37)	43.2 (19/44)	17.2 (5/29)	29.4 (15/51)	35.0 (7/20)	0.064
% Stunted by validated charts (n)***	16.7 (49/293)	20.8 (10/48)	20.5 (9/44)	17.2 (10/58)	13.3 (6/45)	13.8 (8/58)	15.0 (6/40)	0.333
% Stunted (n)	15.7 (46/293)	20.8 (10/48)	20.5 (9/44)	15.5 (9/58)	13.3 (6/45)	13.8 (8/58)	10.0 (4/40)	
% Severely stunted (n)	1.0 (3/293)	0.0 (0/48)	0.0 (0/44)	1.7 (1/58)	0.0 (0/45)	0.0 (0/58)	5.0 (2/40)	
Median body mass index (interquartile range)	16.1 (14.8-17.3)	14.8 (13.2-16.3)	N/A	16.0 (14.7-17.2)	N/A	16.2 (15.2-17.5)	N/A	0.652
% Wasted (n)****	11.8 (8/68)	0.0 (0/2)	N/A	11.1 (4/36)	N/A	13.3 (4/30)	N/A	0.838
HAEMATOLOGY								
Median hemoglobin in g dL ⁻¹ (interquartile range)#	12.0 (11.4-12.7)	12.0 (11.4-12.6)	12.2 (11.4-12.8)	11.8 (11.2-12.4)	12.1 (11.3-12.8)	12.3 (11.5-13)	12 (11.5-12.5)	0.274
% Anemic (n)*****#	34.5 (86/249)	41.0 (16/39)	33.3 (12/36)	44 (22/50)	35.1 (13/37)	21.2 (11/52)	34.3 (12/35)	0.232
IMMUNOCHEMICAL								
% Fecal occult blood test positive	41.2 (61/148)	46.9 (15/32)	44.0 (11/25)	32.0 (8/25)	27.3 (6/22)	48.2 (13/27)	47.1 (8/17)	0.489
PARASITOLOGY								
Schistosomiasis								
% <i>S. mansoni</i> infection by urine-CCA (n)~	80.5 (231/287)	82.6 (38/46)	75.0 (33/44)	87.7 (50/57)	79.1 (34/43)	79.0 (45/57)	77.5 (31/40)	0.663
% Egg patent <i>S. mansoni</i> infection (n)~~	44.3 (127/288)	39.1 (18/46)	36.4 (16/44)	46.6 (27/58)	35.7 (15/42)	45.8 (27/59)	61.5 (24/39)	0.163

Mean egg (95% confidence interval)~~	449.5 (330.1-568.9)	215.2 (108.1)	568.6 (156.2-981.1)	430.4 (170.9-690.0)	505.8 (202.6-809.1)	505.8 (202.6-809.1)	656.3 (284.5-1028.1)	0.241
<i>S. mansoni</i> intensity~~								
% Negative (n)	55.9 (161/288)	60.9 (28/46)	63.6 (28/44)	53.5 (31/58)	64.3 (27/42)	54.2 (32/59)	38.5 (15/39)	
% Light (n)	10.1 (29/288)	4.4 (2/46)	9.1 (4/44)	13.8 (8/58)	7.1 (3/42)	10.2 (6/59)	15.4 (6/39)	
% Medium (n)	11.8 (34/288)	13.0 (6/46)	6.8 (3/44)	8.6 (5/58)	14.3 (6/42)	13.6 (8/59)	15.4 (6/39)	
% Heavy (n)	22.2 (64/288)	21.7 (10/46)	20.5 (9/44)	24.1 (14/58)	14.3 (6/42)	22.0 (13/59)	30.8 (12/39)	
Malaria								
% Malaria (n)^	65.2 (122/187)	88.9 (24/27)	82.6 (19/23)	65.9 (29/44)	63.0 (17/27)	43.2 (16/37)	58.6 (17/29)	0.003
% <i>P. falciparum</i> (n)	65.2 (122/187)	88.4 (24/27)	82.6 (19/23)	65.9 (29/44)	63.0 (17/27)	43.2 (16/37)	58.6 (17/29)	0.008
% Mixed (n)	11.2 (21/187)	18.5 (5/27)	8.7 (2/23)	15.9 (7/44)	7.4 (2/27)	8.1 (3/37)	6.9 (2/29)	0.648
Giardiasis								
% <i>Giardia duodenalis</i> infection (n)^^	21.4 (63/294)	14.9 (7/47)	14.9 (7/47)	18.6 (11/59)	25 (11/44)	23.3 (14/60)	35.1 (13/37)	0.193
20m-SHUTTLE RUN TEST								
Median VO2max in mL kg ⁻¹ min ⁻¹ (interquartile range)	45.4 (42.9-48.0)	45.7 (43.9-47.9)	46.0 (43.6-48.9)	45.4 (43.0-47.5)	47.0 (42.9-49.5)	45.4 (43.8-47.5)	42.1 (40.8-45.0)	< 0.001
Males	47.5 (43.9-49.0)	47.5 (45.5-49.2)	48.4 (45.9-50.4)	46.3 (44.8-49)	48.0 (46.4-50.0)	47.25 (43.8-49.7)	43.2 (41.7-46.4)	0.005
Females	43.9 (41.5-46.3)	44.6 (42.9-45.7)	43.9 (41.8-46)	43.9 (41.5-47.0)	43.9 (42.9-47.5)	44.8 (42.9-46.3)	41.5 (39.9-43.8)	0.100

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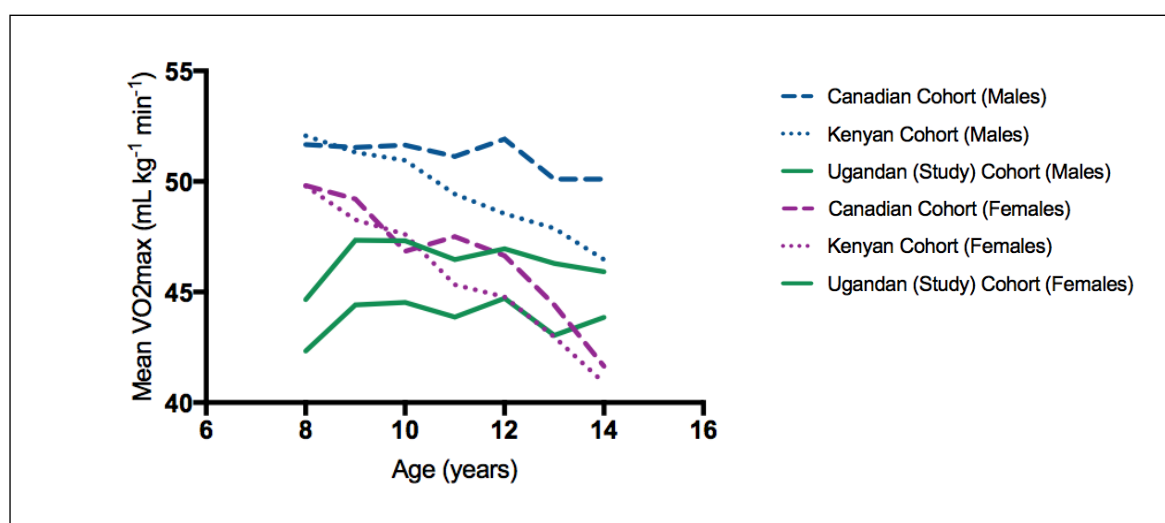
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*Indicates significance of differences among the villages by Kruskal-Wallis or Chi-squared analysis, paired T test or ANOVA. Statistically significant differences ($P \leq 0.05$) indicated in **bold**. **As defined by height-for-age Z-scores ≤ 2 S.D. below mean.³⁷ ***According to validated stunting charts based on height-for-age Z-score: 'stunted' ($\leq 2 - > 3$ S.D. below mean), 'severely stunted' (≤ 3 S.D. below mean).³⁶ ****As defined by BMI-for-age Z-scores ≤ 2 S.D. below mean.³⁷ *****As per standardised hemoglobin cut-offs for age: < 11.5 g/dL (5 - 11y), < 12.0 g/dL (12 - 14y). #Hemoglobin adjusted for altitude.⁴⁰ ~As per urine-cathodic circulating antigen testing. ~~As per dual Kato-Katz examination. Intensity defined by egg: 1 - 99 = light; 100 - 399 = medium, ≥ 400 = heavy.²⁹ ^As per malaria rapid diagnostic testing. ^^As per Giardia/Cryptosporidium Quik Chek test.

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295 Figure 2. Comparison of mean VO₂max between Ugandan (study), Kenyan & Canadian
 296 cohorts by gender & age (Canadian & Ugandan data sourced from Leger et al. & Bustinduy et
 297 al., respectively).^{2, 11}

298

299 Associations between Infection, Nutritional Status, & Aerobic Capacity

300 Unadjusted and multivariable-adjusted analyses examining VO₂max as an outcome
 301 were performed using linear regression. Covariates studied included *S. mansoni* egg patent
 302 infection, fecal occult blood, malaria and stunting (based on validated charts). The analyses
 303 were stratified by gender due to the differences in aerobic capacity between males and
 304 females (S3 Table), and by altitude for the purposes of this study. Model selection was
 305 performed using a stepwise procedure, followed by Akaike's Information Criterion (AIC) as
 306 the model selection criterion. The model with the lowest AIC was selected. Tables 2 and 3
 307 and S4 Table summarize these findings.

308 On unadjusted analysis, *S. mansoni* egg patent infection was a negative predictor of
 309 VO₂max (Coeff -1.28, 95% CI -2.20 – 0.36, P = 0.007). Increasing *S. mansoni* intensity of
 310 infection correlated with decreasing VO₂max (Coeff -0.496 95% CI -0.862 - -0.132, P <
 311 0.05). No other covariates demonstrated significant associations with VO₂max. The

312 correlation between *S. mansoni* egg patent infection and VO₂max remained when adjusted
313 for the presence of fecal occult blood, malaria, stunting (based on validated charts), and
314 anemia (Coeff -4.91, 95% CI -6.31 – 2.07, P < 0.001, Table 2). Similarly, for girls, *S.*
315 *mansoni* egg patent infection was associated with VO₂max on unadjusted (Coeff -1.91, 95%
316 CI -3.12 - -0.70, P = 0.002) and multivariable-adjusted (Coeff -5.04, 95% CI -8.80 - -1.28, P
317 = 0.011) analyses (S4 Table). For boys, no significant correlations with VO₂max were
318 identified. For schools residing at low altitudes, *S. mansoni* egg patent infection negatively
319 correlated with VO₂max on both unadjusted (Coeff -1.30, 95% CI -2.39 - -0.21, P = 0.02)
320 and multivariable-adjusted (Coeff -3.96, 95% CI -6.56 - -1.368, P = 0.004) analyses. For
321 schools residing at high altitude, malaria infection positively correlated with VO₂max on both
322 unadjusted (Coeff 2.83, 95% CI 0.49 – 5.17, P = 0.019) and multivariable-adjusted (Coeff
323 5.52, 95% CI 0.08 – 10.96, P = 0.047) analyses (Table 3).

324

325 [Associations between Infection, Anemia, Fecal Occult Blood, & Nutritional Status](#)

326 Logistic regression was used to explore the association between fecal occult blood,
327 anemia and stunting with infection status, with each covariate being recorded as
328 dichotomous variables. *S. mansoni* egg patent infection positively correlated with fecal occult
329 blood (OR 0.04, 95% CI 4.01 – 20.37, P < 0.05). *S. mansoni* egg patent infection was
330 positively associated with anemia on unadjusted analysis (OR 1.85, 95% CI 1.08 – 3.15, P =
331 0.02), as was fecal occult blood (OR 1.51, 95% CI 1.11 – 2.07, P = 0.01). Multivariable-
332 adjusted analysis revealed fecal occult blood to be the only positive predictor of anemia (OR
333 1.96, 95% CI 1.11 – 3.43, P = 0.02, S6 Figure).

334 Logistic regression was also used to analyse stunting (based on validated charts) as
335 an outcome. *S. mansoni* egg patent infection positively correlated with stunting (OR 2.49,
336 95% CI 1.30 - 4.77, P = 0.01) on unadjusted analysis, however this association did not
337 remain when adjusted for the presence of fecal occult blood, malaria, and anemia (OR 0.75,
338 95% CI 0.17 – 3.39, P = 0.71, S5 Table, S6 Figure).

339 TABLE 2: Linear Regression Models with VO2max as the Outcome.

	Unadjusted Analysis				Multivariable-adjusted Analysis			
	Coefficient	95% CI		P Value	Coefficient	95% CI		P Value
<i>S. mansoni</i> egg patent infection*	-1.279	-2.199	-0.360	0.007	-4.191	-6.312	-2.070	< 0.001
Fecal occult blood	-1.181	-0.767	0.404	0.542	0.404	-0.533	1.342	0.392
Malaria [^]	0.142	-1.057	1.341	0.815	-0.811	-2.824	1.203	0.424
Stunting [~]	-0.534	-1.650	0.583	0.348	-0.615	-2.934	1.704	0.598
Anemia [#]	-0.650	-1.663	0.363	0.208	0.364	-1.595	2.323	0.711

340

341 Statistically significant differences ($P \leq 0.05$) indicated in **bold**. *As per dual Kato-Katz examination. [^]As per342 malaria rapid diagnostic testing. [~]According to validated stunting charts based on height-for-age Z-score ≤ 2 S.D.343 below mean.³⁶ [#]As per standardised hemoglobin cut-offs for age: < 11.5 g dL⁻¹ (5 - 11y), < 12.0 g dL⁻¹ (12 - 14y).344 Hemoglobin adjusted for altitude.⁴⁰ For multivariable-adjusted analysis: n = 68. P Value = 0.009. R-squared =

345 0.2142. Adjusted R-squared = 0.1508. Akaike's Information Criterion = 373.447.

346

347 TABLE 3: Linear Regression Models with VO2max as the Outcome, Stratified by Altitude.

	Unadjusted Analysis				Multivariable-adjusted Analysis			
	Coefficient	95% CI		P Value	Coefficient	95% CI		P Value
<i>S. mansoni</i> egg patent infection*								
Low altitude	-1.299	-2.389	-0.208	0.020	-3.962	-6.556	-1.368	0.004
High altitude	-0.971	-2.712	0.770	0.271	0.452	-5.102	6.007	0.866
Fecal occult blood								
Low altitude	-0.610	-1.349	0.128	0.104	-0.226	-1.362	0.911	0.690
High altitude	0.592	-0.333	1.518	0.205	0.694	-1.094	2.482	0.424
Malaria [^]								
Low altitude	-0.938	-2.320	0.444	0.182	-2.121	-4.390	0.148	0.066
High altitude	2.832	0.494	5.170	0.019	5.524	0.084	10.964	0.047
Stunting [~]								
Low altitude	-0.448	-1.749	0.853	0.498	-0.126	-2.715	2.463	0.922
High altitude	-0.719	-2.875	1.438	0.510	-0.842	-6.230	4.547	0.746
Anemia [#]								
Low altitude	-0.924	-2.145	0.297	0.137	0.891	-1.418	3.201	0.440
High altitude	-0.326	-2.076	1.424	0.711	-1.834	-5.384	1.717	0.291

348

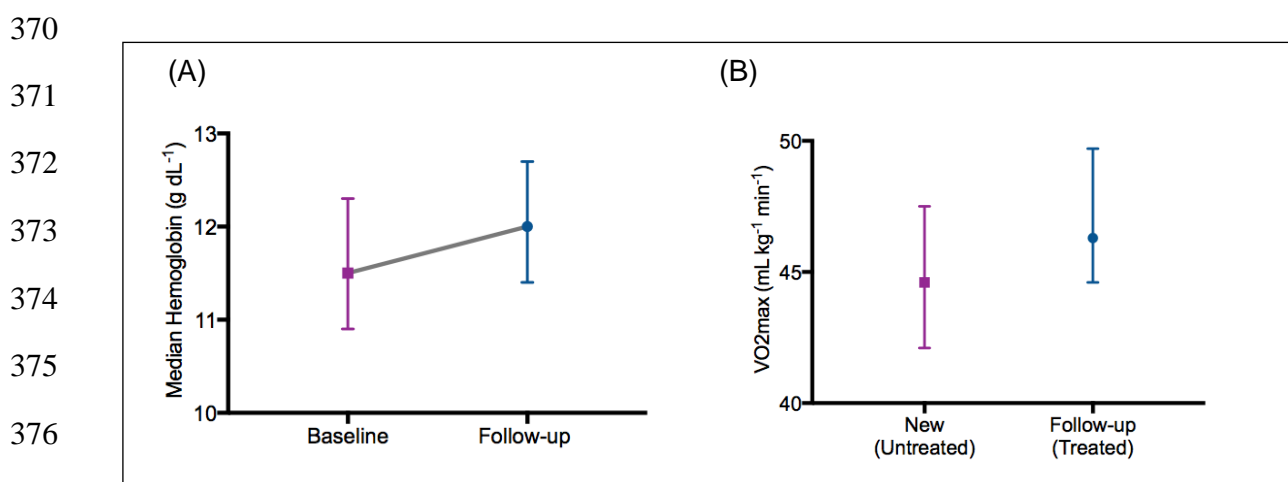
349 Statistically significant differences ($P \leq 0.05$) indicated in **bold**. *As per dual Kato-Katz examination. [^]As per350 malaria rapid diagnostic testing. [~]According to validated stunting charts based on height-for-age Z-score ≤ 2 S.D.351 below mean.³⁶ [#]As per standardised hemoglobin cut-offs for age: < 11.5 g dL⁻¹ (5 - 11y), < 12.0 g dL⁻¹ (12 - 14y).352 Hemoglobin adjusted for altitude.⁴⁰ For multivariable-adjusted analysis: **Low altitude: n = 45. P Value = 0.022.**

353 **R-squared = 0.277. Adjusted R-squared = 0.184. AIC = 246.900.** High altitude: n = 23. P Value = 0.202. R-
 354 squared = 0.326. Adjusted R-squared = 0.128. Akaike's Information Criterion = 125.111.
 355

356 Comparison between Baseline & Follow-up

357 The prevalence of egg patent *S. mansoni* infection was similar at baseline and follow-
 358 up (20.8% vs 25.0%, $P = 0.053$). Median hemoglobin was significantly higher at follow-up
 359 (10.7 g dL^{-1} vs 10.2 g dL^{-1} , $P < 0.001$, Figure 2). Similarly, the prevalence of anemia was
 360 lower at follow-up (69.3% vs 72.9%, $P = 0.001$), particularly for those residing at low altitude.
 361 There was no difference in the prevalence of fecal occult blood between the two timepoints
 362 (22.9% vs 31%, $P = 0.584$, S2 Table).

363 In those residing at low altitude, median VO_2max declined between baseline and
 364 follow-up ($47.0 \text{ mL kg}^{-1} \text{ min}^{-1}$ vs $48.7 \text{ mL kg}^{-1} \text{ min}^{-1}$, $P < 0.001$), however remained similar
 365 between the two time-points in those residing at high altitude ($46.3 \text{ mL kg}^{-1} \text{ min}^{-1}$ vs 46.3 mL
 366 $\text{kg}^{-1} \text{ min}^{-1}$, $P = 0.349$, S2 Table). Median VO_2max was higher in those who had been treated
 367 two weeks prior at baseline, compared with those who were newly recruited to the study
 368 ($46.3 \text{ mL kg}^{-1} \text{ min}^{-1}$, IQR 44.6 - 49.7 $\text{mL kg}^{-1} \text{ min}^{-1}$ vs $44 \text{ mL kg}^{-1} \text{ min}^{-1}$, IQR 42.1 - 47.5 mL
 369 $\text{kg}^{-1} \text{ min}^{-1}$, $P < 0.001$, Figure 3).



377
 378 Figure 3: (A) Median hemoglobin at baseline & follow-up. (B) Scatter plot of VO_2max for
 379 follow-up & new participants with median & interquartile range.

380

381 **DISCUSSION**

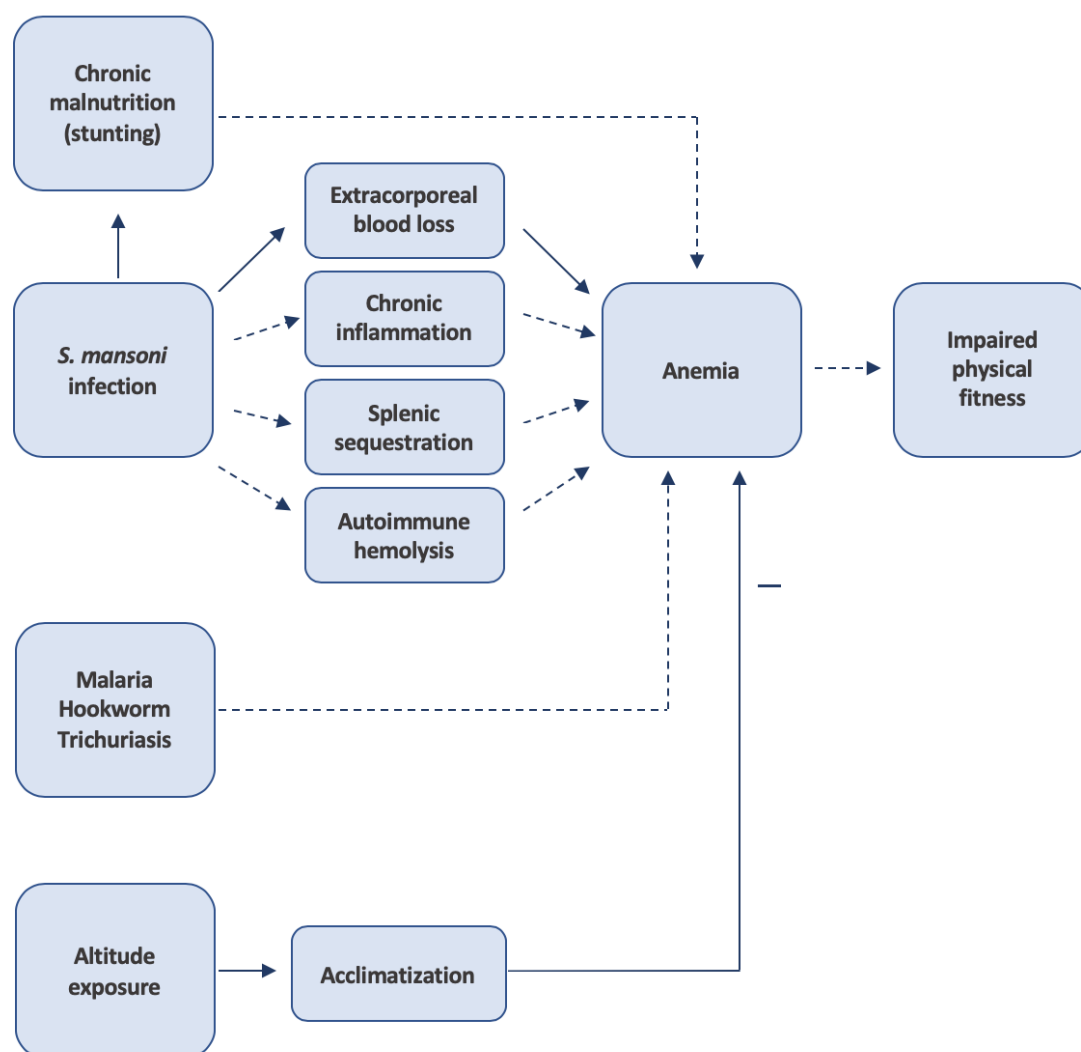
382 Chronic childhood morbidity secondary to *Schistosoma mansoni* infection has been
383 previously overshadowed by a lack of feasible morbidity metrics adaptable to the pediatric
384 population living within resource-poor settings. This study has shown that *S. mansoni* egg
385 patent infection is associated with decreased aerobic capacity in Ugandan schoolchildren,
386 with lower aerobic capacities seen in Ugandan compared with Canadian children. The
387 20mSRT proved to be a feasible and easily-implementable tool that may be harnessed for
388 the identification of *S. mansoni*-related morbidity within the school setting.

389 Negative correlations between all *S. mansoni* infection intensities and VO₂max were
390 found in our study, highlighting the important contribution of light intensity infections to *S.*
391 *mansoni*-related morbidity.^{3, 4} These findings were based on the traditional Kato-Katz
392 method which can miss up to 20-40% of active infections.⁴¹ However, in the presence of
393 infections of moderate-high intensity as was predominantly the case in this study, both urine-
394 CCA and parasitological examination maintain high levels of accuracy.⁴²

395 The pathway between *Schistosoma mansoni* infection and decreased aerobic
396 capacity is multifactorial and complex. Anemia is a known downstream effector of *S.*
397 *mansoni* infection and has been shown to be associated with decreased aerobic capacity.²
398 Fecal occult blood is a proxy marker of intestinal inflammation and mechanism for anemia in
399 *S. mansoni* infection.^{27, 30, 43} *S. mansoni* egg patent infection and fecal occult blood both
400 positively correlated with anemia in our study. Furthermore, *S. mansoni* egg patent infection
401 was linked with stunting; another known pathway for anemia causation in *S. mansoni*
402 infection.² Figure 4 integrates the findings of this study with current knowledge to suggest a
403 potential, albeit simplified, pathophysiological basis for reduced physical fitness in children
404 living in *S. mansoni*-endemic areas.

405 Previous studies have demonstrated a reduction in anemia, nutrition-related
406 morbidity, fecal occult blood and increase in physical performance following praziquantel
407 therapy.^{18, 24, 30, 34, 44, 45} A reassuring decline in the prevalence of anemia was noted in the
408 follow-up cohort after treatment for schistosomiasis at baseline. Furthermore, higher aerobic

409 capacities were seen in those who had been recently treated, compared with those who
 410 were newly recruited to the study, emphasizing the reversibility of functional morbidities. It is
 411 important to note however that disentangling chronic morbidity and the effects of
 412 interventions in low resource settings is a challenging task. Chronic morbidity is confounded
 413 by polyparasitic infections, nutritional deficiencies and numerous other factors, such as
 414 socioeconomic status and food scarcity, which were unable to be accounted for within the
 415 constraints of this study.^{3, 4, 5, 46, 47}



416
 417

418 *Figure 4: Conceptual pathway for impaired physical fitness in S. mansoni infection in children.*

419 *Note: broken arrows represent relationships described elsewhere.*

420

421 Those children residing at high altitude exhibited higher aerobic capacities compared
422 with those residing at low altitude. In the former, *S. mansoni* infection did not have a
423 negative effect on aerobic capacity. With increasing altitude, barometric pressure and
424 atmospheric partial pressure of oxygen decline, resulting in an increase in erythropoietin
425 production. This occurs via the release of hypoxia inducible factor-alpha. Erythropoietin
426 stimulates the bone marrow to increase iron turnover and production of nucleated red blood
427 cells, thereby increasing red blood cell mass.^{48, 49, 50} These adaptations may transpire at
428 altitudes as low as ~1000m.³² Such acclimatization may have dampened the deleterious
429 effect of *S. mansoni* infection upon aerobic capacity in the children living at a higher altitude.

430 This study has several limitations. The small sample size achievable within the time
431 frame has limited the strength of the inferences one can make from the findings, particularly
432 with regard to baseline and follow-up cohorts. Nevertheless, the sample size calculation
433 performed at the outset was achieved, and these findings provide a robust indication for
434 further investigation into the pathway linking *S. mansoni* infection with physical fitness in
435 children living in *S. mansoni*-endemic areas. In addition, testing resource availability was
436 limited due to the unforeseen need of the local clinic to use the resources for medical
437 indications. No specific method for ensuring the children reached their maximal aerobic
438 capacity was employed. Such methods are usually time-consuming and cumbersome and
439 were therefore purposely avoided as a means of maintaining the external validity of the
440 20mSRT as a school-based morbidity metric. The time period between baseline and follow-
441 up testing was brief, limiting the speculations one could make with regard to outcomes
442 following previous exposure to infection and treatment.

443 Areas requiring further investigation include: 1) the development of more rigorous
444 diagnostic tests capable of detecting light infections and demonstrating antigenic cure,
445 thereby illustrating treatment efficacy, 2) the innovation and application of feasible morbidity
446 metrics with the ability to identify sequelae of *S. mansoni* infections of all intensities, 3) the
447 degree of impact of various altitudes upon VO₂max and interplay of these associations with
448 parasitic infections and anemia, and 4) extended baseline-follow-up comparisons to

449 delineate the effects of treatment upon physical fitness within *S. mansoni*-endemic areas at
450 different altitudes.

451 This is the first study to document a relationship between *S. mansoni* infection and
452 decreased aerobic capacity at high and low altitudes. Altitude acclimatization may be
453 partially protective of this effect. Whilst the cause of impaired physical performance is
454 multifactorial, this study provides evidence to support the important contribution that *S.*
455 *mansoni* infection has toward childhood morbidity. The lower aerobic capacities seen in the
456 Ugandan children compared with Kenyan and Canadian children emphasize the inherent
457 need for morbidity assessment in children residing within *S. mansoni*-endemic areas.
458 Furthermore, a recent malacological survey identified schistosomiasis transmission in
459 regions with an altitude beyond 1400m, indicating the need for the geographical expansion
460 of morbidity assessment.^{35, 51, 52} Widespread deployment of the 20mSRT throughout school
461 settings represents a promising means by which schistosomiasis-related childhood morbidity
462 may be rapidly detected and managed appropriately within these areas.

463

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474

475 **DISCLOSURES REGARDING REAL OR PERCEIVED CONFLICTS OF INTEREST**

476 The authors of this paper have no conflicts of interest they wish to disclose.

477

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707 **SUPPORTING INFORMATION**

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709 S1 Table. Demographic, Hematologic, Immunochemical, Parasitological & 20m-Shuttle Run Test Findings in Villages of the Bulisa District at Low
710 Altitude Compared with High Altitude.

Parameter	Total (n=304)	Low Altitude (n=210)	High Altitude (n=94)	P Value*
DEMOGRAPHY				
Median age in years (interquartile range)	11 (10-12)	11 (10-13)	11 (10-12)	0.876
% Female (n)	49.7 (151/304)	50.0 (105/210)	48.9 (46/94)	0.864
ANTHROPOMETRY				
Median height in centimeters (interquartile range)	134 (128.5-140.5)	135.5 (128.7-142.1)	133 (127.6-137.6)	0.046
% Stunted by HFA Z-score (n)**	36.7 (79/215)	39.5 (60/152)	30.2 (19/63)	0.197
% Stunted by validated charts (n)***	16.7 (49/293)	16.5 (33/200)	17.2 (16/93)	0.450
% Stunted (n)	15.7 (46/293)	15.0 (30/200)	17.2 (16/93)	
% Severely stunted (n)	1.0 (3/293)	1.5 (3/200)	0.0 (0/93)	
Median body mass index (interquartile range)	16.1 (14.8-17.3)	16.1 (14.8-17.3)	14.8 (13.2-16.3)	0.435
% Wasted (n)****	11.8 (8/68)	12.1 (8/66)	0.0 (2/2)	0.600
HAEMATOLOGY				
Median hemoglobin in g dL ⁻¹ (interquartile range)#	11.6 (10.7-12.4)	12.1 (11.4-12.7)	12.0 (11.4-12.7)	0.739
% Anemic (n)#	34.5 (86/249)	33.0 (57/173)	38.2 (29/76)	0.426
IMMUNOCHEMICAL				
% Fecal occult blood test positive (n)	41.2 (61/148)	42.6 (40/94)	38.9 (21/54)	0.654
PARASITOLOGY				
Schistosomiasis				
% <i>S. mansoni</i> infection by urine-CCA (n)~	80.5 (231/287)	80.3 (159/198)	80.9 (72/89)	0.906
% Egg patent <i>S. mansoni</i> infection (n)~~	44.3 (127/288)	47.0 (94/200)	37.5 (33/88)	0.135
Mean epg (95% confidence interval)	449.5 (330.1-568.9)	527.2 (366.4-687.9)	273.1 (137.5-408.8)	0.133

<i>S. mansoni</i> intensity~~				
% Negative (n)	55.9 (161/288)	53.0 (106/200)	62.5 (55/88)	
% Light (n)	10.1 (29/288)	12.0 (24/200)	5.7 (5/88)	
% Medium (n)	11.8 (34/288)	11.0 (22/200)	13.6 (12/88)	
% Heavy (n)	22.2 (64/288)	24.0 (48/200)	18.2 (16/88)	
Malaria				
% Malaria (n)^	65.2 (122/187)	60.9 (81/133)	75.9 (41/54)	0.051
% <i>P. falciparum</i> (n)	65.2 (122/187)	60.9 (81/133)	75.9 (41/54)	0.015
% Mixed (n)	11.2 (21/187)	10.5 (14/133)	13.0 (7/54)	0.768
Giardiasis				
% <i>Giardia duodenalis</i> infection (n)^	21.4 (63/294)	22.2 (45/203)	19.8 (18/91)	0.128
20M-SHUTTLE RUN TEST				
Median VO ₂ max in mL kg ⁻¹ min ⁻¹ (interquartile range)	45.4 (42.9-48.0)	44.8 (42.1-47.5)	46.3 (43.4-48.7)	0.031
<i>Males</i>	47.5 (43.9-49.0)	46.4 (43.8-49.0)	47.9 (46.0-49.6)	0.078
<i>Females</i>	43.9 (41.5-46.3)	43.9 (41.5-45.7)	44.3 (42.9-46.3)	0.258

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*Indicates significance of differences among the villages by Kruskal-Wallis or Chi-squared analysis, paired T test or ANOVA. Statistically significant differences ($P \leq 0.05$) indicated in **bold**. **As defined by height-for-age Z-scores ≤ 2 S.D. below mean.³⁷ ***According to validated stunting charts based on height-for-age Z-score: 'stunted' ($\leq 2 - > 3$ S.D. below mean), 'severely stunted' (≤ 3 S.D. below mean).³⁶ ****As defined by BMI-for-age Z-scores ≤ 2 S.D. below mean.³⁷ #As per standardised hemoglobin cut-offs for age: < 11.5 g dL⁻¹ (5 - 11y), < 12.0 g dL⁻¹ (12 - 14y). Hemoglobin adjusted for altitude.⁴⁰ ~As per urine-cathodic circulating antigen testing. ~~As per dual Kato-Katz examination. Intensity defined by epg: 1 - 99 = light; 100 - 399 = medium, ≥ 400 = heavy.²⁹ ^As per malaria rapid diagnostic testing. ^As per Giardia/Cryptosporidium Quik Chek test.

720 S2 Table. Demographic, Hematologic, Anthropometric, Immunochemical, Parasitological &
 721 20m-Shuttle Run Test Findings in Baseline & Follow-up Cohorts.
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Parameter	Baseline (n=96)	Follow-up (n=96)	P Value*
DEMOGRAPHY			
Median age in years (interquartile range)	11 (9.5-12)	11 (9.5-12)	
Low altitude	11 (9-12)	11 (9-12)	
High altitude	11 (10-12)	11 (10-12)	
% Female (n)	51.0 (49/96)	51.0 (49/96)	
Low altitude	48.5 (16/33)	48.5 (16/33)	
High altitude	52.4 (33/63)	52.4 (33/63)	
HAEMATOLOGY			
Median hemoglobin in g dL ⁻¹ , adjusted (interquartile range)#	10.2 (9.6-11.7)	10.7 (9.7-12.1)	<0.001
Low altitude	11.8 (11.0-12.3)	12.5 (11.9-13.1)	<0.001
High altitude	11.5 (10.6-11.9)	112.0 (11.2-12.6)	<0.001
% Anemic, adjusted (n)#	47.9 (23/48)	69.3 (25/75)	0.001
Low altitude	42.9 (9/21)	20.8 (5/24)	0.002
High altitude	51.9 (14/27)	39.2 (20/51)	0.098
IMMUNOCHEMICAL			
% Fecal occult blood test positive	22.9 (11/48)	31.0 (18/58)	0.584
Low altitude	28.6 (6/21)	35.0 (7/20)	0.774
High altitude	18.5 (5/27)	29.0 (11/38)	0.137
PARASITOLOGY			
% <i>S. mansoni</i> infection by urine-CCA (n)~	62.5 (30/48)	76.1 (67/88)	<0.001
Low altitude	57.1 (12/21)	69.0 (20/29)	0.005
High altitude	66.7 (18/27)	79.7 (47/59)	0.001
% Egg patent <i>S. mansoni</i> Infection (n)~~	20.8 (10/48)	25.0 (22/88)	0.053
Low altitude	28.6 (6/21)	17.2 (5/29)	N/A
High altitude	14.8 (4/27)	28.8 (17/59)	0.006
Mean eggs per gram (95% confidence interval)~~	49.8 (-13.1-112.6)	251.5 (86.4-416.5)	0.375
Low altitude	75.4 (-64.6-215.5)	344.7 (-41.6-731.0)	0.277
High altitude	29.8 (-11.6-71.1)	205.6 (47.1-364.1)	0.663
<i>S. mansoni</i> intensity~~			
% Negative (n)	79.2 (38/48)	75.0 (66/88)	
% Light (n)	14.6 (7/48)	5.7 (5/88)	
% Medium (n)	2.1 (1/48)	6.8 (6/88)	
% Heavy (n)	4.2 (2/48)	12.5 (11/88)	
Low Altitude			
% Negative (n)	71.4 (15/21)	82.8 (24/29)	
% Light (n)	23.8 (5/21)	3.5 (1/29)	

% Medium (n)	0.0 (0/21)	0.0 (0/29)	
% Heavy (n)	4.8 (1/21)	13.8 (4/29)	
High Altitude			
% Negative (n)	85.2 (23/27)	71.2 (42/59)	
% Light (n)	7.4 (2/27)	6.8 (4/59)	
% Medium (n)	3.7 (1/27)	10.2 (6/59)	
% Heavy (n)	3.7 (1/27)	11.9 (7/59)	
% <i>Giardia duodenalis</i> infection (n) ^{^^}	20.8 (10/48)	14.9 (14/94)	1.000
Low altitude	13.3 (3/21)	12.5 (4/32)	0.732
High altitude	25.9 (7/27)	16.1 (10/62)	0.992
20M SHUTTLE RUN TEST			
Median VO ₂ max in mL kg ⁻¹ min ⁻¹ (interquartile range)	47.45 (45.4-50.3)	46.3 (43.9-49.1)	0.001
Low altitude	48.7 (46.3-52.0)	47.0 (43.9-48.7)	<0.001
High altitude	46.3 (43.9-48.7)	46.3 (43.9-49.5)	0.349

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724 Associations determined by linear regression. *Indicates significance of differences among the villages by

725 Kruskal-Wallis or Chi-squared analysis, paired T test or ANOVA. Statistically significant differences ($P \leq 0.05$)726 indicated in **bold**. #As per standardised hemoglobin cut-offs for age: < 11.5 g dL⁻¹ (5 - 11y), < 12.0 g dL⁻¹ (12 -727 14y). Hemoglobin adjusted for altitude.⁴⁰ ~As per urine-cathodic circulating antigen testing. ~~As per dual Kato-728 Katz examination. Intensity defined by eggs per gram (epg): 1 - 99 = light; 100 - 399 = medium, ≥ 400 = heavy.²⁹729 ^{^^}As per *Giardia*/*Cryptosporidium* Quik Chek test.

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751 S3 Table. Comparison of Mean VO₂max between Study Participants & Reference Canadian
 752 Cohort.
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Age	Gender	Canadian Cohort		Study Cohort		P Value
		n	Mean VO ₂ max (S.D.)	n	Mean VO ₂ max (S.D.)	
7	Male	297	51.23 (3.34)	2	46.30 (3.39)	<0.001
	Female	299	50.26 (2.63)	1	N/A	N/A
8	Male	303	51.67 (3.91)	9	44.66 (4.03)	<0.001
	Female	308	49.82 (3.44)	14	42.33 (3.05)	<0.001
9	Male	322	51.54 (4.39)	20	47.34 (4.28)	<0.001
	Female	322	49.20 (3.24)	22	44.42 (2.77)	<0.001
10	Male	404	51.64 (4.23)	30	47.32 (3.75)	<0.001
	Female	335	46.84 (2.76)	28	44.53 (4.10)	0.006
11	Male	386	51.13 (4.53)	23	46.47 (3.65)	<0.001
	Female	382	47.51 (4.04)	22	43.87 (4.18)	<0.001
12	Male	341	51.92 (5.16)	29	46.95 (3.78)	<0.001
	Female	292	46.65 (4.17)	29	44.72 (3.44)	0.005
13	Male	325	50.10 (5.21)	19	46.29 (3.51)	<0.001
	Female	298	44.42 (4.76)	19	43.05 (4.03)	0.1568
14	Male	289	50.11 (5.20)	20	45.92 (3.86)	<0.001
	Female	260	41.65 (4.72)	16	43.85 (3.57)	0.026
15	Male	333	50.20 (6.07)	1	48.80 (N/A)	<0.001
	Female	260	41.16 (5.07)	1	41.50 (N/A)	N/A

754 Canadian data obtained from Leger et al., 1988. Differences determined by one-way T test. Statistically
 755 significant differences ($P \leq 0.05$) indicated in **bold**. S.D. = Standard Deviation.
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772 S4 Table. Linear Regression Models with VO₂max as the Outcome, Stratified by Gender.

	Unadjusted Analysis				Multivariable-adjusted Analysis			
	Coefficient	95% CI	P Value	Coefficient	95% CI	P Value		
<i>S. mansoni</i> egg patent infection*								
Males	-0.842	-2.084	0.400	0.182	-2.407	-5.150	0.337	0.083
Females	-1.912	-3.123	-0.700	0.002	-5.038	-8.794	-1.283	0.011
Fecal Occult Blood								
Males	-0.077	-0.878	0.724	0.848	0.090	-1.233	1.412	0.891
Females	-0.442	-1.234	0.349	0.269	0.343	-0.988	1.673	0.601
Malaria[^]								
Males	-0.493	-2.039	1.054	0.529	-0.877	-3.524	1.770	0.504
Females	0.759	-0.942	2.460	0.378	-0.260	-3.592	3.071	0.874
Stunting[~]								
Males	-0.229	-1.966	1.508	0.795	-0.366	-3.541	2.809	0.815
Females	-0.345	-1.678	0.987	0.609	-1.251	-4.586	2.085	0.448
Anemia[#]								
Males	0.134	-1.261	1.529	0.849	1.731	1.000	4.462	0.205
Females	-1.264	-2.601	0.072	0.063	-0.311	-3.444	2.822	0.840

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774 Statistically significant differences ($P \leq 0.05$) indicated in **bold**. *As per dual Kato-Katz examination. [^]As per775 malaria rapid diagnostic testing. [~]According to validated stunting charts based on height-for-age Z-score ≤ 2 S.D.776 below mean.³⁶ [#]As per standardised hemoglobin cut-offs for age: < 11.5 g dL⁻¹ (5 - 11y), < 12.0 g dL⁻¹ (12 - 14y).777 Hemoglobin adjusted for altitude.⁴⁰ For multivariable-adjusted analysis: Males: n = 36. P Value = 0.257. R-

778 squared = 0.188. Adjusted R-squared = 0.053. AIC = 195.429. Females: n = 32. P Value = 0.052. R-squared =

779 0.330. Adjusted R-squared = 0.201. AIC = 176.918.

780 S5 Table. Linear Regression Models with Stunting (by validated charts) as the Outcome.

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	Unadjusted Analysis				Multivariable-adjusted Analysis			
	Odds Ratio	95% CI		P Value	Odds Ratio	95% CI		P Value
<i>S. mansoni</i> egg patent infection*	2.491	1.302	4.771	0.006	0.752	0.167	3.390	0.711
Fecal occult blood	1.292	0.867	1.927	0.208	1.215	0.623	2.369	0.568
Malaria^	0.651	0.307	1.382	0.264	0.681	0.181	2.560	0.570
Anemia#	1.391	0.665	2.908	0.381	1.233	0.322	4.726	0.760

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783 Statistically significant differences ($P \leq 0.05$) indicated in **bold**. *As per dual Kato-Katz examination. ^As per784 malaria rapid diagnostic testing. #As per standardised hemoglobin cut-offs for age: $< 11.5 \text{ g dL}^{-1}$ (5-11y), $< 12.0 \text{ g}$ 785 dL^{-1} (12-14y). Hemoglobin adjusted for altitude.⁴⁰ For multivariable-adjusted analysis: AIC = 73.21548. $n = 70$. P

786 value = 0.92. Pseudo R-squared = 0.0144. likelihood ratio chi-squared test = 0.92.

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830 S6 Figure. Adjusted Odds Ratios for Anemia (A) and Stunting (B; by validated charts).

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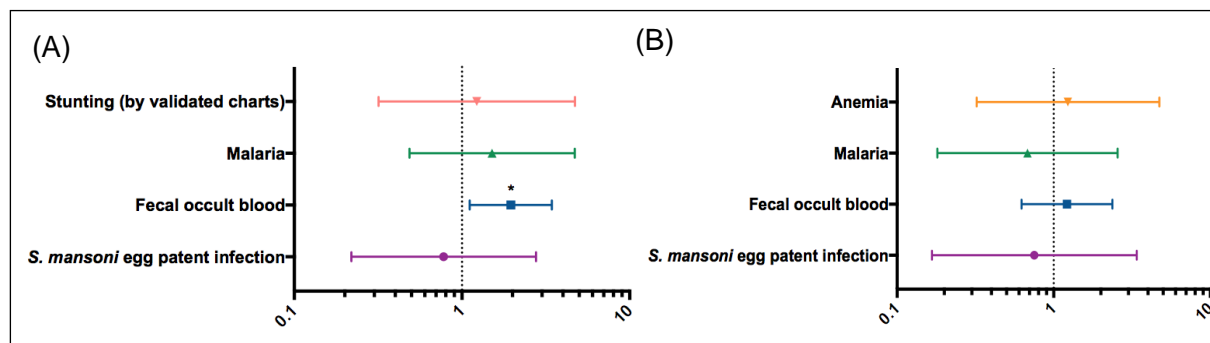
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837 The final models were controlled for (a) *S. mansoni* egg patent infection, fecal occult blood, malaria and stunting

838 (by validated charts), & (b) *S. mansoni* egg patent infection, fecal occult blood, malaria and anemia. *OR 1.96;

839 95% CI 1.11 - 3.43, **P = 0.020**.