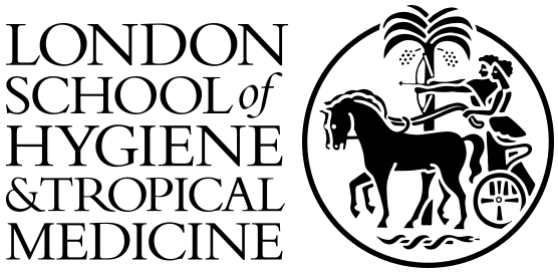

The effect of helminth infections and their treatment on metabolic outcomes: results of a cluster-randomised trial

Richard E Sanya[1,2], Emily L Webb[3], Christopher Zziwa[1], Robert Kizindo[1], Moses Sewankambo[1], Josephine Tumusiime[1], Esther Nakazibwe[1], Gloria Oduru[1], Emmanuel Niwagaba[1], Prossy Kabuubi Nakawungu[1], Joyce Kabagenyi[1], Jacent Nassuuna[1], Bridgious Walusimbi[1], Irene Andia-Biraro[1,2], Alison M Elliott[1,4]; for the LaVIISWA trial team

[1]Immunomodulation and Vaccines Programme, Medical Research Council/ Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit Entebbe, Uganda.

[2]Department of Internal Medicine, College of Health Sciences, Makerere University, Kampala, Uganda.

[3]MRC Tropical Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, United Kingdom.

[4]Department of Clinical Research, London School of Hygiene and Tropical Medicine, United Kingdom.

Corresponding author: Dr Richard E Sanya, MRC/UVRI and LSHTM Uganda Research Unit, Plot 51-59 Nakiwogo road, P. O. Box 49 Entebbe Uganda. Email: Richard.Sanya@mrcuganda.org

SUMMARY

In a cluster-randomised trial, intensive (compared to standard) anthelminthic treatment increased LDL-cholesterol. In observational analyses schistosome and *Strongyloides stercoralis* infections were associated with reduced serum lipids; heavy schistosome infection with lower blood pressure. Helminth elimination may promote cardiovascular disease risk.

ABSTRACT

Background: Helminth infection may influence cardiometabolic risk through effects on inflammation and metabolism**.** We hypothesised that helminths are protective and their treatment detrimental to metabolic outcomes.

Methods: We conducted a cluster-randomised trial in 26 fishing communities, Lake Victoria, Uganda. We investigated effects of community-wide intensive (quarterly single-dose praziquantel, triple dose albendazole) versus standard (annual single-dose praziquantel, six-monthly single-dose albendazole) anthelminthic treatment on metabolic outcomes, and observational associations between helminth infection and metabolic outcomes. The primary outcome, homeostatic model assessment of insulin resistance (HOMA-IR) and secondary outcomes (including blood pressure, fasting blood glucose and lipids) were assessed in a survey conducted after four years of intervention among individuals ≥10 years.

Results: We analysed 1898 participants. The intervention had no effect on HOMA-IR (adjusted geometric mean ratio [95%CI] 0.96 [0.86,1.07] p=0.42) but resulted in higher mean LDL-cholesterol in the intensive arm (2.86 vs 2.60 mmol/L, adjusted mean difference [95%CI] 0.26 [-0.03,0.56] p=0.08). Lower LDL-cholesterol levels were observed in *S. mansoni* (2.37 vs 2.80 mmol/L, -0.25 [-0.49,-0.02] p=0.04) and *Strongyloides* infected (2.34 vs 2.69mmol/L, -0.32 [-0.53,-0.12] p=0.003) participants compared with uninfected. *S. mansoni* infection was associated with lower total cholesterol levels (4.24 vs 4.64 mmol/L, -0.25 [-0.44,-0.07] p=0.01). Participants with moderate to heavy *S. mansoni* infection had lower triglycerides, LDL-cholesterol and diastolic blood pressure levels.

Conclusions: Helminth infections improve lipid profiles and may lower blood pressure. Further studies to confirm causality and investigate mechanisms will contribute to understanding the epidemiological transition and may suggest new approaches to prevent cardiometabolic disease.

Clinical trials registration: ISRCTN47196031

KEY WORDS: Helminths; *Schistosoma mansoni*; Diabetes; Cardiovascular disease; Africa

INTRODUCTION

Non-communicable diseases accounted for 72.3% of deaths globally in 2016 [1]. Ischaemic heart disease and cerebrovascular disease are the highest contributors to this mortality and morbidity [1]. Metabolic disorders such as type 2 diabetes (T2D) and dyslipidaemia are important cardiovascular disease risk factors. In 2017 an estimated 425 million people had diabetes worldwide and the number is projected to increase - disproportionately in low and middle income countries (LMIC) - to 629 million by 2045 [2]. Dyslipidaemia, which results in atherosclerosis, is the leading risk factor for myocardial infarction [3] and stroke [4].

Chronic, low-grade, obesity-driven inflammation has been implicated in the aetiology and progression of insulin resistance and T2D [5]. Atherosclerosis results from a chronic inflammatory state mediated by macrophages in the vascular sub-endothelium combined with high levels of lipids in the systemic circulation [6]. Lipids are utilised by and involved in mediation of immune processes; therefore inflammation may influence lipid levels in the circulation [7]. Modulation of these inflammatory processes may delay the development of T2D and atherosclerosis.

Over a billion people are helminth-infected worldwide, predominantly in LMIC [8]. Helminths have co-evolved with humans over millions of years so that they survive in the human host but mostly cause only subtle harm. To ensure survival, helminths modify type 2 and regulatory immune responses in the human host [9]. With these immunomodulatory properties, helminths may be able to annul the inflammation that results in metabolic disorders and therefore confer protection [10]. Studies in experimental animals support this hypothesis. Mice infected with *Schistosoma mansoni* [11], *Nippostrongylus brasiliensis* [12] and *Litomosoides sigmodontis* [13] had decreased insulin resistance and improved glucose tolerance compared to uninfected mice. Infection of mice with *S. mansoni* cercariae [14] and intra-peritoneal inoculation of *S. mansoni* eggs [15] resulted in lower blood lipid levels

than in uninfected/un-inoculated controls. In mice, *S. mansoni* infection also reduced development of atherosclerotic lesions [14] and ES-62, a product from the filarial nematode *Acanthocheilonema vitae*, caused a 60% reduction in aortic atherosclerotic lesions [16].

In humans, published studies investigating the effect of helminths on metabolic outcomes are few and observational, except for a single trial. In China, history of *Schistosoma japonicum* infection was associated with lower levels of fasting blood glucose, glycated haemoglobin (HbA1c) and insulin resistance, and lower prevalence of diabetes and metabolic syndrome [17], while chronic infection with this helminth was associated with lower serum triglycerides and total cholesterol [18]. Among Australian Aboriginals, *Strongyloides stercoralis* infection was associated with a lower likelihood of diabetes [19] and treatment of *Strongyloides* worsened glycaemic status [20]. Among the Tsimane of the Bolivian Amazon, helminth infection was inversely associated with serum lipid levels [21]. Chronic infection with the trematode *Opisthorcis felineus* was associated with lower serum cholesterol levels and diminished atherosclerosis in a post-mortem study in Russia [22]. In Indonesia, infection with soil-transmitted helminths (STH) was associated with lower insulin resistance and body mass index (BMI) [23]. The only trial to date, conducted in Indonesia, showed no effect of albendazole treatment for STH on insulin resistance, BMI or waist circumference overall, but increased insulin resistance in individuals infected with STH at baseline [24].

Observational studies cannot demonstrate causality and are prone to bias from unmeasured confounders. The only previous trial was done in a setting with high prevalence of STH. However, other parasitic infections such as *S. mansoni*, may have a different impact on metabolic outcomes because of the different location of adult worms and inflammatory and regulatory elements of their life cycles. We therefore aimed to investigate, in a high *S. mansoni* prevalence setting, the effect of helminths and their treatment on metabolic outcomes in individuals aged ≥10 years. We also conducted observational analyses to assess cross-sectional associations between helminths and metabolic outcomes.

METHODS

Study setting and design

This was a two-arm cluster-randomised trial of community-wide intensive versus standard anthelminthic treatment conducted in 26 Lake Victoria fishing villages of Koome sub-county, Mukono district, Uganda (ISRCTN47196031). This population is ethnically diverse with the majority from central Uganda (of Bantu ethnic origin). There is some acculturation as different ethnic groups live together and use Luganda as the *lingua franca*. The main economic activity is fishing with a minority involved in agriculture. Villages are well defined, geographically separate and close to the lake. The residents live in temporary housing made from wood (locally obtained) and roofed with iron sheets or plastic. Houses are built close together. The island communities trade with mainland communities (both nearby and far) in fish and general merchandise.

The protocol has been published [25]. Briefly, 13 villages were randomised to intensive and 13 to standard intervention. Intensive treatment comprised praziquantel 40mg/kg single-dose administered using an extended height pole (which extended treatment to include pre-school age-groups) and albendazole 400mg triple-dose, both quarterly. Standard treatment comprised single-dose praziquantel (40mg/kg) annually and single-dose albendazole (400mg) bi-annually. Trial interventions started in September 2012. Originally, the trial was designed to investigate the effects of three years' intervention on allergy-related outcomes and helminth-related morbidity but interventions were extended for an extra year allowing us to assess their impact on metabolic outcomes.

Randomisation and masking

This was an open trial. Villages were randomised in a 1:1 ratio using restricted randomisation to ensure balance for village size, previous community-wide anthelminthic treatment and distance from the sub-county health centre [25].

Exposures and outcomes

The exposures of interest were anthelminthic intervention (for the trial) and helminth infections (for observational analyses). The primary outcome was insulin resistance measured by the homeostatic model assessment of insulin resistance (HOMA-IR) [26], calculated as *(fasting serum insulin (μU/ml) x fasting glucose (mmol/L)) / 22.5*. Secondary outcomes were fasting blood glucose, glycated haemoglobin (HbA1c), fasting serum lipids (triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol), blood pressure, body mass index (BMI), waist circumference and waist-hip ratio; and (for the trial) helminth infection status.

Procedures

The effects of helminths and anthelminthic intervention were assessed in a household survey conducted in all study villages after four years of intervention. We selected 70 households per village by simple random sampling using STATA (College Station Texas, US) (Supplementary methods). Permission for household participation was sought from each household head or another adult in the household if the head was absent. Household members aged ≥10 years were invited to participate.

After obtaining written informed consent from each household member (and assent from individuals aged 10-17 years), a questionnaire was administered. Data were collected on socio-demographic characteristics, diet, exercise, lifestyle, personal and family history of diabetes and hypertension. Participants' blood pressure (BP), weight, height, waist and hip circumference were measured using standardised procedures (Supplementary methods). Peripheral venous blood was collected after an overnight fast for measurement of the primary and secondary outcomes (Supplementary methods).

Each participant was requested to provide one stool sample, from which duplicate slides were made and examined independently by two experienced technicians using the Kato Katz method. Stool real-time

polymerase chain reaction (PCR) was also used to detect *S. mansoni*, hookworm (*Necator Americanus*) and *Strongyloides Stercoralis* infection (Supplementary methods).

Statistical methods

For this survey, we planned to recruit 1950 participants (Supplementary methods). Statistical analyses were done using STATA v13; all analyses allowed for within-cluster correlations. The trial analysis was by intention-to-treat and measured cluster-level differences. For continuous outcomes, means were calculated for each village (cluster-specific means) and the mean of these within each study arm was used as a summary measure of the outcome in that study arm. T-tests were used to compare cluster-specific means between arms, with corresponding 95% confidence intervals computed. Continuous outcomes with skewed cluster-specific mean distributions were log-transformed before analysis and results back-transformed to give geometric mean ratios. For binary outcomes we calculated risk ratios by dividing the mean of the cluster-specific proportions in the intensive arm by that in the standard arm. P-values were calculated from t-tests comparing cluster-specific proportions, and confidence intervals using a Taylor series approximation to estimate standard errors. For all outcomes, the effects of the intervention were additionally adjusted for age and sex using a two-stage approach [27].

The individual level observational analysis was performed to assess helminths as risk factors for metabolic disease. Potential confounders were identified based on a causal diagram (supplementary figure 1). Crude and adjusted associations were estimated using linear regression models fitted for each worm separately. Stata "svy" commands were used to allow for clustering of participants within villages, and for the non-self-weighting survey design due to variable village sizes. For adjusted analyses, only risk factors/ confounders crudely associated with the outcome with p-value≤0.15 were included in final models. No corrections were made for multiple testing.

Ethical considerations

Ethical clearance was granted by Uganda Virus Research Institute Research Ethics Committee (reference GC/127/17/01/573), London School of Hygiene and Tropical Medicine (reference 9917) and Uganda National Council for Science and Technology (reference HS 2185). Permission to conduct the work was granted by community leaders in all study villages.

RESULTS

Between April and November 2017, 70 households were randomly selected from each village except in two villages with fewer households where all were selected. Of eligible households and eligible individuals in those households, 71.3% (1276/1790) and 87.0% (1898/2181) agreed to participate respectively. We examined 1817/1898 (95.7%) participants and 88.8% (1686/1898) provided blood samples after an overnight fast. Numbers of participants providing data were balanced across trial arms (figure 1).

Characteristics of participants are shown in table 1. This is a young population with mean age 31.5 years (SD 11) considering that individuals <10 years were excluded. There are more males than females and the main occupation is fishing; the majority (69%;1309/1898) reported daily contact with the lake. Activity levels were high: 48.4% (920/1898) reported vigorous physical activity at least weekly, with mean number of days 2.8 (SD 2.7). Diet mainly consists of fish (eaten on average 4.8 days a week) and is low in fruit (on average one day a week). The majority of participants (64.2%; 1218/1898) reported having lived in the village in which they were surveyed throughout the four-year intervention period. Only 14.9% (283/1898) had ever undergone BP measurement and 4.2% (80/1898) had previously had blood sugar levels tested.

Participants living in intensive anthelminthic intervention villages had lower *S. mansoni* prevalence than those in standard intervention villages (stool Kato Katz, intensive 21.9%, standard 35.6%, p=0.02; stool PCR, intensive 37.3%, standard 56.0%, p=0.01). Similar effects were observed for hookworm (stool PCR, intensive 2.3%, standard 4.8%, p=0.03) and *Strongyloides* (stool PCR, intensive 4.8%, standard 9.0% p=0.02). Around half of *S. mansoni* infections were of light intensity (intensive 12.2%, standard 17.4%). The intervention had no effect on *Trichuris trichiura* (table 2).

There was no evidence of a difference in HOMA-IR between the study arms (table 3). However, there was some evidence of a difference in mean LDL-cholesterol, higher in the intensive arm (2.86 versus 2.60mmol/l, adjusted mean difference [95% CI] 0.26 [-0.03,0.56] p=0.08). No differences were seen between trial arms for the other metabolic parameters (table 3). Further analysis of the metabolic outcomes categorised as binary (diabetes, impaired fasting glucose, hypertension, obesity and metabolic syndrome) showed no differences between trial arms (supplementary table 1).

Key associations from our observational analysis are shown in table 4; all associations tested are shown in supplementary table 2. *S. mansoni*-infected participants had lower total cholesterol levels than uninfected participants (4.24mmol/L vs 4.64mmol/L, crude mean difference [95%] -0.40 [-0.62,-0.19] p=0.001). Strong evidence for this association remained after adjusting for age, sex, occupation, residence, diet, exercise, family history of obesity, paternal and maternal tribe (-0.25 [-0.44 -0.07] p=0.01). *S. mansoni* infection was associated with lower LDL-cholesterol (2.37 vs 2.80mmol/L, -0.25 [-0.49,-0.02] p=0.04) but not with HDL-cholesterol. *Strongyloides* infection was associated with lower LDL-cholesterol levels (p=0.003). Participants with heavy *S. mansoni* infection intensity had lowest triglyceride levels (p=0.0004) and lowest diastolic BP (p=0.01). Participants with moderate *S. mansoni*

infection intensity had lowest LDL-cholesterol levels (p=0.04). Co-infection with multiple (increasing) helminth species was associated with lower total and LDL-cholesterol (trend p=0.02).

Four serious adverse events (SAEs) were reported in the first three years of the anthelminthic intervention [28]. In the fourth year of the intervention, no SAEs were reported.

DISCUSSION

This is the first trial to investigate effects of an anthelminthic intervention on metabolic outcomes in an *S. mansoni* endemic, high-transmission, setting. We found no effect of four years of intensive versus standard anthelminthic treatment on insulin resistance, but there a modest increase in LDL-cholesterol in the intensive versus standard arm. Consistent with this, there was strong observational evidence of association between *S mansoni* infection and lower levels of total cholesterol and LDL-cholesterol. The lowest levels of triglycerides and diastolic blood pressure were observed among participants with heavy *S. mansoni* infection and the lowest levels of LDL-cholesterol among those with moderate *S. mansoni* intensity. *Strongyloides* infection was also inversely associated with LDL-cholesterol. A dose-response relationship was observed between increasing numbers of helminth species detected and lower cholesterol levels.

The effect of the intervention on LDL-cholesterol and consistency of this with our cross-sectional observations strongly suggests a causal link between helminth infection and lipid profiles. Our results, in a setting dominated by schistosomiasis, accord with findings in experimental animals [14, 29] and with associations observed between intestinal nematode infection and lipids in humans [30, 31]. One possible mechanism is direct consumption of lipids by helminths. Schistosomes do not synthesise cholesterol and rely on the host for their supply [32]. However, the effect of schistosomes is likely not limited to direct consumption, with immunological effects implicated. La Flamme *et al*. showed that chronic exposure to *S. mansoni* eggs reduced serum cholesterol in mice with changes due to egg-

induced increased uptake of LDL by macrophages [29]. It has been suggested that helminths might modulate production of naturally occurring antibodies to cholesterol [33]. Helminths resident in the lumen might hinder lipid absorption from the gut directly. In addition, there is evidence that helminth infection influences intestinal microbiome [34] which also impacts blood lipids [35]. Studies investigating the influence of helminths on the microbiome and how that relates to lipid metabolism would provide a deeper understanding of the underlying mechanisms.

An unanticipated finding was the association between heavy *S. mansoni* infection intensity and lower diastolic BP. Essential hypertension accounts for 90% of hypertension cases. The aetiology is not well understood, but it is hypothesised that inflammation may cause essential hypertension [36]. Two pathways are proposed. Inflammation of the renal interstitium results in monocyte/macrophage infiltration of renal perivascular fat, oxidative stress and loss of peritubular capillaries. This may lead to medullary hypoxia, impaired sodium excretion and consequently, hypertension [37]. Secondly, inflammation results in monocyte/macrophage infiltration of arterial walls leading to arterial stiffness. Arterial stiffness triggers angiotensin II which results in hypertension. Helminths may influence these pathways via their immunomodulatory properties. Helminths may also indirectly influence blood pressure through effects on the intestinal microbiome. Gut microbiota digest fibre and release short chain fatty acids which, on absorption into the circulation stimulate the release of renin, a major component of the renin angiotensin aldosterone system [38]. We recommend studies to further explore the relationship between helminth infection and BP.

We were surprised to find no impact of anthelminthic treatment or of helminths on insulin resistance, given the strong evidence of effects from animal models and evidence of increased insulin resistance following STH treatment among participants in the Indonesian trial. Perhaps the most probable explanation lies in the transmission dynamics of schistosomiasis in this transmission “hot-spot” setting; and in the biology of schistosomes, as distinct from STH. In this trial, we observed a reduction in

helminth prevalence in the standard arm over time, as well as in the intensive arm [25, 28] and this may have weakened any chance of seeing a differential effect of trial interventions on the metabolic outcomes. As well, single stool Kato Katz analysis has low sensitivity in detecting *S. mansoni* infection. As previously reported, the more sensitive urine circulating cathodic antigen (CCA) used after three years of intervention suggested persistent (albeit reduced intensity) infection in over 80% of participants in both trial arms, presumably due to on-going transmission and re-infection. Moreover, schistosomes differ from STH in that they reside in the vasculature and treatment does not result in immediate expulsion from the body. Immunological changes induced by helminths persist even after treatment of the worms. *Schistosoma* egg antigen elicits reduced insulin resistance in an animal model in the absence of live worms, and *Schistosoma* egg antigen is persistent: liver egg counts were almost unchanged 26 weeks after treatment in a mouse model [39]; in humans, antibody to egg antigen was detectable eight years after curative treatment of schistosome infection [40]. Therefore, effects of schistosome infection may persist after treatment of adult worms with praziquantel. Furthermore, animal models investigating effects of helminths on insulin resistance have tended to use obese models. By contrast, fishing community populations are generally young, slim and active and therefore at low risk of metabolic disorders.

Our results in this high schistosomiasis transmission setting, namely strong observational associations and supportive suggestion of a treatment effect for lipid profiles, contrasting with lack of association or treatment effect for insulin resistance, could be explained if the former depends predominantly upon active schistosome infection, and the latter upon exposure to schistosome antigen.

Strengths of our study include the robust trial design, large sample size and intense helminth exposure. However, on-going helminth transmission and cluster-level randomisation limited our ability to determine effects of helminth elimination and more focused, individually-randomised trials would be useful to assess this further. While multiple outcomes were assessed, risking false positive findings, the

coherence of results on lipid profiles within the study, and when compared to other studies, is persuasive. Finally, we cannot rule out a direct effect of praziquantel and albendazole on metabolic outcomes, although no prior evidence suggests this.

Taken together, our findings have important implications. They provide an understanding on how anthelminthic treatment may impact metabolic health, thus increasing the burden of non-communicable diseases and accelerating the epidemiological transition. Helminth infections may be beneficial to lipid metabolism and BP control in humans. Identification of potentially protective interactions and the underlying mechanisms is important for the development of future therapies.

NOTES

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DISCLAIMER

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Table 1: Characteristics of participants aged ≥10 years enrolled in the survey on metabolic outcomes in the Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA) cluster-randomised trial

Cluster-level characteristics	Study arm	
Household-level characteristics	**Intensive**	**Standard arm**
Household size (median, IQR)	2 (1-3)	2 (1-3)
Individual-level characteristics	**(N=964)**	**(N=934)**
Sex, male	516 (53.5%)	494 (52.9%)
Age in years (mean, SD)	32 (11.0)	31 (11.0)
Age in years, grouped		
10-19	105 (10.9%)	110 (11.8%)
20-29	324 (33.6%)	324 (34.7%)
30-39	311 (32.3%)	283 (30.3%)
40+	224 (23.2%)	217 (23.2%)
Occupation		
Child/student	50 (5.2%)	71 (7.6%)
Housewife	103 (10.7%)	96 (10.3%)
Fishing or lake related	366 (38.0%)	365 (39.1%)
Shops, salons, artisans, service providers	68 (7.1%)	95 (10.2%)
Bars, restaurants, food providers, entertainment	70 (7.3%)	86 (9.2%)
Agriculture, lumbering, charcoal	225 (23.3%)	167 (17.8%)
Professional	20 (2.1%)	11 (1.2%)
Unemployed	18 (1.9%)	18 (1.9%)
Other	44 (4.6%)	25 (2.7%)
Residence		
Always lived in the village	84 (8.7%)	80 (8.6%)
Has lived only in the village throughout the intervention period	526 (54.6%)	528 (56.3%)
Has lived elsewhere in the sub-county during the intervention period	32 (3.2%)	41 (4.4%)
Lived outside the study area during the intervention period	322 (33.4%)	285 (30.5%)
Place of birth (if participant has not always lived in the village)		
Fishing village	28 (2.9%)	24 (2.6%)
Other rural village	757 (78.5%)	743 (79.6%)
Town	76 (7.9%)	65 (7.0%)
City	19 (2.0%)	22 (2.4%)
First five years (if participant has not always lived in the village) (mv,13)		
This village	4 (0.4%)	8 (0.8%)
A fishing village	27 (2.8%)	24 (2.6%)
Other rural village	747 (77.5%)	733 (78.5%)
Town	78 (8.1%)	66 (7.1%)
City	19 (2.0%)	22 (2.4%)
Age of participant when he/she moved to this village (mean, SD)	24 (11.2)	23 (11.3)
Maternal tribe (grouped by region)		
Central	342 (35.5%)	336 (36.0%)
Western	156 (16.3%)	138 (14.8%)
Eastern	215 (22.3%)	190 (20.3%)
Northern	90 (9.3%)	112 (12.0%)
Non-Ugandan	157 (16.3%)	154 (16.5%)
Do not know	4 (0.4%)	4 (0.4%)
Paternal tribe (grouped by region)		
Central	387 (40.2%)	364 (39.0%)

Western	165 (17.1%)	163 (17.5%)
Eastern	213 (22.1%)	172 (18.4%)
Northern	93 (9.7%)	108 (11.6%)
Non-Ugandan	105 (10.9%)	125 (13.4%)
Do not know	1 (0.1%)	2 (0.2%)
Self-reported treatment for worms		
Ever treated for worms	866 (89.8%)	795 (85.1%)
Number of times treated with albendazole in the last 12 months (mean, SD)	1 (0.8)	2 (1.4)
Number of times treated with albendazole in the last 4 years (mean, SD)	8 (5.4)	4 (2.8)
Number of times treated with praziquantel in the last 12 months (mean, SD)	2 (1.4)	0.5 (0.6)
Number of times treated with praziquantel in the last 4 years (mean, SD)	8 (5.4)	2 (1.6)
Frequency of lake contact (mv, 41)		
Every day	630 (65.3%)	679 (72.7%)
Almost every day	161 (16.7%)	136 (14.6%)
Once a week	120 (12.5%)	72 (7.7%)
Once a month	33 (3.4%)	19 (2.0%)
Less than once a month	3 (0.3%)	4 (0.4%)
Ever had blood sugar measured (mv, 30)		
Yes	43 (4.5%)	37 (4.0%)
No	905 (93.8%)	879 (94.1%)
Do not know	2 (0.2%)	2 (0.2%)
Blood sugar measured in the past 12 months		
Yes	18 (1.9%)	13 (1.4%)
No	26 (2.7%)	25 (2.7%)
History of diabetes (mv, 30)		
Yes	4 (0.4%)	3 (0.3%)
No	932 (96.7%)	909 (97.3%)
Do not know	14 (1.5%)	6 (0.6%)
Ever had blood pressure measured (mv, 30)		
Yes	147 (15.3%)	136 (14.6%)
No	802 (83.2%)	782 (83.4%)
Do not know	1 (0.1%)	0
Blood pressure measured in the past 12 months (mv, 30)		
Yes	66 (6.9%)	61 (6.5%)
No	81 (8.4%)	75 (8.0%)
History of hypertension (mv, 30)		
Yes	20 (2.1%)	24 (2.6%)
No	925 (96.0%)	890 (95.3%)
Do not know	5 (0.5%)	4 (0.4%)
Frequency of exercise / participation in vigorous physical activity (mv, 30)		
Every day	19 (2.0%)	8 (0.9%)
Almost every day	193 (20.5%)	194 (21.2%)
Once a week	305 (32.5%)	177 (19.3%)
Once a month	305 (18.3%)	187 (20.4%)
Less than once a month	237 (25.2%)	333 (36.4%)
Number of days in a week a participant performs vigorous physical activity (mean SD)	3.0 (2.7)	2.6 (2.7)
Hours spent per day performing vigorous physical activity (mean, SD)	3.4 (3.4)	2.9 (3.4)
Diet (in a typical week) (mv, 30)		
Number of days you eat fruit (mean, SD)	1.0 (1.5)	0.8 (1.4)
Number of servings of fruit you eat on one of those days (mean, SD)	0.5 (0.7)	0.4 (0.7)

Number of days you eat vegetables (mean, SD)	0.8 (1.3)	0.4 (1.0)
Number of days you eat fish (mean, SD)	4.8 (2.3)	4.8 (2.2)
Number of days you eat meat (mean, SD)	0.3 (0.9)	0.4 (1.1)
Type of oil or fat that is most often used for meal preparation in the household or where the participant eats (mv, 30)		
Vegetable oil	845 (87.7%)	794 (85.0%)
Other oils	14 (1.5%)	10 (1.1%)
None in particular	23 (2.4%)	13 (1.4%)
None used	54 (5.6%)	78 (8.3%)
Don't know	14 (1.5)	23 (2.5%)
Ever smoked (either pipe or cigarette) (mv, 30)		
Yes	175 (18.2%)	168 (18.0%)
No	775 (80.4%)	750 (80.3%)
Currently smoking tobacco products daily	147 (15.3%)	128 (13.7%)
Ever taken alcohol (mv, 30)	482 (50.0%)	423 (45.3%)
Currently drinking alcohol	406 (42.1%)	352 (37.7%)
Maternal history of diabetes (mv, 30)		
No history	801 (83.1%)	764 (81.8%)
History of diabetes	30 (3.1%)	39 (4.2%)
Do not know	119 (12.3%)	115 (12.3%)
Paternal history of diabetes (mv, 30)		
No history	785 (81.4%)	790 (84.6%)
History of diabetes	28 (2.9%)	25 (2.7%)
Don't know	137 (14.2%)	103 (11.0%)
Maternal history of hypertension (mv, 30)		
No history	688 (71.3%)	669 (71.6%)
History of hypertension	148 (15.4%)	137 (14.7%)
Don't know	114 (11.8%)	112 (12.0%)
Paternal history of hypertension (mv, 30)		
No history	764 (79.3%)	775 (83.0%)
History of hypertension	52 (5.4%)	40 (4.3%)
Don't know	134 (1.5%)	103 (11.0%)
Maternal history of obesity/ overweight (mv, 30)		
No history	811 (84.1%)	774 (82.9%)
History of obesity/ overweight	14 (1.5%)	14 (1.5%)
Don't know	125 (13.0%)	130 (13.9%)
Paternal history of obesity/ overweight (mv, 30)		
No history	805 (83.5%)	803 (86.0%)
History of obesity/ overweight	4 (0.4%)	8 (0.9%)
Don't know	141 (14.6%)	107 (11.5%)

mv, missing values; SD, Standard deviation

Table 2: Effect of intensive versus standard anthelminthic treatment on helminth prevalence in the metabolic survey of the Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA) cluster-randomised trial (cluster-level analysis) (n=1853)

Outcome		%		Crude risk ratio (95% CI)	P-value	*Adjusted risk ratio (95% CI)	*P-value
		Intensive arm	Standard arm				
Schistosoma mansoni, stool Kato Katz		21.9	35.6	0.62 (0.41, 0.92)	0.02	0.71 (0.54, 0.93)	0.02
Schistosoma mansoni, stool PCR		37.3	56.0	0.67 (0.51, 0.89)	0.007	0.76 (0.63, 0.94)	0.01
S. mansoni intensity stool Kato Katz	Light	12.2	17.4				
	Moderate	4.9	11.4				
	Heavy	4.8	6.8				
Trichuris trichiura, stool Kato Katz		7.4	8.1	0.91 (0.41, 2.02)	0.82	0.78 (0.36, 1.68)	0.50
Hookworm, stool PCR		2.3	4.8	0.47 (0.22, 1.01)	0.03	0.48 (0.23, 1.01)	0.03
Strongyloides stercoralis, stool PCR		4.8	9.0	0.54 (0.34, 0.86)	0.01	0.52 (0.31, 0.87)	0.02

*CI, Confidence intervals; *Adjusted for age, sex and baseline helminth prevalence **Baseline prevalence measured using stool PCR*

Table 3: Effect of intensive versus standard anthelminthic treatment on metabolic outcomes in the metabolic survey of the Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA) cluster-randomised trial (cluster-level analysis) (n=1853)

Outcome	mean		Crude mean difference/geometric mean ratio (95% CI)	P-value	Adjusted mean difference/geometric mean ratio (95% CI)*	P-value*
	Intensive	Standard				
HOMA – IR (glucose x insulin/22.5)	GM 1.24**	GM 1.30**	GMR 0.96 (0.85, 1.07)***	0.43	aGMR 0.96 (0.86, 1.07)***	0.42
Fasting glucose (mmol/L)	4.78	4.76	0.02 (-0.16, 0.20)	0.85	0.01 (-0.17, 0.19)	0.90
Glycated haemoglobin (mmol/m)	30.72	30.56	0.16 (-2.09, 2.41)	0.88	0.14 (-2.11, 2.40)	0.90
Triglycerides (mmol/L)	GM 0.98**	GM 0.98**	GMR 1.00 (0.94, 1.06)***	0.95	aGMR 0.97 (0.85, 1.11)***	0.63
Total cholesterol (mmol/L)	4.52	4.33	0.19 (-0.16, 0.54)	0.27	0.19 (-0.16, 0.54)	0.28
LDL – Cholesterol (mmol/L)	2.86	2.60	0.27 (-0.03, 0.56)	0.08	0.26 (-0.03, 0.56)	0.08
HDL – Cholesterol (mmol/L)	GM 1.20**	GM 1.20**	GMR 1.01 (0.87, 1.17)***	0.94	aGMR 1.01 (0.87, 1.17)***	0.94
Systolic blood pressure (mmHg)	115.27	116.13	-0.86 (-2.84, 1.12)	0.38	-1.02 (-2.72, 0.68)	0.22
Diastolic blood pressure (mmHg)	76.40	76.37	0.03 (-1.25, 1.31)	0.97	-0.12 (-1.34, 1.10)	0.84
Body mass index (kg/m2)	23.34	23.34	0.01 (-0.50, 0.51)	0.99	-0.08 (-0.58, 0.42)	0.74
Waist circumference (cm)	80.00	80.04	-0.04 (-1.49, 1.41)	0.95	-0.32 (-1.70, 1.07)	0.64
Waist-hip Ratio	0.85	0.85	0.00 (0.00, 0.01)	0.96	0.00 (-0.01, 0.00)	0.72

*CI, Confidence intervals; GM, Geometric mean; GMR, Geometric mean ratio; aGMR, adjusted geometric mean ratio; *Adjusted for age and sex; **Geometric means used because of skewed cluster-specific means; *** Geometric mean ratios used because of skewed cluster-specific means*

Table 4: Associations between helminth infection and metabolic outcomes

		Mean	Crude mean difference (95% CI)*	P value	Adjusted mean difference (95% CI)**	P value**
HOMA-IR						
S. mansoni, stool Kato Katz	Uninfected (n=1065)	GM 1.90				
	Infected (n=440)	GM 1.69	-0.05 (-0.12, 0.02)	0.12	0.05 (-0.05, 0.15)	0.28
S. mansoni, stool PCR	Uninfected (n=793)	GM 1.62				
	Infected (n=694)	GM 2.06	-0.10 (-0.21, 0.01)	0.07	-0.01 (-0.08, 0.06)	0.77
S. mansoni intensity, stool Kato Katz	Uninfected (n=1065)	GM 1.90				
	Light (n=230)	GM 2.07	0.04 (-0.09, 0.17)		0.09 (-0.07, 0.25)	
	Moderate (n=121)	GM 1.20	-0.20 (-0.35, -0.05)		-0.04 (-0.19, 0.12)	
	Heavy (n=89)	GM 1.61	-0.07 (-0.21, 0.06)	0.07	0.07 (-0.11, 0.25)	0.69
T. trichiura, stool Kato Katz	Uninfected (n=1383)	GM 1.82				
	Infected (n=122)	GM 2.00	0.04 (-0.08 0.17)	0.50	0.08 (-0.05, 0.20)	0.21
Hookworm, stool PCR	Uninfected (n=1309)	GM 1.83				
	Infected (n=55)	GM 1.76	-0.02 (-0.17, 0.14)	0.83	0.11 (-0.18, 0 .40)	0.45
Strongyloides stercoralis stool PCR	Uninfected (n=1385)	GM 1.89				
	Infected (n=101)	GM 1.25	-0.18 (-0.40, 0.035)	0.10	0.04 (-0.16, 0.24)	0.70
Infection with multiple helminth species (*S. mansoni* [PCR], *T. trichiura*, Hookworm and *S. stercoralis)*	Helminth uninfected (n=655)	GM 2.12				
	Infected with any one	GM 1.58	-0.13 (-0.23, -0.03)		-0.04 (-0.12, 0.04)	

	helminth (n=611)					
	Infected with any two helminths (n=155)	GM 1.90	-0.05 (-0.18, 0.09)		0.13 (0.03, 0.23)	
	Infected with any three or four helminths (n=17)	GM 1.11	-0.28 (-0.58, 0.02)	<0.01	-0.22 (-0.66, 0.23)	0.05
Infection with multiple helminth species (testing for trend)			-0.07 (-0.12, -0.02)	0.01	0.01 (-0.04, 0.06)	0.61
Triglycerides (mmol/L)						
S. mansoni, stool Kato Katz	Uninfected (n=1065)	GM 1.02				
	Infected (n=440)	GM 0.90	-0.05 (-0.12, 0.01)	0.12	-0.05 (-0.14, 0.03)	0.21
S. mansoni, stool PCR	Uninfected (n=793)	GM 1.00				
	Infected (n=694)	GM 0.95	-0.02 (-0.07, 0.02)	0.28	-0.04 (-0.08, 0.01)	0.09
S. mansoni intensity, stool Kato Katz	Uninfected (n=1065)	GM 1.02				
	Light (n=230)	GM 0.95	-0.03 (-0.15, 0.08)		-0.05 (-0.18, 0.08)	
	Moderate (n=121)	GM 0.98	-0.02 (-0.11, 0.08)		0.00 (-0.09, 0.09)	
	Heavy (n=89)	GM 0.72	-0.15 (-0.23, -0.08)	<0.01	**-0.13 (-0.20, -0.07)**	**<0.01**
T. trichiura, stool Kato Katz	Uninfected (n=1383)	GM 0.99				
	Infected (n=122)	GM 0.87	-0.06 (-0.11, -0.00)	0.04	-0.05 (-0.13, 0.04)	0.29
Hookworm, stool PCR	Uninfected (n=1309)	GM 0.97				
	Infected (n=55)	GM 0.67	-0.17 (-0.30, -0.03)	0.02	-0.08 (-0.25, 0.09)	0.32
Strongyloides stercoralis, stool PCR	Uninfected (n=1385)	GM 0.97				
	Infected (n=101)	GM 0.95	-0.01 (-0.09, 0.08)	0.84	-0.05 (-0.15, 0.05)	0.32

Infection with multiple helminth species (*S. mansoni* [PCR], *T. trichiura*, Hookworm and *S. stercoralis)*	Helminth uninfected (n=655)	GM 0.99				
	Infected with any one helminth (n=611)	GM 0.97	-0.01 (-0.04, 0.03)		-0.01 (-0.05, 0.02)	
	Infected with any two helminths (n=155)	GM 0.87	-0.05 (-0.12, 0.01)		-0.07 (-0.15, 0.02)	
	Infected with any three or four helminths (n=17)	GM 0.65	-0.18 (-0.37, 0.01)	0.23	-0.20 (-0.49, 0.09)	0.50
Infection with multiple helminth species (testing for trend)			-0.03 (-0.05, 0.00)	0.06	-0.03 (-0.07, 0.01)	0.12
Total cholesterol (mmol/L)						
S. mansoni, stool Kato Katz	Uninfected (n=1065)	4.64				
	Infected (n=440)	4.24	-0.40 (-0.62, -0.19)	<0.01	**-0.25 (-0.44, -0.07)**	**0.01**
*S. mansoni, s*tool PCR	Uninfected (n=793)	4.69				
	Infected (n=694)	4.32	-0.37 (-0.63, -0.11)	0.007	**-0.28 (-0.53, -0.03)**	**0.03**
S. mansoni intensity*,* stool Kato Katz	Uninfected (n=1065)	4.64				
	Light (n=230)	4.34	-0.30 (-0.54, -0.07)		-0.19 (-0.42, 0.05)	
	Moderate (n=121)	4.17	-0.48 (-0.77, -0.19)		-0.33 (-0.59, -0.08)	
	Heavy (n=89)	4.10	-0.55 (-0.87, -0.23)	0.01	-0.33 (-0.62, -0.04)	0.06
T. trichiura, stool Kato Katz	Uninfected (n=1383)	4.53				
	Infected (n=122)	4.39	-0.14 (-0.42, 0.15)	0.33	0.00 (-0.25, 0.24)	0.99
Hookworm, stool PCR	Uninfected (n=1309)	4.53				

	Infected (n=55)	4.06	-0.47 (-0.76, -0.18)	0.003	-0.22 (-0.53, 0.09)	0.16
Strongyloides stercoralis, stool PCR	Uninfected (n=1385)	4.53				
	Infected (n=101)	4.24	-0.29 (-0.61, 0.03)	0.07	-0.22 (-0.53, 0.08)	0.15
Infection with multiple helminth species (*S. mansoni* [PCR], *T. trichiura*, Hookworm and *S. stercoralis)*	Helminth uninfected (n=655)	4.71				
	Infected with any one helminth (n=611)	4.37	-0.34 (-0.62, -0.06)		**-0.27 (-0.53, -0.01)**	
	Infected with any two helminths (n=155)	4.23	-0.48 (-0.83, -0.13)		**-0.32 (-0.63, -0.01)**	
	Infected with any three or four helminths (n=17)	3.75	-0.97 (-1.49, -0.44)	0.01	-0.53 (-1.08, 0.02)	0.11
Infection with multiple helminth species (testing for trend)			-0.29 (-0.48, -0.09)	<0.01	**-0.20 (-0.36, -0.03)**	**0.02**
LDL – Cholesterol (mmol/L)						
S. mansoni, stool Kato Katz	Uninfected (n=1065)	2.80				
	Infected (n=440)	2.37	-0.43 (-0.74, -0.12)	0.01	**-0.25 (-0.49, -0.02)**	**0.04**
*S. mansoni, s*tool PCR	Uninfected (n=793)	2.87				
	Infected (n=694)	2.45	-0.42 (-0.78, -0.05)	0.03	-0.28 (-0.57, 0.01)	0.06
S. mansoni intensity*,* stool Kato Katz	Uninfected (n=1065)	2.80				
	Light (n=230)	2.49	-0.32 (-0.60, -0.03)		-0.23 (-0.46, 0.00)	
	Moderate (n=121)	2.18	-0.62 (-0.97, -0.28)		**-0.39 (-0.72, -0.05)**	
	Heavy (n=89)	2.34	-0.46 (-0.91, -0.01)	<0.01	-0.14 (-0.51, 0.23)	**0.04**
T. trichiura, stool Kato Katz	Uninfected (n=1383)	2.66				

	Infected (n=122)	2.69	0.03 (-0.32, 0.37)	0.87	0.05 (-0.22, 0.33)	0.7
Hookworm, stool PCR	Uninfected (n=1309)	2.67				
	Infected (n=55)	2.13	-0.55 (-0.79, -0.30)	<0.01	0.08 (-0.19, 0.35)	0.55
Strongyloides stercoralis, stool PCR	Uninfected (n=1385)	2.69				
	Infected (n=101)	2.34	-0.35 (-0.58, -0.12)	0.004	**-0.32 (-0.53, -0.12)**	**0.003**
Infection with multiple helminth species (*S. mansoni* [PCR], *T. trichiura*, Hookworm and *S. stercoralis)*	Helminth uninfected (n=655)	2.90				
	Infected with any one helminth (n=611)	2.48	-0.42 (-0.82, -0.02)		-0.27 (-0.55, 0.02)	
	Infected with any two helminths (n=155)	2.44	-0.46 (-0.78, -0.13)		**-0.29 (-0.54, -0.05)**	
	Infected with any three or four helminths (n=17)	1.96	-0.94 (-1.57, -0.31)	0.02	-0.52 (-1.14, 0.10)	0.10
Infection with multiple helminth species (testing for trend)			-0.30 (-0.53, -0.07)	0.01	**-0.19 (-0.35, -0.04)**	**0.02**
HDL – Cholesterol (mmol/L)						
S. mansoni, stool Kato Katz	Uninfected (n=1065)	GM 1.81				
	Infected (n=440)	GM 1.82	0.09 (-0.14, 0.14)	0.98	0.05 (-0.04, 0.14)	0.26
*S. mansoni, s*tool PCR	Uninfected (n=793)	GM 1.83				
	Infected (n=694)	GM 1.79	-0.01 (-0.16, 0.14)	0.92	0.00 (-0.09, 0.09)	0.96
S. mansoni intensity*,* stool Kato Katz	Uninfected (n=1065)	GM 1.81				
	Light (n=230)	GM 1.80	-0.01 (-0.10, 0.09)		0.06 (-0.03, 0.14)	
	Moderate (n=121)	GM 2.19	0.08 (-0.08, 0.24)		0.12 (-0.01, 0.26)	

	Heavy (n=89)	GM 1.49	-0.08 (-0.34, 0.17)	0.02	-0.07 (-0.22, 0.09)	0.07
T. trichiura, stool Kato Katz	Uninfected (n=1383)	GM 1.83				
	Infected (n=122)	GM 1.62	-0.06 (-0.18, 0.07)	0.38	0.00 (-0.12, 0.12)	0.97
Hookworm, stool PCR	Uninfected (n=1309)	GM 1.84				
	Infected (n=55)	GM 2.02	0.04 (-0.18, 0.26)	0.70	-0.03 (-0.13, 0.08)	0.57
Strongyloides stercoralis, stool PCR	Uninfected (n=1385)	GM 1.81				
	Infected (n=101)	GM 1.79	-0.01 (-0.10, 0.09)	0.92	-0.04 (-0.13, 0.05)	0.36
Infection with multiple helminth species (*S. mansoni* [PCR], *T. trichiura*, Hookworm and *S. stercoralis)*	Helminth uninfected (n=655)	GM 1.82				
	Infected with any one helminth (n=611)	GM 1.83	0.00 (-0.16, 0.17)		0.00 (-0.10, 0.10)	
	Infected with any two helminths (n=155)	GM 1.70	-0.03 (-0.16, 0.11)		-0.02 (-0.11, 0.07)	
	Infected with any three or four helminths (n=17)	GM 1.75	-0.02 (-0.24, 0.21)	0.86	0.05 (-0.19, 0.28)	0.89
Infection with multiple helminth species (testing for trend)			-0.01 (-0.10, 0.09)	0.88	-0.00 (-0.06, 0.05)	0.89
Diastolic blood pressure (mmHg)						
S. mansoni, stool Kato Katz	Uninfected (n=1065)	76.30				
	Infected (n=440)	75.86	-0.44 (-1.89, 1.01)	0.54	0.72 (-1.40, 2.84)	0.49
*S. mansoni, s*tool PCR	Uninfected (n=793)	76.35				
	Infected (n=694)	75.88	-0.46 (-1.48, 0.56)	0.36	0.56 (-0.84, 1.95)	0.42

S. mansoni intensity, stool Kato Katz	Uninfected (n=1065)	76.30				
	Light (n=230)	76.58	0.27 (-1.08, 1.63)		1.25 (-0.71, 3.22)	
	Moderate (n=121)	76.75	0.45 (-2.56, 3.47)		1.55 (-2.35, 5.46)	
	Heavy (n=89)	72.84	-3.46 (-4.81, -2.12)	<0.01	**-2.29 (-3.91, -0.68)**	**0.01**
T. trichiura, stool Kato Katz	Uninfected (n=1383)	76.40				
	Infected (n=122)	72.97	-3.43 (-5.64, -1.22)	<0.01	-1.45 (-3.58, 0.69)	0.18
Hookworm, stool PCR	Uninfected (n=1309)	76.35				
	Infected (n=55)	72.44	-3.90 (-7.22, -0.59)	0.02	2.20 (-0.92, 5.33)	0.16
Strongyloides stercoralis, stool PCR	Uninfected (n=1385)	76.09				
	Infected (n=101)	76.60	0.51 (-2.67, 3.69)	0.74	-0.56 (-3.25, 2.14)	0.68
Infection with multiple helminth species (*S. mansoni* [PCR], *T. trichiura*, Hookworm and *S. stercoralis)*	Helminth uninfected (n=655)	76.44				
	Infected with any one helminth (n=611)	76.34	-0.10 (-1.22, 1.02)		0.87 (-0.80, 2.53)	
	Infected with any two helminths (n=155)	74.07	-2.37 (-4.33, -0.41)		0.08 (-2.21, 2.38)	
	Infected with any three or four helminths (n=17)	70.78	-5.66 (-12.24, 0.91)	0.10	-4.11 (-10.33, 2.11)	0.47
Infection with multiple helminth species (testing for trend)			-0.94 (-1.70, -0.18)	0.02	-0.26 (-1.13, 0.61)	0.54

*CI, Confidence intervals; GM, Geometric mean; PCR, Polymerase chain reaction; *Both crude and adjusted results allowed for the survey design i.e. weighting and clustering. **Adjusted for the following variables: **HOMA-IR** (age, sex, occupation, residence, lake contact, treatment for worms, treatment with coartem, BMI, family history of DM, maternal and paternal tribe); **Triglycerides** (age, sex, occupation, residence, diet, treatment for worms, family history of obesity, paternal and maternal tribe); **Total cholesterol** (age, sex, occupation, residence, diet, exercise, family history of obesity, paternal and maternal*

tribe); ***LDL – Cholesterol*** *(age, sex, occupation, diet, exercise, treatment for worms, treatment with coartem, parental tribe);* ***HDL – Cholesterol*** *(age, sex, occupation, residence, diet, treatment for worms, treatment with coartem, parental tribe);* ***Diastolic blood pressure*** *(age, sex, occupation, residence, lake contact, treatment for worms, paternal tribe, BMI); There was no evidence of association between helminth infection and fasting blood glucose, glycated haemoglobin, systolic blood pressure, body mass index, waist circumference and waist-hip ratio (shown in supplementary table 2)*

FIGURE

Title: Figure 1: Flow chart of the survey on metabolic outcomes in the Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA) cluster-randomised trial

Legend:

** In two villages, the total number of households per village was less than 70 and therefore all households (41 and 69 respectively) were invited to participate*

Figure 1