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Lule, Swaib A; Namara, Benigna; Akurut, Helen; Lubyayi, Lawrence; Nampijja, Margaret; Akello, Florence; Tumusiime, Josephine; Aujo, Judith C; Oduru, Gloria; Mentzer, Alexander J; +3 more... Smeeth, Liam; Elliott, Alison M; Webb, Emily L; (2019) Blood pressure risk factors in early adolescents: results from a Ugandan birth cohort. *Journal of human hypertension*. ISSN 0950-9240 DOI: <https://doi.org/10.1038/s41371-019-0178-y>

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# Blood pressure risk factors in early adolescents: results from a Ugandan birth cohort

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Received: 5 July 2018 / Revised: 25 January 2019 / Accepted: 11 February 2019  
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## Abstract

We aimed to investigate life-course factors associated with blood pressure (BP) among Ugandan adolescents. Between 9th April 2003 and 24th November 2005, 2507 pregnant women from Entebbe municipality and Katabi sub-county were enrolled into a deworming trial. The resulting 2345 live-born offspring were followed to age 10 or 11 years, when between 20th May 2014 to 16th June 2016, BP was measured following standard protocols. Factors associated with BP were assessed using multivariable linear regression. BP was measured in 1119 adolescents with a median age of 10.2 years. Mean systolic BP and diastolic BP was 105.9 mmHg (standard deviation (SD) 8.2) and 65.2 mmHg (SD 7.3), respectively. Maternal gestational body mass index (BMI), higher maternal education status and family history of hypertension were positively associated with adolescent BP. Childhood (age  $\leq 5$  years) malaria was associated with lower adolescent systolic BP. Factors measured at time of BP measurement positively associated with systolic BP were age, BMI, waist circumference and Trichuris (whipworm) infection; higher vegetable consumption was associated with lower systolic BP. Results for diastolic BP were similar, except higher fruit, rather than higher vegetable consumption was associated with lower diastolic BP and there was no association with waist circumference or Trichuris infection. In summary, life-course exposures were associated with adolescent BP in this tropical birth cohort. Malaria early in life could impact later BP. Interventions initiated early in life targeting individuals with family history of hypertension, aiming to reduce adiposity (in pregnancy and adolescence) and promoting fruit and vegetable consumption might contribute to reducing the risk of high BP and subsequent CVDs.

## Introduction

Once uncommon in Africa [1], high blood pressure (BP) and cardiovascular diseases (CVDs) have escalated on the continent over recent decades [2], affecting populations at younger ages than in more affluent countries [3]. The rising burden of high BP in Africa has been attributed to a transition from active to more sedentary lifestyles and a rise in unhealthy dietary practices [2]. Data on individual level BP risk factors in African adolescents and children are sparse.

Although high BP is less common in children and adolescents than in adults, it initiates early in life, persists into adulthood [4] and predicts adulthood hypertension [5]. Diagnosis of CVDs is uncommon until middle-age, yet its antecedents, mainly cardiovascular and metabolic changes, begin early in life [6]. Globally, the high BP burden in younger age groups has risen [7], with estimated prevalence of 1–25% among African children and adolescents [8].

**Supplementary information** The online version of this article (<https://doi.org/10.1038/s41371-019-0178-y>) contains supplementary material, which is available to authorized users.

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Severe persistent high BP is associated with increased risk of stroke and heart failure [9]; treatment reduces long-term sequelae [9]. In children and adolescents, high BP is often asymptomatic and unnoticed, despite international recommendations for regular BP measurement from three years of age [10]. Hypertension diagnosis is commonly missed or inaccurately classified in children and adolescents [11]. Consequently, over 75% of high BP among children and adolescents remains undiagnosed worldwide [12].

Earlier studies, mainly in adults, have demonstrated the role of established risk factors for high BP such as obesity [13] and physical activity [14]. There is little literature on childhood and adolescent BP determinants from Africa; in particular the impact of childhood infections (of special importance in Africa) remains understudied and unknown.

Childhood and adolescence are opportune periods for high BP control or prevention before clinical manifestation of hypertension or related CVDs. Identification of life-course BP risk factors unique to Africa is needed for the development of appropriate BP control strategies. We used longitudinally collected data from the Entebbe Mother and Baby Study (EMaBS), a large tropical birth cohort, to describe factors associated with adolescent BP.

## Methods

### Study design, setting and population

This longitudinal observational study investigated perinatal and life-course factors associated with BP among adolescents born in Wakiso district, Uganda. The EMaBS was a randomised double-blind placebo-controlled factorial trial [ISRCTN32849447], designed to investigate effects of worms and their treatment in pregnancy and childhood on response to childhood vaccines and on infections [15].

The study was conducted in Entebbe municipality and Katabi sub-county (a peninsula on the northern shores of Lake Victoria). In 2003–2005, 2507 women attending Entebbe Hospital antenatal clinic, in their second or third trimester were invited, enrolled and randomised to receive albendazole (400 mg) or placebo and praziquantel (40 mg/kg) or placebo [15].

Data were collected prenatally from women and resulting 2345 live-born offspring followed from birth. As previously described [16], at 15 months offspring were randomised to receive quarterly single-dose albendazole or placebo up to age five years. Disease events were recorded at the study clinic annually and when the child reported to the clinic with an illness. Children continued under follow-up (seen at routine annual visits and when sick) after trial completion. Between 20th May 2014 and 16th June 2016, additional data, including BP measurements, anthropometry, puberty,

physical activity and diet were collected from 10- and 11-year-olds. Enrolment into the BP study was postponed for those with malaria (fever with malaria parasites) or other illness until they were well after being treated by the study team. Clinic based field workers conducted home visits and telephone calls to remind participants of their annual visit and also invite them to participate in the BP study. Participants who then attended their 10- or 11-year annual visit during the BP study period were then invited to enrol and take part in the BP study at that visit. Adolescents participated once, on their first 10 or 11-year annual visit occurring during the study period.

### Study procedures

Birth weight was measured and recorded immediately after birth in Entebbe hospital or from child health cards for deliveries conducted elsewhere [17]. Weight and height at 10/11 years were measured with scales (Seca, Hamburg, Germany) and stadiometers (Seca 213, Hamburg Germany), respectively. Waist circumference was measured to the nearest 0.1 cm using a Seca tape measure (Seca 201, Hamburg, Germany). BMI was calculated as weight in kilograms (kg) divided by height squared ( $m^2$ ). Trained clinicians examined and performed Tanner staging [18].

Whole-genome genotyping of 1391 EMaBS samples was conducted at the Wellcome Trust Sanger Institute using Illumina HumanOmni2.5M-8 ('octo') Beadchip arrays, version 1.1 (Illumina Inc., San Diego, USA). Sickle-cell trait was imputed using a merged 1000 Genomes and African-specific reference panel [19].

For participants taking part in the BP study from the 21st January 2015 to 23rd December 2015, extra data on fat mass (FM), fat-free mass (FFM) and total body water mass (TBW) were collected by trained nurses using a segmental body composition analyser machine (SBCAM) (TANITA BC-418, TANITA Corporation, Tokyo Japan). Briefly, participants stood barefooted on the posterior electrode base while holding two anterior electrodes handles of the SBCAM. Fat mass index = FMI ( $kg/m^2$ ), fat-free mass index = FFMI ( $kg/m^2$ ) and total body water mass index = TBWI ( $kg/m^2$ ) were computed.

Stool and blood samples were collected from women at enrolment and annually from children. Stool was examined for helminth ova and *Strongyloides* larvae using Kato-Katz [20] and charcoal culture [21] methods, respectively. Blood was examined for malaria parasites using Leishman's stains [16]. Modified Knott's method [22] was used for *Mansonia perstans*. Maternal HIV status at enrolment and children's HIV status after 18 months of age were assessed using a rapid serial testing algorithm described elsewhere [21, 23]. In infancy, HIV status was determined using polymerase chain reaction [21].

At the 10- or 11-year annual visit, three BP measurements (at ~5 min intervals) were taken after 5 min rest using automated devices (Omron M6), with appropriate sized cuffs [5], by trained nurses following standard protocols described elsewhere [17].

For clinical care purposes, means of the three systolic BP and three diastolic BP measurements were calculated and BP percentiles determined using Centre for Disease Control height charts and 2004 updated National Health and Nutrition Examination Survey BP tables specific for sex, age and height [5, 10]. Those with mean systolic BP or diastolic BP  $\geq 95$ th percentile (“high BP”) had their BP re-measured on up to two extra days, 1–2 weeks apart. “Pre-hypertension” was defined as systolic or diastolic BP  $\geq 90$ th but  $< 95$ th percentile. Those with persistent high BP on three different days were referred for specialist attention. Lifestyle modification was recommended for participants with systolic or diastolic BP  $\geq 90$ th percentile.

For data analysis purposes, the means of the second and third systolic/diastolic BP readings on day 1 were used: day 1 second and third BP readings were lower than the first BP reading but similar to each other [17].

Ethical approval was granted by the Uganda Virus Research Institute Science and Ethics Committee; the Uganda National Council for Science and Technology; and the London School of Hygiene and Tropical Medicine. Written informed assent and consent were obtained.

## Statistical methods

Data were collected on pre-coded questionnaires and analysed with Stata 14.2 (College Station, TX, USA). Chi-squared tests (for categorical variables) and *t*-tests (for continuous variables) were used to compare characteristics of cohort members who participated and did not participate in the BP study.

Study outcomes were mean systolic BP and mean diastolic BP, based on the second and third day-one measurements. The decision was made to model these two continuous BP outcome variables rather than to dichotomise outcomes (for example, into normal versus hypertensive) as an analysis using these binary outcomes would be underpowered. Maternal, perinatal and offspring life-course factors considered as exposures and potential confounders were: maternal and adolescent socio-demographic and anthropometric characteristics; EMaBS trial interventions (praziquantel or albendazole); sickle-cell trait; illnesses and infections from birth to time of BP measurement; and body composition, puberty stage, diet, sleep pattern and physical activity at time of BP measurement. Area of residence was grouped into urban versus rural area using zones based on topography and settlements generated from geographical positioning system data [24]. Household socioeconomic

index was generated using principal components analysis of building materials, household size and items owned [23]. Birth season was dichotomised into dry (rainfall below monthly median) and wet (rainfall above monthly median) season. Malaria infection in childhood (age  $\leq 5$  years) was investigated as clinical malaria (history of fever within the last 48 h or axillary temperature  $\geq 37.5$  °C and parasitaemia) and asymptomatic malaria (parasitaemia without fever at any annual visit up to 5 years). Information on diet was obtained as the number of days in a typical week over the previous month for which a given food was consumed. Puberty was grouped into pre-pubertal (stage 1) or pubertal (stages 2–5) for breast or pubic hair development using Tanner methods [18].

Linear regression analysis was used. Data satisfied the assumptions for linear regression. Crude associations were examined for each covariate and a 20% significance level used for selecting covariates for multivariable models. Adolescents’ sex, age and BMI were confounders a priori. Multivariable analysis followed a hierarchical causal approach adding factors sequentially (Fig. 1).

Because of a large proportion of missing data, puberty and body composition variables were not included in model building for other exposures but their effects were each adjusted for variables included in the final multivariable model. Multicollinearity was assessed by considering the change in standard error, when potentially multicollinear variables were included in the same model.

The study was approved by the Research and Ethics Committee of the Uganda Virus Research Institute, the Uganda National Council for Science and Technology and the London School of Hygiene & Tropical Medicine. Consent and assent were obtained for study participation.

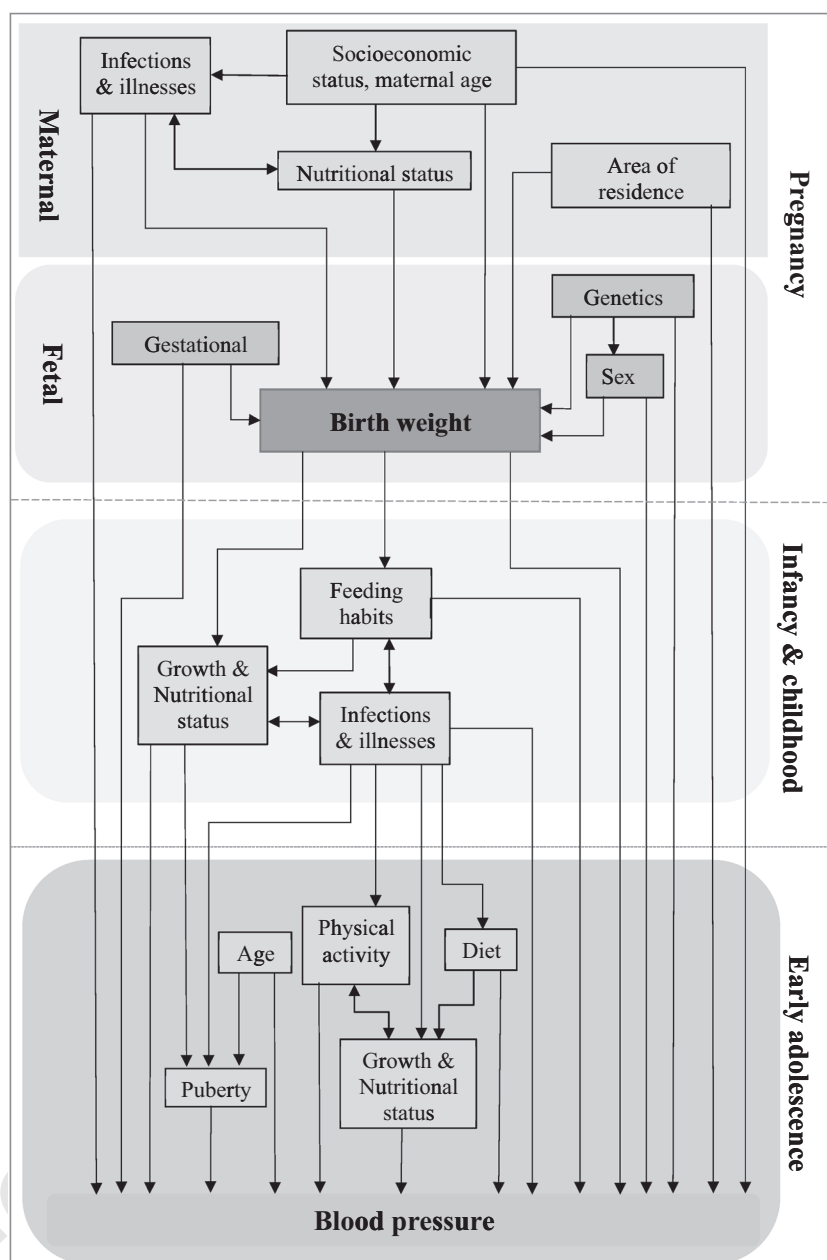
## Results

### Participant characteristics

A total of 1119 EMaBS participants were enrolled into the BP study: 583 (52%) were males; 1100 (98.3%) singletons; 18 (2%) HIV positive; and 344 (31%) mixed feeding by 6 weeks. EMaBS adolescents participating in the BP study were similar to non-participants, except that mothers of participants were more likely to be of higher education status or married/cohabiting; offspring were less likely to be HIV positive or of a multiple birth, details published earlier [17].

At age 10/11 (median participant age 10.2 years (interquartile range (IQR): 10.0–10.9)), 117 (11%) were attending boarding schools, 441 (72%) were pre-pubertal stage for pubic hair development and 178 (65%) of girls were pre-pubertal stage for breast development. Mean BMI was

Fig. 1 Conceptual framework



242 15.8 kg/m<sup>2</sup> (SD 1.9) and mean waist circumference 58.1 cm  
 243 (SD 4.9). Body composition data were available for 176  
 244 (16%) participants, with mean fat mass index 2.9 kg/m<sup>2</sup> (SD  
 245 1.2), fat-free mass index 12.8 kg/m<sup>2</sup> (SD 1.4) and total body  
 246 water mass index 9.5 kg/m<sup>2</sup> (SD 0.9).

247 Over the previous month, starchy staple foods, animal  
 248 proteins, fruit, vegetables and sugar drinks were consumed  
 249 on average for 6.9 days/week (SD 0.8), 2.2 days/week (SD  
 250 1.7), 3 days/week (SD 2.2), 3.4 days/week (SD 2.3) and  
 251 1.7 days/week (SD 2.1), respectively. Nearly all adolescents  
 252 (98%) reported adding salt to cooked food.

253 Mean systolic BP was 105.9 mmHg (SD 8.2) and mean  
 254 diastolic BP was 65.2 mmHg (SD 7.3). There was no

255 difference in mean systolic BP ( $P$ -value = 0.971) or dia-  
 256 stolic BP ( $P$ -value = 0.141) between males and females.  
 257 None of the adolescents had had a prior BP measurement or  
 258 high BP diagnosis.

### 259 Prevalence of high BP

260 Using day 1 BP readings, the prevalence of pre-  
 261 hypertension and high BP was 63 (10.8%) and 42 (7.2%),  
 262 respectively, among males, and 54 (10.1%) and 52 (9.7%),  
 263 respectively, among females. After extra measurements on  
 264 the second and third visits and taking loss to follow-up into  
 265 account, pre-hypertension prevalence was estimated as

266 2.2% in males and 0.7% in females; high BP prevalence  
267 was 0.4% in males and 1.8% in females.

## 268 Risk factors for high BP

269 Tables 1 and 2 show the relationship between examined  
270 characteristics and BP (systolic or diastolic) in adolescents.  
271 Maternal factors crudely positively associated with adoles-  
272 cent systolic BP were gestational BMI and education status;  
273 both remained associated with systolic BP after adjustment  
274 for other maternal factors. The trial interventions during  
275 pregnancy (albendazole and praziquantel) and early child-  
276 hood (albendazole) had no effect on systolic or diastolic BP.

277 Characteristics at the time of BP measurement showing a  
278 crude positive association with systolic BP were age, BMI,  
279 waist circumference, family history of high BP, body  
280 composition variables and puberty stage covariates. In  
281 multivariable analysis, systolic BP increased, on average,  
282 by 1.35 mmHg, 95% CI (0.32, 2.39) for each 1-year  
283 increase in adolescents' age; by 0.78 mmHg (0.42, 1.14) per  
284 unit increase in BMI; and by 0.21 mmHg (0.08, 0.35) per  
285 centimetre increase in waist circumference. Family history  
286 of high BP remained associated with increased SBP,  $\beta =$   
287 1.84 (0.12, 3.56) after adjustment for maternal and child-  
288 hood factors. Body composition and puberty stage covari-  
289 ates were no longer associated with systolic BP on adjusting  
290 for adolescents' age, BMI and waist circumference.

291 Lifestyle factors crudely associated with increased sys-  
292 tolic BP were increased animal-protein consumption,  
293 increased consumption of sugared drinks and attending a  
294 boarding school rather than a day school. Increased fruit and  
295 vegetable consumption were associated with reduced sys-  
296 tolic BP. After adjusting for confounders, systolic BP  
297 reduced, on average, by 1.13 mmHg (-2.15, -0.10) among  
298 adolescents who consumed vegetables for 3–7 days/week  
299 (versus 0–2 days/week).

300 Current infection with *Trichuris* was positively asso-  
301 ciated with systolic BP after adjusting for confounders ( $\beta =$   
302 3.48 mmHg (0.79, 6.18)). Systolic BP dropped by  
303 1.24 mmHg (-2.32, -0.17) among adolescents who had  
304 malaria in childhood compared to those who had not. Both  
305 clinical and asymptomatic malaria were independently  
306 associated with lower BP in multivariable analysis. Weight  
307 and height at 10 and 11 years of age were reduced among  
308 adolescents with childhood clinical and or asymptomatic  
309 malaria (Supplementary Table 1). Compared to those with  
310 no asymptomatic malaria, having asymptomatic malaria in  
311 childhood was associated with, on average, a 3.2 cm  
312 reduction in height, 95% CI (-4.5, -2.0) and a 2.1 kg  
313 reduction in weight, 95% CI (-3.0, -1.9). The effect of  
314 childhood malaria on adolescent BP was weaker on  
315 adjusting for adolescent BMI (Supplementary Table 2).

316 Genetic data were available for 802 (72%) participants of  
317 whom 141 (18%) had sickle-cell trait (HbAS) and 661  
318 (82%) normal haemoglobin (HbAA). Sickle-cell trait was  
319 not associated with systolic BP ( $\beta = -0.28$  mmHg (-1.79,  
320 1.23)), even after adjusting for age and sex. HbAS was  
321 inversely associated with malaria (Supplementary Table 3):  
322 in those with HbAA, 63% had clinical or asymptomatic  
323 malaria up to 5 years compared to 51% with HbAS ( $P =$   
324 0.008).

325 Findings for diastolic BP were broadly similar to those  
326 for systolic BP, with the exceptions that higher fruit rather  
327 than vegetable consumption was associated with lower  
328 diastolic BP, and there was no association with waist cir-  
329 cumference or *Trichuris* infection. No associations were  
330 observed between adolescent BP and any of the other fac-  
331 tors considered in this population (Tables 1 and 2).

## 332 Discussion

333 Persistent high BP and pre-hypertension were unusual in  
334 early adolescence in this setting. Maternal gestational BMI  
335 and education status at enrolment, participant's family his-  
336 tory of hypertension, and adolescents' age and BMI at BP  
337 measurement were positively associated with both systolic  
338 BP and diastolic BP. Malaria parasitaemia in childhood, and  
339 increased vegetable and fruit consumption were inversely  
340 associated with systolic BP and diastolic BP, respectively.  
341 Concurrent *Trichuris* infection was positively associated  
342 with systolic BP but not with diastolic BP. There were no  
343 effects of anti-helminth trial interventions (in pregnancy or  
344 childhood) on adolescent BP and no associations between  
345 prior helminth infection (in pregnancy or childhood) and  
346 adolescent BP.

347 Our findings are consistent with several earlier studies  
348 [25, 26]. We have shown that consuming vegetable and  
349 fruits for 3–7 days/week was associated with lower systolic  
350 BP and diastolic BP, respectively. Our results support  
351 findings from a cross-sectional study that consuming fruits  
352 and vegetables (>400 g/day) lowers systolic BP and dia-  
353 stolic BP in adults [26]. We have shown a positive asso-  
354 ciation of BP with maternal gestational BMI, and adolescent  
355 BMI and waist circumference at the time of BP measure-  
356 ment, consistent with earlier studies [13].

357 Malaria parasitaemia in childhood was associated with  
358 lower BP in early adolescence, consistent with findings  
359 from a cross-sectional study among 5–18-year-old Ugandan  
360 students, which reported that current asymptomatic malaria  
361 was associated with lower BP [25]. Our study was under-  
362 powered to detect the effect of current parasitaemia on BP,  
363 with only 22 (2.1%) adolescents had parasitaemic at the  
364 time of BP measurement.

**Table 1** Factors investigated for association with systolic BP among adolescents from the Entebbe Mother and Baby Study ( $N = 1119$ )

| Factors                                 | Mean BP (SD)       | Crude $\beta$ (95% CI) | $P$ -value         | Adjusted $\beta$ (95% CI)  | $P$ -value       |
|---|--------------------|------------------------|--------------------|----------------------------|------------------|
| Level 1: Maternal factors at enrolments |                    |                        |                    |                            |                  |
| Age (years)                             | 0.06 (−0.03, 0.15) | 0.178                  | 0.02 (−0.07, 0.12) | 0.604                      |                  |
| Household SES<br>( $n = 1104$ )         |                    | 0.23 (−0.16, 0.63)     | 0.245              |                            |                  |
| Parity                                  | 0.04 (−0.23, 0.31) | 0.751                  |                    |                            |                  |
| Body mass index<br>( $n = 1110$ )       |                    | 0.27 (0.13, 0.42)      | <0.001             | <b>0.26 (0.11, 0.40)</b>   | <b>&lt;0.001</b> |
| Education status                        |                    |                        |                    |                            |                  |
| None ( $n = 28$ )                       | 104.5 (8.7)        | −0.54 (−3.65, 2.56)    |                    | <b>−0.62 (−3.77, 2.53)</b> |                  |
| Primary ( $n = 542$ )                   | 105.0 (7.7)        | Reference              |                    | <b>Reference</b>           |                  |
| Senior ( $n = 438$ )                    | 106.5 (8.2)        | 1.45 (0.42, 2.48)      |                    | <b>1.43 (0.39, 2.47)</b>   |                  |
| Tertiary ( $n = 109$ )                  | 108.2 (9.8)        | 3.19 (1.51, 4.87)      | <0.001             | <b>3.14 (1.45, 4.84)</b>   | <b>&lt;0.001</b> |
| Marital status                          |                    |                        |                    |                            |                  |
| Single ( $n = 116$ )                    | 104.7 (7.6)        | −1.34 (−2.92, 0.25)    |                    |                            |                  |
| Married/cohabiting ( $n = 967$ )        | 106.0 (8.3)        | Reference              |                    |                            |                  |
| Separated/widowed ( $n = 35$ )          | 105.3 (6.1)        | −0.78 (−3.56, 1.99)    | 0.229              |                            |                  |
| Area of residence                       |                    |                        |                    |                            |                  |
| Urban ( $n = 770$ )                     | 106.0 (8.3)        | Reference              |                    |                            |                  |
| Rural ( $n = 336$ )                     | 105.5 (8.0)        | −0.47 (−1.52, 0.59)    | 0.386              |                            |                  |
| Alcohol use                             |                    |                        |                    |                            |                  |
| No ( $n = 775$ )                        | 105.8 (8.4)        | Reference              |                    |                            |                  |
| Yes ( $n = 343$ )                       | 106.0 (7.8)        | 0.15 (−0.90, 1.19)     | 0.781              |                            |                  |
| Infections                              |                    |                        |                    |                            |                  |
| HIV                                     |                    |                        |                    |                            |                  |
| Uninfected ( $n = 1002$ )               | 106.0 (8.3)        | Reference              |                    | Reference                  |                  |
| Infected ( $n = 117$ )                  | 104.8 (7.2)        | −1.17 (−2.74, 0.41)    | 0.146              | −0.88 (−2.48, 0.72)        | 0.279            |
| Asymptomatic malaria                    |                    |                        |                    |                            |                  |
| Uninfected ( $n = 991$ )                | 105.8 (8.2)        | Reference              |                    |                            |                  |
| Infected ( $n = 109$ )                  | 106.2 (8.6)        | 0.42 (−1.20, 2.05)     | 0.609              |                            |                  |
| Schistosomiasis                         |                    |                        |                    |                            |                  |
| Uninfected ( $n = 908$ )                | 105.8 (8.3)        | Reference              |                    |                            |                  |
| Infected ( $n = 204$ )                  | 106.2 (7.9)        | 0.35 (−0.90, 1.61)     | 0.578              |                            |                  |
| Hookworm                                |                    |                        |                    |                            |                  |
| Uninfected ( $n = 662$ )                | 105.8 (8.1)        | Reference              |                    |                            |                  |
| Infected ( $n = 450$ )                  | 105.9 (8.4)        | 0.10 (−0.89, 1.09)     | 0.844              |                            |                  |
| Ascaris                                 |                    |                        |                    |                            |                  |
| Uninfected ( $n = 1084$ )               | 105.9 (8.3)        | Reference              |                    |                            |                  |
| Infected ( $n = 28$ )                   | 105.7 (6.7)        | −0.17 (−3.27, 2.92)    | 0.912              |                            |                  |
| Intervention one                        |                    |                        |                    |                            |                  |
| Placebo ( $n = 566$ )                   | 105.5 (8.2)        | Reference              |                    | Reference                  |                  |
| Albendazole ( $n = 553$ )               | 106.2 (8.3)        | 0.67 (−0.29, 1.63)     | 0.173              | 0.84 (−0.12, 1.80)         | 0.087            |
| Intervention two                        |                    |                        |                    |                            |                  |
| Placebo ( $n = 564$ )                   | 106.0 (8.1)        | Reference              |                    |                            |                  |
| Praziquantel ( $n = 555$ )              | 105.8 (8.4)        | −0.20 (−1.16, 0.77)    | 0.686              |                            |                  |
| Level 2: Factors in childhood           |                    |                        |                    |                            |                  |
| Birth weight ( $n = 932$ )              | 0.73 (−0.33, 1.80) | 0.178                  | 0.18 (−0.93, 1.29) | 0.751                      |                  |
| Sex                                     |                    |                        |                    |                            |                  |
| Male ( $n = 583$ )                      | 105.9 (7.5)        | Reference              |                    | Reference                  |                  |
| Female ( $n = 536$ )                    | 105.9 (9.0)        | −0.02 (−0.98, 0.95)    | 0.971              | 0.12 (−1.18, 0.94)         | 0.819            |
| Sickle-cell trait                       |                    |                        |                    |                            |                  |
| HbAA ( $n = 661$ )                      | 106.0 (8.4)        | Reference              |                    |                            |                  |
| HbAS ( $n = 141$ )                      | 105.8 (7.9)        | −0.28 (−1.79, 1.23)    | 0.717              |                            |                  |
| Season of birth                         |                    |                        |                    |                            |                  |
| Dry ( $n = 651$ )                       | 106.1 (8.1)        | Reference              |                    |                            |                  |
| Wet ( $n = 468$ )                       | 105.5 (8.3)        | −0.56 (−1.54, 0.42)    | 0.261              |                            |                  |
| Place of delivery                       |                    |                        |                    |                            |                  |
| Entebbe Hospital ( $n = 824$ )          | 105.8 (8.2)        | Reference              |                    | Reference                  |                  |
| Home ( $n = 120$ )                      | 104.9 (8.6)        | −0.86 (−2.43, 0.71)    |                    | −0.37 (−3.71, 2.96)        |                  |
| Others ( $n = 174$ )                    | 106.8 (8.0)        | 0.95 (−0.39, 2.29)     | 0.166              | 0.90 (−0.87, 2.68)         | 0.582            |
| Feeding status (6 weeks of age)         |                    |                        |                    |                            |                  |
| Exclusively breast fed ( $n = 748$ )    | 106.1 (8.2)        | Reference              |                    |                            |                  |
| Mixed fed ( $n = 344$ )                 | 105.4 (8.4)        | −0.70 (−1.75, 0.35)    |                    |                            |                  |
| Weaned ( $n = 14$ )                     | 105.8 (7.1)        | −0.28 (−4.63, 4.08)    | 0.430              |                            |                  |
| Intervention three                      |                    |                        |                    |                            |                  |
| Placebo ( $n = 553$ )                   | 105.5 (8.4)        | Reference              |                    |                            |                  |
| Albendazole ( $n = 554$ )               | 106.1 (8.0)        | 0.61 (−0.36, 1.58)     | 0.218              |                            |                  |

**Table 1** (continued)

| Factors                                       | Mean BP (SD)      | Crude $\beta$ (95% CI) | P-value                  | Adjusted $\beta$ (95% CI)   | P-value      |
|---|-------------------|------------------------|--------------------------|-----------------------------|--------------|
| <b>HIV status</b>                             |                   |                        |                          |                             |              |
| Unexposed (n= 1001)                           | 106.0 (8.3)       |                        | Reference                |                             |              |
| Exposed not infected (n = 100)                | 105.2 (7.3)       | -0.83 (-2.52, 0.86)    |                          | -0.29 (-2.15, 1.57)         |              |
| Infected (n = 18)                             | 102.7 (6.1)       | -3.34 (-7.17, 0.49)    | 0.156                    | -3.85 (-7.81, 0.12)         | 0.157        |
| <b>Malaria infection below 5 years of age</b> |                   |                        |                          |                             |              |
| Clinical or asymptomatic <sup>a</sup>         |                   |                        |                          |                             |              |
| None (n = 456)                                | 106.6 (8.0)       | Reference              |                          | <b>Reference</b>            |              |
| Yes (n = 663)                                 | 105.3 (8.3)       | -1.31 (-2.29, -0.33)   | 0.009                    | <b>-1.24 (-2.32, -0.17)</b> | <b>0.023</b> |
| Clinical malaria <sup>a</sup>                 |                   |                        |                          |                             |              |
| None (n = 474)                                | 106.6 (8.0)       | Reference              |                          | <b>Reference</b>            |              |
| Yes (n = 645)                                 | 105.4 (8.3)       | -1.19 (-2.17, -0.22)   | 0.016                    | <b>-1.08 (-2.15, -0.02)</b> | <b>0.045</b> |
| Episodes of clinical malaria <sup>a</sup>     |                   |                        |                          |                             |              |
| None (n = 474)                                | 106.6 (8.0)       | Reference              |                          | Reference                   |              |
| 1-2 (n = 382)                                 | 105.4 (8.4)       | -1.13 (-2.24, -0.03)   |                          | -1.11 (-2.32, 0.11)         |              |
| $\geq 3$ (n = 263)                            | 105.3 (8.2)       | -1.28 (-2.52, -0.04)   | 0.026 [trend]            | -1.05 (-2.41, 0.31)         | 0.133        |
| Asymptomatic malaria <sup>a</sup>             |                   |                        |                          |                             |              |
| None (n = 983)                                | 106.1 (8.2)       | Reference              |                          | <b>Reference</b>            |              |
| Yes (n = 124)                                 | 103.7 (8.0)       | -2.41 (-3.94, -0.88)   | 0.002                    | <b>-1.95 (-3.70, -0.20)</b> | <b>0.028</b> |
| <b>Schistosomiasis</b>                        |                   |                        |                          |                             |              |
| Uninfected (n = 1076)                         | 105.9 (8.2)       | Reference              |                          |                             |              |
| Infected (n = 33)                             | 104.8 (7.9)       | -1.09 (-3.94, 1.76)    | 0.452                    |                             |              |
| <b>Ascaris</b>                                |                   |                        |                          |                             |              |
| Uninfected (n = 1052)                         | 105.9 (8.3)       | Reference              |                          |                             |              |
| Infected (n = 57)                             | 105.3 (7.3)       | -0.62 (-2.82, 1.57)    | 0.576                    |                             |              |
| <b>Hookworm</b>                               |                   |                        |                          |                             |              |
| Uninfected (n = 1085)                         | 105.9 (8.2)       | Reference              |                          |                             |              |
| Infected (n = 24)                             | 103.8 (8.9)       | -2.06 (-5.38, 1.27)    | 0.225                    |                             |              |
| <b>Trichuris</b>                              |                   |                        |                          |                             |              |
| Uninfected (n = 997)                          | 105.9 (8.2)       | Reference              |                          |                             |              |
| Infected (n = 112)                            | 105.6 (8.6)       | -0.28 (-1.89, 1.33)    | 0.731                    |                             |              |
| <b>Microfilaria</b>                           |                   |                        |                          |                             |              |
| Uninfected (n = 1102)                         | 105.8 (8.2)       | Reference              |                          |                             |              |
| Infected (n = 8)                              | 109.4 (8.9)       | 3.58 (-2.13, 9.28)     | 0.219                    |                             |              |
| <b>Level 3: Factors in adolescence</b>        |                   |                        |                          |                             |              |
| Age   | 2.12 (1.17, 3.08) | <0.001                 | <b>1.35 (0.32, 2.39)</b> | <b>0.009</b>                |              |
| Body mass index                               | 1.27 (1.02, 1.51) | <0.001                 | <b>0.78 (0.42, 1.14)</b> | <b>&lt;0.001</b>            |              |
| Waist circumference                           | 0.46 (0.36, 0.55) | <0.001                 | <b>0.21 (0.08, 0.35)</b> | <b>0.002</b>                |              |
| <b>Family history</b>                         |                   |                        |                          |                             |              |
| High blood pressure                           |                   |                        |                          |                             |              |
| No (n = 1000)                                 | 105.7 (8.1)       | Reference              |                          | <b>Reference</b>            |              |
| Yes (n = 105)                                 | 107.6 (8.3)       | 1.88 (0.24, 3.52)      | 0.025                    | <b>1.84 (0.12, 3.56)</b>    | <b>0.034</b> |
| Diabetes                                      |                   |                        |                          |                             |              |
| No (n = 927)                                  | 105.8 (8.0)       | Reference              |                          |                             |              |
| Yes (n = 186)                                 | 106.4 (9.2)       | 0.69 (-0.61, 1.99)     | 0.296                    |                             |              |
| <b>Body composition analysis<sup>c</sup></b>  |                   |                        |                          |                             |              |
| Fat mass index (n = 176) <sup>b</sup>         |                   | 3.27 (2.29, 4.24)      | <0.001                   | 1.50 (-0.38, 3.38)          | 0.089        |
| Fat-free mass index (n = 176) <sup>b</sup>    |                   | 1.54 (0.65, 2.43)      | 0.001                    | -0.86 (-2.25, 0.54)         | 0.188        |
| Total body water index (n = 176) <sup>b</sup> |                   | 4.20 (2.97, 5.42)      | <0.001                   | 2.51 (-0.24, 5.27)          | 0.052        |
| <b>Adding salt to food</b>                    |                   |                        |                          |                             |              |
| No (n = 20)                                   | 106.2 (7.3)       | 0.36 (-3.28, 4.00)     |                          |                             |              |
| Yes (n = 1086)                                | 105.9 (8.2)       | Reference              | 0.846                    |                             |              |
| <b>Days a fruit is eaten/week</b>             |                   |                        |                          |                             |              |
| 0-2 (n = 543)                                 | 106.3 (8.0)       | Reference              |                          | Reference                   |              |
| 3-7 (n = 541)                                 | 105.5 (8.5)       | -0.83 (-1.82, 0.15)    | 0.098                    | -0.83 (-1.84, 0.19)         | 0.106        |
| <b>Days vegetables eaten/week</b>             |                   |                        |                          |                             |              |
| 0-2 (n = 461)                                 | 106.4 (8.2)       | Reference              |                          | <b>Reference</b>            |              |
| 3-7 (n = 635)                                 | 105.5 (8.3)       | -0.94 (-1.93, 0.05)    | 0.063                    | <b>-1.13 (-2.15, -0.10)</b> | <b>0.029</b> |
| <b>Days animal-protein eaten/week</b>         |                   |                        |                          |                             |              |
| 0-2 (n = 726)                                 | 105.4 (7.8)       | Reference              |                          | Reference                   |              |
| 3-7 (n = 374)                                 | 106.6 (8.8)       | 1.17 (0.16, 2.19)      | 0.024                    | 0.99 (-0.06, 2.04)          | 0.062        |
| <b>Days sugared drinks taken/week</b>         |                   |                        |                          |                             |              |
| None (n = 427)                                | 105.4 (8.1)       | Reference              |                          | Reference                   |              |
| 1-3 (n = 492)                                 | 105.9 (8.0)       | 0.54 (-0.53, 1.61)     |                          | -0.05 (-1.14, 1.05)         |              |
| 4-7 (n = 174)                                 | 107.2 (9.1)       | 1.81 (0.36, 3.26)      | 0.051                    | 0.96 (-0.53, 2.44)          | 0.358        |
| Days a fruit is eaten/week                    |                   | -0.05 (-0.27, 0.18)    | 0.687                    |                             |              |



**Table 1** (continued)

| Factors                                      | Mean BP (SD) | Crude $\beta$ (95% CI) | P-value | Adjusted $\beta$ (95% CI)        | P-value      |
|--|--------------|------------------------|---------|----------------------------------|--------------|
| Days vegetables eaten/week                   |              | -0.18 (-0.39, 0.03)    | 0.085   | -0.19 (-0.40, 0.03)              | 0.081        |
| Days animal-protein eaten/week               |              | 0.21 (-0.07, 0.50)     | 0.138   | 0.10 (-0.20, 0.39)               | 0.502        |
| Days starchy foods eaten/week                |              | 0.14 (-0.45, 0.73)     | 0.636   |                                  |              |
| Days sugared drinks taken/week               |              | 0.23 (0.00, 0.46)      | 0.049   | 0.11 (-0.12, 0.35)               | 0.325        |
| Breast development (girls only) <sup>b</sup> |              |                        |         |                                  |              |
| Pre-pubertal ( <i>n</i> = 178)               | 103.9 (7.8)  | Reference              |         | Reference                        |              |
| Pubertal ( <i>n</i> = 97)                    | 108.0 (10.5) | 4.07 (1.87, 6.26)      | <0.001  | 1.17 (-1.26, 3.59)               | 0.318        |
| Pubic hair development <sup>a</sup>          |              |                        |         |                                  |              |
| Pre-pubertal ( <i>n</i> = 441)               | 104.7 (7.4)  | Reference              |         | Reference                        |              |
| Pubertal ( <i>n</i> = 170)                   | 106.5 (9.3)  | 1.83 (0.42, 3.24)      | 0.011   | 0.51 (-0.96, 1.98)               | 0.486        |
| Snoring                                      |              |                        |         |                                  |              |
| No ( <i>n</i> = 932)                         | 105.8 (8.2)  | Reference              |         | Reference                        |              |
| Yes ( <i>n</i> = 163)                        | 106.3 (8.2)  | 0.53 (-0.83, 1.90)     | 0.444   |                                  |              |
| Duration of night sleep                      |              |                        |         |                                  |              |
| <9 h ( <i>n</i> = 306)                       | 106.1 (8.0)  | Reference              |         | Reference                        |              |
| 9 h ( <i>n</i> = 382)                        | 105.8 (8.8)  | -0.28 (-1.51, 0.96)    |         |                                  |              |
| >9 h ( <i>n</i> = 405)                       | 105.7 (7.7)  | -0.39 (-1.61, 0.83)    | 0.818   |                                  |              |
| Smoking in household                         |              |                        |         |                                  |              |
| No ( <i>n</i> = 962)                         | 106.0 (8.3)  | Reference              |         | Reference                        |              |
| Yes ( <i>n</i> = 147)                        | 104.9 (7.5)  | -1.03 (-2.46, 0.40)    | 0.157   | -0.65 (-2.10, 0.80)              | 0.372        |
| Type of school                               |              |                        |         |                                  |              |
| Day ( <i>n</i> = 117)                        | 105.7 (7.9)  | Reference              |         | Reference                        |              |
| Boarding school ( <i>n</i> = 719)            | 107.5 (10.3) | 1.76 (0.19, 3.34)      | 0.038   | 0.28 (-1.38, 1.95)               | 0.733        |
| Physical education at school                 |              |                        |         |                                  |              |
| No ( <i>n</i> = 385)                         | 105.5 (8.5)  | Reference              |         | Reference                        |              |
| Yes ( <i>n</i> = 719)                        | 106.0 (8.1)  | 0.48 (-0.54, 1.50)     | 0.360   |                                  |              |
| Infections at BP measurement                 |              |                        |         |                                  |              |
| Asymptomatic malaria                         |              |                        |         |                                  |              |
| Uninfected ( <i>n</i> = 1067)                | 106.0 (8.2)  | Reference              |         | Reference                        |              |
| Infected ( <i>n</i> = 22)                    | 103.1 (9.3)  | -2.85 (-6.31, 0.61)    | 0.106   | -1.50 (-5.02, 2.02) <sup>c</sup> | 0.397        |
| Schistosomiasis                              |              |                        |         |                                  |              |
| Uninfected ( <i>n</i> = 964)                 | 105.9 (8.3)  | Reference              |         | Reference                        |              |
| Infected ( <i>n</i> = 112)                   | 105.7 (8.4)  | -0.25 (1.88, 1.38)     | 0.764   |                                  |              |
| Hookworm                                     |              |                        |         |                                  |              |
| Uninfected ( <i>n</i> = 1066)                | 105.9 (8.3)  | Reference              |         | Reference                        |              |
| Infected ( <i>n</i> = 10)                    | 103.8 (10.0) | -2.10 (-7.27, 3.07)    | 0.425   |                                  |              |
| Ascaris                                      |              |                        |         |                                  |              |
| Uninfected ( <i>n</i> = 1073)                | 105.9 (8.3)  | Reference              |         | Reference                        |              |
| Infected ( <i>n</i> = 3)                     | 98.7 (1.6)   | -7.34 (-16.65, 2.17)   | 0.132   | -7.04 (-15.97, 1.88)             | 0.117        |
| Trichuris                                    |              |                        |         |                                  |              |
| Uninfected ( <i>n</i> = 1036)                | 105.8 (8.3)  | Reference              |         | Reference                        |              |
| Infected ( <i>n</i> = 40)                    | 107.9 (8.3)  | 2.16 (-0.46, 4.78)     | 0.106   | <b>3.48 (0.79, 6.18)</b>         | <b>0.010</b> |

Model building followed the hierarchical approach, adding factors sequentially at three levels starting with the distal factors (level 1). Factors at the same level were added to the model at the same time and considered confounders for each other and for proximal factors. A *P*-value < 0.20 was used for considering the inclusions and maintenance of factors in the model

Adjusted  $\beta$  with 95% CI excluding 0 in bold

$\beta$  linear regression coefficient: mean difference in blood pressure (BP) measured in mmHg

<sup>a</sup>Not included in the model together but each was adjusted for all other model variables

<sup>b</sup>Not included in multivariable model building for other exposures because of large proportion of missing information but each was adjusted for variables in the final model building

<sup>c</sup>Not adjusted for body mass index because body mass index is on the causal pathway

**Table 2** Factors investigated for association with diastolic BP among adolescents from the Entebbe Mother and Baby Study ( $N = 1119$ )

|                                    | Mean BP (SD) | Crude $\beta$ (95% CI) | P-value | Adjusted $\beta$ (95% CI) <sup>†</sup> | P-value      |
|------------------------------------|--------------|------------------------|---------|--|--------------|
| <b>(A) Maternal factors</b>        |              |                        |         |  |              |
| Age (years)                        |              | 0.08 (-0.00, 0.15)     | 0.058   | 0.05 (-0.03, 0.13)                     | 0.247        |
| Household SES ( $n = 1104$ )       |              | 0.22 (-0.13, 0.56)     | 0.225   |  |              |
| Parity                             |              | 0.08 (-0.16, 0.32)     | 0.530   |  |              |
| Body mass index ( $n = 1110$ )     |              | 0.16 (0.03, 0.29)      | 0.014   | <b>0.14 (0.01, 0.27)</b>               | <b>0.030</b> |
| Education status                   |              |                        |         |  |              |
| None ( $n = 28$ )                  | 65.1 (9.3)   | 0.44 (-2.32, 3.19)     |         | <b>0.08 (-2.71, 2.89)</b>              |              |
| Primary ( $n = 542$ )              | 64.6 (6.7)   | Reference              |         | <b>Reference</b>                       |              |
| Senior ( $n = 438$ )               | 65.5 (7.5)   | 0.92 (0.01, 1.84)      |         | <b>1.00 (0.07, 1.92)</b>               |              |
| Tertiary ( $n = 109$ )             | 66.8 (8.0)   | 2.14 (0.65, 3.64)      | 0.023   | <b>2.08 (0.57, 3.59)</b>               | <b>0.022</b> |
| Marital status                     |              |                        |         |  |              |
| Single ( $n = 116$ )               | 64.2 (6.4)   | -1.19 (-2.59, 0.21)    |         | -1.26 (-2.69, 0.16)                    |              |
| Married/cohabiting ( $n = 967$ )   | 65.4 (7.4)   | Reference              |         | Reference                              |              |
| Separated/widowed ( $n = 35$ )     | 63.5 (6.0)   | -1.91 (-4.36, 0.54)    | 0.089   | -1.91 (-4.38, 0.54)                    | 0.075        |
| Area of residence                  |              |                        |         |  |              |
| Urban ( $n = 770$ )                | 65.3 (7.5)   | Reference              |         |  |              |
| Rural ( $n = 336$ )                | 64.9 (6.8)   | 0.49 (-1.42, 0.44)     | 0.302   |  |              |
| Alcohol use                        |              |                        |         |  |              |
| No ( $n = 775$ )                   | 65.3 (7.5)   | Reference              |         |  |              |
| Yes ( $n = 343$ )                  | 65.0 (6.6)   | -0.34 (-1.26, 0.59)    | 0.477   |  |              |
| Infections                         |              |                        |         |  |              |
| HIV                                |              |                        |         |  |              |
| Uninfected ( $n = 1002$ )          | 65.2 (7.3)   | Reference              |         |  |              |
| Infected ( $n = 117$ )             | 64.9 (6.5)   | -0.35 (-1.74, 1.05)    | 0.626   |  |              |
| Asymptomatic malaria               |              |                        |         |  |              |
| Uninfected ( $n = 991$ )           | 65.2 (7.4)   | Reference              |         |  |              |
| Infected ( $n = 109$ )             | 64.9 (6.6)   | -0.29 (-1.73, 1.15)    | 0.695   |  |              |
| Schistosomiasis                    |              |                        |         |  |              |
| Uninfected ( $n = 908$ )           | 65.2 (7.1)   | Reference              |         |  |              |
| Infected ( $n = 204$ )             | 65.5 (7.7)   | 0.31 (-0.79, 1.41)     | 0.579   |  |              |
| Hookworm                           |              |                        |         |  |              |
| Uninfected ( $n = 662$ )           | 65.1 (7.1)   | Reference              |         |  |              |
| Infected ( $n = 450$ )             | 65.4 (7.4)   | 0.27 (-0.60, 1.14)     | 0.539   |  |              |
| Ascaris                            |              |                        |         |  |              |
| Uninfected ( $n = 1084$ )          | 65.3 (7.3)   | Reference              |         |  |              |
| Infected ( $n = 28$ )              | 65.1 (5.5)   | -0.18 (-2.90, 2.54)    | 0.896   |  |              |
| Intervention one                   |              |                        |         |  |              |
| Placebo ( $n = 566$ )              | 65.0 (6.9)   | Reference              |         |  |              |
| Albendazole ( $n = 553$ )          | 65.4 (7.7)   | 0.39 (-0.46, 1.24)     | 0.366   |  |              |
| Intervention two                   |              |                        |         |  |              |
| Placebo ( $n = 564$ )              | 65.4 (7.3)   | Reference              |         |  |              |
| Praziquantel ( $n = 555$ )         | 65.0 (7.2)   | -0.44 (-1.29, 0.42)    | 0.315   |  |              |
| <b>(B) Factors in childhood</b>    |              |                        |         |  |              |
| Birth weight ( $n = 932$ )         |              | 0.66 (-0.27, 1.59)     | 0.164   | 0.57 (-0.40, 1.53)                     | 0.246        |
| Sex                                |              |                        |         |  |              |
| Male ( $n = 583$ )                 | 64.9 (7.2)   | Reference              |         | Reference                              |              |
| Female ( $n = 536$ )               | 65.5 (7.4)   | 0.64 (-0.21, 1.49)     | 0.141   | 0.49 (-0.43, 1.42)                     | 0.294        |
| Sickle-cell trait                  |              |                        |         |  |              |
| HbAA ( $n = 661$ )                 | 65.4 (7.1)   | Reference              |         |  |              |
| HbAS ( $n = 141$ )                 | 65.5 (7.4)   | 0.15 (-1.16, 1.46)     | 0.825   |  |              |
| Season of birth                    |              |                        |         |  |              |
| Dry ( $n = 651$ )                  | 65.5 (7.3)   | Reference              |         | Reference                              |              |
| Wet ( $n = 468$ )                  | 64.7 (7.2)   | -0.79 (-1.65, 0.07)    | 0.073   | 0.59 (-1.52, 0.35)                     | 0.214        |
| Place of delivery                  |              |                        |         |  |              |
| Entebbe Hospital ( $n = 824$ )     | 65.1 (7.1)   | Reference              |         |  |              |
| Home ( $n = 120$ )                 | 65.4 (8.5)   | 0.36 (-1.03, 1.76)     |         |  |              |
| Others ( $n = 174$ )               | 65.7 (7.3)   | 0.61 (-0.58, 1.80)     | 0.564   |  |              |
| Feeding status (6 week of age)     |              |                        |         |  |              |
| Exclusive Breast fed ( $n = 748$ ) | 65.4 (7.4)   | Reference              |         |  |              |
| Mixed fed ( $n = 344$ )            | 64.7 (7.0)   | -0.63 (-1.56, 0.30)    |         |  |              |
| Weaned ( $n = 14$ )                | 67.1 (4.4)   | 1.78 (-2.07, 5.63)     | 0.251   |  |              |
| Intervention three                 |              |                        |         |  |              |

Table 2 (continued)

|   | Mean BP (SD) | Crude $\beta$ (95% CI) | P-value | Adjusted $\beta$ (95% CI) <sup>†</sup> | P-value          |
|---|--------------|------------------------|---------|--|------------------|
| Placebo ( <i>n</i> = 553)                             | 64.9 (7.0)   | Reference              |         | Reference                              |                  |
| Albendazole ( <i>n</i> = 554)                         | 65.5 (7.5)   | 0.62 (−0.24, 1.47)     | 0.156   | 0.56 (−0.37, 1.48)                     | 0.233            |
| HIV status  |              |                        |         |  |                  |
| Unexposed ( <i>n</i> = 1001)                          | 65.2 (7.3)   | Reference              |         |  |                  |
| Exposed not infected ( <i>n</i> = 100)                | 65.1 (6.7)   | −0.12 (−1.62, 1.37)    |         |  |                  |
| Infected ( <i>n</i> = 18)                             | 63.5 (5.1)   | −1.71 (−5.10, 1.68)    | 0.609   |  |                  |
| Malaria infection below 5 years of age                |              |                        |         |  |                  |
| Clinical or asymptomatic malaria <sup>a</sup>         |              |                        |         |  |                  |
| No ( <i>n</i> = 456)                                  | 65.9(7.1)    | Reference              |         | <b>Reference</b>                       |                  |
| Yes ( <i>n</i> = 663)                                 | 64.6 (7.3)   | −1.28 (−2.14, −0.41)   | 0.004   | <b>−1.47 (−2.41, −0.53)</b>            | <b>0.002</b>     |
| Clinical malaria <sup>a</sup>                         |              |                        |         |  |                  |
| None ( <i>n</i> = 474)                                | 66.0 (7.2)   | Reference              |         | <b>Reference</b>                       |                  |
| Yes ( <i>n</i> = 645)                                 | 64.6 (7.3)   | −1.38 (−2.24, −0.51)   | 0.002   | <b>−1.33 (−2.26, −0.39)</b>            | <b>0.005</b>     |
| Episodes of clinical malaria <sup>a</sup>             |              |                        |         |  |                  |
| None ( <i>n</i> = 474)                                | 65.9 (7.2)   | Reference              |         | <b>Reference</b>                       |                  |
| 1–2 ( <i>n</i> = 382)                                 | 64.5 (7.3)   | −1.45 (−2.42, −0.47)   |         | <b>−1.53 (−2.59, −0.46)</b>            |                  |
| ≥3 ( <i>n</i> = 263)                                  | 64.9 (7.4)   | −1.02 (−2.12, 0.07)    | 0.011   | <b>−1.03 (−2.22, 0.16)</b>             | <b>0.015</b>     |
| Asymptomatic malaria <sup>a</sup>                     |              |                        |         |  |                  |
| None ( <i>n</i> = 983)                                | 64.5 (7.3)   | Reference              |         | Reference                              |                  |
| Yes ( <i>n</i> = 124)                                 | 64.9 (7.4)   | −1.45 (−2.80, −0.10)   | 0.035   | −1.35 (−2.89, 0.18)                    | 0.082            |
| Schistosomiasis                                       |              |                        |         |  |                  |
| Uninfected ( <i>n</i> = 1076)                         | 65.2 (7.3)   | Reference              |         |  |                  |
| Infected ( <i>n</i> = 33)                             | 64.5 (5.8)   | 0.67 (−3.18, 1.84)     | 0.602   |  |                  |
| Ascaris   |              |                        |         |  |                  |
| Uninfected ( <i>n</i> = 1052)                         | 65.2 (7.3)   | Reference              |         |  |                  |
| Infected ( <i>n</i> = 57)                             | 64.5 (7.1)   | −0.75 (−2.68, 1.18)    | 0.445   |  |                  |
| Hookworm  |              |                        |         |  |                  |
| Uninfected ( <i>n</i> = 1085)                         | 65.2 (7.3)   | Reference              |         | Reference                              |                  |
| Infected ( <i>n</i> = 24)                             | 62.9 (5.8)   | −2.29 (−5.22, 0.64)    | 0.125   | −1.79 (−4.93, 1.35)                    | 0.261            |
| Trichuris   |              |                        |         |  |                  |
| Uninfected ( <i>n</i> = 997)                          | 65.1 (7.2)   | Reference              |         |  |                  |
| Infected ( <i>n</i> = 112)                            | 65.8 (7.7)   | 0.67 (−0.74, 2.09)     | 0.353   |  |                  |
| Microfilaria  |              |                        |         |  |                  |
| Uninfected ( <i>n</i> = 1102)                         | 65.1 (7.2)   | Reference              |         |  |                  |
| Infected ( <i>n</i> = 8)                              | 67.3 (3.3)   | 2.12 (−2.91, 7.14)     | 0.409   |  |                  |
| (C) Factors in adolescence                            |              |                        |         |  |                  |
| Age   |              | 1.85(1.00, 2.70)       | <0.001  | <b>1.53 (0.63, 2.43)</b>               | <b>&lt;0.001</b> |
| Body mass index                                       |              | 0.28 (0.20, 0.36)      | <0.001  | <b>0.74 (0.42, 1.05)</b>               | <b>&lt;0.001</b> |
| Waist circumference                                   |              | 0.88 (0.66, 1.10)      | <0.001  | 0.07 (−0.05, 0.18)                     | 0.279            |
| Family history  |              |                        |         |  |                  |
| High blood pressure                                   |              |                        |         |  |                  |
| No ( <i>n</i> = 1000)                                 | 65.0 (7.2)   | Reference              |         | <b>Reference</b>                       |                  |
| Yes ( <i>n</i> = 105)                                 | 66.7 (7.6)   | 1.65 (0.19, 3.12)      | 0.027   | <b>1.57 (0.08, 3.06)</b>               | <b>0.037</b>     |
| Diabetes  |              |                        |         |  |                  |
| No ( <i>n</i> = 927)                                  | 65.2 (7.2)   | Reference              |         |  |                  |
| Yes ( <i>n</i> = 186)                                 | 65.5 (7.8)   | 0.35 (−0.80, 1.49)     | 0.553   |  |                  |
| Body composition analysis <sup>c</sup>                |              |                        |         |  |                  |
| Fat mass index <sup>b</sup> ( <i>n</i> = 176)         |              | 1.75 (0.83, 2.69)      | <0.001  | 0.87 (−0.73, 2.47)                     | 0.255            |
| Fat-free mass index <sup>b</sup> ( <i>n</i> = 176)    |              | 1.19 (0.40, 1.98)      | 0.003   | 0.28 (−0.90, 1.45)                     | 0.622            |
| Total body water index <sup>b</sup> ( <i>n</i> = 176) |              | 2.13 (0.95, 3.30)      | <0.001  | 1.51 (−0.86, 3.88)                     | 0.180            |
| Adding salt to food                                   |              |                        |         |  |                  |
| No ( <i>n</i> = 20)                                   | 67.4 (6.1)   | 2.19 (−1.04, 5.41)     |         | 2.72 (−0.39, 5.82)                     |                  |
| Yes ( <i>n</i> = 1086)                                | 65.2 (7.3)   | Reference              | 0.184   | Reference                              | 0.083            |
| Days a fruit is eaten/week                            |              |                        |         |  |                  |
| 0–2 ( <i>n</i> = 543)                                 | 65.7 (7.1)   | Reference              |         | <b>Reference</b>                       |                  |
| 3–7 ( <i>n</i> = 541)                                 | 64.7 (7.5)   | −0.98 (−1.85, −0.11)   | 0.028   | <b>−0.96 (−1.83, −0.10)</b>            | <b>0.027</b>     |
| Days vegetables eaten/week                            |              |                        |         |  |                  |
| 0–2 ( <i>n</i> = 461)                                 | 65.4 (7.1)   | Reference              |         |  |                  |
| 3–7 ( <i>n</i> = 635)                                 | 65.1 (7.5)   | −0.27 (−1.15, 0.60)    | 0.540   |  |                  |
| Days animal-protein eaten/week                        |              |                        |         |  |                  |
| 0–2 ( <i>n</i> = 726)                                 | 65.1 (6.9)   | Reference              |         |  |                  |
| 3–7 ( <i>n</i> = 374)                                 | 65.4 (8.0)   | 0.30 (−0.61, 1.20)     | 0.523   |  |                  |

**Table 2** (continued)

|  | Mean BP (SD) | Crude $\beta$ (95% CI) | <i>P</i> -value | Adjusted $\beta$ (95% CI) <sup>†</sup> | <i>P</i> -value |
|--|--------------|------------------------|-----------------|--|-----------------|
| Days sugared drinks taken/week               |              |                        |                 |  |                 |
| None ( <i>n</i> = 427)                       | 65.0 (7.1)   | Reference              |                 | Reference                              |                 |
| 1–3 ( <i>n</i> = 492)                        | 65.2 (7.4)   | 0.25 (–0.70, 1.20)     |                 | 0.12 (–0.84, 1.08)                     |                 |
| 4–7 ( <i>n</i> = 174)                        | 66.0 (7.5)   | 1.06 (–0.23, 2.35)     | 0.271           | 0.54 (–0.75, 1.83)                     | 0.707           |
| Days a fruit is eaten/week                   |              |                        |                 |  |                 |
| Days vegetables eaten/week                   |              | 0.02 (–0.16, 0.1)      | 0.800           |  |                 |
| Days animal-protein eaten/week               |              | 0.14 (–0.11, 0.39)     | 0.284           |  |                 |
| Days starchy foods eaten/week                |              | 0.03 (–0.50, 0.55)     | 0.924           |  |                 |
| Days sugared drinks taken/week               |              | 0.20 (0.00, 0.41)      | 0.048           |  |                 |
| Breast development (girls only) <sup>b</sup> |              |                        |                 |  |                 |
| Pre-pubertal ( <i>n</i> = 178)               | 64.1 (6.1)   | Reference              |                 | Reference                              |                 |
| Pubertal ( <i>n</i> = 97)                    | 67.2 (7.9)   | 3.067 (1.38, 4.76)     | <0.001          | 0.98 (–0.88, 2.84)                     | 0.281           |
| Pubic hair development <sup>b</sup>          |              |                        |                 |  |                 |
| Pre-pubertal ( <i>n</i> = 441)               | 64.1 (6.6)   | Reference              |                 | Reference                              |                 |
| Pubertal ( <i>n</i> = 170)                   | 66.1 (7.6)   | 2.04 (0.82, 3.26)      | 0.001           | 0.68 (–0.62, 1.99)                     | 0.293           |
| Snoring                                      |              |                        |                 |  |                 |
| No ( <i>n</i> = 932)                         | 65.1 (7.2)   | Reference              |                 |  |                 |
| Yes ( <i>n</i> = 163)                        | 65.6 (7.8)   | 0.44 (–0.78, 1.66)     | 0.477           |  |                 |
| Duration of night sleep                      |              |                        |                 |  |                 |
| <9 h ( <i>n</i> = 306)                       | 65.8 (7.6)   | Reference              |                 | Reference                              |                 |
| 9 h ( <i>n</i> = 382)                        | 64.8 (7.1)   | –1.03 (–2.11, 0.06)    |                 | –0.92 (–2.02, 0.18)                    |                 |
| >9 h ( <i>n</i> = 405)                       | 65.2 (7.2)   | –0.79(–1.86, 0.28)     | 0.160           | –0.67 (–1.76, 0.43)                    | 0.240           |
| Smoking in household                         |              |                        |                 |  |                 |
| Non ( <i>n</i> = 962)                        | 65.2 (7.3)   | Reference              |                 |  |                 |
| Yes ( <i>n</i> = 147)                        | 65.0 (6.8)   | –0.21 (–1.46, 1.06)    | 0.745           |  |                 |
| Type of school                               |              |                        |                 |  |                 |
| Day ( <i>n</i> = 117)                        | 65.1 (7.2)   | Reference              |                 | Reference                              |                 |
| Boarding school ( <i>n</i> = 719)            | 66.2 (7.8)   | 1.13 (–0.26, 2.52)     | 0.112           | –0.24 (–1.67, 1.20)                    | 0.737           |
| Physical education at school                 |              |                        |                 |  |                 |
| No ( <i>n</i> = 385)                         | 65.0 (6.9)   | Reference              |                 |  |                 |
| Yes ( <i>n</i> = 719)                        | 65.3 (7.5)   | 0.32 (–0.58, 1.22)     | 0.482           |  |                 |
| Infections at BP measurement                 |              |                        |                 |  |                 |
| Asymptomatic malaria                         |              |                        |                 |  |                 |
| Uninfected ( <i>n</i> = 1067)                | 65.3 (7.3)   | Reference              |                 |  |                 |
| Infected ( <i>n</i> = 22)                    | 64.0 (5.5)   | –1.31 (–4.36, 1.75)    | 0.401           |  |                 |
| Schistosomiasis                              |              |                        |                 |  |                 |
| Uninfected ( <i>n</i> = 964)                 | 65.2 (7.4)   | Reference              |                 |  |                 |
| Infected ( <i>n</i> = 112)                   | 65.0 (5.8)   | –0.19 (–1.62, 1.24)    | 0.791           |  |                 |
| Hookworm                                     |              |                        |                 |  |                 |
| Uninfected ( <i>n</i> = 1066)                | 65.2 (7.3)   | Reference              |                 |  |                 |
| Infected ( <i>n</i> = 10)                    | 64.0 (5.9)   | –1.25 (–5.80, 3.30)    | 0.590           |  |                 |
| Ascaris                                      |              |                        |                 |  |                 |
| Uninfected ( <i>n</i> = 1073)                | 65.2 (7.3)   | Reference              |                 |  |                 |
| Infected ( <i>n</i> = 3)                     | 62.3 (4.3)   | –2.86 (–11.14, 5.42)   | 0.498           |  |                 |
| Trichuris                                    |              |                        |                 |  |                 |
| Uninfected ( <i>n</i> = 1036)                | 65.1 (7.2)   | Reference              |                 |  |                 |
| Infected ( <i>n</i> = 40)                    | 66.4 (9.4)   | 1.23 (–1.07, 3.54)     | 0.294           |  |                 |

Model building followed the hierarchical approach, adding factors sequentially at three levels starting with the distal factors (level 1). Factors at the same level were added to the model at the same time and considered confounders for each other and for proximal factors. A *P*-value < 0.20 was used for considering the inclusion and maintenance of factors in the model

Adjusted  $\beta$  for which 95% CI exclude 0 are highlighted in bold

$\beta$  linear regression coefficient: mean difference in blood pressure (BP) measured in mmHg

<sup>a</sup>Not included in the model together but each was adjusted for all other variables in the model

<sup>b</sup>Not included in multivariable model building for other exposures because of large proportion of missing information; but each was adjusted for variables in the final model building

<sup>c</sup>Not adjusted for body mass index because body mass index is on the causal pathway

365 Sub-microscopic malaria was most likely misclassified as  
366 negative in this population, since in malaria-endemic areas,  
367 asymptomatic malaria often presents as sub-microscopic in  
368 individuals with past malaria infection [27]. We found no  
369 association between sickle-cell trait and adolescent BP;  
370 contrary to the hypothesis advanced by Etyang, who used  
371 sickle-cell trait as an instrumental variable in a Mendelian  
372 randomisation study [28]. In the predominantly adult  
373 populations from Kenya, sickle-cell trait (linked with partial  
374 protection against malaria) was associated with lower BP in  
375 Kilifi (currently a low-moderate but historically a high  
376 malaria transmission area) compared to Nairobi (no malaria  
377 transmission) [29]. The differences in malaria exposure  
378 intensity and participant age distribution between our study  
379 and the Kenyan study could explain our contrasting results.

380 Similar to earlier studies [30, 31], childhood malaria was  
381 associated with reductions in both weight and height, and  
382 some of the inverse association seen in this study may be  
383 explained by this mechanism, or by confounding by  
384 unmeasured factors. The escalating burden of high BP has  
385 coincided with the declining malaria burden on the African  
386 continent [2, 32, 33]. This could be explained by the epi-  
387 demiological transition process on continent, or the effect  
388 could be more direct; the mechanisms remain to be  
389 elucidated.

390 Current but not previous infection with *Trichuris* (a type  
391 of soil transmitted helminth, commonly known as whip-  
392 worm) was associated with increased systolic BP in early  
393 adolescence. To our knowledge, no study has previously  
394 reported such an association. This may reflect short-term  
395 effects (probably arterial stiffness from inflammatory reac-  
396 tion) or it could be a spurious finding due to the many  
397 exposures included in the analysis. The effect of current  
398 *Trichuris* infection on BP is likely not mediated through  
399 increasing BMI (weight or height); there was no difference  
400 in these measures between adolescents with and without  
401 current *Trichuris* infection.

402 Unlike previous studies [34], we found no association  
403 between BP and salt intake. The lack of evidence for this  
404 relationship in our study could be due to measurement error  
405 from self-report, or the fact that nearly everyone added salt  
406 to cooked food. Measuring sodium in a 24-h urine sample  
407 or in commonly consumed local foods would provide a  
408 more accurate reflection of daily intake. Physical activity  
409 was not associated with lower BP, contrary to earlier lit-  
410 erature [35]; sedentary lifestyles are still fairly uncommon  
411 in this population.

412 Previous studies have linked hypertension to socio-  
413 economic determinants (socioeconomic status (SES), edu-  
414 cation, income, urbanisation) [12, 36]. Our study is  
415 consistent with a Uganda study in adults which showed that  
416 BP was not associated with urban residence [37] but con-  
417 trary to studies linking increased BP with low SES [36] and

418 urbanisation [12]. We have shown that higher maternal  
419 education was associated with increased BP in adolescents,  
420 whereas other studies, predominantly from high-income  
421 countries, report an inverse association [36]. Although low  
422 SES and education is associated with hypertension in the  
423 developed world [36], the relationship may be inverse in  
424 less developed countries [38]. In these settings, offspring  
425 from more highly educated households are more likely to  
426 have sedentary lifestyles and unhealthy dietary practices,  
427 and to be obese, compared to offspring from less-educated  
428 households.

429 Strengths of this study included its longitudinal design  
430 with prospectively collected data reducing recall and  
431 reporter bias, the use of robust BP procedures and the  
432 measurement of BP on up to two extra occasions in those  
433 with BP  $\geq$ 95th percentile at the initial visit, to avoid over-  
434 estimation of high BP. It is unlikely that white-coat phe-  
435 nomenon was an issue as participants regularly attend this  
436 clinic for scheduled and/or illness visits. The use of digital  
437 machines reduced differences in BP reading between  
438 operators which can occur with auscultation.

439 Study limitations include the possibility of residual  
440 confounding by unmeasured factors (such as glomerular  
441 filtration rate (GFR)). The GFR could not be estimated as  
442 creatinine was only measured for a subgroup of the parti-  
443 cipants. The use of digital BP machines may overestimate  
444 BP; however, digital devices used in this study were cali-  
445 brated twice annually. A large number of statistical tests  
446 were undertaken; thus, some findings may be due to mul-  
447 tiplicity. However, it is reassuring that most findings are  
448 consistent with previous literature, albeit from different  
449 settings. Not inviting all adolescents (those with pre-  
450 hypertension or normal BP on day 1) for up to two extra  
451 BP measurements might have resulted in an under-  
452 estimation in the overall prevalence of pre-hypertension and  
453 hypertension. We modelled BP as a continuous outcome,  
454 since analysing high or pre-hypertensive BP versus normal  
455 BP as a binary outcome (or outcomes) would be under-  
456 powered, consequently our findings may not necessarily  
457 reflect associations with hypertensive disease.

458 In summary, routine BP screening which is seldom  
459 conducted for adolescents at health care visits remains vital  
460 in the control and prevention of CVDs later in life. Similar  
461 life-course factors to those observed in high-income settings  
462 (such as adiposity and diet) affect both systolic BP and  
463 diastolic BP among African adolescents. Interventions  
464 during pregnancy, childhood and early adolescence could  
465 be vital in the control and prevention of later high BP.  
466 Multiple intervention strategies initiated during pregnancy  
467 and the early postnatal period and continued across a life-  
468 time could be fundamental in the control of adulthood  
469 hypertension and CVDs.

470 **Summary**471 **What is known about the topic**

- 472 • High blood pressure and cardiovascular diseases
- 473 (CVDs) are increasing in Africa.
- 474 • Scarcity of data on BP risk factors among African
- 475 children and adolescents.
- 476 • The risk factors for high BP may differ from those seen
- 477 in high-income non-tropical settings.
- 478

479 **What this paper adds**

- 480 • Malaria infection in childhood is associated with
- 481 reduced blood pressure among adolescents. Effects of
- 482 childhood malaria on later blood pressure may be
- 483 partially mediated through chronic reduction in weight
- 484 and height.
- 485 • Current infection with *Trichuris* is associated with
- 486 increased blood pressure.
- 487 • Interventions during pregnancy, childhood and early
- 488 adolescence could be vital in the prevention of high BP
- 489 later in life.
- 490

491 **Acknowledgements** We thank all staff, participants and parents/  
 492 guardians in the EMaBS, Entebbe Hospital midwives, the community  
 493 field teams (Entebbe and Katabi), MRC/UVRI, Uganda Research Unit  
 494 staff, and Mulago Hospital staff. We thank all individuals involved in  
 495 the generation and curation of the genotype and imputed data  
 496 including Adrian VS Hill, Manjinder Sandhu, Deept Gurdasani,  
 497 Tommy Carstensen, Allan Muhwezi, Beatrice Nassanga and staff at  
 498 the Wellcome Sanger Institute and Wellcome Centre for Human  
 499 Genetics.

500 **Funding** This work was supported by: the Wellcome Trust (Grant  
 501 Numbers: 064693, 079110, 95778, to Alison M. Elliott; 106289/Z/14/  
 502 Z, to Liam Smeeth; and 098504/Z/12/Z, to Alexander Mentzer); UK  
 503 Medical Research Council and UK Department for International  
 504 Development (Grant Number: MR/K012126/1, to Emily L. Webb);  
 505 and Commonwealth Scholarship Commission (Grant Number: UGCS-  
 506 2015-808, to Swaib A. Lule).

507 **Compliance with ethical standards**

508 **Conflict of interest** The authors declare that they have no conflict of  
 509 interest.

510 **Publisher's note:** Springer Nature remains neutral with regard to  
 511 jurisdictional claims in published maps and institutional affiliations.

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- 514 aetiology of hyperpiesia and arteriosclerosis. *Lancet*. 1929;213:6–7.
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