www.sciencemag.org/content/350/6263/970/suppl/DC1

Supplementary Materials for

Helminth infection, fecundity, and age of first pregnancy in women

Aaron D. Blackwell, * Marilyne A. Tamayo, Bret Beheim, Benjamin C. Trumble, Jonathan Stieglitz, Paul L. Hooper, Melanie Martin, Hillard Kaplan, Michael Gurven

*Corresponding author. E-mail: blackwell@anth.ucsb.edu

Published 20 November 2015, *Science* **350**, 970 (2015)
DOI: 10.1126/science.aac7902

This PDF file includes:

Materials and Methods
Supplementary Text
Figs. S1 to S8
Tables S1 to S7
References (*31–44*)
Captions for Databases S1 and S2

Other Supplementary Materials for this manuscript include the following:
(available at www.sciencemag.org/content/350/6263/970/suppl/DC1)

Databases S1 and S2

Materials and Methods

Study Population

Tsimane are a rapidly expanding (3.6% annual growth rate (*31*)) population of about 15,000 forager-horticulturalists that live along the Maniqui River and surrounding areas in lowland Bolivia. Tsimane are predominately a natural fertility population, with a total fertility rate of 9.1 children per women (*16, 25, 32*). Birth control, mostly in the form of Depo-Provera, is available from some health workers and in pharmacies in town, yet less than 5% of reproductive age women reported using it in the last year. Low birth control usage is largely due to a combination of lack of knowledge about its use, cost, and cultural valuation of large family size. Tubal ligation became available in the last few years in one village near a Catholic mission, but very few women have chosen sterilization. Other forms of modern birth control are almost never used: for example in interviews with ~150 Tsimane women, only two had ever tried using a condom, and each on only one occasion (Lisa McAllister, personal communication). All Tsimane breastfeed their infants, with a mean weaning age of 19 months (*33*).

Tsimane are largely self-sufficient and subsist primarily by hunting, fishing, and cultivation of plantains, rice, and manioc. Since 2002, the Tsimane have been participants in the on-going Tsimane Health and Life History Project (THLHP: http://www.unm.edu/~tsimane). All Tsimane residing in study villages are eligible to participate in the study, and most choose to do so at least once. The Tsimane ethnographic context and project details, including methods of demographic collection, have been described in detail elsewhere (*32, 34, 35*).

Ethics Approval

The study was reviewed and approved by the Gran Consejo Tsimane, the governing body overseeing Tsimane affairs, and by the institutional review boards of the University of California, Santa Barbara, and the University of New Mexico. Informed consent was obtained at two levels. In each study community, community meetings were held describing the study. Communities decided collectively whether the project would be allowed. To date, all communities that have been approached have approved the project. Individuals in the study also gave informed consent during medical visits and again before each procedure.

Medical Surveillance

Study participants were seen by the mobile THLHP biomedical team who visited Tsimane villages roughly once per year from 2004-2013. Individual women in the study were seen by physicians between one and seven times (mean 2.2±1.3), excluding demographic interviews, which sometimes occurred between medical rounds. Patients seen by THLHP physicians were given routine physical exams (patient history, symptom investigation and clinical diagnoses, blood pressure and temperature, height and weight). Hemoglobin was measured with a QBC Autoread Plus Dry Hematology system (QBC Diagnostics). Following on-site analysis of participant blood and fecal samples, physicians administered vitamins and medications as warranted.

Parasite Diagnosis

At every medical exams fecal samples were analyzed for the presence of helminth eggs, larvae, protozoa, and other parasites by direct identification on wet mounts. Duplicate mounts were prepared with 0.9% saline solution and iodine solution, respectively, and examined at 100x and 400x (*35, 36*). Beginning in 2007, fecal samples were also preserved in 10% formalin solution following direct identification, and later analyzed using a modified Percoll (Amersham Pharmacia) technique (*37*). As we report elsewhere, the Percoll method is slightly more sensitive, but does not produce systematic biases in parasite identification (*35*). We therefore combine results from both methods for our analyses. Three limitations in our parasite identification are worth noting: since the project overall was designed to collect a wide array of medical data, and was not focused on parasites alone, quantitative egg counts were not recorded through much of the project period, so parasite burden was not determined. Additionally, given project logistics that involved a mobile medical team and participants unable to participate over multiple days, only a single fecal sample was collected per individual, perhaps inflating false negatives. Finally, since the two species of hookworm, *Ancylostoma duodenale* and *Necator americanus*, cannot be distinguished without molecular techniques, we refer simply to hookworm in the manuscript.

About 20% of individuals positive for helminth infection received treatment with antihelminthics (Table S1). Reasons included physician discretion, occasional shortages of medical supplies, and the fact that often patients would leave the health examination before fecal analysis was complete. Albendazole and mebendazole were also sometimes prescribed for other conditions, such as suspicion of a parasitic infection without a positive diagnosis, lice, anemia, or as prophylaxis, such that about 12% of individuals without a hookworm or *A. lumbricoides* received an antihelminthic.

Although associated with anemia and other morbidities, helminth infections among the Tsimane are frequently asymptomatic, and patients themselves often do not know they are infected. While outwardly asymptomatic, Tsimane have extremely elevated immunoglobulin E, associated with Th2 biasing (*35*), and helminth infections in this population have been previously shown to alter the odds of infection with other parasites and disease conditions (*11, 17*).

Identification of pregnancies

Pregnancy status was determined during medical visits through patient or family member report, with pregnancy tests administered when suspected by the physician. THLHP physicians estimated conception and days pregnant based on time since last menstruation. Pregnancies were cross-validated against later demographic and census interviews recording ages and birth dates of children in all villages. By cross-checking against the demographic interviews we were also able to record pregnancies that occurred between medical visits (n=144), as well as a handful of pregnancies (n=16) that were undetected during medical visits, 13 of which were in the first trimester at the time of the visit. Cross-checking the two data sources also allowed us to verify estimates of conception dates using both dates of birth and dates of last menstruation recorded during medical visits.

Exclusion criteria

After first screening to include only women with both fecal parasite and pregnancy data, 36 additional Tsimane women were excluded: we excluded one 42 year-old woman known to have had a tubal ligation, four women who had Depo-Provera shots during the study period, and 31 women who had previously given birth but had not had a pregnancy for more than six years. These 31 were excluded based on the possibility that they might have used birth control without reporting it, or might have had other underlying fertility issues. The 31 excluded women were slightly older (mean age 41.7±7.6 years), had slightly fewer past pregnancies (6.3±2.9), more hookworm (60.8%), and less *A. lumbricoides* (7.8%) than women retained in the study (Table S1). The final sample includes 561 multiparous and 425 nulliparous women. After the exclusions, age specific fertility in the included sample is slightly higher than previous estimates for the Tsimane populations as a whole (Figure S1). Additional details and descriptive statistics are given in Table S1.

Data preparation.

For analysis, data were structured as intervals between medical visits and conception events, with participants entering analysis at the time of fecal exam, to avoid counting time backwards to the start of the inter-pregnancy interval. Since events (conceptions) were not observed, but instead occurred sometime after observations of parasite status, parasite status and other covariates at conception were assumed to be the last observed infection status prior to the conception, with the constraint that the fecal examination had to have occurred after the previous birth (i.e. during the interbirth interval). In order to determine whether this attribution was appropriate, we examined whether observations of parasite infection were predictive of continued infection for extended periods of time (Figure S2A). Using data from all Tsimane women over age 15, we examined whether infection at one time point was predictive of infection at later time points. Of those infected with *Ascaris lumbricoides* at time zero, 36% were infected one year later, compared to 14% of those uninfected at time zero. For hookworm, 63% of those infected at time zero were infected a year later, compared to 45% of those uninfected (Figure S2C). Controlling for community, study year, age, and receipt of treatment, *Ascaris lumbricoides* infection was predictive of continued or subsequent infection for up to 5.5 years (e.g., 0.5 to 1.5 years later (OR = 3.43, CI 2.17-5.37, $p < 0.001$), 1.5 to 2.5 years later (OR = 3.52, CI 2.12-5.79, $p < 0.001$), and 2.5 to 3.5 years later (OR = 2.23, CI = 1.29-3.80, $p<0.001$)). Hookworm infection was predictive of infection 0.5 to 1.5 (OR = 2.19, CI 1.63-2.94, $p < 0.001$), and 1.5 to 2.5 years later (OR = 1.50, CI = 1.08-2.08, $p=0.015$).

Since some women were treated with antihelminthics (mebendazole or albendazole), antiprotozoals (metronidazole or tinidazole), and antibiotics (amoxicillin, benzathine penicillin, ciprofloxacin, cotrimoxazole, erythromycin, or ampicillin), we checked to see whether treatment affected these results. Controlling for community, age, and study year, treatment with an antihelminthic was associated with a reduced likelihood of infection with hookworm a year later (OR = 0.56, CI = 0.33-0.98, $p = 0.05$), and was marginally associated with a reduced likelihood of *A. lumbricoides* infection (OR = 0.54, CI = 0.26-1.06, $p = 0.09$). Treatment with an antibiotic was also associated with reduced odds of *A.*

lumbricoides infection (OR = 0.46, CI = 0.25-0.94, p = 0.02). However, in real world terms, the effectiveness of treatment was limited. Of those with hookworm, 63% of untreated individuals were infected a year later, while treatment reduced this to 58%. For uninfected individuals, 45% were infected a year later without treatment, and 39% with treatment. For *A. lumbricoides*, of those infected and not treated, 41% were infected a year later, while treatment reduced this to 31%. Of those without *A. lumbricoides*, 16% were infected a year later, compared to 9% in those who were treated. Antiprotozoals were not associated with altered odds for either helminth infection. Inclusion of treatment in models did not substantially alter the odds ratios for infection one year later given infection at time zero.

Given these results, we decided that cases which did not have a pregnancy within 2.5 years after the fecal exam should be considered censored, since parasite status might be unknown (Figure S2B). These cases end with a censored observation 2.5 years after the fecal exam. Below, we perform additional robustness checks to determine whether this decision affects results. We also include treatment as a covariate in our models.

Data Analysis.

Data on pregnancy hazard was analyzed using recurrent events Cox-proportional hazard models with a counting process (*38*). The counting process permits not only repeat pregnancies, but also time-varying covariates. Analysis was done in R 3.1.2 (http://cran.us.r-project.org/) using *coxph* and *Surv* in the *survival* package. Since events (conceptions) were not observed, but instead occurred between observations of parasite status, parasite status at conception was assumed to be the last observed infection status prior to the conception, with the constraint that this observation had to have occurred after the previous birth (i.e. during the interval) and within 2.5 years of the conception. All models included cluster terms for repeat observations on the same individual and for village, to control for geographical non-independence. Since some covariates had missing observations, multiple imputation by chained equations (the *mice* package) was used to impute missing values for BMI, education, Spanish ability, and hemoglobin (*39*) (Table S1). Models with these covariates were run on 100 imputed datasets, with results pooled for reporting. Other covariates were included or excluded from models as described below.

Supplementary Text

Modelling the effects of infection on hazard of next pregnancy following a birth.

We first evaluated the effect of age on pregnancy hazard, to determine whether the hazard of pregnancy varied with age, and whether this variation was linear or better described with a transformation to the model age term. Overall, model fit was improved considerably by adding a transformed age^4 term, given non-linear changes in fecundity with age (Figure S3).

Next we assessed whether other variables that might be expected to influence interbirth intervals or infection prevalence would modify hazard ratios associated with parasite infection (Table S2). Some observations or individuals were missing data for some covariates. Rather than exclude cases with missing covariate information, which would reduce power and potentially introduce bias, we used multiple imputation by chained equations (MICE) to impute missing values (*39*). The number of imputed values

for each variable are shown in Table S1. Imputations were iterated 100 times and parameter values from all iterations were pooled for reporting. Overall, imputation did not affect results, as complete case analysis produced similar parameter values and significance levels.

The control variables evaluated included two indicators of energetic or nutritional status (BMI and blood hemoglobin) to determine whether condition affects conception hazard, as well as to evaluate whether the effects of helminths are mediated by their effects on health. We include three measures of acculturation and market access (years of formal education, Spanish ability, and village distance to the main market town of San Borja), since acculturation can affect both access to medications and family planning, as well as cultural values and behaviors that could affect work and living conditions. Three variables capturing receipt of medications were included, with medications classified as antihelminthics (mebendazole or albendazole), antiprotozoals (metronidazole or tinidazole) or antibiotics (amoxicillin, benzathine penicillin, ciprofloxacin, cotrimoxazole, erythromycin, or ampicillin). A month variable was also included, modelled with a penalized spline (p-spline), to control for seasonal variation throughout the year. All models included cluster terms for community and individual to control for clustering by community and repeat observations on the same individual. Control variables were checked for significance as well as by model AIC. We also checked for significant interactions between each infection and age terms with transformations ranging from age^1 to age^6, and for interactions between hookworm and *Ascaris* infection. A final model was chosen by stepwise AIC, which included controls for formal education, Spanish ability, distance to market, antihelminithic treatment, and season, with an interaction between *A. lumbricoides* infection and age (Table S2.)

Overall, the choice of control variables had little effect on infection-related parameter values. Hazard ratios for hookworm ranged from 0.70 to 0.79. *A. lumbricoides* hazard ratios at age 20 ranged from 1.51 – 1.64, with parameter values ranging from 0.66 - 0.70 for the interaction between *A. lumbricoides* and age. Both parameters were highly significant in every model. As a final check, we ran models including only one type of infection (hookworm or *A. lumbricoides*). Parameters in these models were not significantly different (Table S2).

Controlling for age and coinfection, in our sample, hookworm infection is associated with lower BMI (β = - 0.77 kg/m2, $p < 0.001$) and hemoglobin (β = -0.19 g/dL, $p = 0.005$), while *A. lumbricoides* is not (β = -0.34 kg/m2, $p = 0.180$; β = -0.07 g/dL, $p = 0.413$). However, hemoglobin and BMI were not significant in any model predicting pregnancy hazard, and did not mediate the effects of infection. In the multiparous model, years of education, Spanish ability, and distance to the market town were all retained by AIC. Years of formal education (HR = 0.92, CI 0.85-0.98, $p = 0.013$) and Spanish ability (HR = 0.75, CI 0.59-0.96, $p = 0.021$) both predicted reduced hazards of pregnancy and longer interbirth intervals. After controlling for individual level acculturation, pregnancy hazard decreased with increasing distance from market (HR = 0.96, CI 0.92-1.01, $p = 0.098$). Despite these effects, none of these variables mediated the effects of helminth infection.

Treatment with an anthelminthic was associated with reduced hazard of conception (HR = 0.75, CI 0.58-0.97, $p = 0.027$). However, including treatment in the model did not significantly modify the effect size of the infection parameters. Additionally, there were

no significant interactions between receipt of treatment and infection with either helminth species. As an additional check for interactions, we excluded women who had received treatment. Excluding these women reduces power (n = 406; obs = 732, pregnancies = 326), but does not appreciably alter parameter values (Hookworm: HR = 0.74, p = 0.008; *A. lumbricoides*: HR = 1.61, p = 0.033; *A. lumbricoides* x Age HR = 0.72 p =0.076). The results suggest that treatment is having its own effect, independent of infection, either by serving as a proxy for some additional unmeasured variable, such as health related behaviors or other infections, or possibly by directly affecting fecundity in some manner.

We also found a significant effect of observation month on pregnancy hazard, with conceptions at their highest in September and October (Figure S4). To examine this more closely, we ran models in which season predicted infection (see below, Table S6). Only *A. lumbricoides* showed evidence of seasonality, with detection rates at their highest in drier months (May-August), peaking in June (Figure S4). To determine whether separate seasonal patterns in both *A. lumbricoides* and conceptions might create the illusion of an association of *A. lumbricoides* with pregnancy hazard we compared models both with and without the seasonal control (Table S2). The inclusion of this control did not appreciably alter relationships with either parasite (Tables S2 and S5), suggesting that seasonality does not explain the association. Similarly, we examined whether the seasonality in *A. lumbricoides* might be driving the seasonality in births. However, controlling for *A. lumbricoides* had little effect on the seasonality of conceptions, suggesting birth seasonality and *A. lumbricoides* seasonality are largely independent.

Modeling the effect of infection on age of first pregnancy.

Following the procedure used to test control variables on pregnancy hazard for multiparous women, we tested control variables for effects on age of first pregnancy for nulliparous women (Table S3). For nulliparous women, years of education is potentially a problematic control variable, since becoming pregnant may cause women to leave school earlier, reversing the causal relationship with education. We therefore also examined whether village level prevalence of Spanish among women or village average education level for women affected age of first pregnancy. As with later pregnancy risk, seasonality was apparent and significant in models, and had a similar pattern. Since BMI changes with age, particularly around adolescence, BMI was transformed first into Tsimane age and sex specific z-scores (BMIZ) generated from 28,266 observations from 9,351 children (following methods in (*40*)). Of the variables examined only season and treatment with antihelminthics were significant. Both had little effect on infection-related parameters (Table S3).

Association between helminth infections, other diseases, and hazard of pregnancy.

Many study participants presented at medical visits with multiple comorbidities. Past work has shown that helminth infections are associated with altered odds for other infections, including *G. lamblia* (*11*, *17*), suggesting that helminths might affect fertility indirectly, by altering risk of comorbidities. To investigate this possibility, we investigated whether helminth infections were associated with altered odds of comorbid conditions, whether comorbid conditions were associated with altered hazards of conception, and whether the inclusion of comorbid conditions in models would mediate

helminth-associated hazard ratios. We categorized medical ICD-10 codes given by project physicians, and analyzed all categories with infectious etiology with over 2% prevalence (Table S4). Giardia was diagnosed by the presence of *G. lamblia* in microscopic examinations of fecal samples. Analyses include only women age 15-50.

Both hookworm and *A. lumbricoides* were associated with reduced odds of *G. lamblia* infection (OR = 0.49, $p < 0.001$; OR = 0.64, $p = 0.07$). Hookworm was associated with increased odds of respiratory infection (OR = 1.52, $p = 0.03$) and gastrointestinal illness (OR = 1.40, $p = 0.06$). Other common diagnoses, including urinary tract infections, vaginal yeast infections, other fungal infections, and vaginal or pelvic inflammation (vaginitis) were not associated with helminth infections. To investigate this last category in more detail, we analyzed data on a subsample of 206 women who received Papanicolaou (PAP) tests (see (*41*)), neither hookworm nor *A. lumbricoides* infection was associated with altered odds of a PAP test positive for inflammation, regardless of inflammatory etiology.

Despite some associations with helminth infection, none of the other infectious categories was significantly associated with altered hazards of conception (Table S4), and none mediated the effects of either hookworm or *A. lumbricoides*. While this may seem surprising for some diagnoses, it may simply be that unlike helminth infections, most of these diagnoses are acute, rather than chronic, meaning that diagnoses at a single time point, approximately once per year, have little relevance for fecundity over a period of a year or more. Giardia infection, for example, does not predict increased odds of giardia infection one year later (OR = 0.93, CI = 0.60-1.42, $p = 0.75$), unlike both hookworm and *A. lumbricoides* which are predictive of infection for longer periods of time.

Model Robustness Checks: Assessing the impact of censoring after a medical exam.

A key assumption of our models is that helminth infections persist for some length of time, such that infection status at a single time point is relevant for assessing conception hazard at later time points. Based on the findings in Figure S2, we set a cutoff of 2.5 years between parasite observation and subsequent pregnancy before cases were considered censored. To test whether this choice affected model outcomes, we ran a series of models with varying cut-offs (Figure S5). As the cut-off becomes more stringent, e.g. requiring that the fecal exam was more priximate to the subsequent conception, the number of non-censored inter-pregnancy intervals (IPIs) declines, particularly under one year, since most individuals were examined about once per year (median time between visits = 1.41 years, mode = 1.06). Thus, with the cutoff at 2.5 years, 405 non-censored intervals are included in IPI model and 87 in the Age of first reproduction (AFR) model. At one year this drops to 284 and 49. When the cut-off is 0.5 years the sample is reduced considerably, to 139 intervals in the IPI and 26 in the AFR model.

It is worth noting that, particularly in the AFR model, the effect size for infection increases as the cut-off becomes narrower, suggesting that more exact measures of parasite status immediately before conception might yield stronger effects than we have chosen to report (Figure S5), and providing further evidence that infection affects conception prospectively. However, when the sample becomes too small, certainty in parameter estimates decreases. Setting the cut-off at 2.5 years strikes a reasonable balance, and retains most of the sample for both datasets.

Model Robustness Checks: Testing for secular changes.

We next wanted to verify that our results were not influenced by secular changes. For example, if both infection levels and pregnancy hazard were changing with time as a result of some third variable (such as acculturation) this might create the illusion of an association between these variables. To check this we ran our *coxph* model with calendar time as the time variable, rather than time since last birth (for the IPI model) or age (for the AFR model). The survival algorithm calculates hazards by comparing individuals at-risk at the time of an event. In the case of the above model, individuals are at risk together if they are at the same time point in their inter-pregnancy interval. In contrast, when using secular time, individuals are at risk together if their intervals overlap in calendar time (Figure S6). Changing the time counter changes which individuals are considered at risk together. Since all individuals in the calendar time model experience the same secular changes, this should control for the possibility of secular changes as confounds.

In the multiparous models, parameters were not significantly altered by using calendar time, compared to the IPI time model (for hookworm, HR = 0.78, CI 0.65-0.95, p = 0.011; for *A. lumbricoides* at age twenty HR = 1.51, CI 1.14-2.02, p = 0.004; *A. lumbricoides* x age HR = 0.70, CI 0.54-0.91, p = 0.007; Table S5). Similarly, parameters in the age of first pregnancy model were not substantially different (for hookworm HR = 0.36, CI 0.21-0.54, p<0.001; for *A. lumbricoides* HR = 2.80, CI 1.81-4.31, p<0.001). The primary difference between the two accounting methods, therefore, is in the interpretation of the Kaplan-Meier curve itself. Using time since last birth or age allows for a direct biological interpretation of the Kaplan-Meier curve in terms of birth intervals or age. These are therefore the models we report in the body of the paper.

Effects of pregnancy on infection.

Since a number of animal studies have shown that reproductive effort may affect susceptibility to parasites (e.g. *34*) and such effects could create the illusion of effects of infection on pregnancy, we also tested for reverse causality, in which pregnancy impacts the likelihood of becoming newly infected. We reasoned that if pregnancy altered the likelihood of infection, then women who had given birth more recently might be more or less likely to be infected, creating a spurious association between infection and conception. In essence, infection might serve as a proxy for recent pregnancy. We first used binomial generalized linear mixed models to examine the predictors of infection (Table S6). In these models, currently pregnant women were more likely to have hookworm (OR = 1.91, p = 0.02), but there was no significant association with *A. lumbricoides*. To examine these associations more closely, we centered observations on the midpoint of each pregnancy and used generalized additive models to examine the likelihood of infection based on timing relative to the pregnancy (Figure S8). Controlling for age, coinfection, season, and repeat measures, we find that hookworm infections vary across the peri-pregnancy period while *A. lumbricoides* infections do not (p-spline hookworm, p = 0.002, *A. lumbricoides* p = 0.140). Odds of hookworm infection were lower before pregnancy and then increase during pregnancy. After the pregnancy, odds of hookworm infection are increased relative to the mean.

These results suggest that pregnancy does alter the odds of infection, or at least the odds of detection (e.g. egg output (*43*)). To determine whether this might explain the

associations found with conception, we returned to the Cox proportional hazard model with calendar time as the time counter, noted above. We added a non-linear spline term for time since last pregnancy to this model (Table S5, Figure S7). Adding this control does not alter the significance or direction of the coefficients, but does partially mediate the effect-size of *A. lumbricoides* and education (though not hookworm). Is this mediation due to effects of pregnancy on infection, or something else? We next examined whether odds of infection varied across the inter-pregnancy interval, with time since last pregnancy. We checked for both linear and non-linear effects and found that time since last pregnancy was not a significant predictor of odds of infection in any model. Finally, we used multistate Markov models (MSM)(*44*) to examine the effect of pregnancy on likelihood of transitions from uninfected to infected states across medical visits. Models controlled for BMI, age, and coinfection status. Pregnancy was not significantly associated with transitions from uninfected to infected states for either parasite using MSM models (Table S7).

Given these results, we conclude that rather than pregnancy affecting infection, women with hookworm occasionally clear their infections, during which time they are more likely to become pregnant. However, they quickly become re-infected and return to similar prevalence as non-pregnant women. The mediation effect of IPI in the calendar time model is likely due to the fact that IPI is itself a product of infection, education, and individual characteristics (such as baseline fecundity or health).

Are fertility and likelihood of infection determined by unobserved individual characteristics?

Another possible explanation for our results is that some characteristic of individuals affects both fertility and likelihood of infection. Some examples might include pleiotropic genetic factors or individual differences in early life experiences which affect life history trajectories. To examine this possibility we tested whether past parity (e.g. previous pregnancies) was associated with altered odds of helminth infection, reasoning that if similar factors were affecting both fertility and infection then past fertility would be associated with higher or lower odds of infection. Controlling for age, age^2, community, Spanish ability, study year, and repeat observations, number of past births was not predictive of either hookworm (OR = 0.98 per birth, CI 0.90-1.08, p = 0.65) nor *A. lumbricoides* (OR = 1.05 per birth, CI 0.93-1.18, p = 0.46) infection. This result was not modified by adding or removing control variables or including age interactions or non-linear age terms.

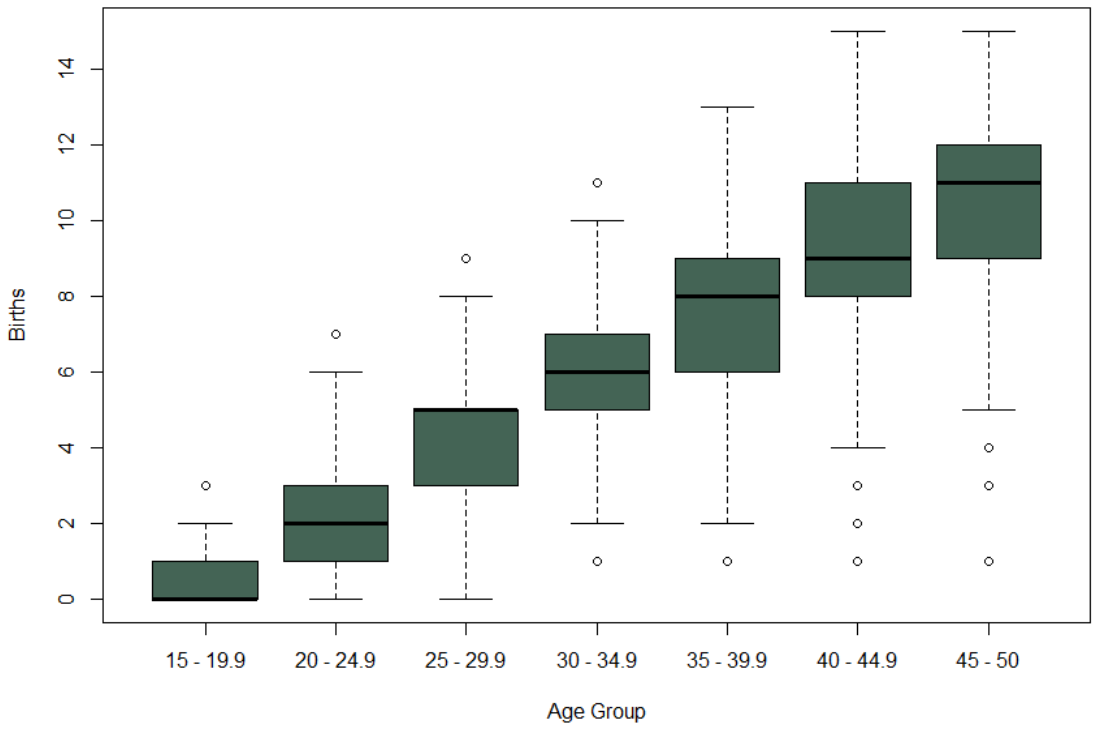

Fig. S1. Births by age group for women in this study.
Fertility is slightly higher than Tsimane average TFR of 9.1, since women who had not given birth for six years or more were excluded from analysis.

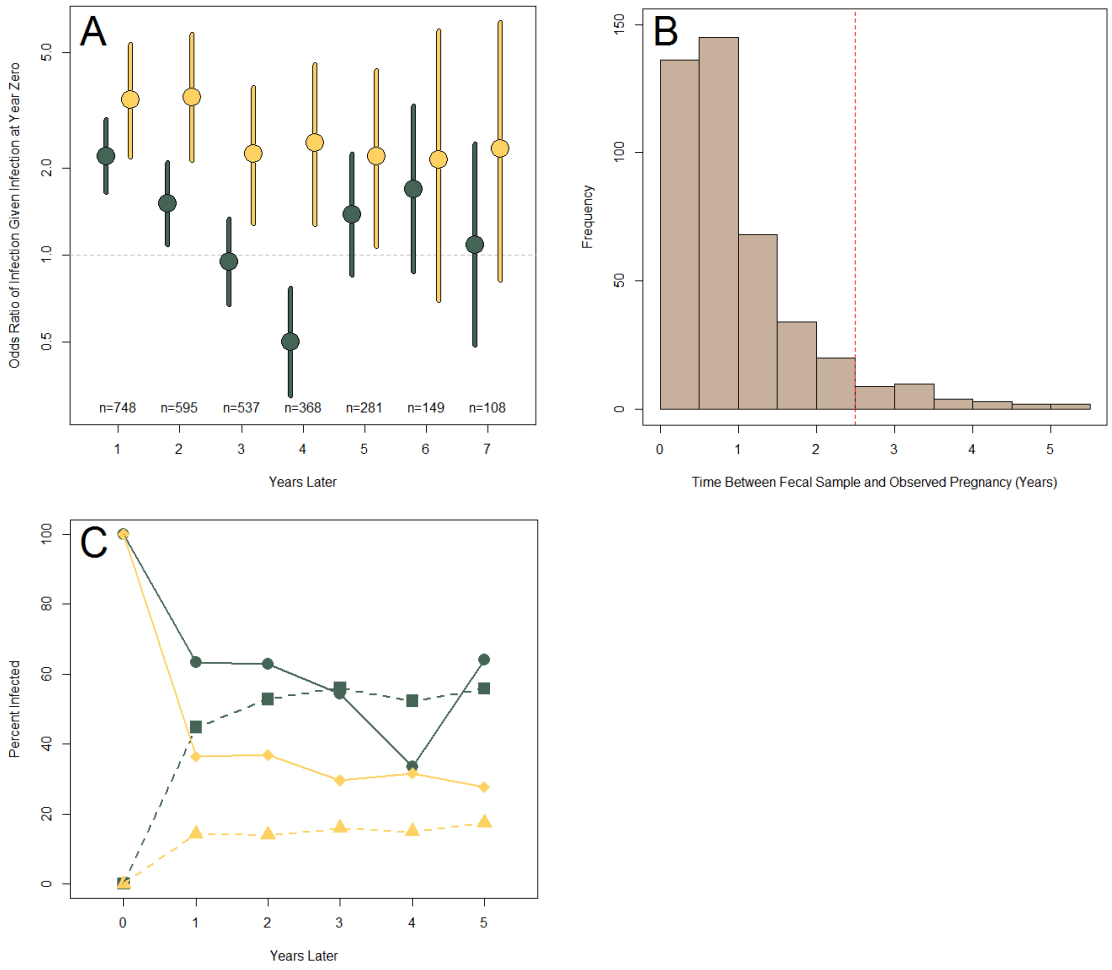

Fig. S2 Persistence of infection.

A) An observation of parasite infection is predictive of likelihood of infection for several years after the observation. *Ascaris lumbricoides* infection (yellow) at time zero is a significant predictor of continued infection for up to 5.5 years. Hookworm infection (green) is significantly predictive for up to 2.5 years. B) Histogram of time between fecal exams and subsequent pregnancies. Infection status at conception was determined based on the most recent status prior to the conception. In most instances this was within one year, but in some instances there was a longer interval prior to conception. For the primary analyses we excluded cases with observations more than 2.5 years prior to conception (dashed red line). C) Percent of individuals infected with hookworm (green) or *Ascaris lumbricoides* (yellow) given infection status at time zero; Solid lines indicate infected at time zero, dashed lines indicate uninfected at time zero.

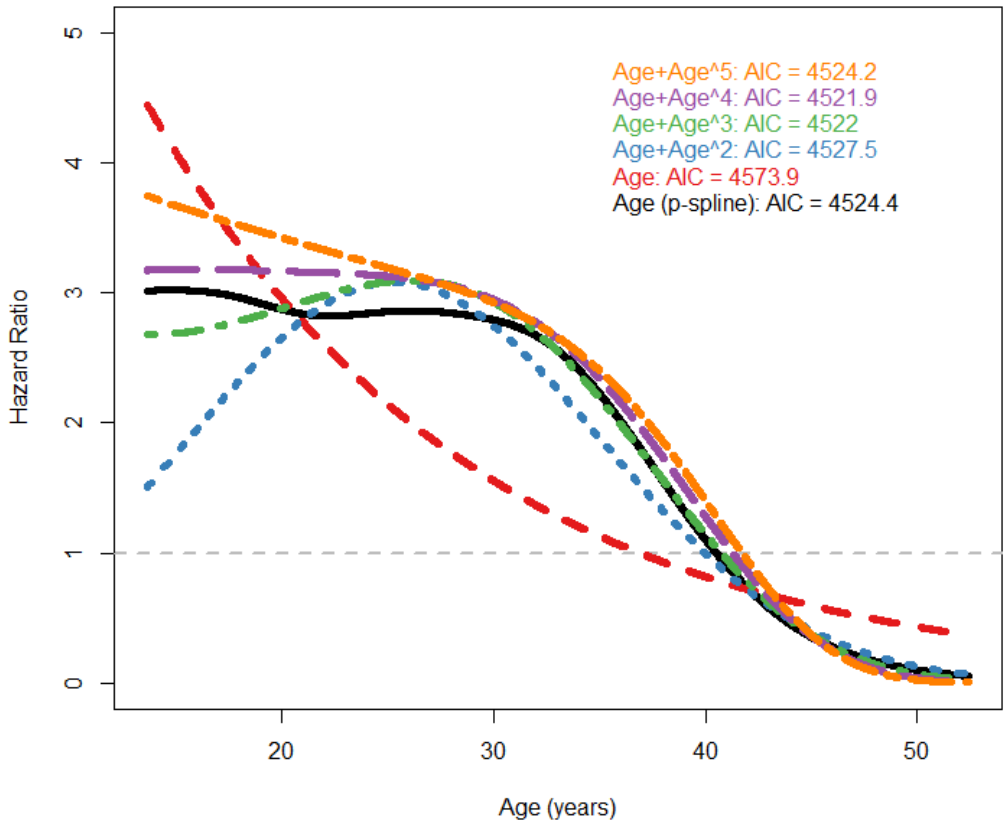

Fig. S3. Evaluation of transformations of the age term in Cox-proportional hazard models.

Lines show the hazard ratio for pregnancy at a given age for each transformation. The lowest AIC is obtained with the inclusion of an age^4 term.

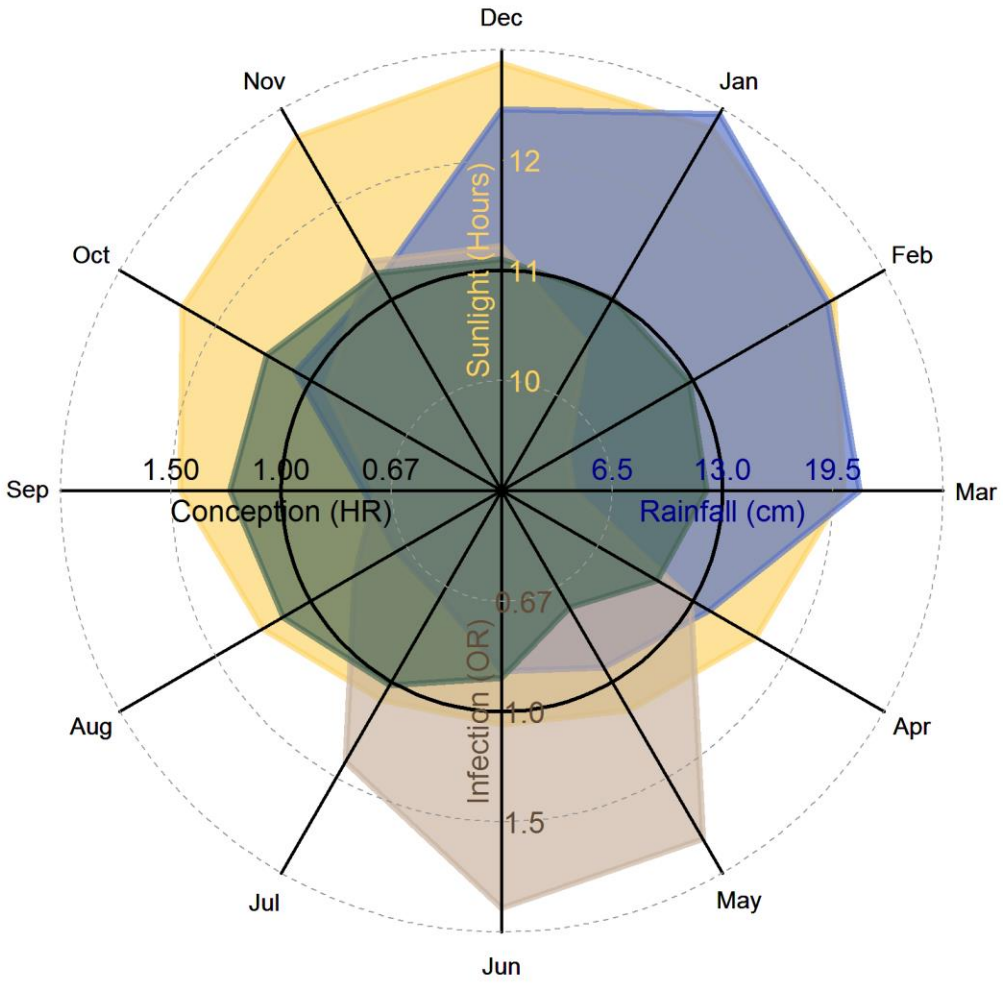

Fig. S4. Conception hazard ratio and helminth infection by month.

A. lumbricoides infections (brown) are highest in the drier months, with a peak in June and July. Conceptions (green) also show some seasonality, peaking in September and October, with resulting births peaking in June and July. Average monthly rainfall recorded in San Borja, Bolivia, for 2000-2012 (blue) and hours of sunlight (yellow) are shown for comparison. Conception hazard was estimated with a p-spline in the model in Table 1. Odds ratio for *A. lumbricoides* infection and hookworm infection were estimated with cyclical cubic splines (Table S8). Note that the axes for ratios are logged. No seasonality was found for hookworm.

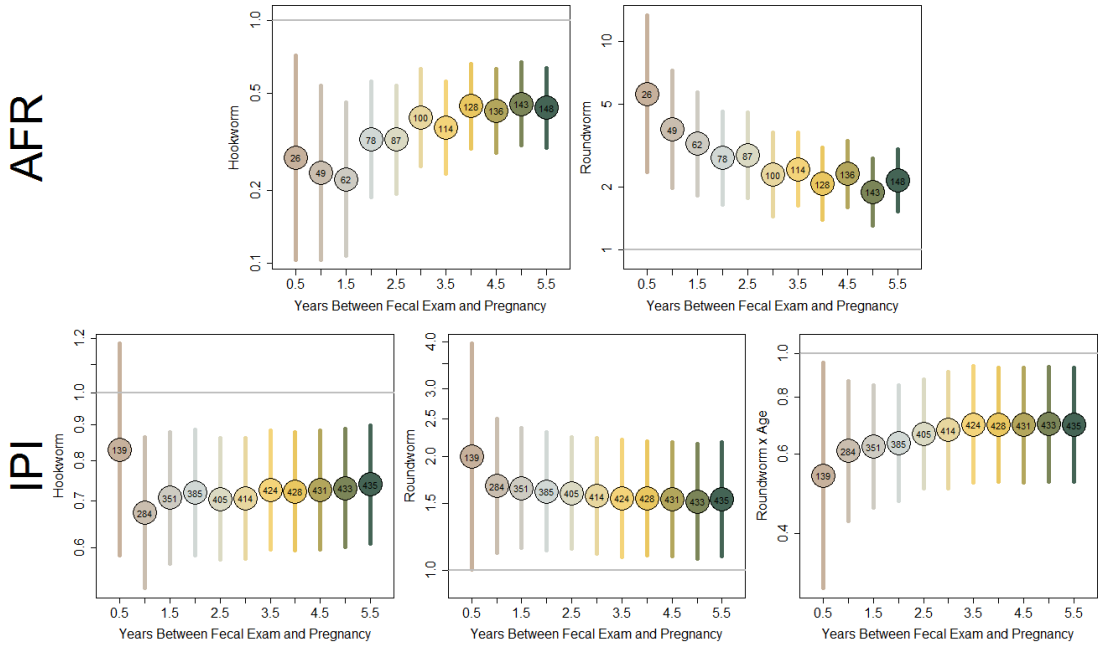

Fig. S5. Parameter values (hazard ratios) from models with varying censoring cutoffs.

Figures in the top row are parameters in age of first reproduction (AFR) models, while figures in the bottom row show parameters in inter-pregnancy interval (IPI) models. Intervals were considered censored if more than the allotted time-cutoff had passed between a fecal observation and the subsequent conception. The x-axis indicates the cutoff. Circles indicate the parameter value, with the number in the circle indicating the number of non-censored intervals included in the model. Lines indicate the 95% confidence intervals for the parameter.

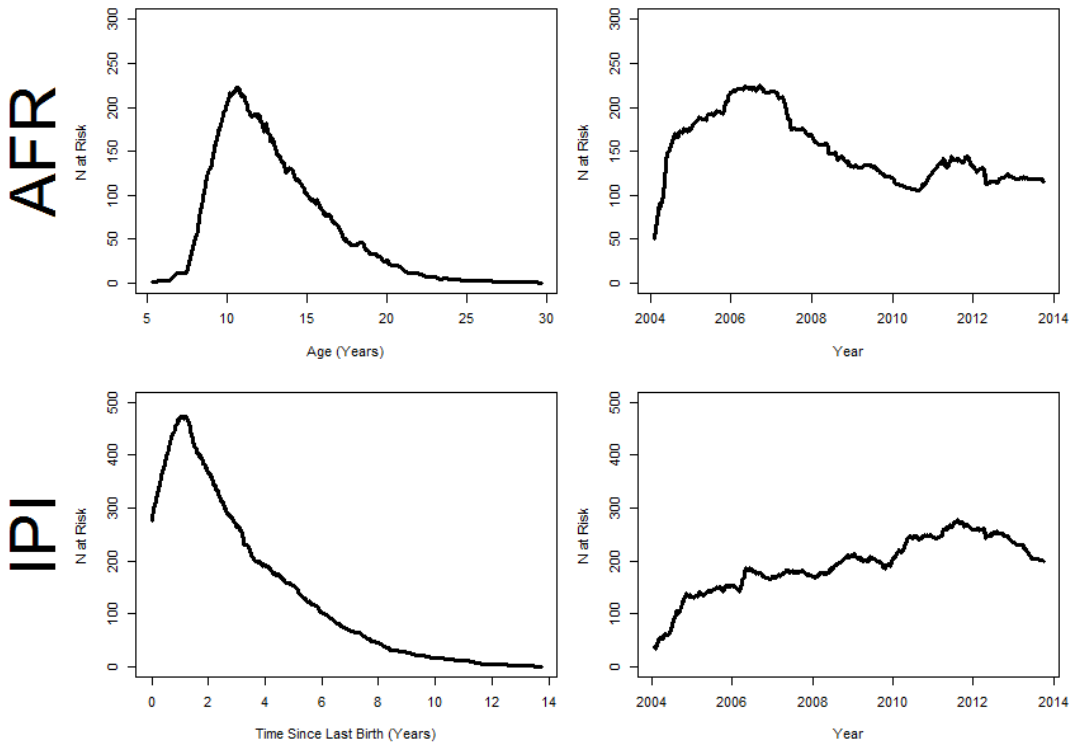

Fig. S6. Individuals at risk in Cox-proportional hazards models using different time counters.

Left, time since last birth as the time counter. Right, calendar time as the time counter. In the models on the left, individuals at risk initially increase since individual are considered at risk when they have a medical visit with a fecal parasite exam, not at time zero. The choice of time counter affects the interpretation of Kaplan-Meier curves, but does not substantially affect hazard ratios for covariates (Table S5).

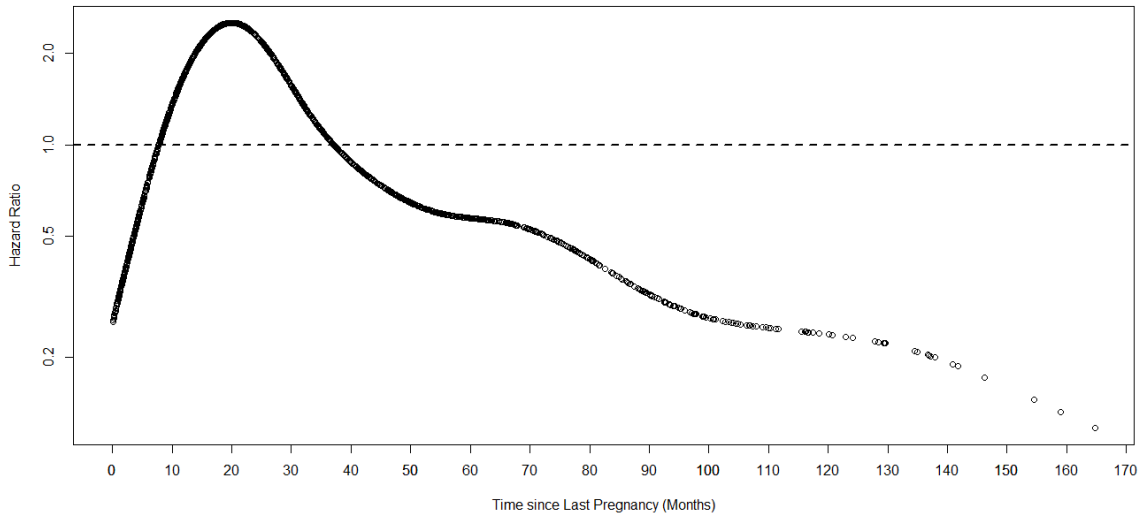

Fig. S7. Non-linear effect of time since last birth on conception hazard.
From the model in Table S5.

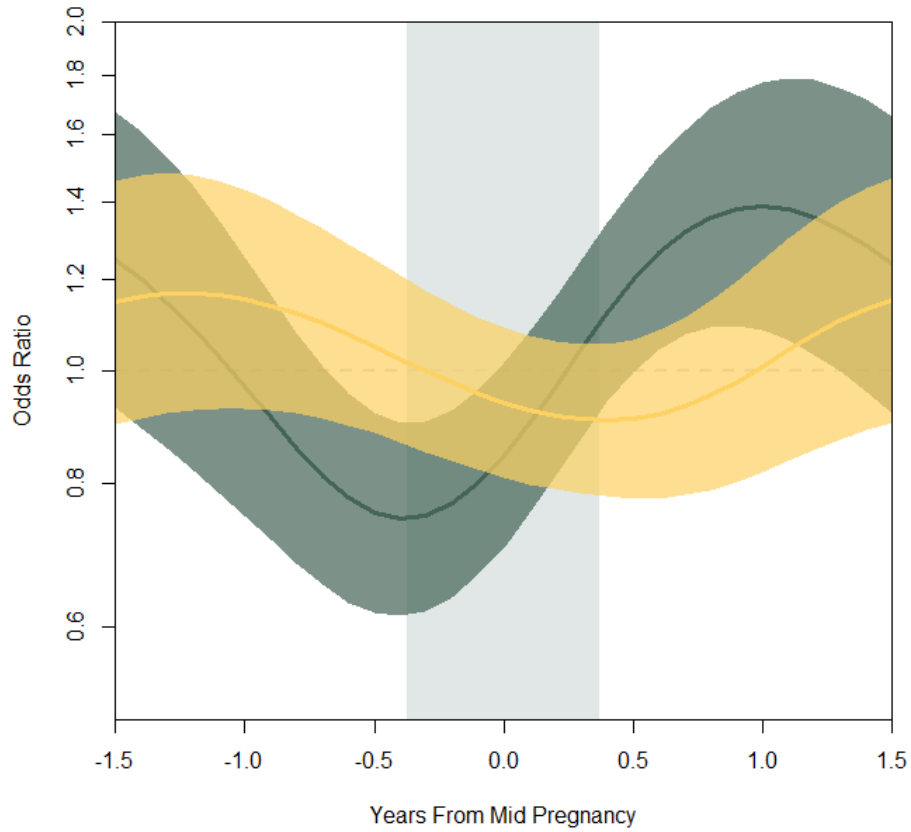

Fig. S8. Predicted probability of helminth infection by reproductive status, controlling for age, season, coinfection, and repeat observations.

Colors indicate *A. lumbricoides* (yellow) or hookworm (green). Observations are centered on the midpoint of a pregnancy (shaded region). Models are generalized additive mixed models with cyclical splines for infection. Polygons show 95% confidence intervals for the prediction.

Table S1. Descriptive statistics for the nulliparous and multiparous samples of Tsimane women.

	Nulliparous		Multiparous								
	All Ages	**Missing Values**	**All Ages**	**13 – 19**	**20 – 24**	**25 – 29**	**30 – 34**	**35 – 39**	**40 - 45**	**45-50**	**Missing Values**
Observations[a]	639	--	1623	124	209	217	232	291	362	188	--
Individuals[b]	425	--	561	64	122	117	116	172	211	131	--
Birth Intervals Starting[c]	--	--	756	72	105	97	112	159	162	49	--
New Pregnancies[d]	87	--	405	37	75	83	77	74	53	6	--
Age in Years (SD)	13.1 (3.6)	0	35.4 (9.3)	18 (1.5)	22.6 (1.4)	27.4 (1.5)	32.4 (1.4)	37.8 (1.4)	42.4 (1.4)	47.6 (1.9)	0
Previous Pregnancies (SD)	0	0	6.8 (3.5)	1.4 (0.6)	2.7 (1.3)	4.5 (1.6)	6.2 (1.8)	7.8 (2.4)	9 (2.4)	10.1 (2.5)	0
Hookworm Prevalence (%)	47	0	48.9	39.1	40.3	42.2	41.6	49.1	58.6	55.8	0
***Ascaris* Prevalence (%)**	25	0	19.5	25	19.9	26.2	23.1	18.8	15	15.8	0
Hookworm and *Ascaris* (%)	10	0	9.8	10.2	12.3	12.7	8.2	8.5	9.6	8.5	0
Antihelminth [e,f]		0	20.1 / 11.8	10.2 / 7.3	9.3 / 7.3	8.6 / 6.5	12.2 / 5.8	21.8 / 13.1	29.8 / 17.2	31.5 / 16.9	0
Antiprotozoal [e,g]		0	9.7 / 13.1	4.7 / 6.7	5.5 / 7.4	2.0 / 9.9	5.9 / 8.0	11.5 / 13.6	14.2 / 19.2	15.5 / 17.4	0
Antibiotic [e,h]		0	15.1 / 15.9	14.1 / 19.9	9.7 / 13.4	8.6 / 11.0	13.7 / 13.2	18.8 / 17.8	20.0 / 18.4	14.2 / 16.3	0
Height in cm (SD)	135.8 (12.9)	136	151.2 (4.6)	150.2 (4.7)	150.2 (4.6)	150.8 (4.4)	151.4 (4.3)	151.7 (4.5)	151.5 (4.6)	151.3 (4.7)	45
Weight in kg (SD)	35.8 (12.3)	136	55.4 (8.9)	50.1 (5.5)	51.4 (6.4)	54.8 (7.8)	57 (9.3)	57.1 (10.1)	56.7 (9.5)	55.6 (8.3)	53
BMI (SD)	18.9 (3.3)	136	24.2 (3.5)	22.2 (2.2)	22.8 (2.6)	24.1 (3.1)	24.8 (3.6)	24.8 (4)	24.7 (3.7)	24.3 (3.3)	53
Hb in g/dL (SD)	12.2 (1.4)	192	12.7 (1.2)	12.5 (1.2)	12.4 (1.2)	12.6 (1.3)	12.7 (1.1)	12.7 (1.2)	12.9 (1.2)	12.8 (1.1)	374
Yrs Formal Education (SD)	2.9 (2.2)	151	1.3 (1.8)	2.7 (2.4)	2.2 (2.1)	2 (2.4)	1.5 (1.7)	0.8 (1.3)	0.6 (1.1)	0.5 (0.9)	109
Speaks Spanish (%)	46	151	43.2	59	47.9	50.4	44.5	42.4	37.5	33.9	109

[a] Observations of infection status, BMI, and pregnancy status. Means for age, previous pregnancies, height, weight, and BMI are means of all observations, and may include repeated data on the same individual. Prevalences reported here are similarly by observation, and not by individual.

[b] Unique individuals appearing in the age category. Due to the longitudinal dataset, some individuals appear in more than one age group, so the total N is smaller than the sum of the Ns from each age group

[c] Birth intervals beginning in this age group. Intervals begin on the birth date of the last offspring. Since some intervals overlap multiple age categories, this number may be lower that the number of unique individuals in that category.

[d] Intervals ending in recorded pregnancies. Intervals without recorded pregnancies are considered right censored.

[e] For all treatments, numbers indicate the percent of helminth infected individuals treated and the percent without helminth infection treated

[f] Mebendazole or albendazole. [g] Metronidazole or tinidazole. [h] Amoxicillin, benzathine penicillin, ciprofloxacin, cotrimoxazole, erythromycin, or ampicillin.

Table S2. Cox proportional hazard models examining the effects of infection on pregnancy hazard, with various control variables

	No Controls	BMI	Hb	Years Education	Spanish	Location	Month (Cyclical)
Age (decades) [a]	1.09 (0.86-1.37)	1.11 (0.88-1.40)	1.09 (0.86-1.37)	0.99 (0.79-1.24)	1.05 (0.83-1.32)	1.09 (0.86-1.38)	1.09 (0.86-1.37)
Age^4 (decades) [a]	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)
Hookworm	0.76** (0.62-0.93)	0.75** (0.62-0.92)	0.76** (0.62-0.92)	0.70*** (0.57-0.86)	0.71*** (0.58-0.87)	0.76** (0.63-0.94)	0.76** (0.62-0.93)
*A. lumbricoides (*At Age 20)	1.54** (1.11-2.15)	1.52** (1.09-2.12)	1.51* (1.08-2.10)	1.57** (1.13-2.19)	1.53** (1.10-2.14)	1.55** (1.11-2.18)	1.53** (1.10-2.13)
A. lumbricoides x Age (decades) [a]	0.66** (0.50-0.88)	0.67** (0.50-0.88)	0.67** (0.51-0.89)	0.66** (0.50-0.87)	0.67** (0.51-0.89)	0.66** (0.50-0.87)	0.67** (0.50-0.88)
BMI		0.99 (0.95-1.02)					
Hemoglobin (g/dL)			0.90 (0.75-1.08)				
Education (Years)				0.88*** (0.83-0.94)			
Speaks Spanish					0.65*** (0.53-0.80)		
Distance to Town (10 km)						0.99 (0.95-1.04)	
Month (P-spline, df=5)							***
Model AIC	4515.03	4516.19	4514.72	4496.84	4499.71	4516.90	4513.19

Values are the exp(β) and 95% confidence intervals. Models also include GEE cluster terms for individual and village. All models include data on 561 individuals, 756 birth intervals, 405 with observed first pregnancies.

[a]Age was continuous to the nearest hundredth of a year, but is shown in decades to make the parameters more easily interpretable.

[t] $p \leq 0.10$; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table S2, continued. Cox proportional hazard models examining the effects of infection on pregnancy hazard, with various control variables

	Anti-helminthis	Anti-protozoal	Anti-biotic	Full	AIC Best Fit	Only Hookworm	Only *Ascaris*
Age (decades) [a]	1.09 (0.86-1.37)	1.09 (0.86-1.38)	1.10 (0.87-1.39)	1.02 (0.81-1.28)	1.00 (0.80-1.25)	0.91 (0.74-1.13)	1.00 (0.80-1.25)
Age^4 (decades) [a]	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)	0.95*** (0.93-0.96)
Hookworm	0.79* (0.65-0.97)	0.76** (0.62-0.93)	0.78** (0.63-0.95)	0.75** (0.60-0.92)	0.74** (0.60-0.91)	0.75** (0.61-0.92)	
A. lumbricoides (At Age 20)	1.58** (1.13-2.23)	1.54** (1.10-2.16)	1.53** (1.10-2.13)	1.60** (1.12-2.27)	1.64** (1.16-2.33)		1.62** (1.14-2.29)
A. lumbricoides x Age (decades) [a]	0.67** (0.50-0.89)	0.66** (0.50-0.88)	0.66** (0.50-0.88)	0.69** (0.52-0.91)	0.68** (0.51-0.89)		0.70** (0.53-0.92)
Treatment with Antihelminthic	0.77* (0.59-1.00)			0.76* (0.58-0.98)	0.75* (0.58-0.97)	0.75* (0.58-0.97)	0.69** (0.54-0.89)
Treatment with Antiprotozoal		0.98 (0.76-1.25)		1.02 (0.79-1.30)			
Treatment with Antibiotic			0.85 (0.66-1.10)	0.90 (0.70-1.16)			
BMI				0.99 (0.96-1.03)			
HB				0.94 (0.76-1.16)			
Education (Years)				0.92* (0.86-0.99)	0.92* (0.86-0.99)	0.92* (0.86-0.99)	0.93* (0.87-0.99)
Speaks Spanish				0.74* (0.57-0.95)	0.74* (0.57-0.95)	0.73* (0.56-0.94)	0.74* (0.58-0.96)
Distance to Town (10 km)				0.96t (0.91-1.00)	0.96t (0.91-1.00)	0.96t (0.92-1.01)	0.95* (0.91-1.00)
Month (P-spline, df=5)				***	***	***	***
Model AIC	4513.27	4517.00	4515.18	4496.21	4490.80	4493.36	4496.88

Values are the exp(β) and 95% confidence intervals. Models also include GEE cluster terms for individual and village. All models include data on 561 individuals, 756 birth intervals, 405 with observed first pregnancies.

[a]Age was continuous to the nearest hundredth of a year, but is shown in decades to make the parameters more easily interpretable.

[t] $p \leq 0.10$; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table S3. Cox-proportional hazard models for age of first pregnancy

	No Controls	BMI	Hb	Spanish	Formal Education	Location	Village Education	Village Spanish %
Hookworm	0.34*** (0.21-0.56)	0.34*** (0.20-0.56)	0.31*** (0.18-0.55)	0.33*** (0.20-0.56)	0.33*** (0.20-0.54)	0.35*** (0.21-0.58)	0.34*** (0.20-0.56)	0.33*** (0.20-0.56)
A. lumbricoides	2.72*** (1.70-4.33)	2.68*** (1.67-4.32)	2.67*** (1.67-4.26)	2.74*** (1.72-4.36)	2.75*** (1.74-4.34)	2.69*** (1.70-4.27)	2.73*** (1.72-4.34)	2.73*** (1.72-4.33)
BMI (Z-score)		1.09 (0.86-1.38)						
Hemoglobin (g/dL)			0.93 (0.78-1.10)					
Speaks Spanish				0.90 (0.55-1.47)				
Formal Education (Years)					0.96 (0.87-1.06)			
Distance to Town (10 km)						0.98 (0.89-1.09)		
Village Mean Women's Education							0.96 (0.69-1.33)	
Village Women's Spanish (%)								0.75 (0.25-2.25)
Model AIC	683.02	680.55	683.33	684.65	684.02	684.93	684.93	684.69

Values are the exp(β) and 95% confidence intervals. Models also include GEE cluster terms for individual and village. All models include data on 425 individuals, 87 with observed first pregnancies.
^{t} $p \leq 0.10$; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table S3, continued. Cox-proportional hazard models for age of first pregnancy

	Anti-helminthis	Anti-protozoal	Anti-biotic	Month (Cyclical)	All	AIC Best Fit	Only Hookworm	Only *Ascaris*
Hookworm	0.36*** (0.21-0.60)	0.33*** (0.20-0.54)	0.35*** (0.22-0.57)	0.33*** (0.20-0.54)	0.31*** (0.17-0.58)	0.34*** (0.20-0.58)	0.38*** (0.23-0.64)	
A. lumbricoides	2.81*** (1.75-4.52)	2.53*** (1.59-4.03)	2.61*** (1.64-4.15)	2.92*** (1.84-4.63)	2.54*** (1.58-4.08)	3.06*** (1.91-4.91)		2.74*** (1.72-4.37)
BMI (Z-score)					1.11 (0.88-1.40)			
Hemoglobin (g/dL)					0.97 (0.78-1.19)			
Speaks Spanish					1.01 (0.50-2.05)			
Formal Education (Years)					0.93 (0.81-1.07)			
Distance to Town (10 km)					0.89 (0.77-1.03)			
Village Mean Women's Education					1.39 (0.75-2.59)			
Village Women's Spanish (%)					0.18 (0.01-2.40)			
Treatment with Antihelminthic	0.46^{t} (0.20-1.04)				0.52 (0.23-1.19)	0.43* (0.19-0.97)	0.49t (0.22-1.12)	0.37** (0.17-0.79)
Treatment with Antiprotozoal		0.57 (0.27-1.19)			0.61 (0.30-1.23)			
Treatment with Antibiotic			0.58 (0.30-1.12)		0.72 (0.35-1.52)			
Month (P-spline; df=2)				***	***	***	***	***
Model AIC	680.88	682.54	681.92	678.85	683.59	675.82	697.78	693.43

Values are the exp(β) and 95% confidence intervals. Models also include GEE cluster terms for individual and village. All models include data on 425 individuals, 87 with observed first pregnancies.

^{t} $p \leq 0.10$; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table S4. Association between (a) helminth infection and medical diagnoses and (b) between medical diagnosis and hazard of conception

Disease / Disease Category	Prevalence (%)	OR With Hookworm[a]		OR With *A. lumbricoides* [a]		HR for Conception[b]	
		OR	p	OR	p	HR	p
Giardia	26.4	0.49*** (0.35-0.72)	<0.001	0.64[t] (0.40-1.04)	0.07	1.09 (0.85-1.38)	0.50
Respiratory Infection	16.2	1.52* (1.01-2.15)	0.03	1.14 (0.74-1.82)	0.58	0.91 (0.71-1.16)	0.45
Gastrointestinal Illness	25.5	1.40[t] (1.00-2.01)	0.06	0.93 (0.61-1.48)	0.75	1.14 (0.92-1.42)	0.23
Urinary Tract Infection	17.2	1.02 (0.69-1.56)	0.90	0.89 (0.51-1.49)	0.70	1.11 (0.88-1.40)	0.36
Vaginal Yeast Infection	4.2	0.61 (0.29-1.28)	0.17	1.22 (0.44-3.07)	0.70	0.94 (0.57-1.55)	0.81
Other Fungal Infection	4.2	1.30 (0.67-2.62)	0.47	0.44[t] (0.18-1.15)	0.10	0.83 (0.55-1.24)	0.35
Vaginal or Pelvic Inflammation	7.0	0.71 (0.41-1.32)	0.28	1.08 (0.50-2.32)	0.86	0.98 (0.71-1.35)	0.90

[a] OR for the disease given infection with hookworm or *A. lumbricoides*, controlling for age, study year, community, and repeat measures

b. HR for conception given a disease diagnosis in Cox-proportional hazard models, controlling for observation month, age, hookworm, *A. lumbricoides*, anthelminthic treatment, education, Spanish ability, village location, community, and repeat measures.

[t] $p \leq 0.10$; * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table S5. Cox-proportional hazard model with calendar time as the time counter

	No Birth Interval Control				Controlling for Time Since Last Birth			
Covariate	**HR**	**95% CI**		**p**	**HR**	**95% CI**		**p**
Age (decades) [a]	1.05	0.86	1.29	0.623	1.04	0.84	1.30	0.702
Age^4 (decades) [a]	0.95	0.93	0.96	<0.001	0.95	0.93	0.97	<0.001
Hookworm	0.78	0.65	0.95	0.011	0.80	0.65	0.98	0.027
A. lumbricoides (At Age 20)	1.51	1.14	2.02	0.004	1.60	1.15	2.24	0.006
A. lumbricoides x Age	0.70	0.54	0.91	0.007	0.67	0.51	0.88	0.004
Antihelminthic	0.76	0.60	0.97	0.030	0.77	0.59	0.99	0.044
Education (Years)	0.91	0.85	0.97	0.003	0.90	0.84	0.96	0.003
Speaks Spanish	0.83	0.66	1.06	0.131	0.83	0.64	1.07	0.145
Distance to Town (10km)	0.95	0.91	0.99	0.026	0.95	0.91	1.00	0.037
Time Since Last Birth (P-spline)[b]	--	--		--	--	--		<0.001
Month (P-spline, df=5)	--	--		<0.001	--	--		<0.001

[a]Age was continuous to the nearest hundredth of a year, but is shown in decades to make the parameters more easily interpretable.
[b]See Figure S7
[t] p = 0.10; * p = 0.05; ** p = 0.01; *** p = 0.001

Table S6. Binomial generalized additive mixed models for hookworm and *A. lumbricoides* infection.

	Hookworm				*A. lumbricoides*			
Covariate	**OR**	**95% CI**		**p**	**OR**	**95% CI**		**p**
Age (decades) [a]	1.37	1.06	1.77	0.02	0.94	0.68	1.31	0.74
BMI	0.94	0.89	1.00	0.07	1.03	0.96	1.12	0.39
Pregnant Now	2.24	1.22	4.12	<0.01	1.21	0.58	2.55	0.61
A. lumbricoides Now	1.11	0.66	1.88	0.68				
Hookworm Now					1.05	0.62	1.79	0.85
Pregnant Last Year	0.89	0.53	1.49	0.65	1.49	0.79	2.83	0.22
Hookworm Last Year	1.72	1.14	2.57	<0.01	0.76	0.45	1.30	0.32
A. lumbricoides Last Year	0.87	0.51	1.49	0.61	2.79	1.56	5.00	<0.00
Month (cyclic cubic spline)	--	--		0.43	--	--		<0.01

[a]Age was continuous to the nearest hundredth of a year, but is shown in decades to make the parameters more easily interpretable.
[t] p = 0.10; * p = 0.05; ** p = 0.01; *** p = 0.001

Table S7. Hazard ratios for covariates from multistate Markov models examining likelihood of transition between uninfected and infected states.

	Hookworm			*A. lumbricoides*		
Covariate	**HR**	**95% CI**		**HR**	**95% CI**	
Age (decades)[a]	1.24	1.04	1.48	0.91	0.72	1.16
BMI	0.94	0.89	0.98	1.00	0.95	1.07
Pregnancy	0.81	0.56	1.18	1.26	0.77	2.05
A. lumbricoides Infected	0.75	0.50	1.11			
Hookworm Infected				0.82	0.53	1.27

[a]Age was continuous to the nearest hundredth of a year, but is shown in decades to make the parameters more easily interpretable.
[t] p = 0.10; * p = 0.05; ** p = 0.01; *** p = 0.001

Database S1: AFRdata.csv

Contains the age of first reproduction dataset. Note that subject IDs and communities have been anonymized with random ID numbers, and dates have been rounded to month and year to protect participant identities. Data contains the complete dataset prior to censoring and imputation of missing values.

Database S2: IPIdata.csv

Contains the age of first reproduction dataset. Note that subject IDs and communities have been anonymized with random ID numbers, and dates have been rounded to month and year to protect participant identities. Data contains the complete dataset prior to censoring, exclusion of women with long inter-birth intervals, and imputation of missing values.

REFERENCES AND NOTES

1. H. J. A. Carp, C. Selmi, Y. Shoenfeld, The autoimmune bases of infertility and pregnancy loss. *J. Autoimmun.* **38**, J266–J274 (2012). Medline doi:10.1016/j.jaut.2011.11.016

2. A. Sen, V. A. Kushnir, D. H. Barad, N. Gleicher, Endocrine autoimmune diseases and female infertility. *Nat. Rev. Endocrinol.* **10**, 37–50 (2014). Medline doi:10.1038/nrendo.2013.212

3. T. T. Jiang, V. Chaturvedi, J. M. Ertelt, J. M. Kinder, D. R. Clark, A. M. Valent, L. Xin, S. S. Way, Regulatory T cells: New keys for further unlocking the enigma of fetal tolerance and pregnancy complications. *J. Immunol.* **192**, 4949–4956 (2014). Medline doi:10.4049/jimmunol.1400498

4. A. L. Veenstra van Nieuwenhoven, M. J. Heineman, M. M. Faas, The immunology of successful pregnancy. *Hum. Reprod. Update* **9**, 347–357 (2003). Medline doi:10.1093/humupd/dmg026

5. P. J. Hotez, P. J. Brindley, J. M. Bethony, C. H. King, E. J. Pearce, J. Jacobson, Helminth infections: The great neglected tropical diseases. *J. Clin. Invest.* **118**, 1311–1321 (2008). Medline doi:10.1172/JCI34261

6. S. M. Geiger, C. L. Massara, J. Bethony, P. T. Soboslay, O. S. Carvalho, R. Corrêa-Oliveira, Cellular responses and cytokine profiles in *Ascaris lumbricoides* and *Trichuris trichiura* infected patients. *Parasite Immunol.* **24**, 499–509 (2002). Medline doi:10.1046/j.1365-3024.2002.00600.x

7. R. M. Maizels, M. Yazdanbakhsh, Immune regulation by helminth parasites: Cellular and molecular mechanisms. *Nat. Rev. Immunol.* **3**, 733–744 (2003). Medline doi:10.1038/nri1183

8. L. J. Wammes, F. Hamid, A. E. Wiria, B. de Gier, E. Sartono, R. M. Maizels, A. J. Luty, Y. Fillié, G. T. Brice, T. Supali, H. H. Smits, M. Yazdanbakhsh, Regulatory T cells in human geohelminth infection suppress immune responses to BCG and *Plasmodium falciparum*. *Eur. J. Immunol.* **40**, 437–442 (2010). Medline doi:10.1002/eji.200939699

9. E. van Riet, F. C. Hartgers, M. Yazdanbakhsh, Chronic helminth infections induce immunomodulation: Consequences and mechanisms. *Immunobiology* **212**, 475–490 (2007). Medline doi:10.1016/j.imbio.2007.03.009

10. J. A. Fernández-Niño, A. J. Idrovo, Z. M. Cucunubá, P. Reyes-Harker, Á. P. Guerra, L. I. Moncada, M. C. López, S. M. Barrera, L. J. Cortés, M. Olivera, R. S. Nicholls, Paradoxical associations between soil-transmitted helminths and *Plasmodium falciparum* infection. *Trans. R. Soc. Trop. Med. Hyg.* **106**, 701–708 (2012). Medline doi:10.1016/j.trstmh.2012.07.012

11. A. D. Blackwell, M. Martin, H. Kaplan, M. Gurven, Antagonism between two intestinal parasites in humans: The importance of co-infection for infection risk and recovery dynamics. *Proc. Biol. Sci.* **280**, 20131671 (2013). Medline doi:10.1098/rspb.2013.1671

12. V. O. Ezenwa, A. E. Jolles, Opposite effects of anthelmintic treatment on microbial infection at individual versus population scales. *Science* **347**, 175–177 (2015). Medline doi:10.1126/science.1261714

13. L. J. Wammes, H. Mpairwe, A. M. Elliott, M. Yazdanbakhsh, Helminth therapy or elimination: Epidemiological, immunological, and clinical considerations. *Lancet Infect. Dis.* **14**, 1150–1162 (2014). Medline doi:10.1016/S1473-3099(14)70771-6

14. J. McFalls, A. Joseph, M. H. McFalls, *Disease and Fertility* (Academic Press, Orlando, FL, 1984).

15. M. Forbes, Parasitism and host reproductive effort. *Oikos* **67**, 444–450 (1993). doi:10.2307/3545356

16. L. McAllister, M. Gurven, H. Kaplan, J. Stieglitz, Why do women have more children than they want? Understanding differences in women's ideal and actual family size in a natural fertility population. *Am. J. Hum. Biol.* **24**, 786–799 (2012). Medline doi:10.1002/ajhb.22316

17. M. Martin, A. D. Blackwell, M. Gurven, H. Kaplan, in *Primates, Pathogens, and Evolution*, J. Brinkworth, K. Pechenkina, Eds. (Springer, New York, 2013), pp. 363–387.

18. A. Møller, Ectoparasites increase the cost of reproduction in their hosts. *J. Anim. Ecol.* **62**, 309–322 (1993). doi:10.2307/5362

19. H. Hurd, Host fecundity reduction: A strategy for damage limitation? *Trends Parasitol.* **17**, 363–368 (2001). Medline doi:10.1016/S1471-4922(01)01927-4

20. P. Neuhaus, Parasite removal and its impact on litter size and body condition in Columbian ground squirrels (*Spermophilus columbianus*). *Proc. Biol. Sci.* **270** (suppl. 2), S213–S215 (2003). Medline doi:10.1098/rsbl.2003.0073

21. L. Krishnan, L. J. Guilbert, T. G. Wegmann, M. Belosevic, T. R. Mosmann, T helper 1 response against *Leishmania major* in pregnant C57BL/6 mice increases implantation failure and fetal resorptions. Correlation with increased IFN-gamma and TNF and reduced IL-10 production by placental cells. *J. Immunol.* **156**, 653–662 (1996). Medline

22. R. Avitsur, R. Yirmiya, The immunobiology of sexual behavior: Gender differences in the suppression of sexual activity during illness. *Pharmacol. Biochem. Behav.* **64**, 787–796 (1999). Medline doi:10.1016/S0091-3057(99)00165-3

23. M. Baudoin, Host castration as a parasitic strategy. *Evolution* **29**, 335–352 (1975). doi:10.2307/2407221

24. Materials and methods are available as supplementary materials on *Science* Online.

25. H. Kaplan, P. L. Hooper, J. Stieglitz, M. Gurven, "The causal relationship between fertility and infant mortality: Prospective analyses of a population in transition," in *Population in the Human Sciences: Concepts, Models, Evidence*, Philip Kreager, B. Winne, S. Ulijaszek, C. Capelli, Eds. (Oxford Univ. Press, Oxford, 2015), pp. 361–378.

26. S. M. Geiger, N. D. Alexander, R. T. Fujiwara, S. Brooker, B. Cundill, D. J. Diemert, R. Correa-Oliveira, J. M. Bethony, *Necator americanus* and helminth co-infections: Further down-modulation of hookworm-specific type 1 immune responses. *PLOS Negl. Trop. Dis.* **5**, e1280 (2011). Medline doi:10.1371/journal.pntd.0001280

27. H. J. McSorley, A. Loukas, The immunology of human hookworm infections. *Parasite Immunol.* **32**, 549–559 (2010). Medline

28. K. B. H. Clancy, L. D. Klein, A. Ziomkiewicz, I. Nenko, G. Jasienska, R. G. Bribiescas, Relationships between biomarkers of inflammation, ovarian steroids, and age at menarche in a rural Polish sample. *Am. J. Hum. Biol.* **25**, 389–398 (2013). Medline doi:10.1002/ajhb.22386

29. J. Stieglitz, B. C. Trumble, M. E. Thompson, A. D. Blackwell, H. Kaplan, M. Gurven, Depression as sickness behavior? A test of the host defense hypothesis in a high pathogen population. *Brain Behav. Immun.* **49**, 130–139 (2015). 10.1016/j.bbi.2015.05.008 Medline doi:10.1016/j.bbi.2015.05.008

30. E. C. Shattuck, M. P. Muehlenbein, Human sickness behavior: Ultimate and proximate explanations. *Am. J. Phys. Anthropol.* **157**, 1–18 (2015). 10.1002/ajpa.22698 Medline doi:10.1002/ajpa.22698

31. M. Gurven, C. von Rueden, J. Stieglitz, H. Kaplan, D. E. Rodriguez, The evolutionary fitness of personality traits in a small-scale subsistence society. *Evol. Hum. Behav.* **35**, 17–25 (2014). Medline doi:10.1016/j.evolhumbehav.2013.09.002

32. M. Gurven, H. Kaplan, A. Z. Supa, Mortality experience of Tsimane Amerindians of Bolivia: Regional variation and temporal trends. *Am. J. Hum. Biol.* **19**, 376–398 (2007). Medline doi:10.1002/ajhb.20600

33. A. Veile, M. Martin, L. McAllister, M. Gurven, Modernization is associated with intensive breastfeeding patterns in the Bolivian Amazon. *Soc. Sci. Med.* **100**, 148–158 (2014). Medline doi:10.1016/j.socscimed.2013.10.034

34. M. Gurven, H. Kaplan, J. Winking, D. Eid Rodriguez, S. Vasunilashorn, J. K. Kim, C. Finch, E. Crimmins, Inflammation and infection do not promote arterial aging and cardiovascular disease risk factors among lean horticulturalists. *PLOS ONE* **4**, e6590 (2009). Medline doi:10.1371/journal.pone.0006590

35. A. D. Blackwell, M. D. Gurven, L. S. Sugiyama, F. C. Madimenos, M. A. Liebert, M. A. Martin, H. S. Kaplan, J. J. Snodgrass, Evidence for a peak shift in a humoral response to helminths: Age profiles of IgE in the Shuar of Ecuador, the Tsimane of Bolivia, and the U.S. NHANES. *PLOS Negl. Trop. Dis.* **5**, e1218 (2011). Medline

36. S. Vasunilashorn, E. M. Crimmins, J. K. Kim, J. Winking, M. Gurven, H. Kaplan, C. E. Finch, Blood lipids, infection, and inflammatory markers in the Tsimane of Bolivia. *Am. J. Hum. Biol.* **22**, 731–740 (2010). Medline doi:10.1002/ajhb.21074

37. M. Eberl, M. al-Sherbiny, P. Hagan, S. Ljubojevic, A. W. Thomas, R. A. Wilson, A novel and sensitive method to monitor helminth infections by faecal sampling. *Acta Trop.* **83**, 183–187 (2002). Medline doi:10.1016/S0001-706X(02)00089-X

38. P. Andersen, R. Gill, Cox's regression model for counting processes: A large sample study. *Ann. Stat.* **10**, 1100–1120 (1982). doi:10.1214/aos/1176345976

39. S. Van Buuren, K. Groothuis-Oudshoorn, Multivariate imputation by chained equations. *J. Stat. Softw.* **45**, 1–67 (2011).

40. S. S. Urlacher, A. D. Blackwell, M. A. Liebert, F. C. Madimenos, T. J. Cepon-Robins, T. E. Gildner, J. J. Snodgrass, L. S. Sugiyama, Physical growth of the shuar: Height, weight, and BMI references for an indigenous amazonian population. *Am. J. Hum. Biol*. 10.1002/ajhb.22747 (2015). Medline

41. J. Stieglitz, A. D. Blackwell, R. Quispe Gutierrez, E. Cortez Linares, M. Gurven, H. Kaplan, Modernization, sexual risk-taking, and gynecological morbidity among Bolivian forager-horticulturalists. *PLOS ONE* **7**, e50384 (2012). Medline doi:10.1371/journal.pone.0050384

42. S. C. L. Knowles, S. Nakagawa, B. C. Sheldon, Elevated reproductive effort increases blood parasitaemia and decreases immune function in birds: A meta-regression approach. *Funct. Ecol.* **23**, 405–415 (2009). doi:10.1111/j.1365-2435.2008.01507.x

43. F. Pelletier, K. Page, T. Ostiguy, M. Festa-Bianchet, Fecal counts of lungworm larvae and reproductive effort in bighorn sheep, *Ovis canadensis*. *Oikos* **110**, 473–480 (2005). doi:10.1111/j.0030-1299.2005.14120.x

44. C. Jackson, Multi-state models for panel data: The msm package for R. *J. Stat. Softw.* **38** (2011). doi:10.18637/jss.v038.i08