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Aaron D. Blackwell, University of California Santa Barbara
Marilyne Tamayo, University of Missouri
Bret Beheim, University of New Mexico
Benjamin C. Trumble, University of California Santa Barbara
Jonathan Stieglitz, Tsimane Health and Life History Project
Paul L. Hooper, Emory University
Melanie Martin, University of California Santa Barbara
Hillard Kaplan, University of New Mexico
Michael Gurven, University of California Santa Barbara

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Aaron D. Blackwell\textsuperscript{a,b,c,*}, Marilyne Tamayo\textsuperscript{d}, Bret Beheim\textsuperscript{b,e}, Benjamin C. Trumble\textsuperscript{a,b,c,f,g}, Jonathan Stieglitz\textsuperscript{b,h}, Paul L. Hooper\textsuperscript{b,i}, Melanie Martin\textsuperscript{a,b,c}, Hillard Kaplan\textsuperscript{b,e}, and Michael Gurven\textsuperscript{a,b,c}

\textsuperscript{a}Department of Anthropology, University of California Santa Barbara, CA, USA
\textsuperscript{b}Tsimane Health and Life History Project, San Borja, Bolivia
\textsuperscript{c}Broom Center for Demography, University of California Santa Barbara, CA, USA
\textsuperscript{d}Department of Anthropology, University of Missouri, Columbia, MO, USA
\textsuperscript{e}Department of Anthropology, University of New Mexico, Albuquerque, NM
\textsuperscript{f}Center for Evolutionary Medicine, Arizona State University, Tempe, AZ, USA
\textsuperscript{g}School of Human Evolution and Social Change, Arizona State University, Tempe, AZ, USA
\textsuperscript{h}Institute for Advanced Study in Toulouse, Toulouse, France
\textsuperscript{i}Department of Anthropology, Emory University, Atlanta, GA, USA

Abstract

Infection with intestinal helminths results in immunological changes that influence the odds of comorbid infections, and might also affect fecundity by inducing immunological states supportive of conception and pregnancy. Here we investigate associations between intestinal helminths and fertility in human females, utilizing nine years of longitudinal data from 986 Bolivian forger-horticulturalists, experiencing natural fertility and a 70% helminth prevalence. We find that different species of helminth are associated with opposing effects on fecundity. Infection with roundworm (\textit{Ascaris lumbricoides}) is associated with earlier first births and shortened interbirth intervals, while infection with hookworm is associated with delayed first pregnancy and extended interbirth intervals. Thus, helminths may have important, and sometimes contradictory effects on human fertility, reflecting the physiological and immunological consequences of infection with particular species.

*Corresponding author: blackwell@anth.ucsb.edu.

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Dysregulated immune function, and in particular autoimmune disease, has negative impacts on virtually every aspect of fecundity, including ovarian function, implantation, and pregnancy loss (1, 2). Conversely, healthy pregnancy is also associated with shifts in immunity. During the luteal phase of the menstrual cycle regulatory (Treg) and type 2 (Th2) T-cell responses increase (3). If conception occurs, these shifts continue through pregnancy (4) and help to suppress type 1 (Th1) T cell responses, increasing maternal tolerance of an immunologically distinct fetus (3). Since pregnancy is both affected by and alters immunity, parasites that result in systemic immunological changes might affect fecundity by altering the host’s immune system. Helminths, such as hookworm (Ancylostoma duodenale or Necator americanus) and giant roundworm (Ascaris lumbricoides) infect upwards of 500–800 million people a piece (5), and are associated with such immunological changes: host helper T cell populations generally shift away from Th1 and towards Th2 responses (6, 7), and the suppressive activity of regulatory T cells increases, modulating both Th1 and Th2 responses (8, 9). These shifts can increase or decrease susceptibility to other pathogens, such as malaria (10), giardia (11), and tuberculosis (12), and are associated with reductions in many diseases with inflammatory or auto-immune etiology (13). They also resemble the shifts that occur during pregnancy, suggesting that helminth infections might result in immunological states that favor conception or pregnancy.

In humans, parasites that directly affect either the reproductive organs or the fetus have been investigated, including Wuchereria bancrofti which can cause elephantiasis of the genitals (14). Animal studies have also examined life history changes associated with parasitism (15). Yet, there is little data on the effects of intestinal helminth infections on human fecundity, fertility, or birth spacing. Here we examine prospectively the effect of helminth infection on the fecundity of human females. We use nine years of longitudinal data collected on 986 Tsimane forager-horticulturalist women living in the Amazonian lowlands of Bolivia (Table S1). Tsimane are predominantly a natural fertility population, with infrequent (<5% prevalence) use of pharmaceutical contraceptives, and a total fertility rate of nine births per woman (16). Helminths infect 70% of the population; the two most common infections being hookworm, infecting 56%, and A. lumbricoides, infecting 15–20% (11, 17). Tsimane therefore represent an ideal population for examining the effects of helminth infection on human reproduction.

In both animal and human studies there are examples of parasitism affecting host reproduction, including effects on sexual behavior, brood or litter size, offspring size, incubation periods, conception rates, and pregnancy loss (18–22). In most cases, parasitism reduces host reproduction by compromising reproductive organs or reducing energy budgets (14, 23). However, among Tsimane adults, morbidity from intestinal helminth infections is low, particularly for A. lumbricoides: controlling for age and coinfection, in our sample, hookworm infection is associated with slightly lower BMI ($\beta = -0.77$ kg/m$^2$, p < 0.001) and hemoglobin ($\beta = -0.19$ g/dL, p = 0.005), while A. lumbricoides is not ($\beta = -0.34$ kg/m$^2$, p =0.180; $\beta = -0.07$ g/dL, p =0.413). However, helminth infection is also associated with reductions in other infections, such as G. lamblia (11). We hypothesized that unlike many other infections, intestinal helminths might result in increased fecundity, given associated immunological changes that resemble those occurring during pregnancy,
modulation of inflammatory responses that might impair fertility, and apparently low costs
of infection.

Using Cox-proportional hazards models, we tested whether helminth infection was
associated with changes in birth spacing for 561 multiparous women, and the age of first
pregnancy (AFP) for 425 nulliparous women (24). Consistent with our hypothesis, *A.
lumbricoides* infection was associated with an earlier AFP (HR = 3.06, CI 1.91–4.91, p <
0.001; Figure 1, Table 1) and with increased hazard of pregnancy under age 32 (at age 20:
HR = 1.64, CI 1.16–2.33, p = 0.005). This association declines with age (interaction
between *A. lumbricoides* and age: HR = 0.68 per decade, CI 0.51–0.89, p = 0.006) and
becomes significantly negative by age forty-six (HR = 0.62, CI 0.38–1.00, p = 0.05).
However, these late life negative associations are outweighed by early life positive
associations, such that *A. lumbricoides* infection projected across the lifespan would result
in two more children than for a woman never infected (Figure 2).

In contrast, infection with hookworm was associated with a delayed age of first pregnancy
(HR = 0.33, CI 0.20 – 0.54, p < 0.001), and with a reduced hazard of subsequent
pregnancies at all ages (HR = 0.71, CI 0.58–0.86, p < 0.001). A woman chronically infected
with hookworm would be predicted to have three fewer children than an uninfected woman
(Figure 2). We found no interaction between infections, such that coinfection is associated
with the additive effects of hookworm and *A. lumbricoides*.

These results are not altered by controlling for other likely confounds affecting fecundity or
fecundity altering behaviors, including physical condition, education (a proxy of
acculturation), village location, season, and secular changes, even though these variables do
affect fertility (Table S2–S3, also see (25)). The results are also not mediated by other
comorbid infections or illnesses (Table S4). Twenty percent of infected women were given
antihelminthic medications during medical visits. Receipt of antihelmintics was itself
associated with a lower hazard of conceiving (HR = 0.75, CI 0.58–0.97, p = 0.03); however,
neither controlling for treatment in models, nor excluding these women appreciably altered
hazard ratios from infection with either hookworm or *A. lumbricoides*. The results are also
not driven by changing infection hazard during pregnancy; pregnancy is associated with an
increased likelihood of hookworm infection, particularly in late pregnancy (Table S6; Figure
S8), but this relationship does not mediate the association between infection and conception
hazards (24). Instead it appears that hookworm infected women occasionally clear their
infections, during which time they become pregnant, followed quickly by subsequent
reinfected with hookworm. Finally, these associations are unlikely to be due to consistent
differences between individual women (e.g. genetic pleiotropies), that affect both fertility
and risk of infection, as past parity is unrelated to likelihood of current infection
(hookworm: OR = 0.98 per birth, CI 0.90–1.08, p = 0.65; *A. lumbricoides*: OR 1.05 per
birth, CI 0.93–1.18, p = 0.46).

The finding that hookworm and *A. lumbricoides* have different associations with fecundity
may seem surprising. However, we suggest two reasons why we might observe such a
pattern. First, although helminths are often discussed as if interchangeable, hookworm and
*A. lumbricoides* do not have identical effects on the immune system. While *A. lumbricoides*
is associated with a polarized Th2 response (6), the response to hookworm has been reported as a mixed Th1/Th2 response (26, 27). Hookworm and *A. lumbricoides* also have contradictory effects on other diseases, such as malaria (10). Thus the *A. lumbricoides* response may be more favorable to conception and implantation, as it more closely resembles the immunological state in pregnancy, and less closely resembles pro-inflammatory states that suppress fecundity. Second, hookworm infection may be more costly than *A. lumbricoides*, such that the costs imposed by infection, such as anemia and nutritional loss, outweigh any effect of immune modulation. While we do not have direct measures of parasite load, hookworm is associated with both lower BMI and lower hemoglobin for women in our sample, while *A. lumbricoides* is not. Future studies will need to investigate the importance of parasite burden in these associations.

Although consistent with our hypothesis, it is still surprising to see positive associations between fecundity and *A. lumbricoides* infection, given that most parasites decrease reproduction. However, this association might instead be understood not as *de novo* increases in fecundity, but as the suppression of responses that would otherwise *decrease* fecundity. For example, most organisms down-regulate reproductive effort during acute illness as inflammation leads to the suppression of reproductive function (28). If *A. lumbricoides* infection modulated inflammatory responses, then this might also limit inflammation-induced reproductive suppression, as well as sickness behavior and associated reductions in sexual activity (29, 30). If this were true, then the effects of *A. lumbricoides* might only be observed in the presence of other illnesses or conditions resulting in excess inflammation. An additional possibility is that the increase in fertility represents fecundity compensation, a host response in which reproductive effort is shifted towards earlier ages to compensate for increasing morbidity or mortality (15). However, our analysis cannot fully evaluate these kinds of lifetime or cumulative effects as even our longitudinal sample remains relatively short relative to the lifespan of a human.

Regardless of mechanism, these results suggests that across populations, helminths may have unappreciated effects on demographic patterns, particularly given their high global prevalences (5). If our findings generalize, then it is worth considering the role of helminth infections may play in the demographics of these individuals.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References and Notes**


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


Figure 1.
Associations between infection and likelihood of becoming pregnant. (A–C) Kaplan-Meier curves from cox-proportional hazard models (Table 2), representing the time to first pregnancy (A), and time to subsequent pregnancies at age 25 (B) and age 40 (C). Hazard ratios for conception associated with infection across ages are shown in (D). Colors indicate uninfected (dashed brown), infected with hookworm (solid dark green), or infected with *A. lumbricoides* (solid mustard).
Figure 2.
Reproductive careers predicted from Cox proportional hazard models, showing the expected distributions of reproductive values for hypothetical women with constant parasite status throughout life. Outcomes include: age at first birth (A), interbirth intervals (B), age at last birth (C), age specific fertility (births/woman/year) (D), median cumulative fertility over time (E), and total completed fertility at age 50 (F). Colors indicate uninfected (U; brown), infected with hookworm (H; dark green), infected with *A. lumbricoides* (A; mustard), or coinfectected with hookworm and *A. lumbricoides* (C; light blue). Boxplot whiskers display the
5th and 95th percentiles, bodies the 25th, 50th, and 75th. Predictions are derived from the models in Figure 1.
Cox-proportional hazard models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age of First Pregnancy (n = 425, obs = 639, preg = 87)</th>
<th>Time to Next Pregnancy (n = 561, obs = 1623, preg = 405)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exp(β)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age (decades) *</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Age^4 (decades) *</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hookworm</td>
<td>0.34</td>
<td>(0.20–0.58)</td>
</tr>
<tr>
<td>A. lumbricoides†</td>
<td>3.06</td>
<td>(1.91–4.91)</td>
</tr>
<tr>
<td>A. lumbricoides × Age †</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Treatment with antihelminthic</td>
<td>0.43</td>
<td>(0.19–0.97)</td>
</tr>
<tr>
<td>Education (Years)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Speaks Spanish</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Distance to town (10km)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Season (P-spline)</td>
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</tr>
</tbody>
</table>

Models also include GEE cluster terms for individual and village. See tables S2–S3 for additional excluded variables.

* Age is centered at 20 years. Age was continuous to the nearest tenth of a year, but is shown in decades to make the parameters more easily interpretable.

† For the time to next pregnancy model the roundworm parameter represents the hazard ratio at age 20.