Early-life infectious disease exposure, the "hygiene hypothesis", and lifespan: evidence from hookworm *

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Abstract

Exposure to infectious disease in early life may have long-term ramifications for health and lifespan. However, reducing pathogen exposure may not be uniformly beneficial. The rise of modern sanitation and reduction of infectious diseases has been implicated in increasing levels of allergy and immune dysregulation: termed, the "hygiene hypothesis." This study leverages quasi-experimental variation from combining pre-campaign hookworm exposure with the Rockefeller Sanitary Commission's de-worming campaign in the early 20th century to rigorously examine the impacts of childhood hookworm exposure on adult lifespan and morbidity. Findings show de-worming before age five leads to 2.5 additional months of life in a large sample of adult death records. Further, decreasing hookworm exposure is related to improvements in biomarkers for inflammation and skin-tested allergies, in contrast to predictions of the "hygiene hypothesis". Placebo tests using health outcomes that should not be affected by de-worming do not show similar patterns. Findings provide new, rigorous evidence of the role of early life infectious disease on later life health outcomes, and the mechanisms through which it occurs. Overall, childhood de-worming leads to improvements in morbidity and lifespan decades later.

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1 Introduction

Over the 20th century, the United States experienced dramatic changes in lifespan and health. Most notably, life expectancy at age 10 increased by nearly 20 years over the century (Costa, 2015). People grew taller, experienced less heart disease and had lower infectious disease exposure (Costa, 2000; Crimmins and Finch, 2006; Goldin and Lleras-Muney, 2019). In contrast, autoimmune conditions and allergy rose dramatically (Platts-Mills, 2015). This study rigorously explores the role of infectious disease in these changes, using the Rockefeller Sanitary Commission's (RSC) campaign to eradicate hookworm in the US South as a natural experiment.

Much of the improvement in life expectancy has been attributed to developments in medical science, public health interventions, and the broad decline of inflammatory exposure over time (Alsan and Goldin, 2019; Costa, 2015; Cutler and Meara, 2001; Cutler and Miller, 2005). While infectious diseases present acute threats to mortality, one prominent theory argues that improvements in lifespan may result from reductions in inflammatory exposure early in life. Finch and Crimmins argue for this theory indirectly by noting the negative relationship between cohort-level infant mortality with adult longevity (Crimmins and Finch, 2006; Finch and Crimmins, 2004). However, unifying mechanistic understanding of the role of inflammatory processes in improving lifespan is lacking.

While compelling, the impact of early life inflammatory environment on lifespan is challenging to test directly. Among other difficulties, in studies of birth-year infectious disease exposure due to seasonal variation or the 1918 influenza pandemic it is difficult to separate potential in-utero maternal health shocks (and the well-documented impacts of Barker's fetal origins hypothesis) from individual exposure (Almond and Currie, 2011; Barker, 1995; Barker, 1997; Beach et al., 2022; Bengtsson and Lindström, 2003; Cohen et al., 2010; Mazumder et al., 2010; Myrskylä et al., 2013). Additionally, with these study designs it may be difficult to separate changes in early-life mortality selection from broader changes in the disease environment (Caruso et al., 2005). A further challenge for many of these studies that draw comparisons across 'typical' year-to-year variation in the early-life disease exposure is that infant mortality and early life disease exposure may be correlated with environmental or economic changes that likely have direct impacts on health. Even then, these studies have mixed results on lifespan.

This paper sets out to contribute direct evidence on the role of chronic inflammatory processes on lifespan, and test the implications of chronic inflammatory processes in earlier life on morbidity and auto-immune conditions. Taking an approach similar to Bleakley, 2007's study of de-worming on economic outcomes, I leverage the Rockefeller Sanitary Com-

mission's (RSC) de-worming program in the American South to investigate the long-term effects of de-worming before age 5 on adult lifespan, and explore changes in morbidity, including auto-immune conditions, at older ages. Identification is derived from the combination of pre-intervention hookworm prevalence with the relatively sudden changes in hookworm prevalence in treated areas. Intuitively, areas with higher pre-intervention hookworm prevalence should benefit more from the de-worming campaign - this "dose-response" allows me to attribute changes in later-life outcomes for birth cohorts around the intervention to the impacts of de-worming.

This paper makes several contributions. First, I provide direct evidence on the effect of early-life chronic inflammatory exposure on lifespan. Using data including nearly 4 million deaths, primarily among older adults, from the Berkeley Unified Numident Database, I show that exposure to de-worming in childhood is linked to an additional 0.21 year increase in adult lifespan.[1] I derive similar findings with a parallel approach based on census data, and extended samples covering earlier years of death. This study's emphasis on hookworm has three additional strengths for interpretation: 1) hookworm is a chronic inflammatory exposure rather than an acute infectious disease, 2) mortality attributed to hookworm is nearly-zero, so childhood mortality selection is very limited, and 3) hookworm is very uncommon in adults, suggesting that changes in lifespan can be interpreted as the result of chronic changes due to hookworm, rather than shocks to in-utero health.

Further, using data from two waves of the National Health and Nutrition Examination Survey, I find evidence for long-term improvements in erythrocyte sedimentation rate, a biomarker for inflammation, as well as decreases in skin-tested allergies decades after the de-worming campaign. These persistent changes in immunologic outcomes provide further mechanistic evidence that early-life immune environments can shape lifespan through chronic inflammation.

Notably, this finding is inconsistent with the "hygiene hypothesis", which posits that the reduction in inflammatory exposure and parasites, specifically helminths, plays a large role in the modern increases in allergy and autoimmune conditions (Loukas et al., 2016; Strachan, 1989). To some extent, the theory is appealing as it reconciles the observed declines in infectious disease mortality with increasing autoimmune conditions. While it is a high-profile theory, there is little human evidence over the long-term to support or reject it.

[1]While selection into the BUNMD data on survival into old age potentially biases this estimate, it likely does so downwards and the direction of the estimated effect is likely accurate given the empirical specification. The inclusion of a birth-year fixed effect and the empirical design chosen should account for age-based selection into the sample unless there is substantial selection into the BUNMD sample that is related to RSC campaign exposure, which I empirically verify is not the case. Further, positive mortality selection into representation at older-ages should bias the estimated effects of de-worming downwards.

Contrary to the theory's prediction, I find that reduction in helminth burdens likely is not responsible for the rise of allergy and auto-immune disease in America over the 20th century, and in fact likely contributed to relative reductions in these conditions.

Finally, this paper has direct implications for de-worming policy. Over 400 million people globally live with hookworm (P. J. Hotez et al., 2014). Seminal work finds human capital and short-term health benefits from mass de-worming (Bleakley, 2007; Miguel and Kremer, 2004). However, the value of large-scale de-worming continues to be debated, and long-term evidence on the consequences of de-worming is thin (Croke et al., 2024; Taylor-Robinson et al., 2019). This work provides novel evidence on the long-term consequences of childhood de-worming.

The remainder of this paper proceeds as follows. In Part 2, I explore the lifecycle and relevant epidemiologic considerations of hookworm, and the literature surrounding their health impacts. Part 3 reviews the de-worming intervention by the Rockefeller Sanitary Commission. Part 4 describes the data used and the empirical approach. Part 5 presents empirical results, and Part 6 concludes.

2 Helminths and health

2.1 Hookworm lifecycle, spread, and contemporaneous symptoms

"Hookworm" in the United States typically refers to two species of soil-transmitted helminths: primarily *Necator Americanus* and to a much lesser extent *Ancylostoma duodenale* (P. J. Hotez et al., 2006; Loukas et al., 2016). The lifecycle of the hookworm foregrounds key features of its epidemiology and impact. Hookworm larvae initially infect the host through the skin of the feet (and to a lesser extent, through oral ingestion). After penetrating the skin and entering the bloodstream, they enter the lungs and are swallowed, maturing in the wall of the small intestine where they then excrete eggs via feces (Loukas et al., 2016). Adult worms can survive in the gastrointestinal tract between one and four years (P. J. Hotez et al., 2006). In the right soil conditions, preferably wet and sandy, eggs hatch and larvae develop, restarting the process (P. Hotez, 2008).

As a result, hookworm prevalence is much higher in places with wet, sandy soil types, and they are found infrequently at higher altitudes due to both soil conditions and temperature. The pre-intervention distribution of hookworm prevalence in the US southeast is shown in figure 1. The role of fecal transmission also implicates sewage infrastructure as a potentially important factor in the prevalence of hookworm (P. Hotez, 2008). In the early 20th century, soil and environmental conditions in particular played a large role in determining wide variation in hookworm prevalence across geographic areas (Elman et al., 2014).

Infection burden is much greater in children than adults. In areas where hookworm is

endemic, most individuals who will be infected have been infected before age 5. The impacts of infection are also much larger for young children due to poor underlying iron status and critical periods for the development of the immune system (Brooker et al., 2007; P. J. Hotez et al., 2006).

These infections are rarely fatal, but can have chronic impacts on the health of their hosts (Stephenson et al., 2000).[2] The primary symptom of infection is blood loss, which is linked closely to the amount of worms hosted in the body.[3] This loss of blood often manifests as low weight, protein malnutrition, and lethargy (Loukas et al., 2016).

Other contemporaneous symptoms implicate the immune response to hookworms. Hookworm infection is accompanied by increasing systemic and mucosal eosinophilia and basophilia - increases in the predominant immune cell types responsible for containing and removing helminths (Gaze et al., 2012). However, the net effects of hookworm infection on broader inflammation are uncertain. Some studies suggest that human immune responses to hookworm infection are not very effective at removing all hookworms, but rather assist in limiting the spread. In this framework, immunosuppressive molecules secreted by worms may prevent their removal, and in tandem with the body's own responses may also mitigate the effects of chronic inflammation (Loukas et al., 2016; Wammes et al., 2014). Nonetheless, strong evidence on the long-term net inflammatory effects of helminth infection in humans is sparse.[4]

2.2 Long-term effects of hookworm on health and the hygiene hypothesis

Exposure to hookworm could have long-term effects related to the immune reaction as the body responds, or due to the anemia and calorie loss caused directly by infection.

The long-term effects of changes in hemoglobin and iron status have implications for morbidity, mortality, and wellbeing. Hemoglobin levels have been linked to health outcomes including mortality and psycho-social health, as well as economic productivity (Dong et al., 2008; Thomas et al., 2006). These effects are likely to be non-linear, with reduced impacts of hemoglobin changes above minimum thresholds (Haas and Brownlie, 2001; Strauss and Thomas, 2007).

A larger literature explores the potential ramifications of early life nutrition status on

[2]Case mortality is estimated at 0.0014%.

[3]Blood loss is primarily due to leakage around the site of infection, rather than direct consumption by parasites

[4]Challenge trials find short-term inflammatory responses, with suggestive evidence of initialization of long-term immuno-suppressive signalling cascades which are not realized in the time horizon of these studies (Feary et al., 2009; Gaze et al., 2012). Of note, these studies are occurring in an environment with minimal other external inflammatory stimuli, which likely would not have been the case in the relevant time period for this paper.

later life body composition. A broad literature in economics centers on Barker's fetal origins hypothesis - linking in-utero health shocks to later life body mass index (BMI) and metabolic disease (Almond and Currie, 2011). This paper abstracts somewhat away from the fetal origins hypothesis, as the relevant health shocks are in childhood rather than in-utero, but similarly explores the potentially long reach of early life conditions. The medical literature links childhood nutrition status and health to adult BMI, suggesting potential for persistence into the long-term (Zhao et al., 2012).

However, hemoglobin and nutrition insults due to hookworm are primarily sub-clinical, and while a potential theoretical link may persist into later life, little long-term data has studied the potential for persistence of these changes.

Exposure to chronic inflammatory processes also has potentially important implications for lifespan and morbidity. Crimmins and Finch link changing life expectancy to changing infant mortality, indirectly suggesting early life inflammatory exposure may resonate years later (Finch and Crimmins, 2004). They also suggest that there may be complementarities between early life nutritional status and inflammatory environment for lifespan (Crimmins and Finch, 2006; Strauss and Thomas, 2007). A complementary literature in economics explores the potential ramifications of early life disease exposure on human capital outcomes, including studies of the same de-worming campaign evaluated here by Bleakley (Bleakley, 2007), evaluations of early life malaria, airborne infectious disease exposure, and water purification (S. R. Bhalotra and Venkataramani, 2015; S. R. Bhalotra et al., 2021; Bleakley, 2010; Daysal et al., 2021; Venkataramani, 2012). Nonetheless, while infectious disease environment in early life likely has important implications for cognitive development, direct evidence of the impact of chronic inflammatory processes and lifespan is limited. Furthermore, while the potential mechanistic role of long-term inflammatory changes in linking early life infectious disease and lifespan has been long-theorized, little work to date explores both the long-term immunologic and lifespan consequences of the same exposure.

Complicating analysis of the impacts of early life inflammatory environment is the potential role of a prominent theory known as the "hygiene hypothesis". First theorized by Strachan, the hygiene hypothesis refers to a stylized model that connects decreasing intensity of immune environments with the broad society-wide rise in autoimmune disease over the 20th century. In Strachan's first study, children who grew up in households with more children present were noted to have higher hay fever prevalence, with the implied conclusion attributing the cause to decreased infectious disease exposure (Strachan, 1989). Helminths have acquired particular salience in this discussion. As noted above, the body's inability to clear helminths and the potential for subsequent downregulation of the immune system (instead of overstimulation) has led some to suggest that human immunology and helminths

co-evolved, and that in particular the loss of helminths has led to increased autoimmune disease (Loukas et al., 2016). Proponents of this theory have gone as far as to suggest that de-worming in countries that do not have the medical infrastructure to effectively treat autoimmune disease should be reconsidered (Wammes et al., 2014).

These arguments remain hotly contested. While prominent, testing the hygiene hypothesis is challenging, and many limitations arise interpreting findings from both mice and humans.[5] Human studies of the relationship between helminths and atopy or allergy is very mixed (Briggs et al., 2016; Santiago and Nutman, 2016). Studies with careful immune profiling suggest a potentially delicate balance between the potential pro and anti-inflammatory effects of helminths (Wammes et al., 2016; Yazdanbakhsh et al., 2002). In part, the potential role of other environmental triggers may be important. The theoretical immuno-suppressant effects of helminths may not be realized in an environment where other immune stimuli are common (for example, in the American south circa 1910 but not in the setting of a modern randomized trial in London). The time course over which the potential ramifications of helminths are observed may also contribute to mixed results - the long term and short term effects of a chronic infection may be substantively different.

Taken together, these findings collectively suggest a potentially important role of hookworm for later life health outcomes, with directions that may be different for different health outcomes. Mechanistically, these likely manifest in several important dimensions that this paper explores. First, I focus on lifespan. Then, I turn to explore potential mechanisms that shed light on questions related to long-term hemoglobin, metabolic, and immune regulation with broad ramifications for de-worming policy as well as our understanding of the health consequences of early life disease exposure.

3 The Rockefeller Sanitary Commission's de-worming campaign

The Rockefeller Sanitary Commission for the Eradication of Hookworm Disease (RSC) set out to document the prevalence of hookworm infections in the US South, then treat and remove the burden of the disease (Bleakley, 2007; Elman et al., 2014). At the time, medical recognition of hookworm as a disease was relatively recent, with scientific recognition beginning in the 1870s and effective drugs for control of infection developed by the 1890s (Elman et al., 2014). Initial evidence found that approximately 40% of Southern children

[5]Several notable limitations have made testing the role of the hygiene hypothesis, and the role of helminths, challenging. Murine models have developed wild and wildling mice to test the hygiene hypothesis, finding limited support (Ma et al., 2023). Models of helminth infection have implicated potentially important changes in microbiota (Ramanan et al., 2016). Other natural experiments from human populations in farming environments or birth order, while informative, are difficult contexts to isolate the impacts of a specific exposure (Genuneit et al., 2013; Stein et al., 2016). Studies of child birth order may also be contaminated by socio-economic impacts of birth order (Black et al., 2005).

were affected, and activities proceeded in 11 Southern states (Commission, 1914). While surveillance of worms began, treatment operations and reduction in hookworm burden did not begin in earnest until 1913 (Elman et al., 2014).

The RSC initially began by sampling at least 200 children in each county, but often many more, examining stool microscopically for hookworm ova. Of note, a significant amount of education was required to encourage adoption. While initially skeptical, the RSC found that a "dispensary" setup in which people could be shown the prevalence of worms in their children's stool, and then be administered thymol treatment onsite, caught on and was highly effective (Elman et al., 2014). At the same time, recognizing that hookworm was spread through the soil, the RSC embarked on a campaign to educate parents, children, and physicians about the spread of hookworm, and also invested significantly in latrines and other sanitary measures. This campaign enabled continued identification, treatemnt, and prevention of hookworm even after the first years of activity, leading to the eventual eradication of hookworm in the US south.

In a 2007 paper, Bleakley documents that exposure to the RSC intervention led to contemporaneous increases in children's school enrollment and literacy outcomes, with long-term ramifications for income in midlife (Bleakley, 2007). Further studies investigated the fertility responses to the impacts of reduced hookworm burdens on the return to human capital (Bleakley and Lange, 2009).

However, little work has systematically evaluated the potential long-term health ramifications of de-worming. Notably, studying the de-worming intervention has the potential to directly test hypotheses in human biology relating to the long-term effects of chronic inflammation on lifespan, as well as explore theories for the rise of autoimmune disease.

4 Data & Empirical Approach

4.1 Berkeley Unified Numident Mortality Database

In order to investigate the effects of de-worming exposure on lifespan, I draw on public data from the Berkeley Unified Numident Mortality Database (BUNMD), assembled by the CenSoc project (Breen and Goldstein, 2022; Goldstein et al., 2023). These data are derived from a 2013 transfer of Social Security Administration Numident mortality records to the National Archives and Records Administration. In primary analyses, I draw data from deaths between 1988-2005, the BUNMD "high coverage" years where over 95% of older adult deaths in the United States are included. I relax this restriction and evaluate earlier death years with lower mortality coverage as a robustness check. I also am able to use census data

to verify that selection into the sample is unrelated to the RSC campaign.[6] The sample is weighted at the sex-birthplace-race level to reflect the universe of deaths in the human mortality database (HMD). Critically, for each decedent these data include county of birth, as well as age and date of death. For empirical models, I aggregate birth counties into State Economic Areas (SEAs) with stable borders over time. I restrict to decedents born between 1900-1935 in areas of the American South where the RSC was active and where I have pre-campaign SEA-level hookworm prevalence data. This yields an analytic sample of 3,980,291 individuals, 47% of whom are male, and 27% are Black (table 1).

The distribution of birth years smoothly covers my birth cohorts of interest, the distribution of death years increases slightly over the years covered (Supplement figures A1a,A1b) (Breen and Goldstein, 2022).[7] The average lifespan in this sample is 77.6, somewhat older than the expected lifespan for these birth cohorts, since my primary analysis of the BUNMD conditions on survival until the latter 20th century.[8] It is important to consider that estimates are in a sample of older-age deaths, and abstract away from infant and childhood mortality. Selection into the sample on the basis of older ages of death may bias estimates toward 0 if additional individuals who died earlier than the period of observation due to hookworm were less healthy than those who survived into the observation window. I conduct additional analyses with census data and expanded samples that cover earlier death years to validate results, and birth year fixed effects address cohort-level selection into the sample.

4.2 Census-based survival rates

I conduct complementary analyses using census data to estimate survival rates until the 1960 census. To do this, I construct a dataset at the state of birth by birth-year level, and focus on the subset of states where the RSC was active, so variation in exposure is driven

[6] I conduct the following analysis to verify that selection into the BUNMD sample is unrelated to the exposure of interest. For each State economic area (SEA)-by-birthyear, I estimate the fraction of individuals represented in the BUNMD. For the numerator, I count the number of people in the BUNMD born in a given SEA in a given birth year. For the denominator, I use the 1910-1940 censuses to count how many people are alive from a given birth year in an SEA, in the first census the birth cohort appears in. This ratio thus estimates the fraction of individuals represented in the BUNMD from a given SEA and birth year, and I produce a dataset with one observation per birth-year-by-SEA, which I weight by SEA population. Estimating the primary specification equation 1, the coefficient on SEA baseline hookworm prevalence interacted with effective exposure years is -0.001 with a standard error of 0.002 (t-statistic 0.51), with a constant of 0.273. Selection into the sample on the basis of RSC campaign exposure is rejected.

[7] Estimated shares of deaths covered closely follow counts in each birth cohort (Supplement figure A1c).

[8] Gender differences are consistent with women living longer than men, on average. Nonetheless, limited differences in the sample representation by sex suggest that endogenous selection on older-age mortality may not be particularly concerning in practice. Additionally, these data cover a large fraction of deaths generally, but do particularly well covering deaths around the RSC intervention.

by hookworm prevalence across RSC-active areas. Using full-count census data from 1900, 1910, 1920, and 1930, I construct denominators for the number of people alive in each birth cohort, depending on the birth year using the number of individuals aged 5-15, in order to abstract away from early-life mortality (Ruggles et al., 2024). I then construct numerators based on the number of individuals from a given birth state and birth year in 1960 using the 5% sample of the census. Thus, I create survival rates net of early-life mortality for each birth-year and birth state observation. I include the same set of birth cohorts as the primary specification, from 1900 to 1935. As well as pooled estimates, I repeat this process by sex. Empirically, I weight states by the number of individuals alive at their baseline measurement.

4.3 National Health and Nutrition Examination Survey

For this project, I combine two waves of the National Health and Nutrition Examination Surveys (NHANES) to examine changes in morbidity and investigate potential mechanisms underlying mortality changes. The first two waves of the NHANES were fielded between 1971-1974 and 1976-1980, respectively.

Both surveys are nationally-representative probability samples of the United States, with approximately 32,000 people in the NHANES I, and approximately 21,000 in the NHANES II. The first two waves of the NHANES also include location about state of birth. Unlike the lifespan specification, I use state of birth to assign hookworm prevalence, and thus make comparisons across states. I restrict to individuals born in the contiguous United States. Parallel to the mortality sample specification, I focus on adults who were born between 1900 and 1935, for a total combined sample of 18,377.

These surveys combine questionnaire-based information about health status with detailed anthropometric, clinical, and laboratory evaluations. While not all assessments are done for all individuals due to cost reasons, sampling frames for sub-samples that receive more limited specific tests are random, and thus retain their interpretation as population-representative. The individuals in this sample are older, approximately 57 years old at the time of measurement as seen in table 1. 34% were born in RSC-treated states, 46% are located in urban areas and 39% rural areas, 47% finished high school and 24% are low-income at the time of measurement.

Crucially, the NHANES contains independently assessed biomarkers for health status. I focus on domains of health outcomes that would be most plausibly associated with exposure to hookworm. To evaluate the potential long-term effects of de-worming on nutritional status and anemia, I evaluate body-mass index, and laboratory-assessed measures for hemoglobin. In order to understand the potential impacts on auto-immune conditions, I utilize the number

of positive allergy skin tests out of 8 allergen skin pricks[9] per person conducted in the second wave, and make use of a biomarker for inflammation: erythrocyte sedimentation rate (ESR).[10] I complement these with other placebo outcomes.

4.4 Empirical Strategy

The intuition for these analyses is analogous to a difference-in-differences approach, similar to Bleakley, 2007. While conventional difference-in-differences uses a treatment variable that takes the value of 1 for groups eventually treated, and 0 untreated, I use continuous hookworm prevalence from prior to the intervention that takes values between 0 and 1. Individuals from areas with higher hookworm prevalence should disproportionately benefit from the de-worming campaign. Comparing birth cohorts before and after the de-worming campaign from areas of varying hookworm prevalence enables a causally-interpretable estimate of the long-term consequences of childhood de-worming. The study design treats the initiation of the RSC campaign as an exogenous natural shock - given poor baseline understanding of hookworm and the amount of capital investment needed to intervene, the timing and initiation of the RSC campaign, combined with pre-intervention variation in exposure, is considered exogenous to later health outcomes.

4.4.1 Hookworm prevalence data

Prior to the initiation of the de-worming campaign, the RSC sampled at least 200, but often many more, children in each county. They examined stool microscopically for hookworm ova. Using data digitized by Roodman from the Rockefeller foundation archives, I aggregate counties into State Economic Areas (SEAs) with stable borders over time (Commission, 1914; Roodman, 2018). As shown in figure 1, prevalence varied within and across states before the campaign. Hookworm suitability was primarily a function of land characteristics and temperature: sandy soils were preferable for hookworm reproduction. Note that many of the largest urban centers were excluded from the pre-intervention prevalence data and activity. People born in these areas are also excluded from analysis. Prior analyses of pre-intervention hookworm prevalence found more rural and less Black counties had higher prevalence, but the primary variation was predicted by soil type and number of frost-free days (Elman et

[9]Each person received 8 allergen skin tests, the responses to which were recorded in the NHANES. Tests were considered positive if a wheal formed at the prick site. The eight allergens included House dust, alternaria, cat, dog, ragweed, oak, rye grass, and bermuda grass.

[10]While ESR is the more primitive assessment for inflammation than C-Reactive Protein (CRP), CRP was not measured in the earliest waves of the NHANES. Further, ESR is likely to be more sensitive to chronic inflammation, of particular interest in this study, while CRP is more sensitive to acute inflammation. In practice, ESR and CRP are highly correlated.

al., 2014). I use this pre-intervention hookworm prevalence data in my primary mortality specification.

In other analyses, I take a complementary approach comparing hookworm prevalence across states. To expand my sample to the contiguous United States, I reference complementary hookworm data from army recruits (Kofoid and Tucker, 1921). Analyses of the 11 overlapping states suggests that the supplementary dataset well-approximates systematic county-level data collection from the RSC (supplement figure A2). The primary difference is that army prevalence is lower, on average, than the county data for a given prevalence level. This is likely due to differences in the age of the samples.[11]

4.4.2 Defining under-5 exposure to the RSC campaign

In order to account for 1) partial treatment of children born right before the initiation of the RSC campaign, and 2) the fact that it took several years to achieve high penetrance of deworming, I construct a continuous measure of "effective years" of exposure to the campaign before age 5. To model the increasing efficacy of the campaign over time, I use aggregated data from a subset of counties where repeated follow-ups occurred. In these samples, in 1910 59.7% of children had hookworm, falling to 39.7 in 1915, to 21.7 by 1920. This suggests yearly reduction in hookworm prevalence by a factor of 0.9. The functional form is as follows: $\sum_{y=Y1}^{Y5} \mathbb{1}[y \geq 1912](1 - 0.90^{(y-1912)})$ where $Y1, Y5$ are the years of birth through age 5 respectively. Thus, each individual gets the sum of "effective years" of exposure to the campaign before they reach the age of 5. The functional form is plotted in supplement figure A1d. Analogous to more simpler approaches that use "years of exposure", in the pre-period individuals have 0 effective years, and by 1920 the functional form is essentially flat. Results are robust to using simpler functional forms (supplement table A1).

Note that while this captures the differing average exposure to hookworms an individual would get based on the year relative to the start of the Rockefeller campaign, this does not vary endogenously with regards to specific areas that may have been likely to respond more effectively or less effectively to the RSC campaign. The effective years measure simply captures differences in the *average* effective exposure based on which year of the RSC campaign an individual was exposed to.

4.4.3 Primary analyses of lifespan

The empirical strategy rests on two core ideas. First, it leverages the varying hookworm prevalence across different areas at baseline. Higher prevalence areas stood much more to

[11] Kofoid notes that the burdens identified were the remaining light-intensity residual hookworm burden as hookworms in young soldiers died and they were not re-infected.

benefit from the RSC treatment than lower-prevalence. Second, the study design treats the initiation of the RSC campaign as an exogenous natural shock - given poor baseline understanding of hookworm and the amount of capital investment needed to intervene, the timing and initiation of the RSC campaign is considered exogenous to later health outcomes.

The core specification for the lifespan outcome is as follows [12] :

$$Y_{icst} = \beta(W_c * EffectiveYrsExposed_t) + \theta_{st} + \gamma_c + \epsilon_{ict} \quad (1)$$

Where Y_{icst} is lifespan for an individual i born in state economic area c and state s, in year t. W_c refers to the hookworm prevalence at baseline in SEA indexed by c, and $EffectiveYearsExposed$ is based on birth year and is the effective number of years exposed to the RSC campaign. θ_{st} represents the state of birth-by-year fixed effects, which capture state-specific shocks and time-trends. Note this also absorbs a more conventional birth year fixed-effect. X_i represents covariates of interest - while a general label is used, in lifespan analyses the only covariate used is sex. γ_c are fixed effects for SEA c.[13] These terms are allowed to vary by sex as potentially important sex-specific trends may have been different for males and females during this time (S. Bhalotra et al., 2023; Miller, 2008). In regressions separated by sex, these effects collapse to just one term for birth SEA, state, or year.

Note, γ_c absorbs the baseline worm prevalence, along with observed and unobserved SEA-level characteristics that may be relevant for lifespan and are not changing over time. While there are some concerns for this study about limited coverage of deaths at younger ages and selection into the sample, the birth state by birth year fixed-effect capture cohort-level endogeneity in the probability a given individual is reflected in the data, to the extent it is fixed across a given cohort. θ_{st} also accounts for observed and unobserved state and cohort effects in lifespan, which is important as cohort lifespans are increasing over this period in American history. Since this specification uses RSC-derived baseline hookworm prevalence at the county level, the analytical sample is restricted to RSC-surveyed SEAs where they were active in the American Southeast.

Taken together, the coefficient of interest β can be interpreted as the effect of an additional year of exposure to de-worming on age at death, estimated by comparing across SEAs, but within states, that have differing baseline prevalence of hookworm. Standard errors are clustered at the SEA level.

[12] Several other alternative specifications could reasonably be considered. Results from an alternative specification with a semi-parametric estimate of the relationship between quartiles of baseline worm prevalence and the interaction with effective years, as well as another alternative specification using a simple "pre-post" estimate yield similar results in appendix table A1.

[13] Similar to Bleakley, I aggregate counties into SEAs with stable boundaries over time.

4.4.4 Analyses of morbidity

I use a parallel strategy to the primary analyses of lifespan, in order to evaluate the impacts of de-worming on morbidity. I use a series of biomarkers from the NHANES. Since the NHANES does not have county or SEA of birth, I construct treatments at the state of birth, using state level hookworm prevalence from Kofoid and Tucker, 1921. State data are highly-concordant with averages of county-level data from the RSC (supplement figure A2).

I estimate:

$$Y_{ist} = \beta(W_s * EffectiveYrsExposed_t) + \lambda_t + \gamma_s + \phi X_i + \epsilon_{ist} \quad (2)$$

Where Y_{ist} is the outcome of interest for an individual i born in state s in year t. W_s refers to the hookworm prevalence at baseline in states indexed by s, and $EffectiveYearsExposed$ is based on birth year and is the effective number of years exposed to the RSC campaign. λ_t, γ_s are birth state and birth-year fixed effects, which capture time-invariant state characteristics, and cohort-specific effects. These terms are allowed to vary by sex. One strength of the NHANES is richer socio-economic data. I include X_i as a vector of covariates of interest, including sex, NHANES wave, age, rural/urban status, Black race, educational attainment, and low income level.[14]. Note that γ_s will absorb baseline state hookworm prevalence, along with observed and unobserved state-level characteristics. λ_t will absorb birth year-specific effects. β retains a similar interpretation to the primary specification, as the effect of an additional year of exposure to de-worming on lifespan, estimated by comparing across states that have differing baseline prevalence of hookworm, before and after the de-worming campaign. Standard errors are clustered at the state level.

4.4.5 Empirical assumptions

For either specification, interpreting β as causal demands several assumptions. Similar to difference-in-difference approaches, the empirical structure assumes that the relationship between baseline hookworm prevalence and the outcomes of interest would have evolved similarly in absence of the RSC campaign. Data from an event-study framework in figure 2 suggests that is not unreasonable. Pre-intervention, point-estimates of the relationship between SEA-level hookworm prevalence at baseline and lifespan within each birth cohort do not exhibit a clear pre-trend. As the RSC campaign begins, the relationship between baseline SEA-level hookworm prevalence and lifespan improves positively, following closely the

[14] A simpler specification only controlling age and sex yields nearly-exactly the same results. Given findings from Bleakley and Lange, 2009, I present results with additional socio-economic status controls to yield estimates that are robust to these potential changes. The fact that point-estimates are nearly-identical between the simple and full model provides further evidence of the exogeneity of the treatment estimated

functional form of "effective years" exposed (red squares). Post-intervention, the relationship between baseline hookworm prevalence remains flat.

Additionally, relaxing the event-study framework and dropping the SEA fixed effect enables reduced-form estimates of the varying direct association between baseline hookworm prevalence and lifespan (rather than estimating relative to the pre-period). Before the intervention, the relationship between SEA hookworm prevalence and lifespan is negative, and it moves positively such that baseline hookworm prevalence and lifespan are *uncorrelated* after the intervention completes. This is further evidence that 1) hookworm eradication was successful, and 2) changes in lifespan are caused by successful eradication.

One must also assume that the treatment timing was exogenous, which given the scale and relative rapidity of the RSC campaign is likely plausible. Finally, given the limitations of the mortality data in particular, one must believe that selection into the sample is not endogenous to treatment exposure conditional on the birth cohort fixed effects. While hard to test directly, this assumption appears plausible, and can be verified empirically by comparing estimated fractions of the 1910 SEA population with the counts of those present in the BUNMD mortality sample (see footnote 6).

5 Long-term lifespan and health impacts of the RSC campaign

5.1 Impacts on adult lifespan

In this section, I explore the impacts of the RSC de-worming campaign on lifespan, estimated in the BUNMD sample. Using the primary specification in equation 1, I find one year of de-worming is linked to 0.042 additional life years (0.504 months) (Table 2). This effect is qualitatively large - the full implied impact of 5 years of childhood de-worming exposure is 0.21 additional years of life at older ages, similar to the life expectancy gained by eliminating Alzheimers' disease, half of cerebrovascular disease in older age, or removing lead in-utero Arias et al., 2013; Fletcher and Noghanibehambari, 2023. The point estimates for females are larger than for males (0.046 and 0.036, respectively), though the difference is not statistically significant. This is potentially consistent with the fact that women have conventionally benefited more than men from improvements in the infectious disease environment Goldin and Lleras-Muney, 2019.

Two event-study style analyses support the argument that changes in lifespan are driven by de-worming due to the RSC-campaign. In the top panel of figure 2, an event-study with a full set of fixed-effects from the primary specification examines the change in the estimated relationship between baseline hookworm prevalence and lifespan within each birth cohort, relative to the last birth years before the intervention began. In the 12 preceding years, there is no evidence that the outcomes for areas with more hookworm prevalence

were evolving differently from those with less, supporting the validity of the parallel-trends assumption. After the RSC campaign, the coefficient changes positively, suggesting increases in lifespan related to de-worming that occur shortly after campaign initiation. On the bottom panel, a similar analysis is conducted, but the SEA fixed effects are excluded, so the point estimate of the baseline hookworm prevalence-lifespan relationship can be estimated directly for each birth cohort. A similar pattern is visible - there are no systematic trends related to hookworm prevalence in the pre-period. In the post period, the coefficient goes from negative to essentially 0, suggesting that the relationship between baseline hookworm prevalence and lifespan did not just become more positive, but that large-scale treatment of hookworm rendered baseline hookworm prevalence and lifespan uncorrelated after it occurred.

One potential concern is mean reversion across study areas. Potentially, these results could reflect a condition where some countries at the baseline of measurement had high hookworm infection and high mortality due to a transient shock and re-converged naturally. To account for potential mean reversion, I control for an interaction between the 1912 average life expectancy in each county and the effective exposure metric. Results are presented in panel B of table 2, and are very similar to the primary specification's findings.

Results are also robust to a variety of alternative specifications and functional forms including linear years of exposure before age 5, a binary pre/post specification, and a semi-parametric specification using tertiles of baseline hookworm prevalence. Another potential concern is that broader trends in areas with soil and environmental characteristics that are related to hookworm may be driving the results. Findings are robust to including controls for birth year interacted with rurality, climate, and soil suitability for cultivation from the FAO-GAEZ (supplement table A1).[15] These interactions control for potential differential trends across areas with characteristics that may be related to hookworm prevalence.

A potential concern is that these data do not record lifespans for deaths that occur earlier in the 20th century. If hookworm led additional individuals to die earlier than the period of observation, and those individuals were less healthy than those who would have survived anyways, the effect I find is an underestimate of what one would find if all deaths were observed. Nonetheless, I conduct several extensions to assess the importance of these concerns. In supplement table A2, I estimate a parallel set of results using census data to create survival rates at the birth-state by birth-year level until the 1960 census. Estimates yield similar conclusions to the BUNMD dataset - exposure to the RSC campaign is associated with significant increases in the likelihood of surviving until the 1960 census.

[15]Controls for birth year interacted with rurality, precipitation, temperature, and soil suitability capture potential trends related to characteristics that affect hookworm prevalence that may affect SEA lifespan trajectories over time. In practice, I produce quartiles of the distribution for each characteristic in the sample, and add birth year-by-quartile fixed effects to the primary specification.

I also estimate the impacts of de-worming using a broader sample of the Unified Numident data that expands coverage primarily to younger ages of death (5.3 million obs.), including years before 1988 with lower mortality coverage, and extending coverage to 2007. Findings are very similar, but point estimates are larger, suggesting that the primary estimates from this paper may be underestimating total potential impacts (supplement table A1).[16]

5.2 Impacts on morbidity

Using data from the NHANES I and NHANES II with information on state of birth, I estimate a parallel model to the specification for lifespan, using state hookworm prevalence at baseline. I focus on key health outcomes that are likely to be affected by hookworm. I primarily investigate immunologic outcomes including skin-tests for allergies, as well as erythrocyte sedimentation rate as a biomarker of inflammation. An alternative pathway through which hookworm may affect lifespan is that hookworm may lead to persistent changes in metabolism and iron status, so I also investigate BMI and hemoglobin.

On one hand, chronic inflammatory stressors have been linked to adverse outcomes and deleterious consequences of a 'hyper-active' immune system (Crimmins and Finch, 2006). On the other hand, a widely-cited "hygiene hypothesis" suggests that hookworms and humans co-evolved, and much of the rise of allergy and auto-immune disease can be attributed to their 'loss' in the modern era (Loukas et al., 2016).

Findings in Table 3 estimate the equation 2, and show clear, large inflammatory improvements. Estimating the effect of 1 year of de-worming on the number of skin-tested allergies finds reductions of 0.14. The implied reduction in the number of allergies is substantial: five years of childhood de-worming exposure is estimated to reduce the average number of allergies by nearly 0.75, approximately 1/2 of a standard deviation. I also find each year of de-worming reduces erythrocyte sedimentation rate, a biomarker for inflammation, by 1.5mm/hr later in life, which is significant at a 10% size of test. This implies a reduction by 7.5mm/hr with full campaign exposure (approximately 3/4 of a standard deviation). This is slightly larger than the gap between people born pre-intervention in the South versus the rest of the country.

I additionally explore an alternative set of potential mechanisms that may link hookworm to adult lifespan: whether potential early-life blood loss and nutritional deficits have persistent impacts later into life. Among adults at older-ages, BMI can be interpreted as nutritional status, but can also be interpreted to some extent as a reserve against frailty (Kıskaç et al., 2022; Kopinska et al., 2021). This is particularly true in the 1970s-80s at the

[16]Increased standard errors also suggest increased variance of mortality in early life, compared with mortality in later life.

time of measurement, where relatively few people were obese.

Hemoglobin is a direct measure of the oxygen-binding protein. I find that exposure to de-worming is linked to increased BMI and hemoglobin in adulthood, with full exposure associated with nearly a 1 standard deviation increase in BMI, and a nearly 1/2 standard deviation increase in hemoglobin. This appears to be true for both males and females. The increases in BMI are apparent across the BMI distribution, but de-worming appears to especially reduce incidence of low BMI and increase sub-obese overweight. The prevalence of low BMI (<=20) is reduced by 5.4% for each additional effective year of de-worming exposure, the prevalence of overweight (BMI>=25, BMI<30) increases by 7.8% for each additional effective year of exposure, and estimated increases in obesity (BMI>=30) have positive point estimates between 1-2%, but are not statistically significant. The benefits for hemoglobin appear to be sub-clinical improvements in hemoglobin status. While the point estimates for anemia are negative, they are small and not statistically significant.

In these analyses of the NHANES data, unlike the lifespan analyses, I can control for individual-specific socio-economic and geographic characteristics at the time of measurement [17]. I include these in the estimates shown, but estimates are minimally-affected when a simpler specification without controls is used.

5.3 Placebo outcomes

Finally, I turn to conduct several placebo tests of these results. I examine height, as a potential threat to identification is endogenous changes in the health and socio-economic status of individuals having children as exposure to the de-worming campaign increases. While height is not a perfect placebo outcome, as extreme calorie deprivation can reduce heights, most hookworm infections were not extreme, and height also reflects in-utero health, early life conditions, and characteristics of parents that may be changing in the background (Beach et al., 2022; Martorell, 1995; Strauss and Thomas, 1998). Further, the most critical periods for the determination of height are in-utero and before most people can walk, and thus before people would be exposed to hookworm (Martorell, 2008; Perkins et al., 2016).

I also consider two measures of cholesterol - HDL and total cholesterol, and FEV1/FVC, a pulmonary function test that is sensitive for asthma. These are particularly insightful placebo outcomes since cholesterol and blood pressure in particular respond to diet, health behaviors, and health care access. Lack of results in these findings would suggest that exposure to the RSC campaign is not driven by exposure to individuals with systematically

[17] If adult socio-economic status and location is a potentially important route through which childhood de-worming affects adult morbidity and lifespan, these controls may be over-adjusting. However, empirical evidence of adult SES effects is small, and morbidity results are minimally-affected by inclusion of controls.

different health behaviors.

As seen in Table 4, exposure to the RSC campaign is not significantly related to height, cholesterols, or FEV1/FVC. Null relationships with height suggest that in-utero and very early life nutrition status (and the various forces that may affect it including selection on parental stature) are not driving the observed results. Taken together, placebo tests suggest that other forces that shape health, including in-utero and very early life conditions, diet and other health behaviors that shape cholesterols and blood pressure, likely do not play a large role in the observed results.

6 Discussion and conclusion

This paper explores the long-term ramifications of the Rockefeller Sanitary Commission's de-worming campaign to provide new evidence on the impacts of childhood hookworm infection on lifespan and morbidity. In doing so, I provide novel tests of 1) the linkage between early-life inflammatory exposure with later life morbidity and mortality, and 2) the role of hookworm in the "hygiene hypothesis" and the rise of allergy and autoimmune conditions over the 20th century. I find substantial gains in lifespan at older age, as well as long-term reductions in a biomarker of inflammation and the number of skin-tested allergies, as well as increases in BMI and hemoglobin. Similar changes are not observed in health outcomes that should be unaffected by de-worming.

Exploring the impacts of exposure identified by the interaction of birth year and baseline hookworm prevalence in an SEA, estimates imply that a full year of exposure to the RSC campaign before the age of 5 is linked to an additional 0.18 life years, in a sample of older-age mortality. These data provide a direct test supporting an influential theory advocated by Finch and Crimmins - that cohort-level exposure to inflammatory processes early in life shape changes in lifespan in recent human history (Finch and Crimmins, 2004). Examining morbidity changes finds further support for an extension of their original model - that reduced infectious burdens early in life can lead to persistent improvements in inflammation over the life course (Crimmins and Finch, 2006).

The estimated impact of de-worming on lifespan at older age is large, corresponding roughly to the older-age lifespan lost due to Alzheimer's Disease. These findings are a direct test of, and provide new rigorous evidence for, influential theories that infectious disease burdens early in life shape mortality across the life course (Finch, 2010; Finch and Crimmins, 2004). Notably, this study provides causal evidence for the link between early life infectious disease and adult lifespan, but also finds novel mechanistic evidence for the central role of background inflammation.

Men and women benefit similarly from de-worming, though point estimates are larger

for women. Sex differences in epidemiological and laboratory studies of immunology are becoming increasingly appreciated, in part improvements in women's lifespan relative to men over the 20th century have been attributed to this (Dou et al., 2024; Goldin and Lleras-Muney, 2019; Noymer and Garenne, 2000). The morbidity findings provide mechanistic support for many of the theorized links between early life infectious disease and adult lifespan. Changes in ESR are consistent with long-term changes in chronic, low-grade, inflammation that may raise cardiovascular disease and cancer risk (Fulop et al., 2018; Gurven et al., 2008). Further, changes in early-life health such as nutritional status and hemoglobin may be persistent, leading to long-term benefit (Blackwell et al., 2011; Crimmins and Finch, 2006). In this sample of older adults with relatively low BMI in the 1970s, I interpret increases in BMI as likely positive protections against frailty, especially as changes are concentrated among reducing low weight and sub-obese BMI (Kıskaç et al., 2022; Kopinska et al., 2021).

While the improvements in mortality can be attributed to meaningful observed improvements in underlying health changes from early childhood, it is possible that de-worming may lead to economic benefits that may also play a role (Bleakley and Lange, 2009; Miguel and Kremer, 2004). While I do not have educational attainment and mortality data in the same individuals, it is unlikely that changes in education or income fully explain the observed impacts. In a study of the economic ramifications of under-18 exposure to de-worming, Bleakley finds no long-term impact on educational attainment, but small increases in income. In my analyses of morbidity, I directly control for a variety of potentially relevant socio-economic pathways including education, poverty status, and rurality. These controls minimally impact observed results.

The joint reductions in background inflammation as well as allergies further an argument that helminths may in fact raise allergies through chronic inflammatory processes (Briggs et al., 2016). Notably, these findings contrast sharply with a potential role of hookworm in the "hygiene hypothesis" (Briggs et al., 2016; Loukas et al., 2016; Ramanan et al., 2016; Strachan, 1989; Wammes et al., 2014; Yazdanbakhsh et al., 2002). This study provides rigorous evidence of long-term impacts between hookworm and allergies, in a space where mouse models and short-term human trials are conflicting, and active debate ensues. However, the interpretation of these findings is limited by the context of the RSC de-worming campaign in the early 20th century. The role of hookworm in auto-immune processes may vary in contexts with differing levels of background pathogens (McDade, 2012).

This study also has substantial implications for mass de-worming programs around the globe. The efficacy and cost-effectiveness of mass de-worming has been debated in recent years, with mixed results on the impacts of hookworm on short and medium-term outcomes, and theoretical arguments made that the potential role of hookworm in auto-immune con-

ditions may undermine the value of de-worming (Croke and Atun, 2019; Taylor-Robinson et al., 2019; Wammes et al., 2014). Prior work on the RSC campaign has found long-term improvements in income and contemporaneous improvements in school attendance (Bleakley, 2007), and contemporaneous work on male deaths finds health impacts of de-worming and education may be complementary for adult lifespan (Noghanibehambari and Fletcher, 2024).[18] This study provides evidence for life-long benefits to de-worming, with persistent impacts on health and age at death. These benefits make a strong case for expanded de-worming programs in endemic areas around the globe.

This study has several limitations. One limitation is that the primary source of mortality data primarily draws from the later 20th century, potentially missing earlier-life impacts of hookworm. Hookworm should minimally impact childhood mortality, but may have impacted mid-life mortality, which would not be measured in this paper's primary analysis. Analyses at the state level using census data on survival rates until 1960, which should reflect mid-life mortality, as well as extensions of the Unified Numident sample into earlier years of death, find larger impacts of hookworm exposure relative to the primary sample. Primary estimates are thus possibly underestimates of true lifespan effects.

Another potential limitation is unobserved changes in the health status across cohorts before and after de-worming begins, in a way that is related to hookworm prevalence. I address this in several ways. 1) Using a model that includes state-by-birth year fixed effects in the primary mortality specification, I am able to account for potential state-specific trends and changes over time, and localize the variation used to across-SEAs within states. I also extend the model to include controls for time trends that may be related to SEA characteristics such as rurality, climate, and soil suitability for agriculture. 2) Event-study analyses suggest that in the years before the campaign, and the years after full effects are realized, mortality dynamics are not evolving in a way related to baseline hookworm prevalence. 3) I provide evidence from placebo health outcomes that there were not major changes in health status unrelated to hookworm-specific morbidity.

I conclude that de-worming in early childhood has large life-long benefits for morbidity and mortality. Mechanistic evidence finds support for long-term immunologic improvements due to de-worming, and other health benefits. In this context, hookworm reduces allergies in a way that is not consistent with a role in the "hygiene hypothesis". Potential long-term

[18]This study complements independent, simultaneous work by Noghanibehambari and Fletcher (Noghanibehambari and Fletcher, 2024). Mortality findings are qualitatively similar, though several important differences are notable. I use a sample four times as large, and include both men and women, rather than just men. This is particularly important, as many effects are larger in women. Additionally, this study uniquely explores the long-term health impacts, and potential physiologic mechanisms by which de-worming may affect long-term mortality.

benefits should be considered when evaluating mass de-worming programs.

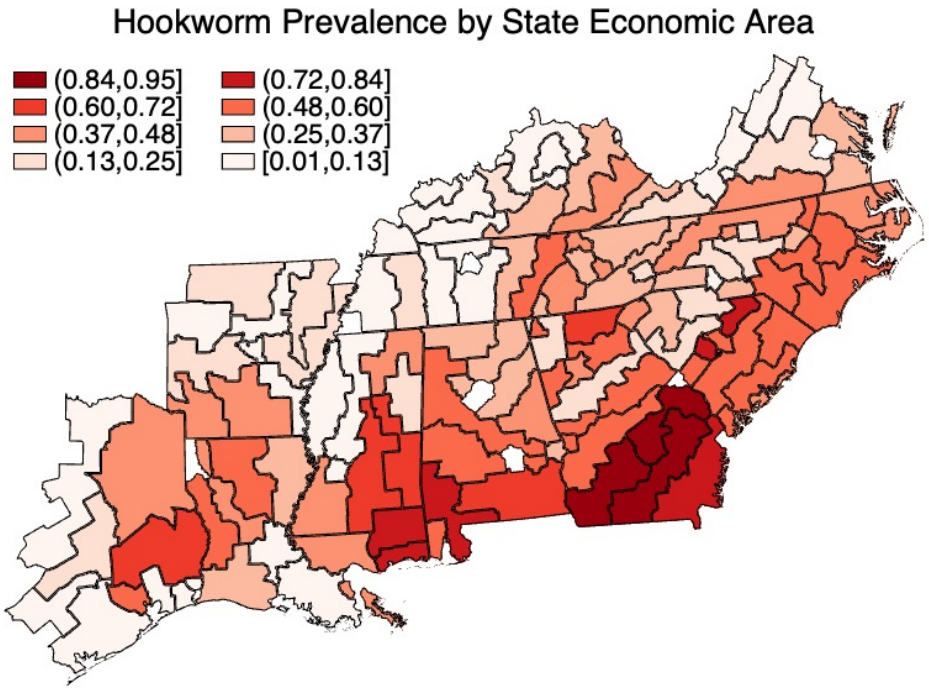

Figure 1: Distribution of pre-intervention hookworm by state economic area

Notes: This figure shows estimates of childhood hookworm prevalence from systematic county surveys of children pre-intervention conducted by the Rockefeller Sanitary Commission. County data are aggregated and displayed at the State Economic Area (SEA). Prevalence data were digitized by Roodman, 2018 from the Rockefeller Foundation Archive (Roodman, 2018).

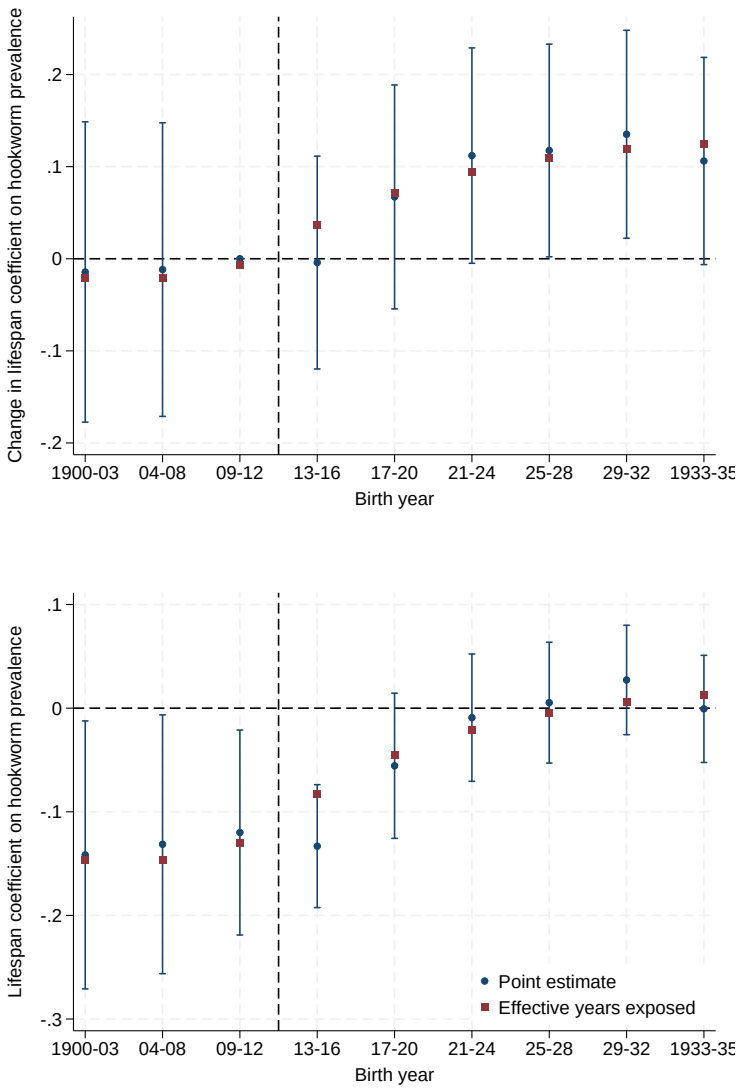

Figure 2: Relationship between baseline hookworm prevalence and lifespan across cohorts

Notes: This figures show estimates of the relationship between *baseline* state economic area (SEA) hookworm prevalence and lifespan for people born in a given SEA, estimated for different birth cohorts. The top panel plots event study estimates, including fixed effects by sex that reflect birth SEA, and birth state-by-birth year. Plotted coefficients are the interaction term between birth year and hookworm prevalence, reflecting the hookworm prevalence coefficient in each birth cohort, relative to the years immediately pre-campaign. The bottom panel relaxes this model, dropping the birth SEA fixed effects. Thus, the relationship between baseline hookworm prevalence and lifespan can be directly estimated and plotted for each birth cohort. Blue markers plot coefficient estimates and 95% confidence intervals within each cohort over time, visualizing the trajectory of the changing relationship between baseline hookworm prevalence and lifespan around the time of RSC campaign initiation. Red squares show the normalized average effective years of exposure in each set of year bins, to map plotted results onto the functional form applied in the primary estimate in table **??**. In order to visualize the functional form of effective years of exposure assigned alongside the point estimates, I regress the effective years on the point estimate, and plot the normalized values. Detailed effective years for each birth cohort are plotted in supplement figure A1d.

Table 1: Summary statistics by sample

	Unified Numident Decedents	**NHANES** Survey Participants
Lifespan (years)	77.6	-
	(7.2)	-
Age (years)	-	57.18
	-	(10.69)
Proportion Male	0.47	0.46
	(0.50)	(0.50)
Proportion Black	0.27	0.15
	(0.45)	(0.35)
Effective Years	2.92	2.34
	(1.34)	(1.85)
Proportion born in RSC State	1	0.34
	-	(0.47)
Proportion in Major Urban Areas	-	0.46
	-	(0.50)
Proportion in Rural areas	-	0.39
	-	(0.49)
Proportion HS Grad+	-	0.47
	-	(0.50)
Proportion College Grad+	-	0.08
	-	(0.28)
Proportion low income	-	0.24
	-	(0.43)
N	3,980,291	18,377

Notes: This table presents summary statistics for individuals in both of the analytic samples used for these analyses. Mortality data are drawn from the Berkeley Unified Numident Mortality Dataset. Morbidity data are drawn from the NHANES I and NHANES II. Individuals represented were born between 1900 and 1935.

Table 2: Change in lifespan per year of exposure to de-worming campaign

	Lifespan (years)		
	All	**Males**	**Females**
A. Primary specification			
SEA Prevalence × Effective Exposure Years	0.042***	0.034**	0.046***
	[0.012]	[0.015]	[0.016]
Constant	77.765***	76.100***	79.191***
	[0.012]	[0.016]	[0.015]
N	3,980,291	1,851,939	2,128,352
Implied effect of full exposure (years)	0.211	0.171	0.228
B. Allow for SEA-specific mean reversion			
SEA Prevalence × Effective Exposure Years	0.042***	0.035**	0.045***
	[0.012]	[0.015]	[0.017]

Notes: This table presents estimates of the effect of exposure to the de-worming campaign on the age of death, first pooled then stratified by sex. Lifespan data are drawn from decedents in the CenSoc Unified Numident file (BUNMD), and include deaths in high-coverage years from 1988-2005. The sample includes decedents born between 1900 and 1935 in the 11 states the RSC was active, in the SEAs where pre-intervention surveys were conducted. Hookworm prevalence is assigned at the SEA of birth. Estimates are conducted using fixed effects by sex that reflect birth SEA, and birth state-by-birth year. Standard errors presented in brackets, clustered at the SEA level. The coefficients presented are the interaction between baseline SEA hookworm prevalence and effective years of exposure, and can be interpreted as the implied effect of one full year of exposure to de-worming. Each individual received up to five years of exposure. Panel B shows the same model estimated allowing for SEA-specific mean reversion based off of SEA lifespan in the year prior to the campaign's initiation.

Table 3: Estimated change in adult morbidity per year exposure to de-worming (before age 5).

	ESR			# of Allergies					
A. Immunologic changes	All	M	F	All	M	F			
Prevalence ×	-1.502*	-2.314*	-1.039	-0.144**	-0.089	-0.184*	-	-	-
Effective exposure years	[0.871]	[1.187]	[1.017]	[0.068]	[0.106]	[0.100]			
N	6,218	2,660	3,558	8,639	4,219	4,420			
Mean	16.95	13.26	19.73	0.55	0.59	0.52			
(SD)	(11.67)	(10.6)	(11.67)	(1.31)	(1.33)	(1.30)			
Implied effect of full exposure (SD)	-0.643	-0.992	-0.445	-0.549	-0.337	-0.702			

	BMI			Hemoglobin			Anemia		
B. BMI & hemoglobin	All	M	F	All	M	F	All	M	F
Prevalence ×	0.927***	1.055***	0.674**	0.143**	0.151	0.127***	-0.012	-0.019	-0.008
Effective exposure years	[0.271]	[0.288]	[0.327]	[0.059]	[0.098]	[0.047]	[0.010]	[0.017]	[0.012]
N	17,450	8,162	9,288	17,068	7,856	9,212	17,068	7,856	9,212
Mean	25.01	24.81	25.18	14.22	14.93	13.61	0.08	0.08	0.07
(SD)	(4.87)	(4.49)	(5.18)	(1.44)	(1.35)	(1.22)	(0.27)	(0.28)	(0.26)
Implied effect of full exposure (SD)	0.952	1.083	0.692	0.496	0.525	0.441	-0.227	-0.359	-0.143

Notes: This table presents estimates of the effect of exposure to the de-worming campaign, first pooled then stratified by sex. Pre-intervention hookworm prevalence is assigned by state of birth. Data are drawn from individuals surveyed in the NHANES I and NHANES II. Models include fixed effects for birth year and birth state, controls for sex, age, rural/urban, status, Black race, educational attainment, and low income level. The coefficients presented are the interaction between baseline state hookworm prevalence and effective years of exposure, and can be interpreted as the implied effects of one full year of exposure to de-worming, and each individual received up to five years of exposure. In panel A: Erythrocyte sedimentation rate (ESR) is a biomarker for inflammation, while the number of allergies reflects the number of positive skin-tested allergies out of 8 potential allergens. In panel B: Body mass index (BMI) is calculated as weight (kg) divided by height(m) squared. Hemoglobin is in grams per 100mL, and anemia is defined as hemoglobin$<$13 for men, and hemoglobin $<$12 for women. Standard errors presented in brackets, clustered at the birth state level.

Table 4: Placebo tests

Variables	Height (m)	Total Cholesterol	HDL	FEV1/FVC
Prevalence ×	0.002	-1.355	-1.829	-0.009
Effective exposure years	[0.006]	[1.404]	[1.292]	[0.007]
N	17,714	15,526	5,695	3,338
Mean	1.64	229.23	50.11	0.76
(SD)	(0.14)	(48.40)	(14.95)	(0.76)

Notes: This table presents estimates of the effect of exposure to the de-worming campaign on health outcomes that should not be directly affected by hookworm. Hookworm prevalence is assigned by state of birth. Data are drawn from individuals surveyed in the NHANES I and NHANES II. Total cholesterol and HDL (high-density lipoprotein) are measured in mg/dL. FEV1/FVC is a ratio that reflects the volume of air expelled in one second of spirometry over the total amount expelled. Models include fixed effects for birth year and birth state, controls for sex, age, rural/urban, status, Black race, educational attainment, and low income level. The coefficients presented are the interaction between baseline state hookworm prevalence and effective years of exposure, and can be interpreted as the implied effects of one full year of exposure to de-worming. Standard errors presented in brackets, clustered at the birth state level.

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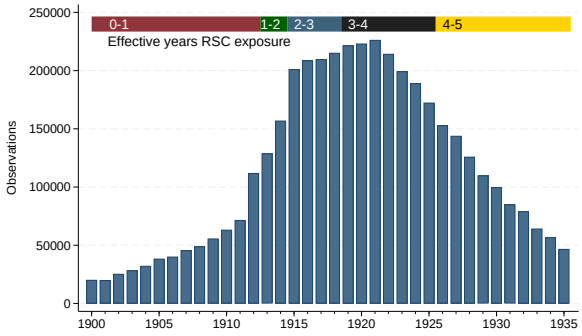
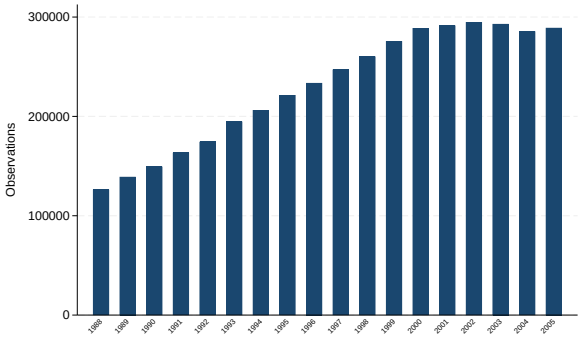
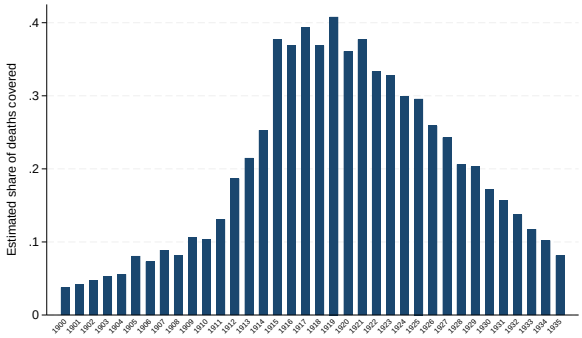


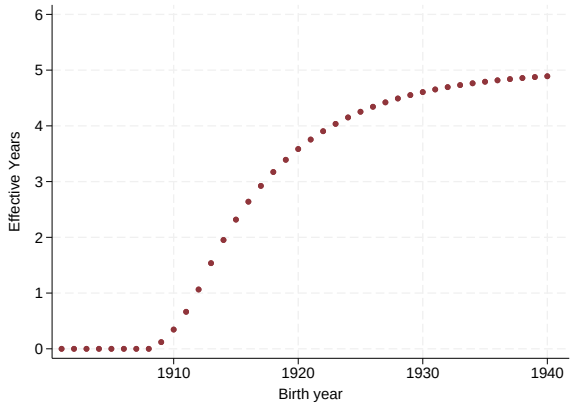
(a) Distribution of birth years



(b) Distribution of death years



(c) Estimated share of deaths covered for each birth year



(d) Effective years of exposure assigned to each birth cohort

Figure A1: Distribution of birth years, share of deaths covered, death years, and effective years of exposure in the analytic sample

Notes: In **panel (a)**: The top bar provides bands of the effective years of RSC campaign exposure that each birth cohort is assigned. The figure plots the count of individuals represented in the analytical sample by birth year. In **panel (b)**: the figure plots estimates of the share of deaths represented of each birth cohort in the analytic sample. For each birth cohort-by-SEA, a proportion is produced where the numerator reflects the number of people born in a given birth-year-by-SEA that are in the high-coverage BUNMD, and the denominator reflects the number of people in an SEA from a given birth year that appear in the first census after age 5 a birth cohort is observed in (to avoid infant mortality). Each birth-year-by-SEA thus has one observation, weighted by population, the distribution of which is plotted. In **panel (c)**: This figure plots the count of individuals represented in the analytical sample by death year. In **panel (d)**: This figure shows the number of effective years of exposure assigned to each birth cohort over time.

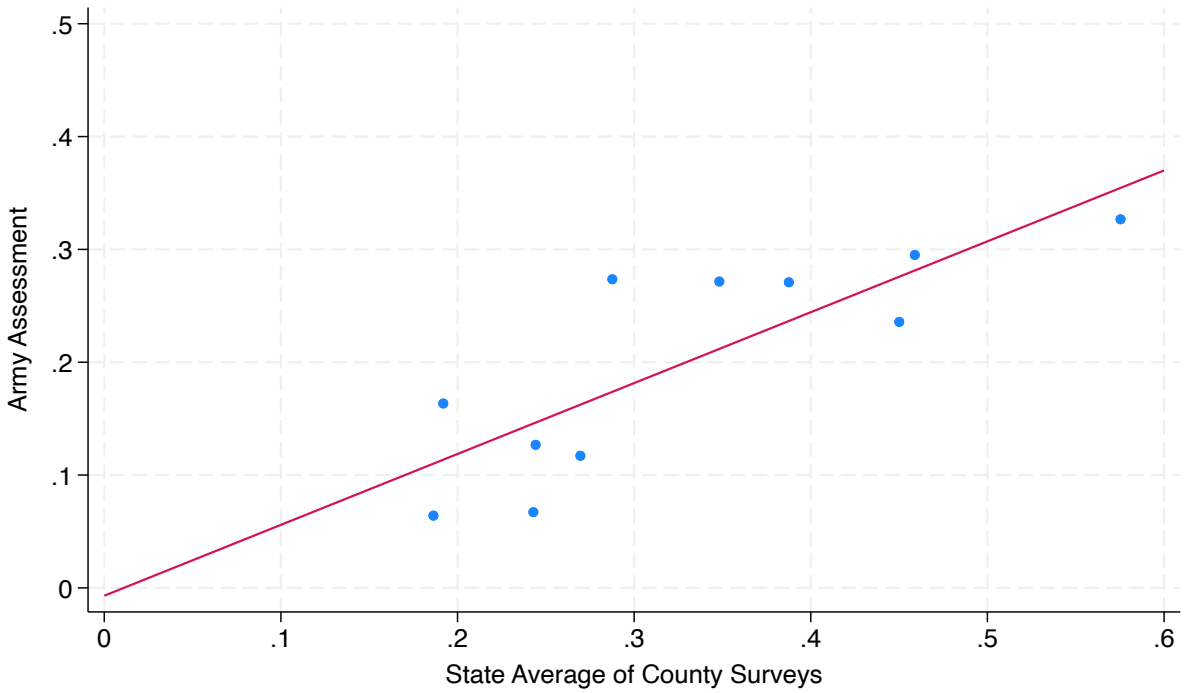


Figure A2: Relationship between army hookworm prevalence and county-level RSC assessed prevalence in overlapping states

Notes: This figure shows the relationship between average hookworm prevalence from systematic RSC surveys of children in each county, and average hookworm prevalence from surveys of army recruits. The line of best fit is included.

Table A1: Coefficients from alternative specifications, inclusion of additional controls, and use of extended samples to estimate the impact of de-worming on lifespan

	Lifespan (years)		
	All	**Males**	**Females**
Panel A. Tests using alternative specifications to estimate the impact of childhood de-worming on lifespan			
A1. Alternate specification: semi-parametric specification			
SEA tertile 1 × Effective Exposure Years (omitted)	-	-	-
SEA tertile 2 × Effective Exposure Years	0.016**	0.014*	0.017**
	[0.006]	[0.008]	[0.008]
SEA tertile 3 × Effective Exposure Years	0.019***	0.017**	0.020**
	[0.007]	[0.008]	[0.009]
N	3,980,291	1,851,939	2,128,352
A2. Alternate specification: pre-post specification			
Baseline SEA prevalence × [1] >2 effective exposure years	0.112**	0.049	0.142**
	[0.048]	[0.049]	[0.061]
N	3,980,291	1,851,939	2,128,352
A3. Alternate specification: linear years of exposure before age 5			
Baseline SEA prevalence × years since 1912	0.028**	0.023**	0.030**
	[0.011]	[0.011]	[0.014]
N	3,980,291	1,851,939	2,128,352
Panel B. Tests adding time trends for additional control characteristics to the primary specification			
B1. Primary specification, add SEA rural quartile × birth-year controls			
SEA Prevalence × Effective Exposure Years	0.038***	0.033**	0.040**
	[0.013]	[0.015]	[0.018]
N	3,980,291	1,851,939	2,128,352
B2. Primary specification, add SEA rural, temperature, precipitation, and suitability for agriculture quartiles × birth year controls			
SEA Prevalence × Effective Exposure Years	0.046***	0.026	0.055***
	[0.013]	[0.017]	[0.017]
N	3,960,391	1,842,320	2,118,071
Panel C. Extending the primary specification to include earlier years of death with lower mortality coverage			
C1. Primary specification, extended samples to earlier death years with lower coverage			
SEA Prevalence × Effective Exposure Years	0.066**	0.061*	0.067**
	[0.028]	[0.033]	[0.030]
N	5,286,010	2,608,623	2,677,387

Notes: This table presents estimates of the effect of exposure to the de-worming campaign, first pooled then stratified by sex. **Panel A1** presents coefficients from an alternative semi-parametric specification using the interaction between tertile of baseline hookworm prevalence and years of exposure, with coefficients relative to the lowest tertile. **Panel A2** presents coefficients from a simplified pre-post difference-in-differences framework, using those with less than 2 effective years of exposure as the reference group. **Panel A3** most closely resembles the paper's primary specification, but uses a linear years of exposure before age 5 term, where the years of exposure are calculated as the birth year-1912, truncated at 0 on the low end and 5 on the high end. **Panel B1** returns to the primary specification, and presents coefficients including interactions between SEA rurality quartile calculated using the 1910 census (and thus available for all SEAs) and birth year. **Panel B2** presents results that add to rurality a series of other quartile-by-birthyear interactions for indicators produced at the county level by Fiszbein, 2022, including temperature, precipitation, and agricultural suitability from the FAO-GAEZ (Fiszbein, 2022). **Panel C1** presents results from estimates using the primary specification on extended samples. Lifespan data are drawn from the CenSoc BUNMD, and extend the high-coverage sample used in the primary specification, which covers deaths 1988-2005, to include lower-coverage years, primarily from 1970-1987, but including through 1940. All empirical specifications reflect the primary specification using SEA fixed-effects that are allowed to vary by sex, and state-by-birth year fixed-effects. Hookworm prevalence is assigned at the SEA. Standard errors presented in brackets, clustered at the SEA level.

Table A2: Estimates of de-worming's impact on mortality rates calculated in the US census

	Survival		
	All	**Males**	**Females**
A. Primary specification			
State Prevalence × Effective Exposure Years	0.051*	0.038	0.064**
	[0.028]	[0.029]	[0.026]
Constant	0.770***	0.738***	0.804***
	[0.008]	[0.008]	[0.007]
N	341	341	341

Notes: This table presents estimates of the effect of exposure to the de-worming campaign, first pooled then stratified by sex. Observations only include RSC-treated states, and calculate the survival from early life (after infant mortality) until 1960 in the census. The empirical specification includes birth year and birth state fixed-effects. Standard errors presented in brackets, clustered at the state level.