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Agricultural intensification and childhood cancer in Brazil

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Over the last several decades, Brazil has become both the world's leading soy producer and the world's leading consumer of hazardous pesticides. Despite identified links between pesticide exposure and carcinogenesis, there has been little population-level research on the effects of pesticide intensification on broader human health in Brazil. We estimate the relationship between expanded soy production—and related community exposure to pesticides—on childhood cancer incidence using 15 y of data on disease mortality. We find a statistically significant increase in pediatric leukemia following expanded local soy production, but timely access to treatment mitigates this relationship. We show that pesticide exposure likely occurs via water supply penetration. Our findings represent only the tip of the iceberg for substantial health externalities of high-input crop production and land use change. Our results are of particular interest in developing contexts with demand for intensified food production systems and underscore the need for stronger regulation of pesticides and increased public health attention to exposure in the broader community.

cancer | agriculture | pesticides | public health

Significance

Pesticides are critical to agricultural intensification but can negatively impact human health. We show that as soy cultivation spread across Brazil, agricultural pesticide exposure was associated with increased childhood cancer mortality among the broader population indirectly exposed to these chemicals. We find that populations were exposed to pesticides through the water supply, but negative health effects were mitigated by access to high-quality cancer treatment centers. Our results support policies to strengthen pesticide regulation, especially in contexts intensifying their food production systems, and increased public health attention to pesticide exposure in the broader community.

Agricultural intensification—increased yields via increased inputs—is a pathway to sustainably increase food supply while minimizing environmental damages (1, 2). Intensification is viewed as having particular promise in developing country contexts characterized by low-input agriculture (3). Even so, policymakers must assess the possible effects of agricultural intensification on community development and human health outcomes (4). One major concern is that agricultural intensification often involves application of pesticides—chemical inputs that kill pests or weeds—with known adverse human health impacts (5–7).

Policymakers and stakeholders may underestimate the cost of intensification for their communities. While considerable research has established the health risks posed by acute exposure to pesticides, e.g., on pesticide poisoning of agricultural workers (6, 8) and on adverse birth outcomes (7), limited empirical evidence has characterized how chronic, low-level exposure from agricultural pesticides affects the broader public's health (9). Focusing only on health outcomes related to short-term or high-dose pesticide exposure underestimates the full community health costs of intensification; indirect, chronic, low-level exposure to some pesticides has long-term negative health outcomes (10).

We provide a population-wide analysis of the association between indirect exposure to agricultural pesticides and cancer. We use 15 y of panel data to study childhood cancer mortality during the expansion of soy cultivation and pesticide use through Brazil's Cerrado and Amazon biomes. Area in soy in the Cerrado tripled from 5 million hectares in 2000 to 15 million hectares in 2019. In the Amazon, the increase was twenty-fold, as soy increased from 0.25 million to 5 million hectares (11) (Fig. 1). Soy expansion typically occurs through conversion of pasture rather than clearing of native forest (12, 13). This conversion is a form of intensification, as cattle production uses relatively few inputs, particularly in terms of pesticides, while input use for soy production is high (14).

Brazil is now the world's leading consumer of highly hazardous pesticides, and the second leading consumer of all pesticides. In part, this massive consumption is because Brazil applies pesticides (per hectare) at a rate 2.3 times higher than the United States and 3 times higher than China, the first and third largest consumers of pesticides by volume, respectively (15, 16). Pesticide use for soy in Brazil has increased since the 2004 approval of genetically engineered glyphosate-resistant soybean varieties (7). Brazilian farmers also apply more inputs per hectare of soy than to other temporary crops, including corn, rice, beans, and sugarcane (7, 14, 17).

We empirically demonstrate the relationship between soy expansion and childhood blood-borne cancers—specifically, acute lymphoblastic leukemia (ALL), the most common childhood blood-borne cancer (18). We find a positive and significant increase in pediatric deaths from ALL following soy expansion, equivalent to 123 additional

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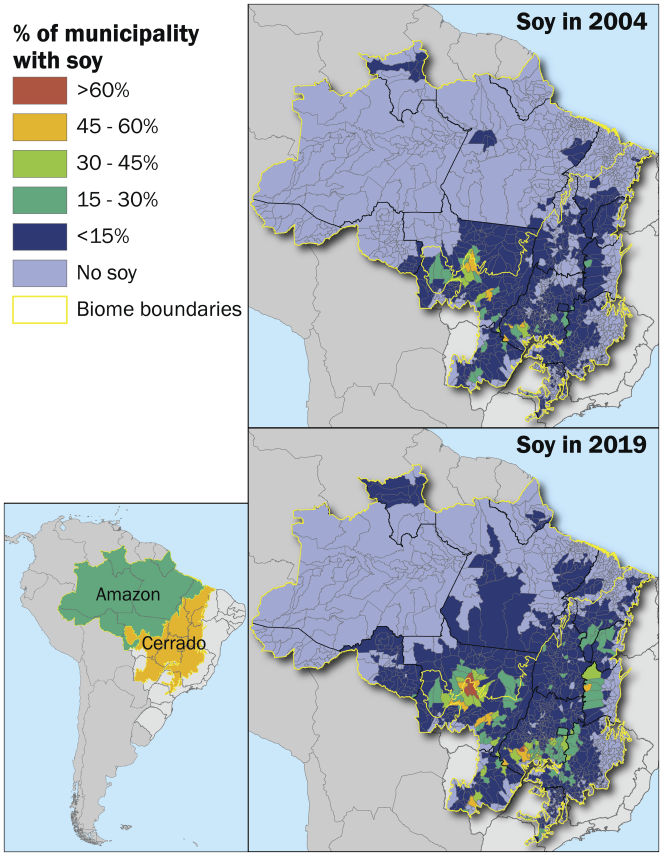

Fig. 1. Percent of municipal area planted in soy in 2004 and 2019 across the Amazon and Cerrado.

deaths of children under age 10 from 2008 to 2019. Leveraging geospatial data on Brazil's river network, we link mortality to soy production upstream in the watershed rather than the administrative region (municipality). This result indicates that a primary source of exposure is through contaminated water supply. We rule out alternative mechanisms of change, including placebo effects or increased production of other, less intensive, crops. Our results support our hypothesis that pesticide exposure is the channel between soy expansion and cancer and that a primary source of exposure is through pesticide contamination in the water supply.

We show a strong and persistent relationship between the arrival of high-intensity agriculture in a region and adverse human health outcomes. Further, we show that this relationship is mitigated by access to good-quality healthcare systems. While ALL is a highly treatable cancer conditional on timely and high-quality care, it is fatal without such care (19). Early treatment stages are intensive, requiring daily administration of medicine that may be achieved through inpatient or outpatient stays. We provide evidence that access to a pediatric oncology center within a daily drive (100 km) mitigates significant increases in fatal outcomes.

Further, pesticides are a textbook example of a good whose use comes with a negative externality (6). Farmers and pesticide producers earn private benefits in the form of profits from continued use and production of pesticides. However, pesticides impose an external cost on vulnerable populations, including fetuses and infants (7, 20, 21) and the elderly (10), particularly through water contamination. Such negative externalities have led to strict governmental control of pesticides in some regions, primarily in rich countries (22). Limited funding for staffing and enforcement, along with increased pressure from lobbying groups, has eroded the power of Brazil's pesticide control over time (16). The combination of restricted oversight, limited healthcare access, a rapidly evolving agricultural production system, and a new chemical technology provides a cautionary tale to regions in similar stages of agricultural intensification. As such, the results in this paper have implications for other regions experiencing or considering adoption or expansion of high-input agriculture.

This paper contributes to a growing body of empirical evidence of the impacts of pesticides on human health (7, 20). In Brazil, several studies have found correlations between pesticide exposure and cancer, either by using data on lagged pesticide sales and cancer mortality (23) or by looking at specific types of tumors like colon (24) or prostate cancer (25). Pesticides are a known risk factor for childhood cancer in particular (26, 27), though the empirical evidence tends to draw on case–control studies and retrospective data on pesticide exposure. Some studies have found a significant relationship between pesticide exposure and ALL (28), including exposure in utero, while other studies have found mixed or negligible effects of paternal exposure on ALL specifically (27, 29). Importantly, none of these studies of pesticides and pediatric ALL use data from Brazil.

We expand the horizon of study beyond time in utero and the first year of life to show that long-term pesticide exposure continues to have robust associations with fatal outcomes for children under the age of 10. While other work (7) has identified impacts of prenatal pesticide exposure on fetal development and adverse birth outcomes, our work shows evidence of this relationship beyond fetal development into infancy and childhood. Moreover, we provide such evidence at scale among populations not directly involved in agricultural production. Our work highlights that hazardous chemical exposure previously identified among nonagricultural populations is indeed associated with adverse human-health outcomes in the broader population. Further, our findings are only the tip of the iceberg, as our results do not account for the nonfatal health implications of environmental pesticide exposure, including cases of ALL that are successfully treated, other forms of cancer, and noncancerous disease that result from pesticide exposure. This study therefore reflects a small part of a much larger environmental health phenomenon.

The limited causal and population-level evidence to date regarding pesticide exposure and cancer risk comes from the complex and multifactorial process of carcinogenesis. Genetic mutations that lead to malignancies (both liquid and solid tumors) can be spurred by a number of causes, including exposure to radiation, pesticides, tobacco, alcohol, and so on refs. 30–32. As such, we do not interpret our results causally. However, we take steps to rule out several potential alternative explanations for the relationship that we find.

Limiting analysis to cases of ALL both accounts for the confounding effects of age and the multifactorial risk for solid tumor development. A number of major cancer risk factors for adults are less of a factor for children, such as radiation exposure, alcohol consumption, and tobacco use. Notably, while the medical literature suggests there is a direct relationship between soy consumption and other types of cancer, little evidence has suggested the presence of a similar relationship with pediatric ALL. Existing research is mixed on whether consumption (either directly or in utero) of soy products poses increased, no change in, or reduced risk of development of ALL (33, 34). Furthermore, soy production in the area is almost exclusively for livestock feed, rather than human consumption, reducing concern over the dietary exposure pathway. We also find no evidence that less input-intensive row crops increase pediatric deaths from ALL. This rules out economic or lifestyle changes associated with crop

agriculture (such as increased exposure to diesel exhaust) as the mechanism through which soy expansion leads to cancer. Last, we directly control for differences in population, municipal climate and development, and regional trends in development.

Results

Pediatric deaths from ALL increased following soy expansion in Brazil's Amazon and Cerrado. We present the coefficient of interest from our primary model specifications in Table 1. We report full regression tables of these models in the supplement.

We find that a 10-percentage-point increase in the municipal area planted in soy is associated with an additional 0.40 deaths from ALL of children under 5 per 10,000 population and an additional 0.21 deaths under 10 per 10,000 population. During this period, the mean level of soy coverage in the sample was 3% with a SD of 8%, and the mean deaths per 10,000 population for children under 5 and 10 were 0.081 and 0.079, respectively. We estimate an unweighted model in *SI Appendix*, Table 4 and find that, at actual soy and population levels, this is equivalent to an additional 123 deaths of children under 10 from 2008 to 2019 across the sample, compared to 226 total deaths in our sample during the period. The binary model shows that a 10-percentage-point increase in municipal area in soy increases the likelihood that a single child in that municipality and year under 5 would die from ALL by 1.3% and the likelihood of death by 1.6% for a child under 10.

We also find a positive relationship between soy production and pediatric deaths from ALL. An increase of 0.10 tons of soy per municipal hectare is associated with a 0.2% higher likelihood that a child under 5 dies of ALL and a 0.3% higher likelihood for children under 10. The mean value of production in the period was 0.11 tons per hectare with a SD of 0.25.

Our primary sample includes all municipalities that were at least 90% contained in the Amazon or Cerrado, excluding those in the state of Goiás. Goiás includes the Federal District and differs from the remainder of the sample economically and in terms of availability of cancer treatment. We discuss this choice further in the supplement. As a robustness test, we include Goiás in the sample and interact soy production with an indicator for Goiás. We find a positive and significant overall relationship, with an imprecise negative interaction coefficient of soy production in Goiás (*SI Appendix*, Table 14).

Table 1. Pediatric deaths from ALL relative to previous 5-y soy production in the municipality and upstream in the Ottobasin

	Under 5		Under 10	
	Per 10,000	Binary	Per 10,000	Binary
Treatment: municipality				
Soy area				
Proportion area in soy	3.978**	0.133**	2.069*	0.163**
	(1.895)	(0.055)	(1.069)	(0.073)
Soy production				
Tons soy per ha	0.382	0.022**	0.228	0.032*
	(0.355)	(0.011)	(0.202)	(0.017)
Observations	8426	8426	8426	8426
Treatment: Upstream Ottobasin				
Soy area				
Proportion own + upstream area in soy	30.284**	0.786*	15.799**	0.875**
	(14.552)	(0.407)	(7.406)	(0.436)
Proportion upstream area in soy	27.038**	0.676*	13.810**	0.735*
	(13.216)	(0.358)	(6.794)	(0.393)
Observations	5566	5566	5566	5566
Municipal FE	X	X	X	X
Meso-region-year FE	X	X	X	X
Controls	X	X	X	X

Note: The unit of observation is the municipality. Observations are weighted by relevant population. Every row presents the coefficient of interest from a distinct model. Ottobasin-level sample limited to municipalities where at least 90% of municipal land area is located within a single Level 4 Ottobasin. Robust standard errors are in parentheses and are clustered at the Level 3 Ottobasin level. Municipalities falling in multiple Ottobasins are considered in their primary Ottobasin for purposes of clustering. *$P < 0.10$, **$P < 0.05$, ***$P < 0.01$.

Surface Water was a Means of Exposure. Next, we investigate whether water sources were a primary method of exposure. We measure soy production upstream within the same watershed (Ottobasin level 3) to more precisely measure pesticide exposure via river and stream networks.

We find that a 10-percentage-point increase in the upstream Ottobasin area in soy precedes an additional 2.70 deaths of children under age 5 per 10,000 population and an additional 1.38 deaths under age 10 per 10,000 population (Table 1). When we include production in the municipality's Level 4 Ottobasin, the increase was 3.03 and 1.58 deaths per 10,000 population for children under five and ten, respectively. This relationship is larger than the effects of municipal-level production. On average, a 10-percentage-point increase in upstream area in soy corresponds to a larger total increase in soy production than a 10-percentage-point increase in municipal area, as the average upstream area in an Ottobasin is 1.35 million hectares, while the average municipality is 0.23 million hectares. However, this should not account for the entirety of the difference, as we measure both municipal and upstream soy as a percent of total area.

We include downstream area in soy production as an additional treatment variable in *SI Appendix*, Table 6 and find no evidence of a relationship between downstream soy production and pediatric deaths from ALL. In the model including all municipalities, we again find a positive and significant relationship between own and upstream soy production and deaths from ALL but no significant coefficient on downstream soy production. In the models only including municipalities that are at least 90% in one watershed, we again find no relationship between downstream soy production and deaths from ALL. The coefficients on own and upstream soy area are no longer significant, but we attribute this to high correlation between upstream and downstream soy production ($\rho = 0.88$) in this sample compared to the sample of all municipalities ($\rho = 0.44$).

Our results suggest that pesticides used in soy production upstream in the Ottobasin reach children living downstream via waterways and water sources.

Cancer Treatment Mitigates Fatalities. The majority of cancer treatment is performed at high-complexity oncology centers (Portuguese acronym CACON) or high-complexity oncology units (Portuguese acronym UNACON), with some complementary treatment done at general hospitals (25).* Across the entirety of Brazil, there are 299 accredited oncology programs, though almost half of those are in the Southeast (Espírito Santo, Minas Gerais, Rio de Janeiro, and São Paulo) (Fig. 2). Pediatric

*Health care is provided in Brazil by public health insurance (the Sistema Único de Saúde, or SUS), though 25% of the population has supplementary private health insurance (35). Public hospitals are free but often have long wait lists for appointments, making receiving timely care difficult. These disparities are more egregious in rural areas and among poor populations (36).

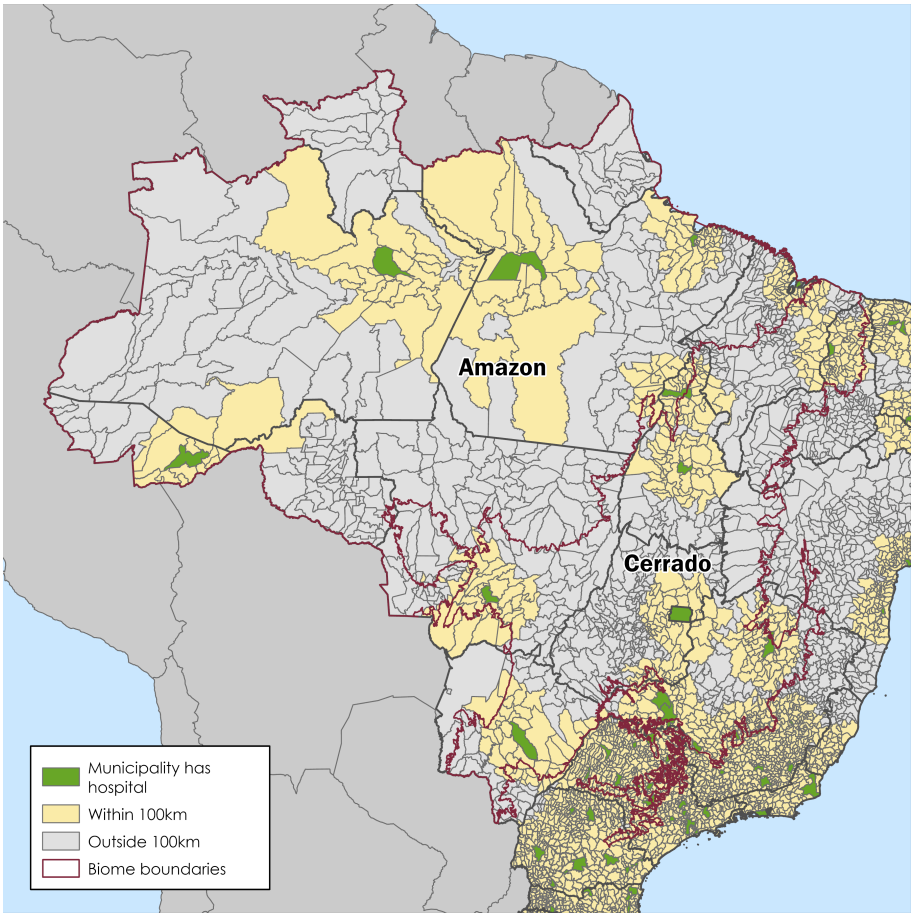

Fig. 2. Municipal-level distance from a hospital treating pediatric oncology in 2005 to 2009.

oncology centers are even fewer and farther between, with 72 in the entire country as of 2017. There are only two cities in the entirety of the Amazon with high-complexity pediatric oncology treatment (CACON or UNACON). In the Cerrado, there are 35 CACON or UNACON, but 31 of these are within the relatively urban states of Bahia, Minas Gerais, and São Paulo, and 26 are in São Paulo alone.

Concentration of UNACONs and CACONs in the wealthier and more populous states of Brazil further exacerbates health disparities seen in the Amazon and the frontier. Socioeconomic status (SES) is inversely related to overall cancer risk (37). Notably, the literature is divided on the relationship between SES and ALL, with some researchers finding higher ALL incidence in higher SES households and others finding the opposite relationship (38, 39). In the context of Brazil, geographic isolation from pediatric CACONs and UNACONs likely limits the kinds of treatments locally available and/or require patients and their families to travel hundreds or thousands of kilometers to seek treatment. Additionally, distance limits the kinds of treatments that are available daily. For example, if there is no hospital that is accredited to administer daily chemotherapy within driving distance, patients may not be able to receive adequate treatment.

We use a slightly broader definition of treatment access by including any hospital that treated more than five pediatric oncology cases over the five-year baseline period (2005 to 2009). We find that the increase in observed pediatric ALL deaths following soy expansion is limited to municipalities that were more than 100 km from a treatment center. This suggests that the relationship between pesticide exposure and fatal cases of ALL weakens as cancer treatment is more available. As ALL is a highly treatable form of cancer, this matches expectations. In municipalities farther than 100 km from a hospital treating pediatric oncology, we find that a 10-percentage-point increase in municipal area in soy corresponds to an additional 0.54 deaths of children under 5 per 10,00 population and an additional 0.32 deaths under 10 per 10,000 population (Table 2). In contrast, in municipalities within 100 km of a relevant hospital, we detect no significant relationship with pediatric deaths from ALL.

We find similar patterns when we consider soy production upstream in the Ottobasin (inclusive of own Level 4 production). We find that a 10-percentage-point increase in upstream area planted in soy was followed by an increase of 4.3 deaths under 5 per 10,000 and 2.3 deaths of children under 10 per 10,000 (in response to soy production in the municipality's Level 4 Ottobasin and upstream in the Level 3 Ottobasin). There was a significant increase in deaths of children under 5 per 10,000 in response to upstream within 100 km of a hospital, although this coefficient was less than one-third of that for municipalities far from a hospital.

Ruling out Alternative Mechanisms. Finally, we implement a series of tests to confirm that our results were driven by our proposed mechanism of pesticide exposure, rather than through endogenous changes that occur in a community when crop agriculture replaces cattle production.

Table 2. Pediatric deaths from ALL relative to previous 5-y soy production in the municipality or upstream in the Ottobasin and distance to hospital

	Under 5		Under 10	
	Per 10,000	Binary	Per 10,000	Binary
Treatment: municipality				
Soy area				
Less than 100 km	0.799	0.041	−0.603	−0.031
	(0.926)	(0.037)	(0.695)	(0.064)
Greater than 100 km	5.365**	0.173**	3.239***	0.248***
	(2.331)	(0.067)	(1.212)	(0.086)
Soy production				
Less than 100 km	−0.140	0.016	−0.388	−0.013
	(0.420)	(0.016)	(0.255)	(0.028)
Greater than 100 km	0.563	0.024*	0.445**	0.048***
	(0.451)	(0.013)	(0.216)	(0.018)
Observations	8426	8426	8426	8426
Treatment: Ottobasin				
Soy area				
Less than 100 km	8.628*	0.282**	2.547	0.118
	(4.825)	(0.128)	(2.610)	(0.160)
More than 100 km	42.799*	1.077*	23.425**	1.310**
	(22.596)	(0.619)	(11.436)	(0.638)
Observations	5566	5566	5566	5566
Municipal FE	X	X	X	X
Meso-region-year FE	X	X	X	X
Controls	X	X	X	X

Note: Unit of observation is the municipality. Observations are weighted by relevant population. Ottobasin-level sample limited to municipalities where at least 90% of municipal land area is located within a single Level 4 Ottobasin. Ottobasin treatment includes area in the municipality's Level 4 Ottobasin and all upstream Level 4 Ottobasins. Robust standard errors are in parentheses and are clustered at the Level 3 Ottobasin level. Municipalities falling in multiple Level 3 Ottobasins are considered in their primary Ottobasin for purposes of clustering. *$P < 0.10$, **$P < 0.05$, ***$P < 0.01$.

We conduct a placebo test to measure whether soy expansion affected pediatric deaths from slips, trips, and falls (ICD-10 codes W00 - W19) (*SI Appendix*, Table 7). The chemicals in pesticides are not a risk factor for these conditions, and the path for soy expansion to influence deaths from this accident is indirectly through socioeconomic conditions and healthcare availability. We find weak evidence that deaths from slips, trips, and falls decreased as area in soy expanded. While it is possible that healthcare availability and quality increased as soy expanded (which would therefore bias our estimates toward zero), it is important to remember that the majority of care that children receive for cases of ALL takes place outside of the municipality at specialized cancer clinics. We therefore take the conservative interpretation that this placebo test does not provide evidence of a placebo effect in this context.

Further, we test the effect of nonsoy annual crops (excluding sugarcane) on pediatric deaths from ALL. Soy is the most heavily treated crop (7, 14), so we would not anticipate a relationship between nonsoy annual crops and pediatric deaths from ALL. According to the Agricultural Census, in the North and Center-West, there is meaningful (> .5% of total area in production) area in pineapple, rice, beans (including black-eyed peas), mandioca, watermelon, and sorghum, none of which are known for heavy pesticide application. (While some pesticides may be applied to these crops, we would expect a crop with lower pesticide intensity to have smaller effects, assuming that both are toxic in comparable ways.) Indeed, we find little evidence of a relationship between these crops and deaths from ALL (*SI Appendix*, Table 8).

We test whether a 1-y lag of soy production is related to pediatric deaths from ALL. The timing from pesticide exposure to deaths from ALL is likely longer than a year, even for young children. Thus, a single-year lag captures the current levels of development in a municipality rather than the child's lifetime exposure to pesticide. We find no statistically significant relationship between the 1-y lagged soy production variables and pediatric deaths from ALL (*SI Appendix*, Table 9).

Finally, we disaggregate the five-year moving average in *SI Appendix*, Table 10. This test could contain information regarding the most critical window of exposure. However, in practice, the autocorrelation in the treatment variable precludes any meaningful information from this test (Born and Breitung q-stat with four lags = 104.96). Indeed, we find no significant coefficients in this model, as would be expected in a model with high multicollinearity.

Discussion

We identify a substantial, statistically significant, and persistent relationship between soy expansion in the Brazilian Amazon and Cerrado and childhood deaths from ALL. The relationship is present for both municipal- and Ottobasin-level soy area and municipal-level soy production. In total, we estimate that 123 children under 10 died from ALL associated with soy exposure between 2008 and 2019. This is roughly half of all reported deaths from ALL of children under 10 in the same period. Through a series of tests, we argue that this effect was due to indirect exposure to pesticides via water sources.

Our results are a narrow estimate of the adverse relationship between soy expansion and human health, focused on only one subset of the population and one particular disease, acute lymphoblastic leukemia (ALL). It is likely that pesticide exposure impacts many other forms of illness that we do not study here, including other forms of cancer, neurological illnesses, and acute pesticide poisoning.

Data scarcity precludes quantifying the human or financial costs of nonfatal cases of ALL, which are substantial (40, 41). Pediatric oncology and hematology are able to use aggressive forms of radiation and chemotherapy to treat cancer in children given the resilience of younger bone marrow. However, exposure to radiation and chemotherapy have lifelong impacts on physical and cognitive development, especially for very young children (under age 3) (40, 41). These effects put even further strain on already-taxed public health systems, especially in poor, rural areas of Brazil. Further, we do not estimate effects in the historic soy-producing regions of Brazil or in nonrural municipalities. Our estimate is therefore a lower bound of the total cost of pesticide exposure to Brazilian public health.

We use soy expansion specifically as our treatment of interest because of the identified direct link between soy production and expanded pesticide application, but we acknowledge that soy can be intercropped with another pesticide-intensive crop, such as corn. This would mean that we might be capturing the effect of both pesticides applied to soy as well as to the second crop. This would transform our interpretation to being the effect of pesticides altogether, with a portion of that total effect attributed to those pesticides applied to soy specifically. This is still consistent with the narrative that the transition from low-input (cattle) production to high-input crop production, which yields pesticide exposure, has deleterious effects on human health. Further, we expand on existing literature by showing a population-level relationship between pesticide exposure and

childhood cancer mortality and provide evidence for the relevant mechanism.

A number of health and agricultural policies at the local and national levels may mitigate the relationship we find. Rural populations benefit from access to timely cancer treatment; increasing access may reduce the number of fatal pediatric ALL cases. Programs to develop registries of all identified diagnoses of cancer, as have been developed in some countries (42), can aid researchers and policymakers in identifying potential cancer clusters, improving the speed and efficiency of public health response. While such programs are costly, they are much more feasible in the context of Brazil's public health system. Medical doctors may consider adopting a standard screening procedure for children in communities with increasing or high soy production. Such a procedure may include annual blood tests to assess immune system health and detect early signs of liquid tumors and parental education on water source safety. Regulation of highly hazardous chemicals may reduce the effects we study here.

Additionally, advising in proper levels of pesticide use by individuals who do not privately benefit from pesticide use may reduce the risk of overapplication. Policymakers may consider stronger controls over pesticide application and tracking of application to better target healthcare interventions.

This study presents strong, quantified evidence of an increase in cancer deaths among the broader, indirectly exposed population that is concurrent with intensified soy production, and thus increased pesticide application. This work underscores the importance of considering the human health implications of agricultural intensification, especially in regions without prior exposure to these methods. In addition, our results point to the lifesaving importance of mitigation (i.e., healthcare access) when communities undergo intensification, although we do not quantify here the cost of nonfatal ALL cases in regions with hospital access.

Materials and Methods

Data. Our data consist of a 15-y (2004 to 2019), municipal-level panel on health outcomes, land use, surface water, and demographics. Mortality data are publicly available from DataSUS (43). These encounters are defined by ICD-10 (International Classification of Disease) diagnosis category codes and stratified by age bins, allowing us to identify fatal cases of lymphoid leukemia (ICD-10 code C91) in the population under ages 5 and 10 at the municipal-year level. Among children (under age 5 and under age 10), these cases should overwhelmingly consist of deaths from ALL (19).

Population data are available from the Brazilian Institute of Geography and Statistics (IBGE), although they are not available annually stratified by age group (44). We impute annual population under 5 and under 10 by multiplying the proportion of the population in that age group in the most recent census (every 5 y) by the annual total population.

We compile data on soy, sugarcane, all other temporary crops, pasture, mining, and natural vegetation using land cover maps from Mapbiomas version 7 (45). Using these data, we can calculate the total number of hectares in the municipality planted in soy as well as control for sugarcane, remaining forest, natural vegetation, and area in pasture. In Brazil, corn is intercropped with soy and is not the dominant cash crop. Land use data reflect this by categorizing land used in a soy-corn rotation as area in soy.

Consistent with prior work, we measure a municipality's upstream exposure to soy within a watershed (7). Watersheds (geographic areas over which rainfall is channeled via rivers and creeks to eventual outflow points) are measured as Ottobasins in Brazil and are available from the Brazilian Institute of Geography and Statistics (IBGE) (46). Level 3 includes catchment areas that overlap between some municipalities, allowing us to measure exposure to agricultural pesticides that occurs outside the municipality of residence (*SI Appendix*, Fig. 1). Within a Level 3 Ottobasin, we leverage the system of Level 4 Ottobasins to identify areas upstream of the municipality (*SI Appendix*, Fig. 2). This corresponds to no upstream area for tributaries (i.e., even-numbered Level 4s). We then measure upstream treatment by overlaying MapBiomas soy area with Level 4 Ottobasin boundaries. We consider both upstream area only and area in the Level 4 in the municipality as well as in the Level 4 Ottobasin of the municipality. When a municipality falls within more than one Level 3 Ottobasin, we assign it the characteristics of the Level 3 Ottobasins according to the proportion of land area within that Ottobasin.

Sample. Our main sample includes municipalities in the Amazon and Cerrado that are classified as "rural" per IBGE categories and have at least 25% of land cover in agriculture. This excludes municipalities that are either urban or highly forested, both of which are likely to have different patterns of cancer rates than our sample of interest.

We exclude municipalities outside the Amazon and Cerrado biomes, which correspond to the Atlantic Forest, Caatinga, Pampa, and Pantanal biomes. These biomes either had established soy production at the beginning of our study period (i.e., the Pampa and Atlantic Forest regions of Paraná, Santa Catarina, and Rio Grande do Sul) or had relatively little soy production throughout the period and significant urbanization and industry that presents a challenge to identification (i.e., the Atlantic Forest and Caatinga portions of Rio de Janeiro, Espírito Santo, Rio Grande do Norte, Paraíba, Pernambuco, and Sergipe).

To avoid contamination of our treatment, we consider soy production beginning in 2004, the year that genetically modified (GM) soy was approved for use in Brazil. This GM soy is herbicide-resistant, allowing farmers to use chemical inputs to control weeds without damaging the growing soy plants. GM soy has been shown to have increased the use of pesticide in Brazil, especially the highly hazardous chemical glyphosate (the active agent in Round-Up), and is linked to increased adverse health outcomes (7). Notably, we are not able to distinguish what proportion of area in cultivation was planted in a GM cultivar, nor can we precisely measure the application rate. Our results are rather based on the average cultivar and application rate at the time of our study.

For two-thirds of municipalities in our sample, at least 90% of their area falls within a single Level 3 Ottobasin. In our Ottobasin analysis, we focus primarily on these municipalities and define their treatment based on the most downstream Level 4 Ottobasin they fall within in their primary Level 3 Ottobasin, but for robustness, we use a sample with all municipalities.

Model. We estimate the effect of soy production on pediatric deaths from ALL using an ordinary least squares (OLS) model with fixed effects:

$$C_{mt} = \alpha S_{m,\overline{t-5}} + \beta X_{mt} + \delta_m + \gamma_{rt} + \epsilon_{mt}. \quad [1]$$

Outcomes C_{mt} are pediatric (under age 5 and under age 10) deaths from ALL in municipality m in year t. We measure deaths per 10,000 of the corresponding population and as a binary indicator that takes a value of one if a child in the municipality died from ALL in that year and zero otherwise.

Our independent variable of interest, $S_{m,\overline{t-5}}$, is the average soy production in municipality m in years $t-1$ to $t-5$. We consider two measures of production: the proportion of municipal hectares in soy production and the total soy production relative to municipal area.

In contrast with much of the previous literature that estimates the acute effects of exposure to an environmental toxin (7, 20, 21), we are interested in the effects of a longer-term exposure. Prior work has noted the empirical challenge of estimating the cumulative effects of long-term exposure, particularly as autocorrelation in the treatment variable challenges the use of distributed lag models (9).

We are interested in mortality due to cases of pediatric ALL, which would generally occur by age 10. Data on cancer mortality are not disaggregated by exact age, so we only know the number of deaths from ALL among children in 5-y bins. Here, we use five-year treatment bins as a proxy for average lifetime exposure. These allow us to measure their exposure to soy production over a critical window given the rapid nature of ALL development in early life. To account for this lag, we include observations of health outcomes beginning in 2009. Such aggregated measures are used in the epidemiology literature to measure

the association between long-term pollution exposure and health outcomes (47–49).

Additionally, we use a continuous treatment variable rather than a binary treatment variable as there is no justifiable switch point across which pesticide exposure dramatically increases its toxicity and carcinogenicity. This prevents us from using an event study-style analysis.

In alternative specifications, we define $S_{m,\overline{t-5}}$ using the area in soy production upstream of the municipality but within the Level 3 Ottobasin. We omit the downstream area in soy from our primary models but include downstream area as an additional treatment variable as a falsification test.

Controls X_{mt} include the proportion of municipal area in natural vegetation, mining, and sugarcane, and municipal population. For all land-cover variables, we use a 5-y moving average to match the treatment variable. We include municipal fixed effects and meso-region-year fixed effects. Meso-regions are unit of analysis that were designated by IBGE. They are smaller than a state and are meant to represent an "individualized area [...] with its own regional identity" (50). We weight observations by the municipal population of the relevant group (e.g., population of children under five for models of deaths under five) using inverse probability weights. SEs are clustered at the Level 3 Ottobasin.[†] When municipalities are located in multiple Ottobasins, we choose the majority Ottobasin.

We consider the role of treatment in mitigating deaths from ALL using a heterogeneity test based on the distance between a municipality and the nearest hospital that treats pediatric cancer.

$$C_{mt} = \alpha S_{m,\overline{t-5}} * Near_m + \alpha S_{m,\overline{t-5}} * Far_m + \beta X_{mt} + \delta_m + \gamma_{rt} + \epsilon_{mt}. \quad [2]$$

We use the set of hospitals that treated at least five pediatric (under 10) cancer cases between 2005 and 2009. This is equivalent to one case per year in the early period of soy expansion. By limiting the treatment to this early period, our analysis may not fully reflect access to treatment in the later period.[‡] However, it avoids endogenous hospital or unit openings based on increased cancer cases. We define municipalities as near a treatment center ($Near_m = 1$) if their municipal centroid is within 100 km of the centroid of a municipality with a pediatric cancer center and far ($Far_m = 1$) otherwise. This distance roughly corresponds to a distance that a family could reasonably travel in a day for treatment.[§]

Because carcinogenesis is a complex and multifactorial process, the tools we used cannot demonstrate a causal link between soy expansion (and pesticide use) and cancer deaths. That said, we take a number of steps to rule out other potential explanations. Municipal fixed effects account for unvarying characteristics such as geological traits. Meso-region-year fixed effects account for different trends in development across regions, which relates to socioeconomic status and treatment access. As discussed, our focus on childhood cases reduces the risk of behavioral factors that might increase risk (e.g., exposure to radiation in the workplace) and our focus on a cancer that can be diagnosed using a relatively straightforward blood test reduces disparities in likelihood of diagnosis. This assumption would also be violated if soy production led to significant migration or population shifts. We find no evidence that rural municipal populations increase with soy production, which would be expected if existing local labor transitioned from cattle to soy production.

Data, Materials, and Software Availability. Previously published data were used for this work. Data on mortality by ICD-10 code, municipality, age group, and year are available directly from DataSUS (43). Data on soy, sugarcane, all other temporary crops, pasture, mining, and natural vegetation come from land cover maps in Mapbiomas version 5 (44). Population data (45), and Data on Ottobasins in Brazil (46) are available from the Brazilian Institute of Geography and Statistics (IBGE).

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[†] For robustness, we also cluster SEs at the municipality. SEs are changed by 0.008 at most and do not change the significance level in any specification.

[‡] This is particularly the case for Goiás and the Federal District, which had three clinics from 2005 to 2009 and eleven in 2015 to 2019. For this reason, we also exclude Goiás from our analysis based on hospital distance.

[§] Actual travel times will vary depending on the road network, but by highway, this distance can be traveled in 1 to 2 h by car or bus.

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