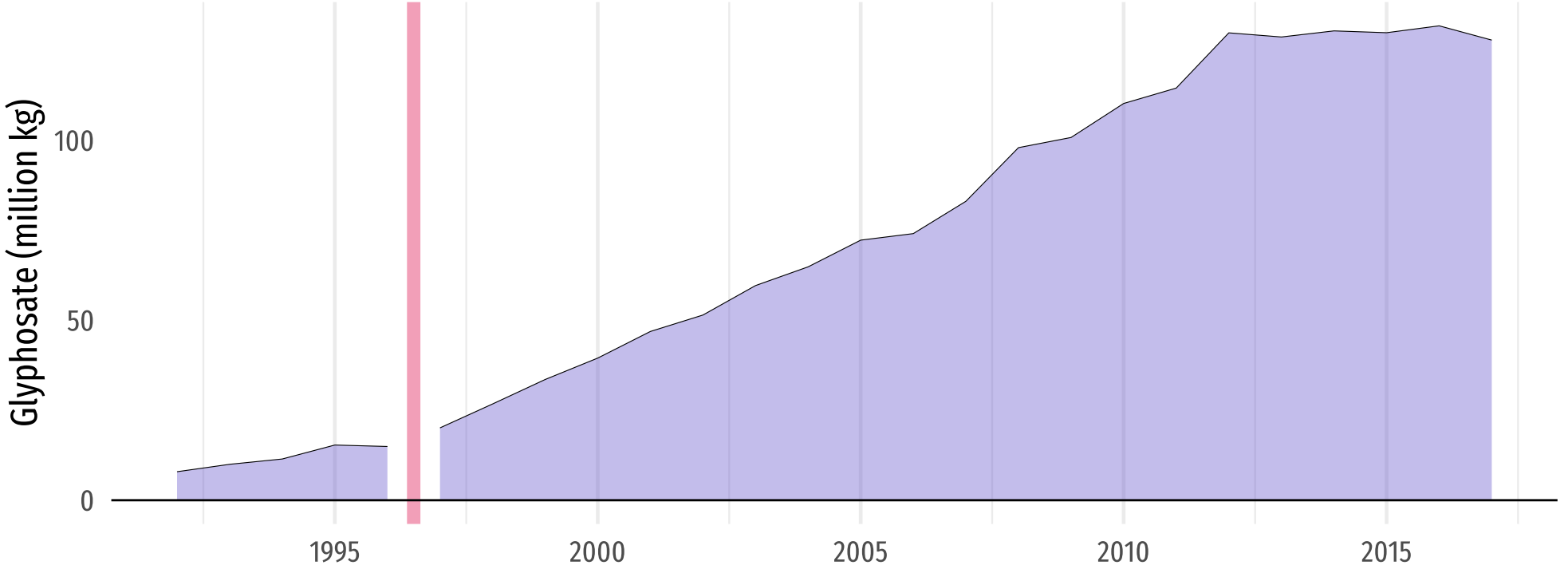
Perinatal health effects of herbicides

Glyphosate and the U.S. roll-out of GM crops

Emmett Reynier // University of Oregon + US EPA
Edward Rubin // University of Oregon

#revolution Introduction of **genetically modified** (GM), **glyphosate**-tolerant seeds from 1996–1998 dramatically reshaped US agriculture.



Big changes: Within two decades, **>90% of corn and soy seeds sold were GM**.
Between 1995 and 2015, **glyphosate** (GLY) **increased 750 percent**.

The GM *miracle*: With GLY-tolerant "Roundup Ready" GM crops, farmers can spray a super potent herbicide ***directly* onto their crops**—throughout the growing season.

Q: So glyphosate (and Roundup) must be safe, right?

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A: Maybe? We're not sure.

Weed Killer, Long Cleared, Is Doubted

Give this article

Glyphosate being sprayed on a field in Suffolk, England. Introduced in the 1970s, it is the most widely used herbicide in the world. Universal Images Group, via Getty Images

2015

Monsanto Weed Killer Roundup Faces New Doubts on Safety in Unsealed Documents

Give this article 354

A scanning machine illuminating a bottle of Roundup, a weed killer, as it moved along a production line at a facility in Antwerp, Belgium, owned by Monsanto. Jasper Juinen/Bloomberg

2017

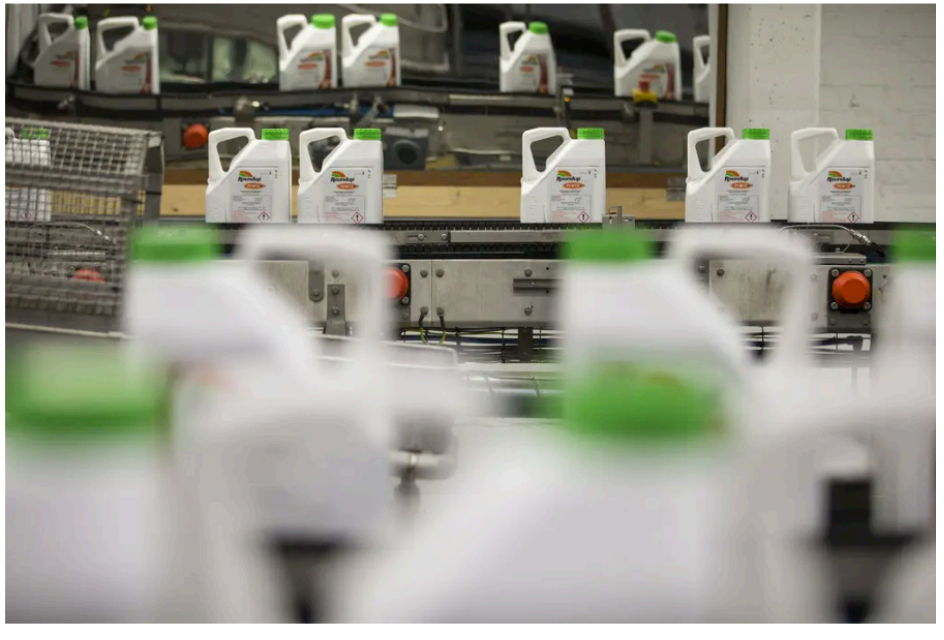
Roundup Weedkiller Is Blamed for Cancers, but Farmers Say It's Not Going Away

After a blockbuster acquisition, Bayer may lose billions over claims that the No. 1 agricultural chemical is unsafe. But its market niche seems secure.

Herbicide containers on Andy Bensend's farm in Dallas, Wis. Mr. Bensend relies on the key ingredient in Roundup — glyphosate — to kill weeds, improve yields and cut costs. Jenn Ackerman for The New York Times

Key Element of Monsanto Weed Killer Not a Carcinogen, European Agency Says

Give this article



Bottles of Roundup weed killer on a production line operated by Monsanto in Belgium. Jasper Juinen/Bloomberg

2017

Roundup Maker to Pay $10 Billion to Settle Cancer Suits

Bayer faced tens of thousands of claims linking the weedkiller to cases of non-Hodgkin's lymphoma. Some of the money is set aside for future cases.

Give this article

Bayer, the world's largest seed and pesticide producer, added Roundup to its portfolio when it acquired Monsanto. Daniel Acker/Bloomberg

2020

Uncertainty goes back to the early days of Roundup.

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- >80% of streams sampled by USGS
- residue in common foods (*e.g.*, Cheerios)
- >90% urine samples (Gerona et al, 2022)

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Further: Much of the health conversation focuses on carcinogenic concerns.

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Results

- Significant **reductions** in average **birth weight** (~30g) and **gestation** (~1.5 days).
- **Largest reductions in expected low-weight births**.
- ⇒ disprop. impacted **female infants** with **Black and/or unmarried parents**.

Literature and contribution

Growing literature on health effects of general pesticides exposure.

Larsen, Gaines, Deschênes (2017, Nature)

Pesticide exposure ↑ adverse birth outcomes.

Chiu et al. (2018, JAMA IM)

High-pest. foods assoc. w/ ↓ probability of birth.

Sagiv et al. (2019, PNAS)

OP-pest. in pregnancy correlate w/ altered brain activation.

Jones (2020, Land)

Premature and low-weight births ↑ w/ insecticide/fungicide.

Taylor (2022, WP)

Insecticides ↑ infant mortality and reduce later-life outcomes.

Frank & Taylor (2022, WP)

DDT ↑ infant mortality.

Literature and contribution

Small existing literature for GLY and health outcomes

1. Lab-based studies (esp. small animals)
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Lab. studies document GLY and adverse reproductive outcomes

- human embryonic, umbilical, and placental cells (Richard *et al.*, 2005; Benachour *et al.*, 2007 & 2009)
- toxicity and slowed developmental in rats (Dallegrave *et al.*, 2003)
- endocrine-disrupting effects on male-mouse reproduction (Pham *et al.*, 2019)
- developmental issues in frogs (Paganelli *et al.*, 2010)

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Camacho & Mejía (2017, JHE)

- Aerial anti-coca GLY campaign Colombia
- ↑ medical visits (derm. and resp.) & miscarriages

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Dias, Rocha, and Soares (2023, REStud)

- Document GLY effects on IMR for six Brazilian states, 2000–2010 (6.3M births)
- Exposure mechanism: water transport—particulary acute in South Am.
- *Average* ↑ in GLY ⇒ 5% ↑ for infant mortality rate (0.88 per 1000 births).

Skidmore, Sims, and Gibbs (2023, PNAS)

- Soy intensification in Brazil ⇒ GLY exposure ⇒ increased pediatric leukemia
- Exposure mechanism: water-supply penetration

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Arbuckle *et al.*, 2001 in *Environmental Health Perspectives*

- *Sample:* Ontario farm population survey (2,110 women; ~4k pregnancies)
- Significant cor. between pre-conception GLY exposure and miscarriage.

Parvez *et al.*, 2018 in *Environmental Health*

- *Sample:* 71 women with "low-risk pregnancies" in central Indiana.
- Detected glyphosate in urine of 66/71 women.
- Association between GLY exposure and gest. length and (not sign. for birth weight).

Gerona *et al.*, 2022 in *Environmental Helath*

- *Sample:* 150 women with "high-risk pregnancies" in Indiana (+1 IL cnty).
- 99% of pregnant women had glyphosate in urine (n=150).
- Higher GLY in urine associated with lower birth-weight percentile and higher NICU risk.

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Gerona *et al.*, 2022

> To our knowledge, there are no animal or human studies which correlate prenatal glyphosate exposure and fetal growth or BWT%ile.
>
> The results warrant further investigation on the effects of GLY exposure in human pregnancies in larger population studies.

Background

History, chemistry, and institutions

1961 Stauffer Chemical Co. patents GLY as a descaling and chelating agent.

1970 John Franz (Monsanto) discovers GLY's herbicidal efficacy.

1974 US EPA approves GLY for use on crops.
Monsanto begins selling GLY-based herbicide as "Roundup".

198* Monsanto develops glyphosate-tolerant crops.
1985 US EPA *almost* lists GLY as a likely carcinogen.

1996 GLY-tolerant (Roundup Ready) GM soybean seeds hit US market.
1997 ↳ GLY-tolerant cotton seeds enter market.
1998 ↳ GLY-tolerant corn seeds first available.

Glyphosate

What is it?

Chem: N-(phosphonomethyl)glycine (an organophosphorous compound).
Main ingredient in Roundup.

How does it work?

- GLY disrupts the enzyme EPSP† synthase.
- Disruption eventually stops active growth.
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Early advertisements: GLY safe for animals because we lack EPSP synthase.

Problem? Bacteria and fungi have EPSPS. Might matter for microbiome and broader ecology.
Human mechanisms may differ from plants...

† 5-enolpyruvylshikimate-3-phosphate synthase

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But also 14.5-15% surfactant POEA.[†]

- Surfactants reduce surface tension in liquid.
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POEA is more toxic to amphibians and fish than glyphosate (also highly toxic to bees).

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Note: Our approach cannot separate GLY exposure from POEA.
↳ Effect of Roundup or an upperbound on GLY toxicity.

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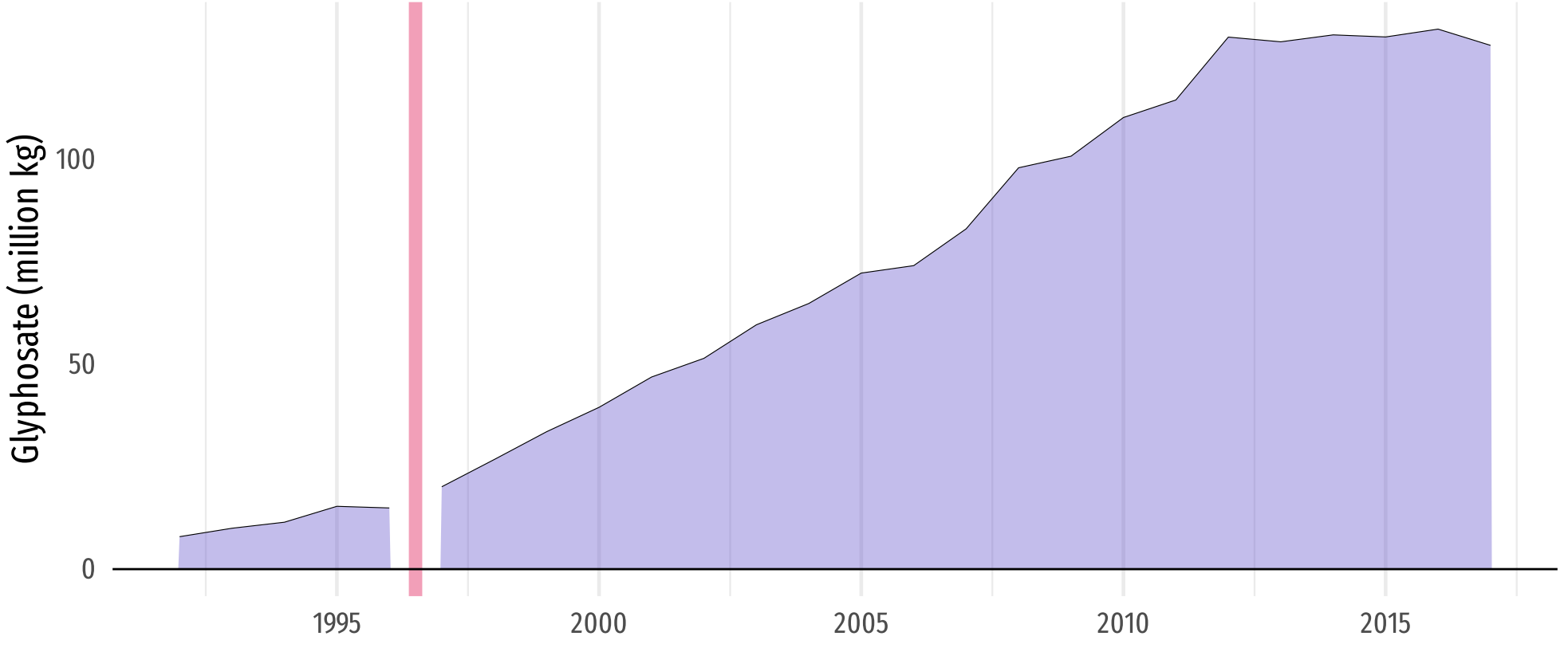
> My primary concern is with the glyphosate in terms of the potential for this work to **blow Roundup risk evaluations** (getting a **much higher dermal penetration than we've ever seen before**. [sic]

William Heydens, toxicologist, Monsanto

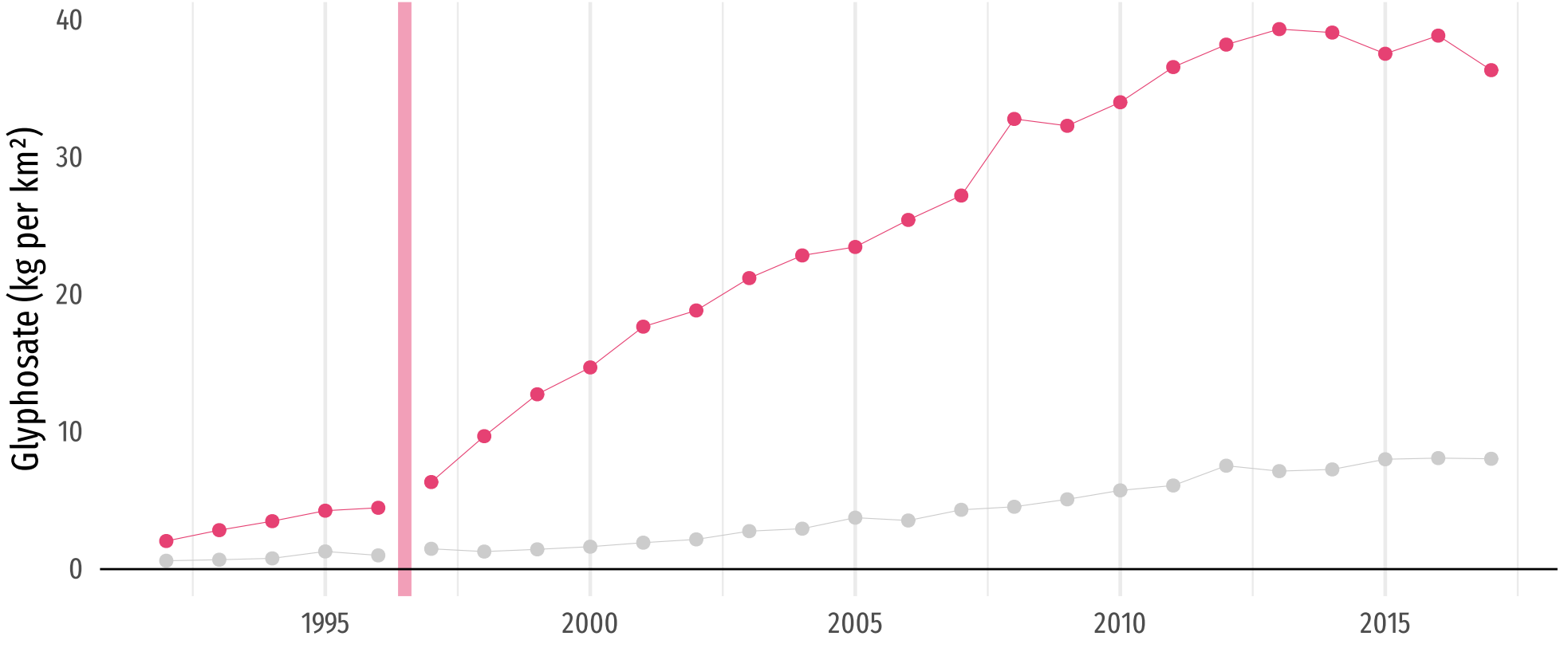
Glyphosate use since 1992

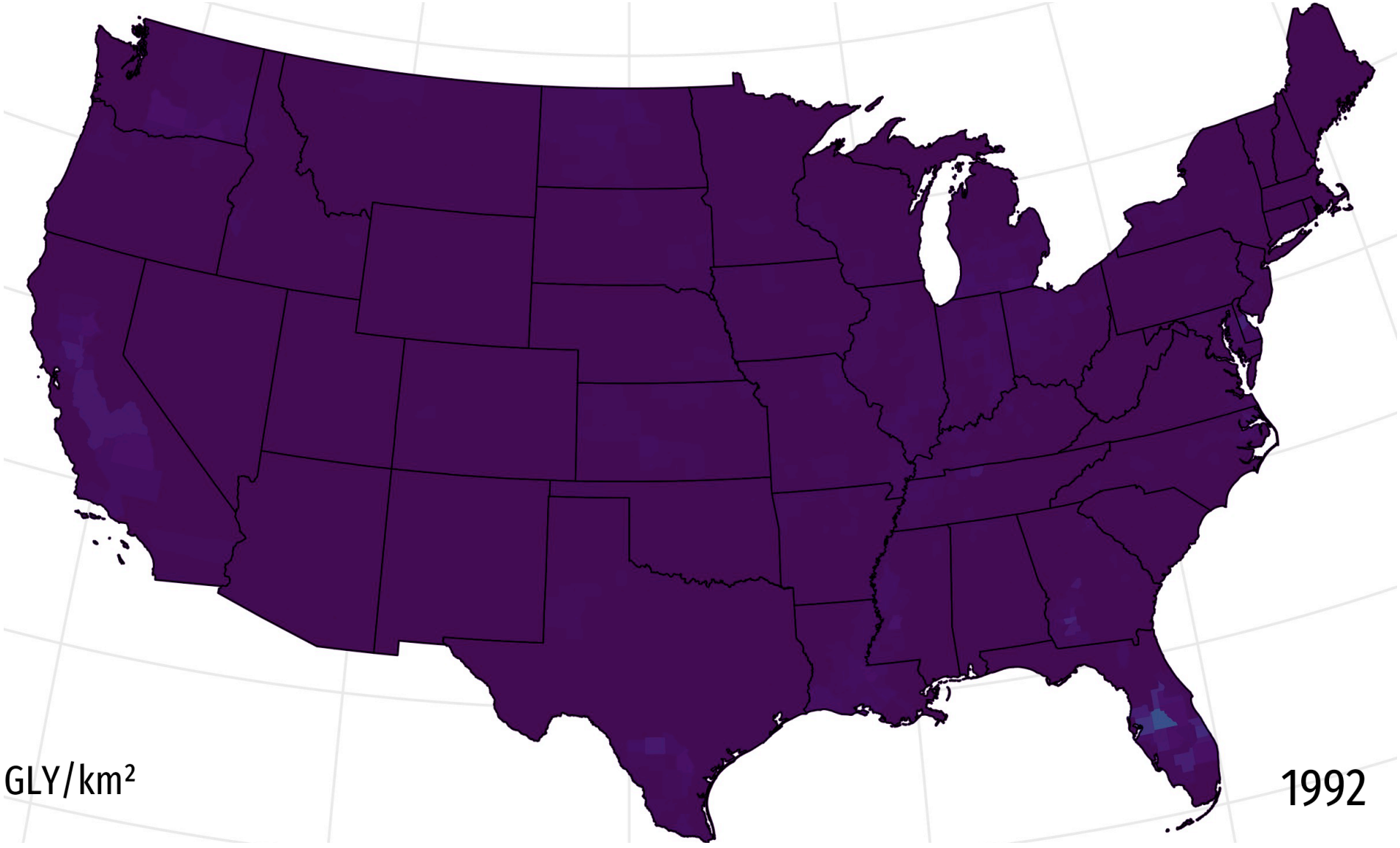
Source: USGS

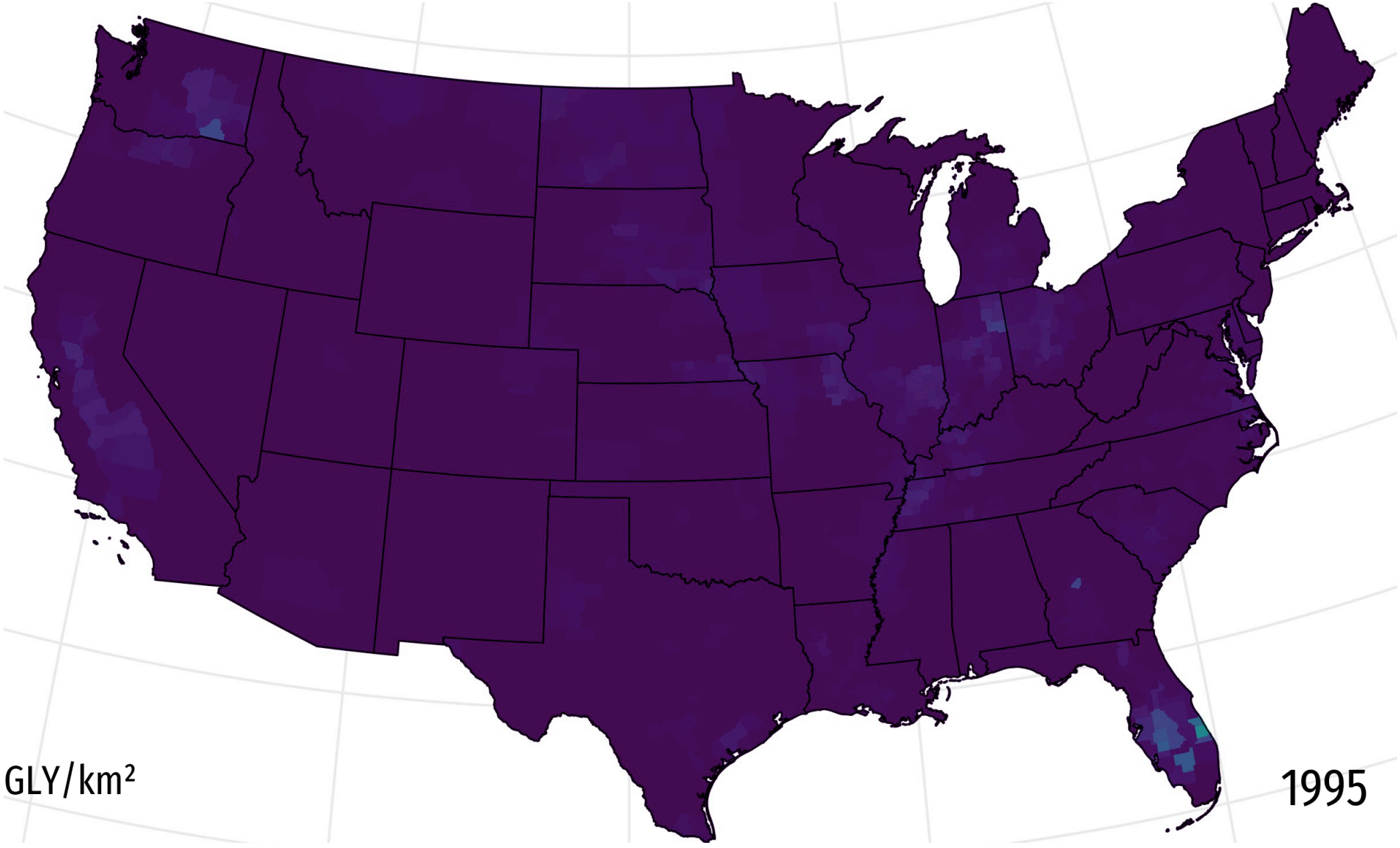


Glyphosate use since 1992: High *vs.* low suitability for GLY-tolerance for GMO crops (CSC)

Sources: USGS & FAO GAEZ




GLY/km²
1992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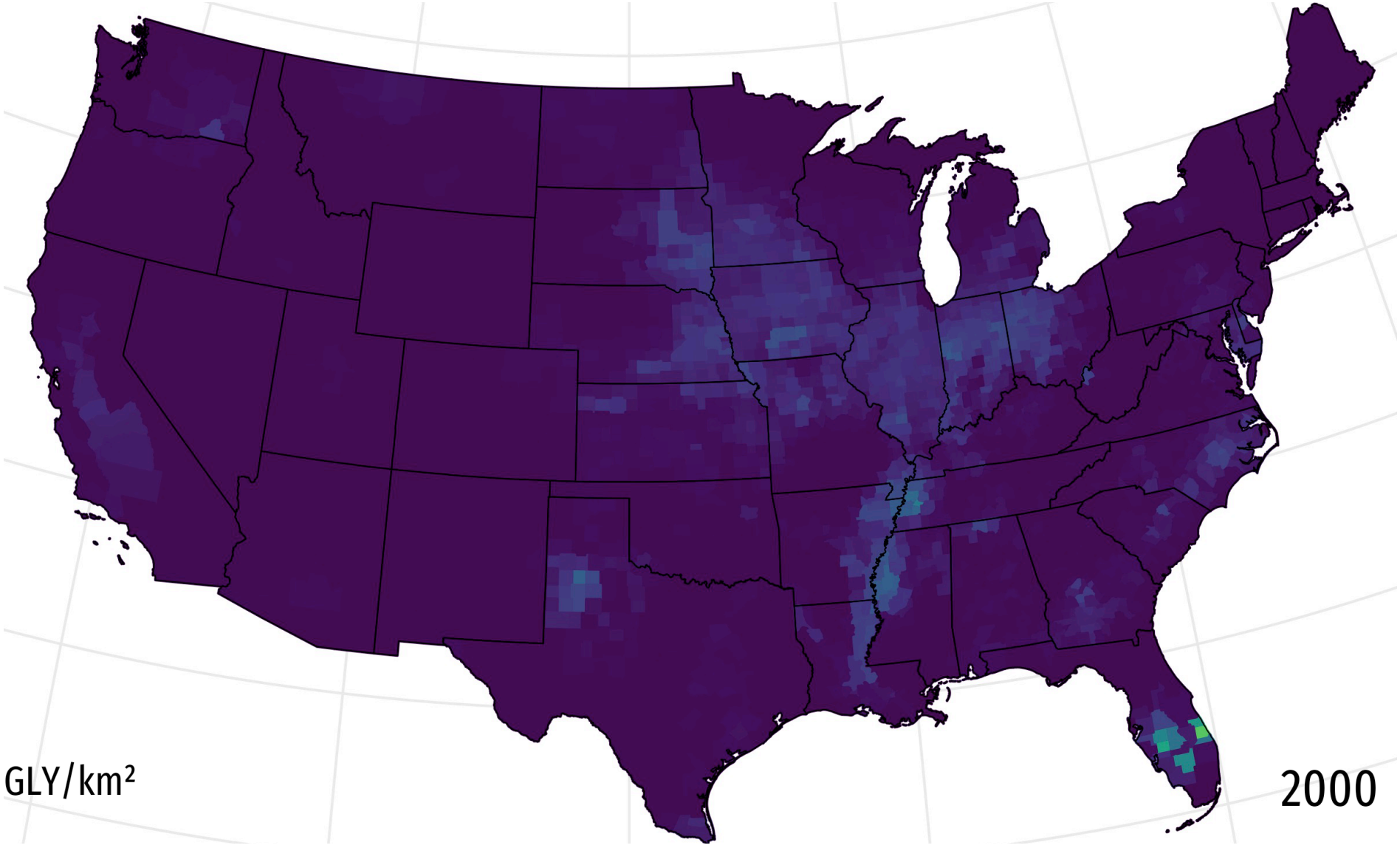
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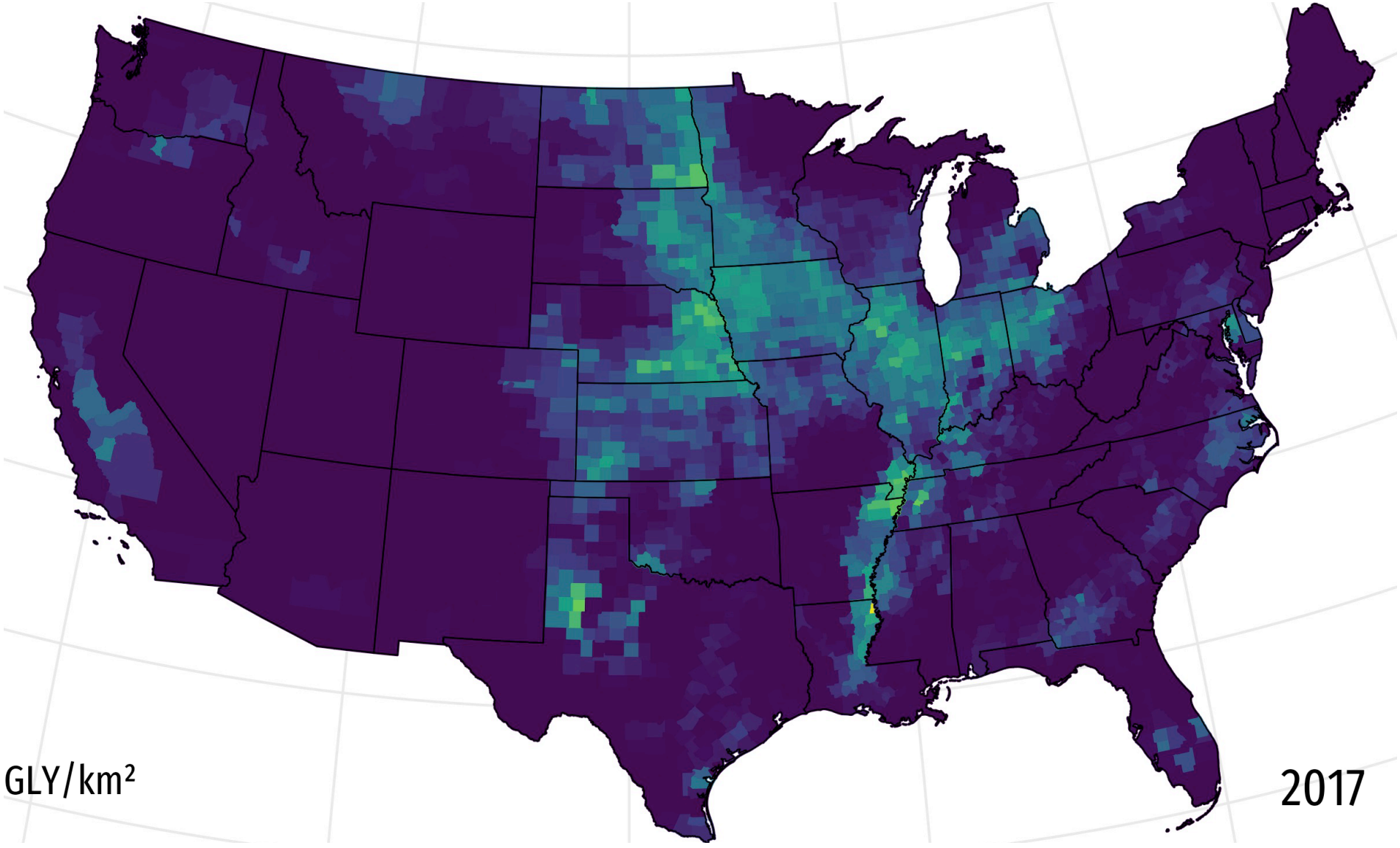
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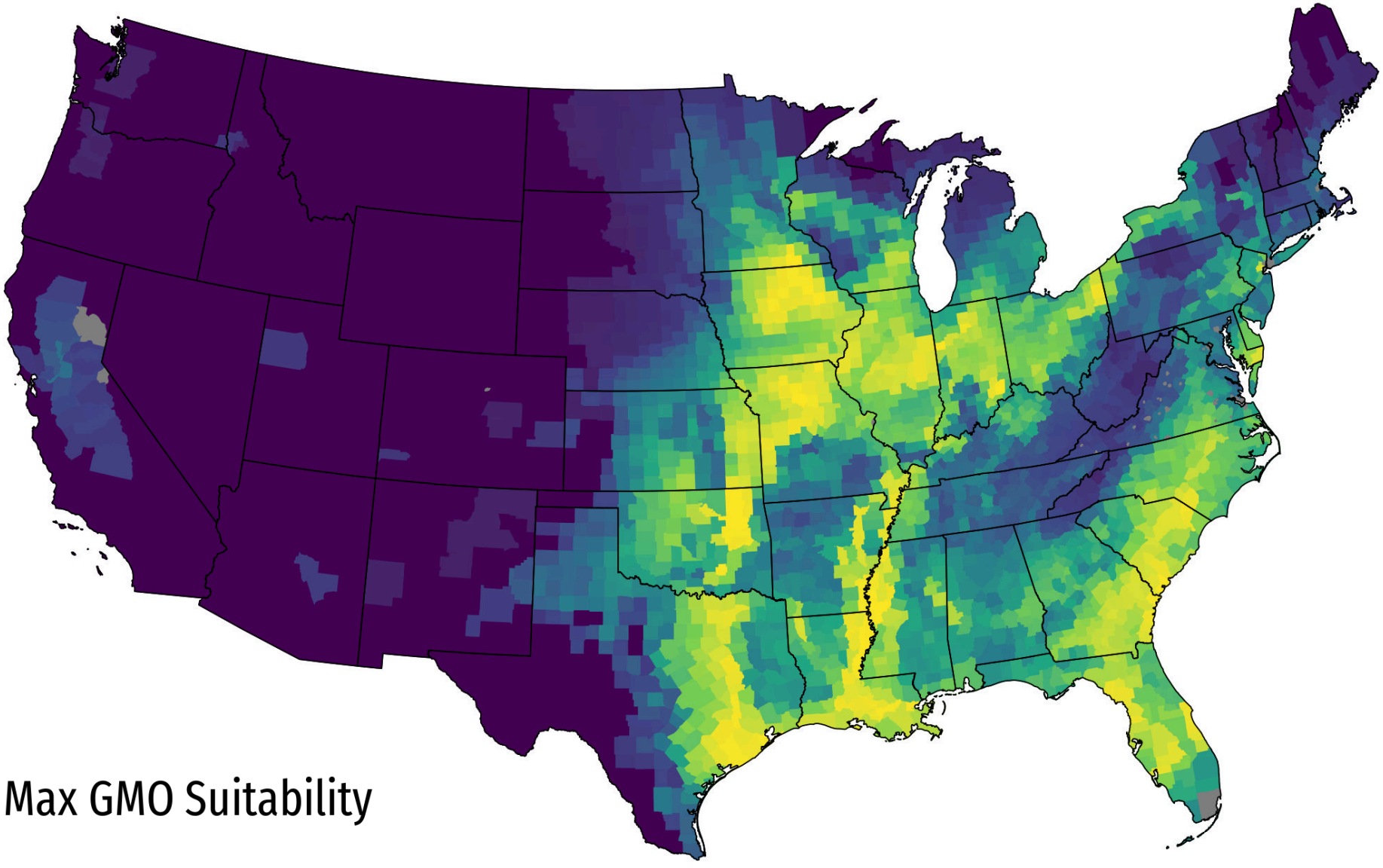
Max GMO Suitability

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$Solution_{2c}$ Re-interpret estimand: The "policy effect" of GLY net of other pesticides.

Data

CDC NCHS vital statistics

- Microdata for US births, 1990–2019, identified at county
- Weight, gestation, sex, parent demographics

USGS Pesticide National Synthesis Project

- County-level pesticide-use estimates (by chemical), 1992-2017
- *Also USGS:* HUC-12 watersheds and a handful of surface-water GLY/AMPA monitors

FAO GAEZ v4 Agro-Ecological Attainable Yield

- Estimated attainable yield by crop
- $= f($soil type, terrain slope class, water supply, inputs $)$

Others

US Census ▸ Intercensal population trends

USDA ▸ Yield and acreage (year $\times$ county $\times$ crop); rural designations

BEA + **BLS** ▸ Employment, income, + unemployment

Empirical strategy

Target equation

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Basic idea of instrument for $GLY_{c(i)t}$ Interact

- Indicator $t \geq 1996$
- County c's yield return to "high input" ag for corn, soy, and cotton (CSC).

$$\Delta\text{Input}_c = (\text{GAEZ yield} \mid \text{High inputs})_c - (\text{GAEZ yield} \mid \text{Low inputs})_c$$

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  - Absent GM, high/low ΔInput counties would have remained on similar trajectories
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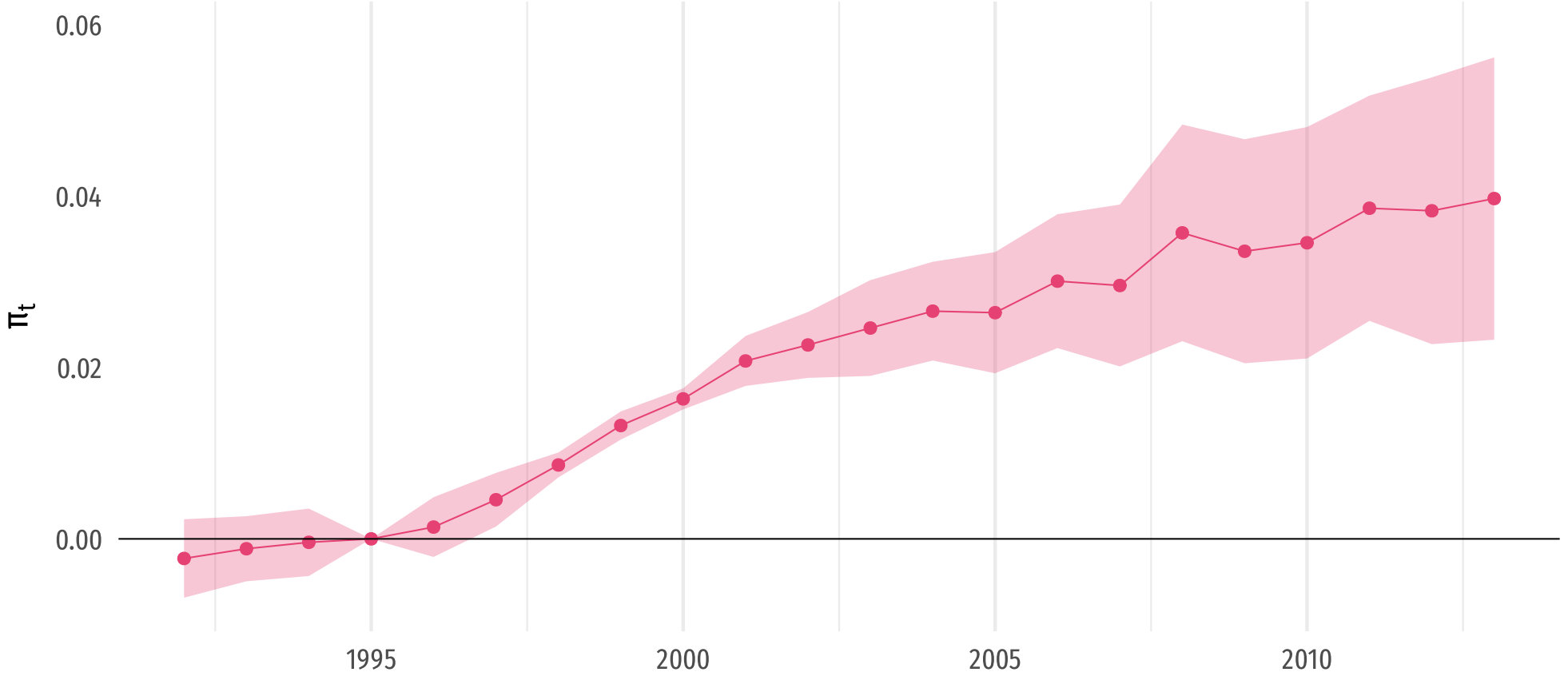
- *Monotonicity:* Higher (GAEZ) suitability weakly ↑ counties' GLY use after 1996. (Plausible.)

Visual first stage High yield returns from inputs predicts GLY adoption post-1996.

Event study $GLY_{c(i)t} = \pi_t\ (\text{GM Return})_{c(i)t} \cdot I(t) + \mu_{c(i)} + \delta_t + \omega_{ict}$



SEs cluster at state and year.

Visual first stage Suitability measure doesn't matter (max *vs.* avg).

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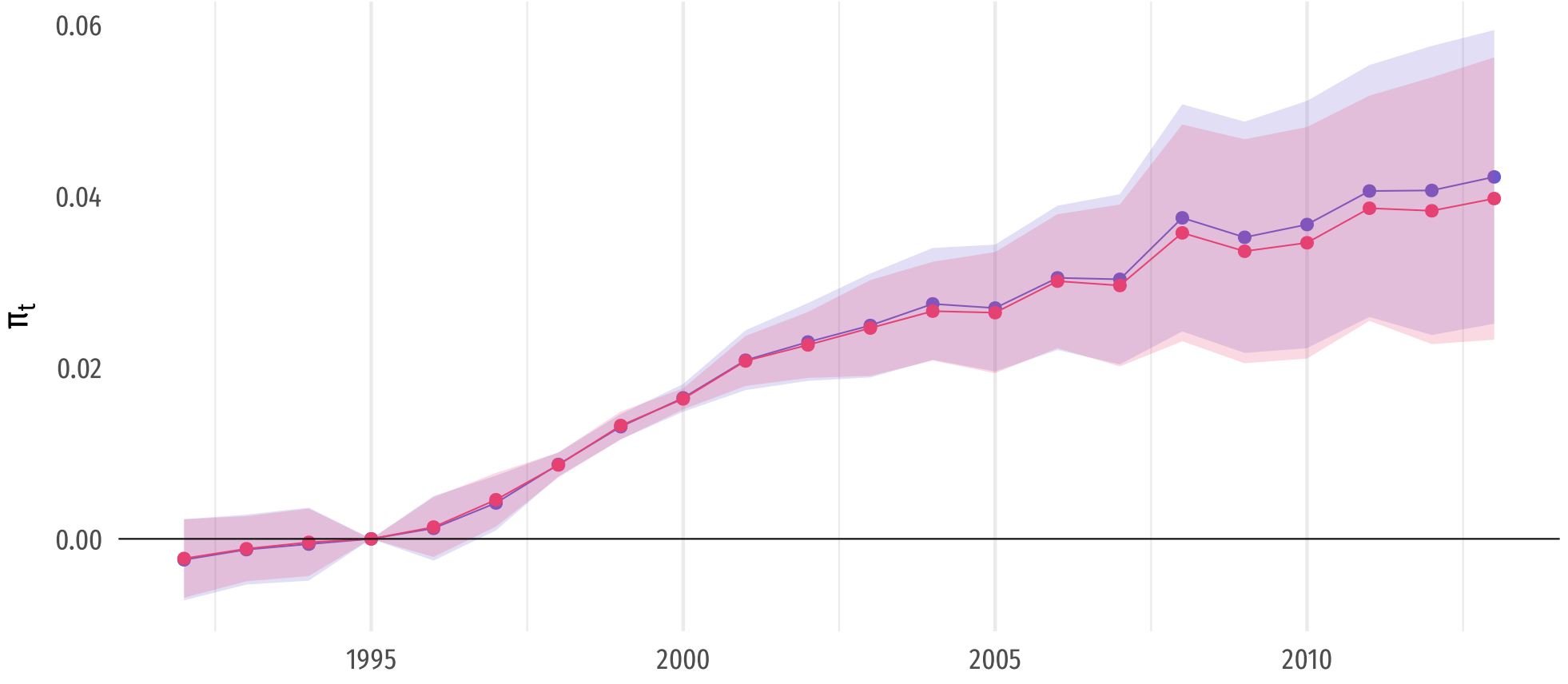

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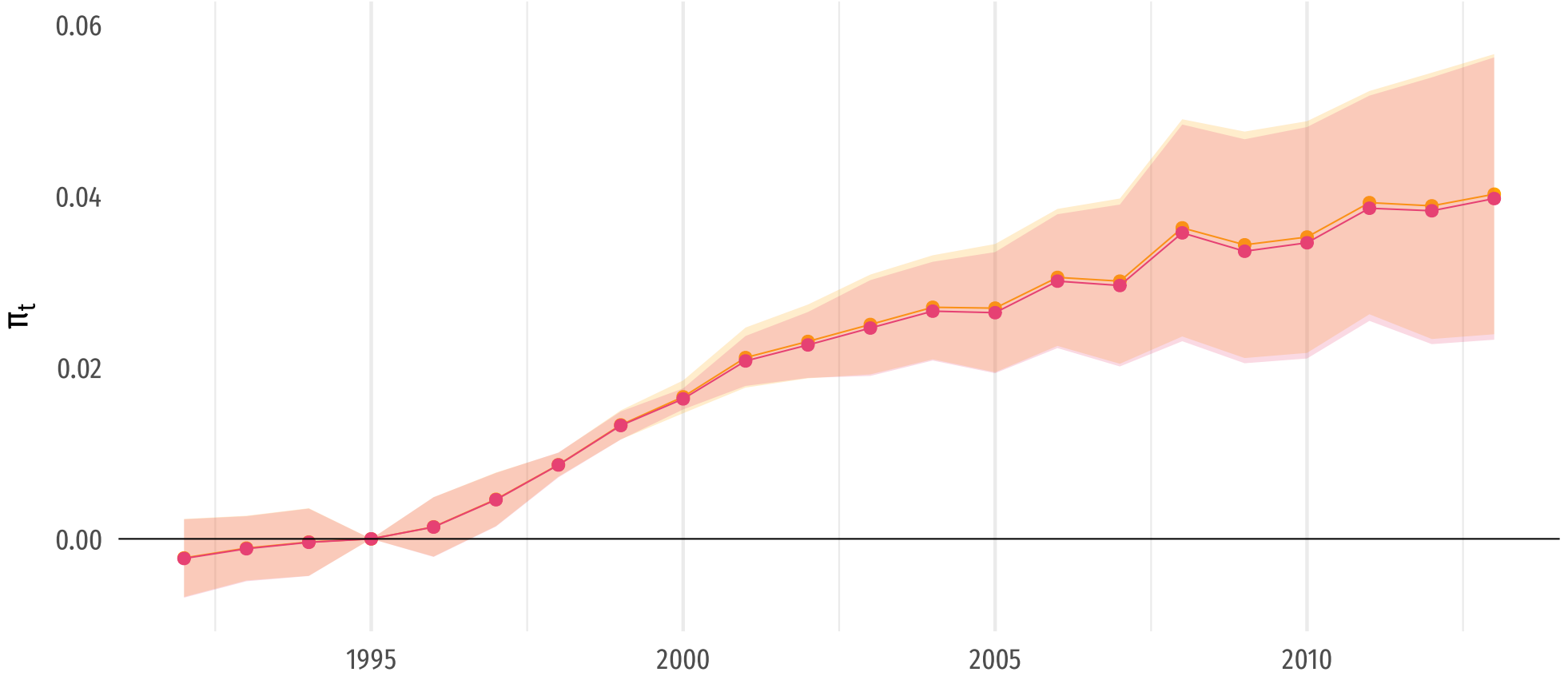

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Visual first stage Restricting to counties east of the 100th meridian tells the same story.

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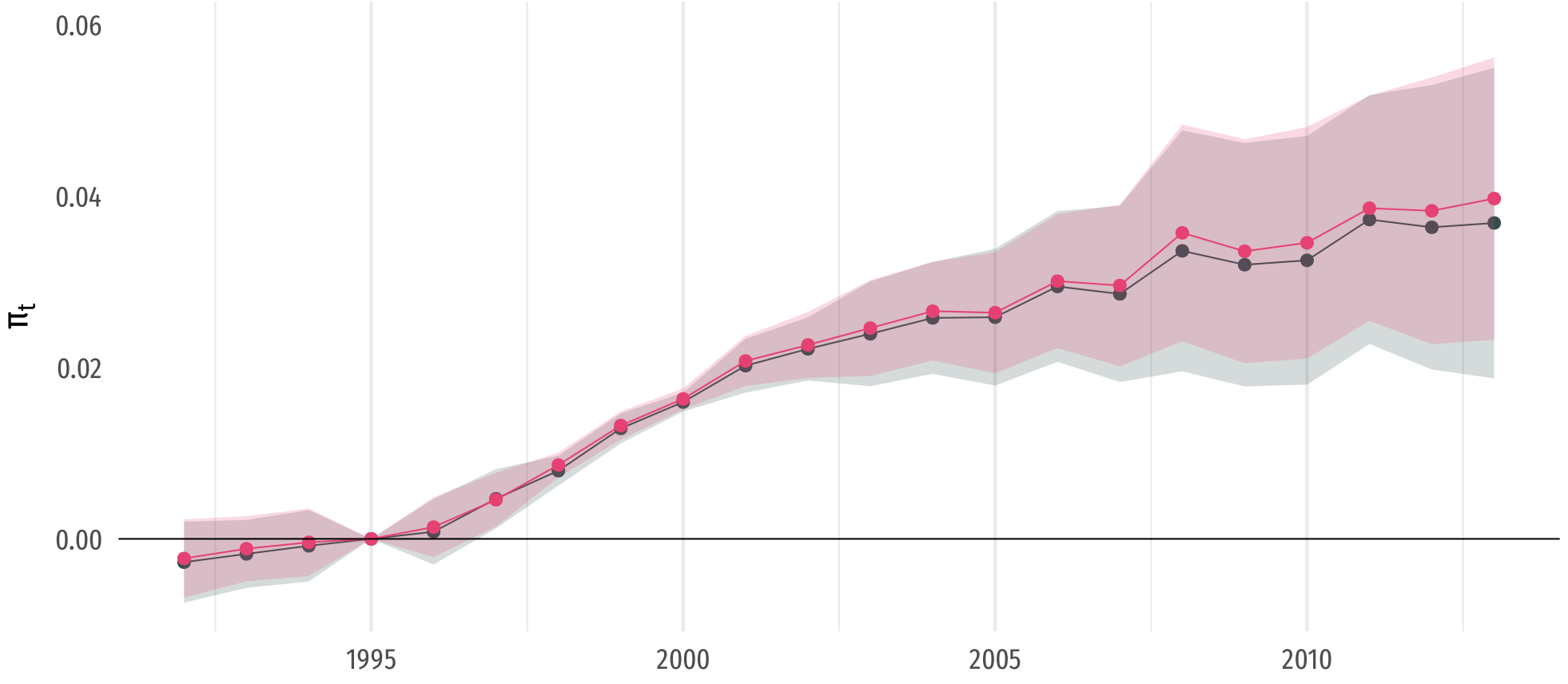
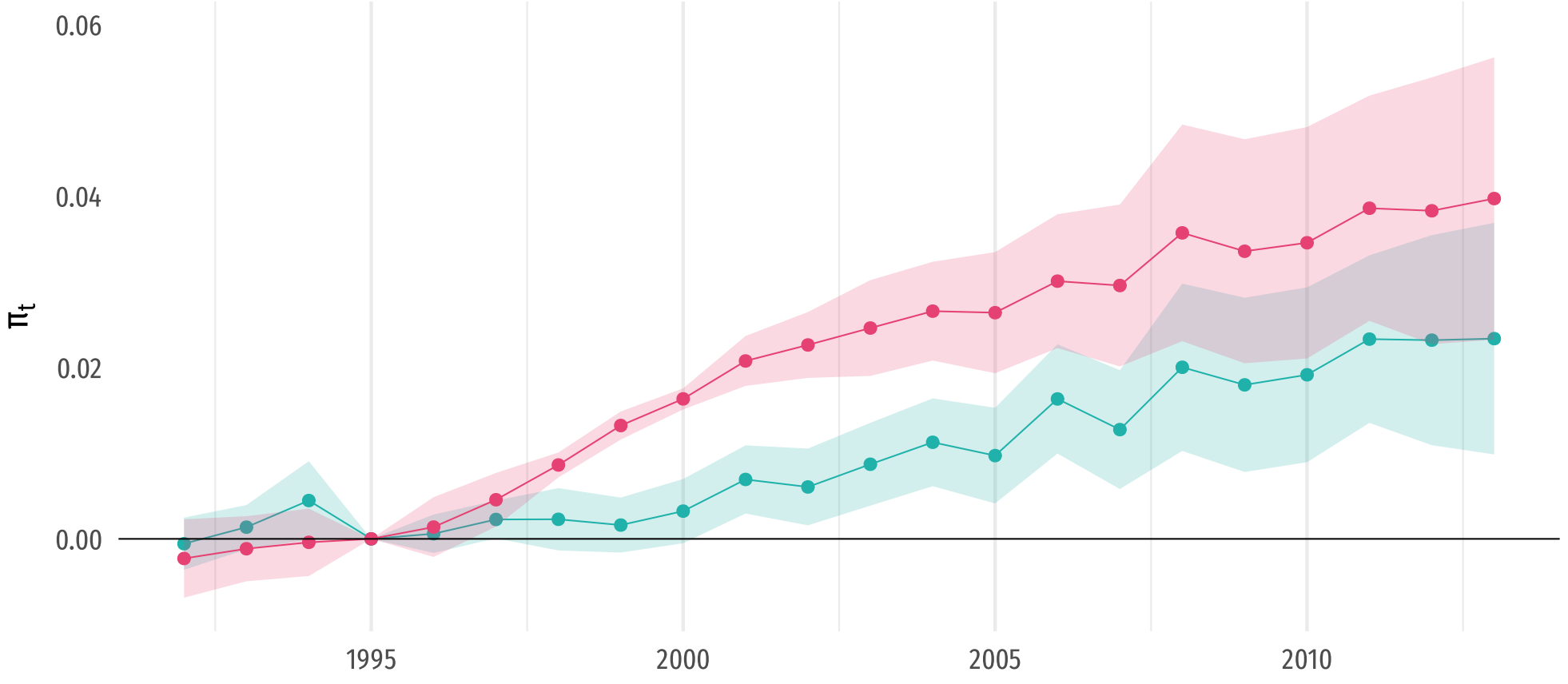


SEs cluster at state and year.

Visual first stage Controlling for non-GLY pesticides tells a similar—but attenuated—story.

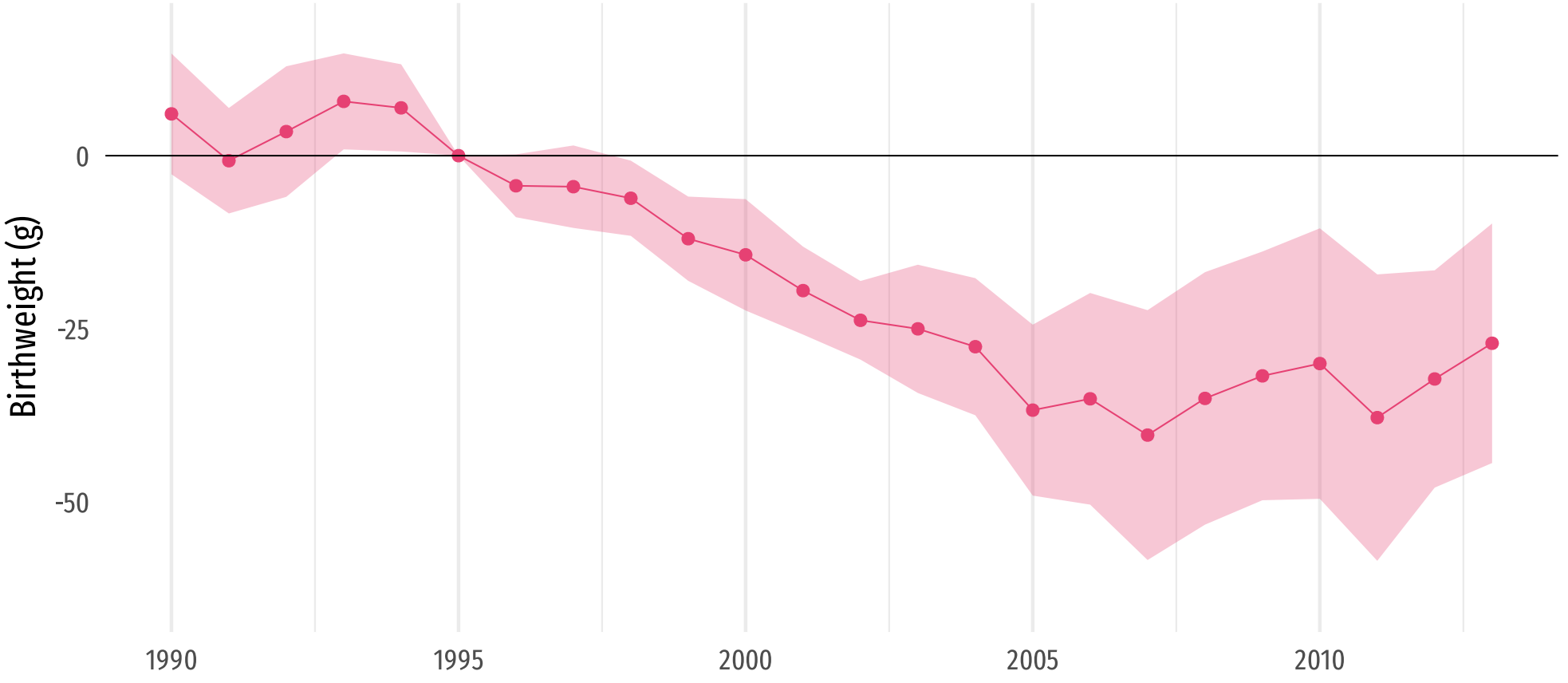
Event study $GLY_{c(i)t} = \pi_t (GM\ Return)_{c(i)t} \cdot I(t) + \mu_{c(i)} + \delta_t + \Lambda X_{ict} + \omega_{ict}$



SEs cluster at state and year.

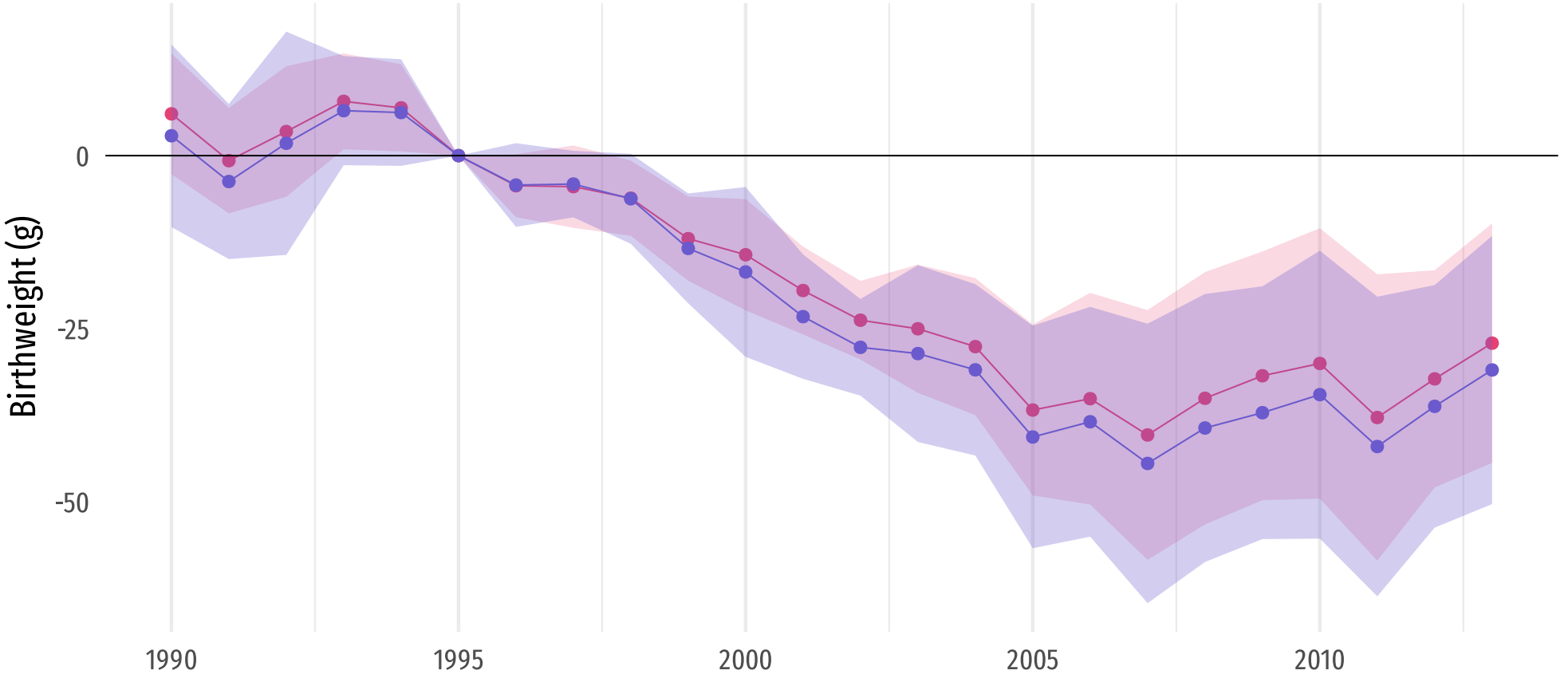
Reduced-form results

Reduced form $\text{Birthweight}_{c(i)t} = \gamma_t \, (\text{GM Return})_{c(i)t} \cdot I(t) + \mu_{c(i)} + \delta_t + \omega_{ict}$



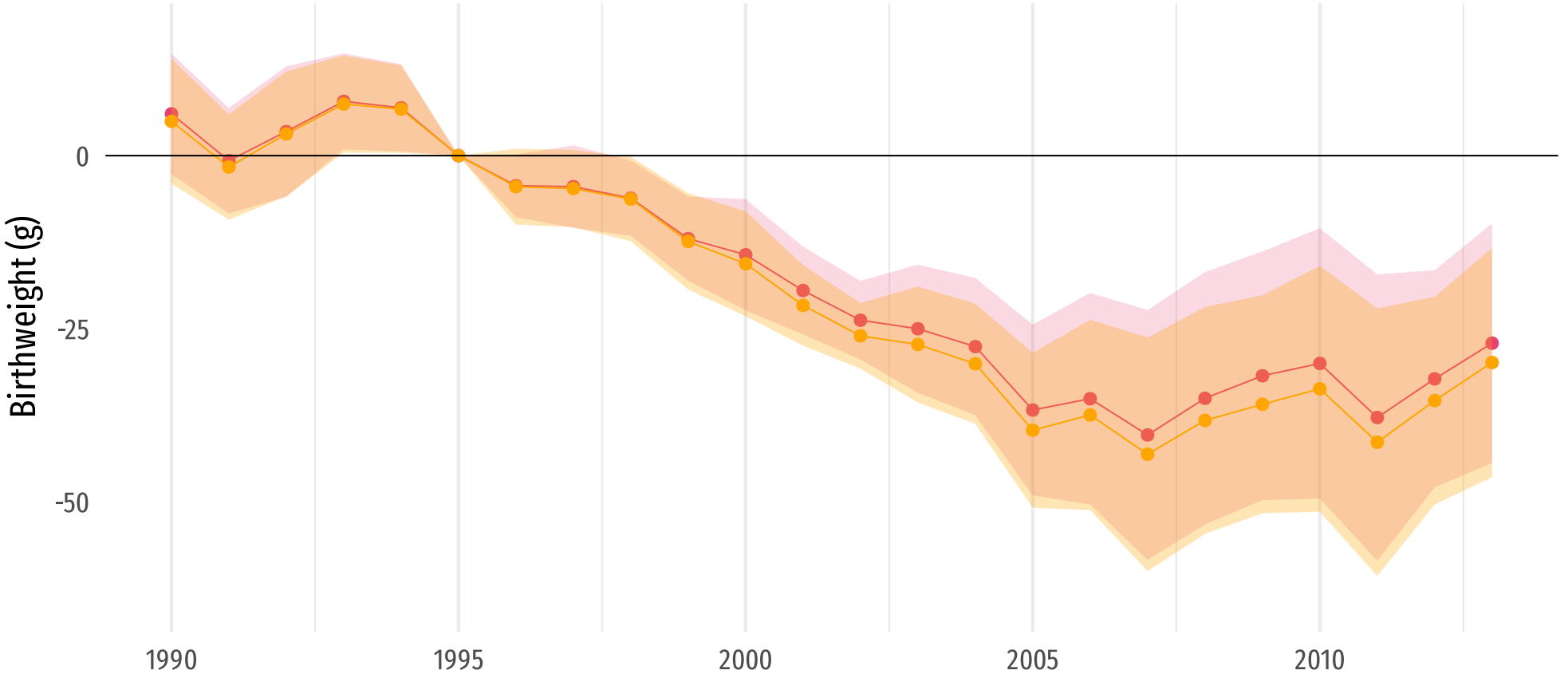
Rural US births. Year-month and county FEs.
SEs cluster at state and year.

Reduced form Birthweight, controlling for local pesticides, (un)employment, and income



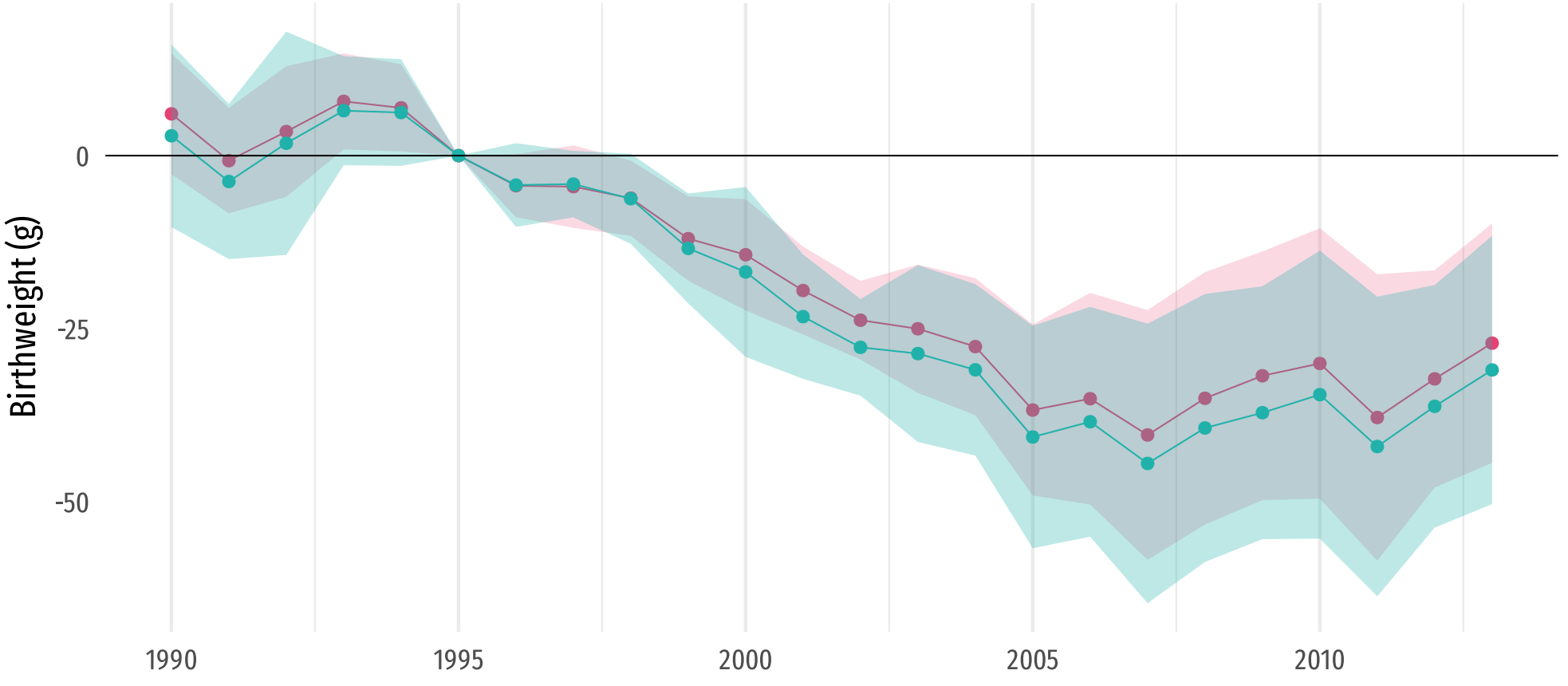
Rural US births. Year-month and county FEs. Controls for pesticides + (un)employment and income.
SEs cluster at state and year.

Reduced form Birthweight, controlling for demographics



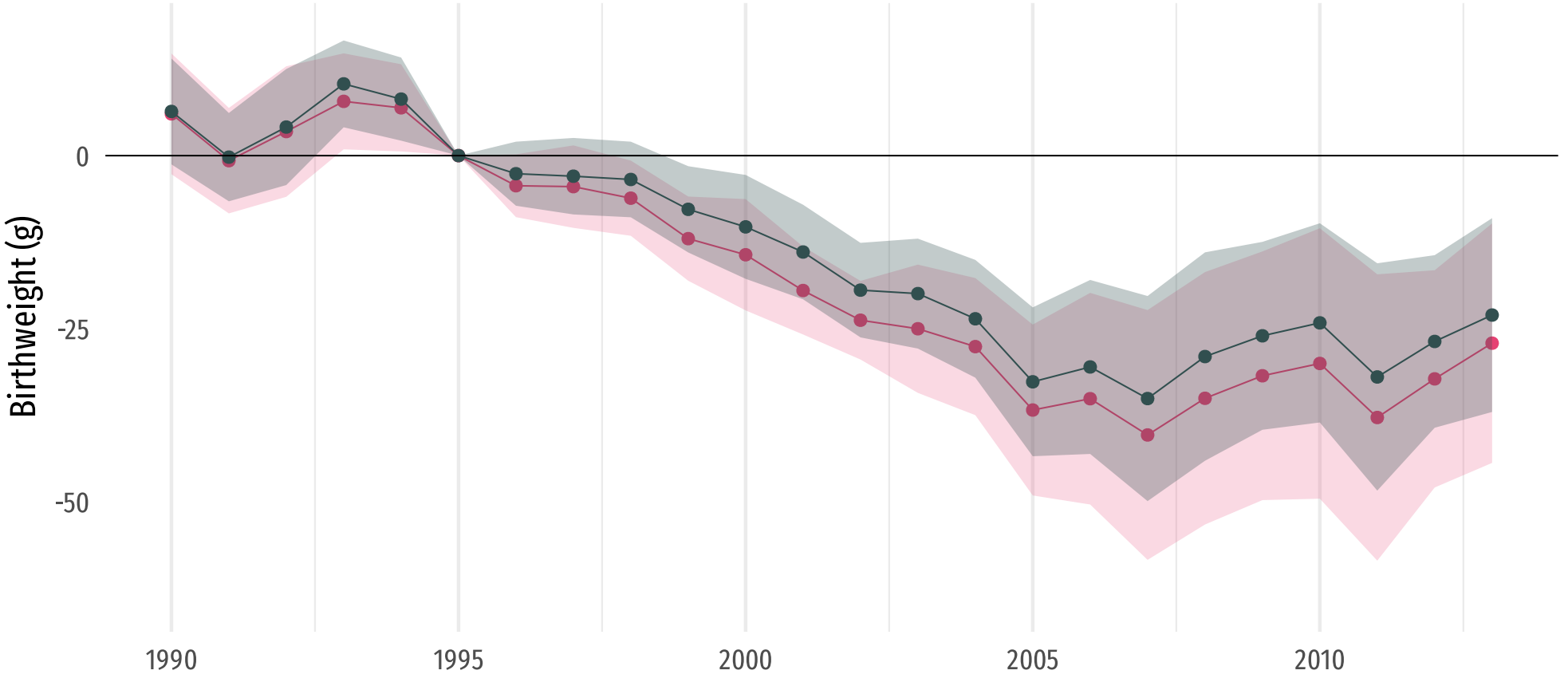
Rural US births. Year-month and county FEs. Controls for sex, birth facility, and parent demographics.
SEs cluster at state and year.

Reduced form Birthweight, all the controls



Rural US births. Year-month and county FEs. Controls for pesticides, (un)employment, income, sex, birth fac., + dem.
SEs cluster at state and year.

Reduced form Birthweight east of the 100th meridian (same controls).



Rural US births. Year-month and county FEs. Controls for pesticides, (un)employment, income, sex, birth fac., + dem.
SEs cluster at state and year.

2SLS Results The effect of GLY on birthweight

Instrumented with mean GM return

	1	2	3	4	5
GLY/km^2	−1,086.4	−1,643.2	−943.0	−1,277.0	−1,363.2
	(208.8)	(405.2)	(216.7)	(640.7)	(486.9)
Controls					
Local pesticides		×		×	×
Employment		×		×	×
Family demog.			×	×	×
Fixed effects					
Yr × Mo + Cnty	×	×	×	×	×
Sample	US	US	US	US	East
N (millions)	11.91	11.90	9.03	9.02	6.99
Implied effect at mean (g)	−27.9	−42.2	−24.2	-32.0	−35.0

In rural counties in 2012, avg. DBWT was 3,309 g and avg. GLY/km^2 0.0257 1,000 kg/km^2 (95th pctl: 0.098).

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2SLS Results The effect of GLY on several outcomes

Instrumented with mean GM return

	1 *BW (g)*	2 *BW Pctl.*	3 *P(Low BW)*	4 *P(V. Low BW)*	5 *Gest (w)*	6 *P(Preterm)*	7 *P(C-section)*
GLY/km^2	-1,376.2	-0.698	0.330	0.075	-9.46	0.963	0.474
	(640.7)	(0.322)	(0.148)	(0.033)	(3.42)	(0.442)	(0.344)
Controls							
Local pesticides	×	×	×	×	×	×	×
Unemployment	×	×	×	×	×	×	×
Family demog.	×	×	×	×	×	×	×
Fixed effects							
Yr × Mo + Cnty	×	×	×	×	×	×	×
Sample	US	US	US	US	US	US	US
Mean in 2012	3,309	0.50	0.081	0.014	38.6	0.207	0.278
Effect at mean	-32.0	-0.016	0.008	0.002	-0.220	0.022	0.011

2SLS Results The effect of GLY on several outcomes

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Question *Who* loses here?

Are lower-weight births losing more?

Relates to Gerona et al., 2022

Should we be concerned for equity?

Idea Predict infants' counterfactual birthweights w. exogenous/observable data.

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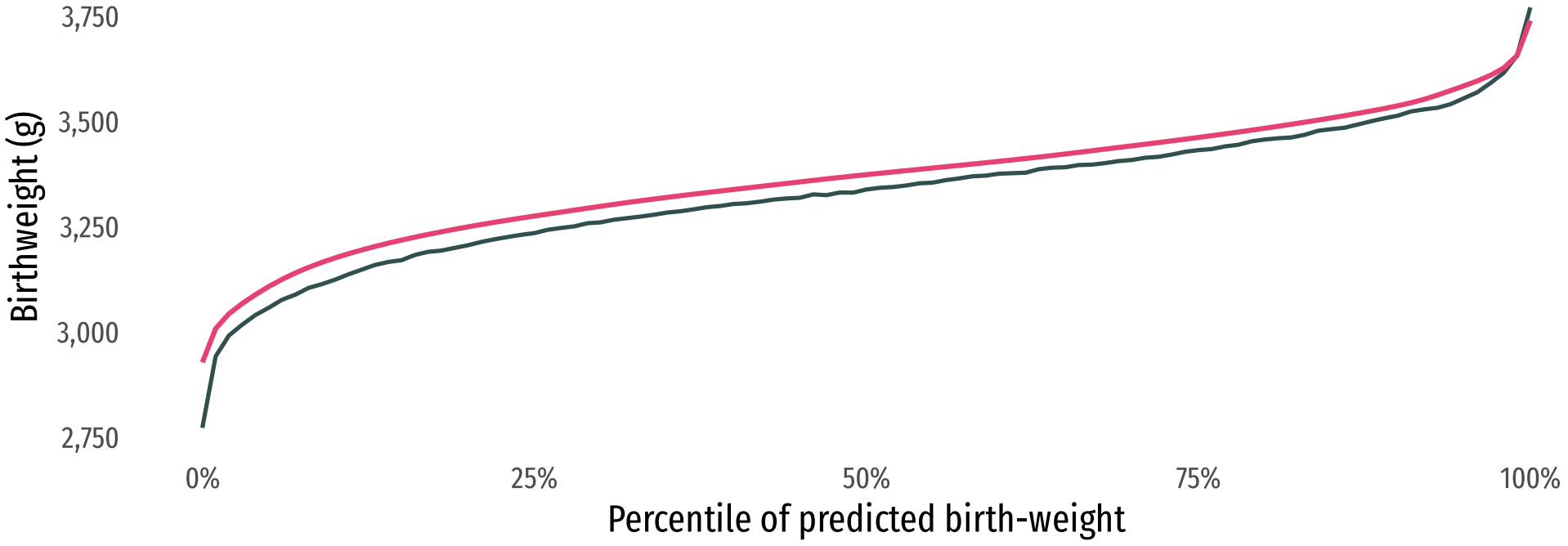

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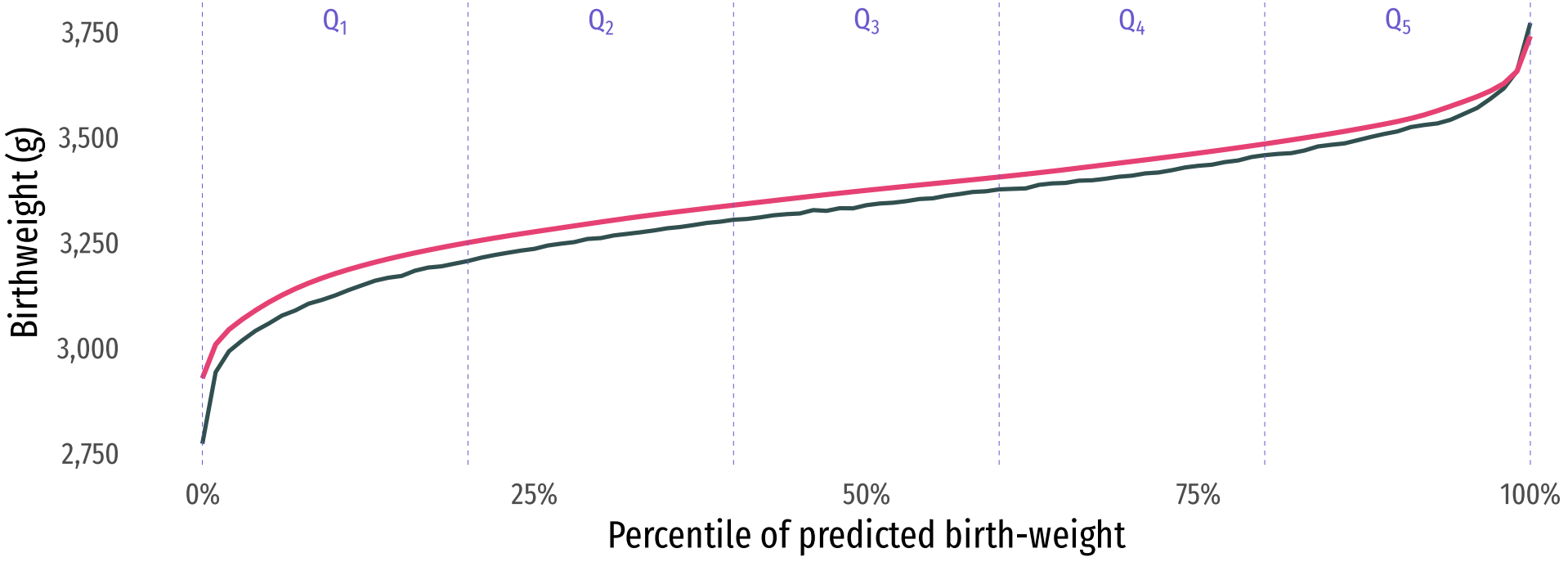

2SLS Results The effect of GLY on birthweight by predicted birth-weight quintile

Instrumented with mean GM return.

	Full sample	Q_1	Q_2	Q_3	Q_4	Q_5
GLY/km^2	-1,376.2	−4,450.7	−2,089.8	−937.9	−662.0	−59.7
	(640.7)	(941.0)	(394.7)	(248.6)	(211.5)	(198.3)
Controls						
Local pesticides	×	×	×	×	×	×
Unemployment	×	×	×	×	×	×
Family demog.	×	×	×	×	×	×
Fixed effects						
Yr × Mo + Cnty	×	×	×	×	×	×
N (millions)	9.01	1.24	1.73	1.88	2.02	2.14
Implied effect at mean (g)	-32.0	−114.4	−53.7	−24.1	−17.0	−1.5
2012 birthweight mean (g)	3,309	3,114	3,245	3,314	3,379	3,496

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N (millions)	9.01	1.24	1.73	1.88	2.02	2.14
Implied effect at mean (g)	-32.0	−114.4	−53.7	−24.1	−17.0	−1.5
2012 birthweight mean (g)	3,309	3,114	3,245	3,314	3,379	3,496

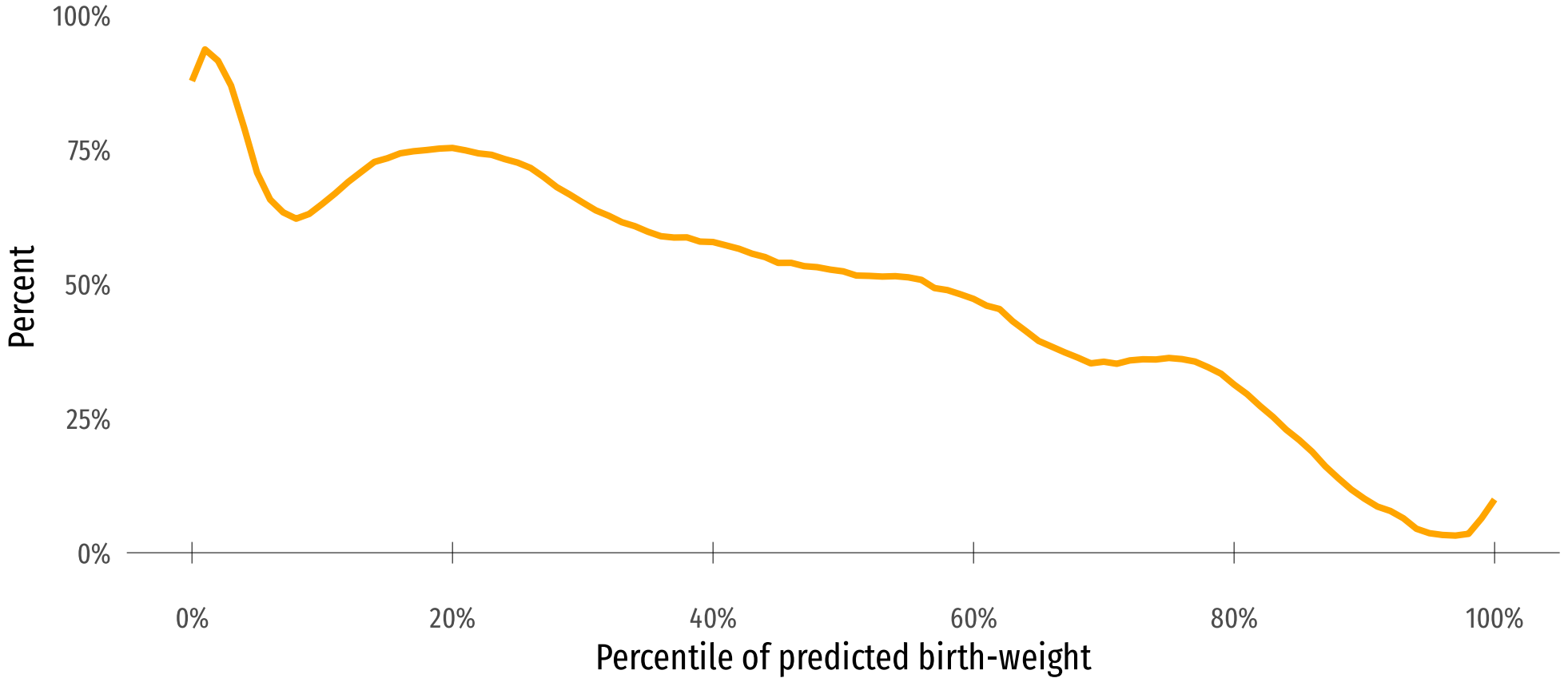
2SLS Results The effect of GLY on gestation by predicted birth-weight quintile

Instrumented with mean GM return.

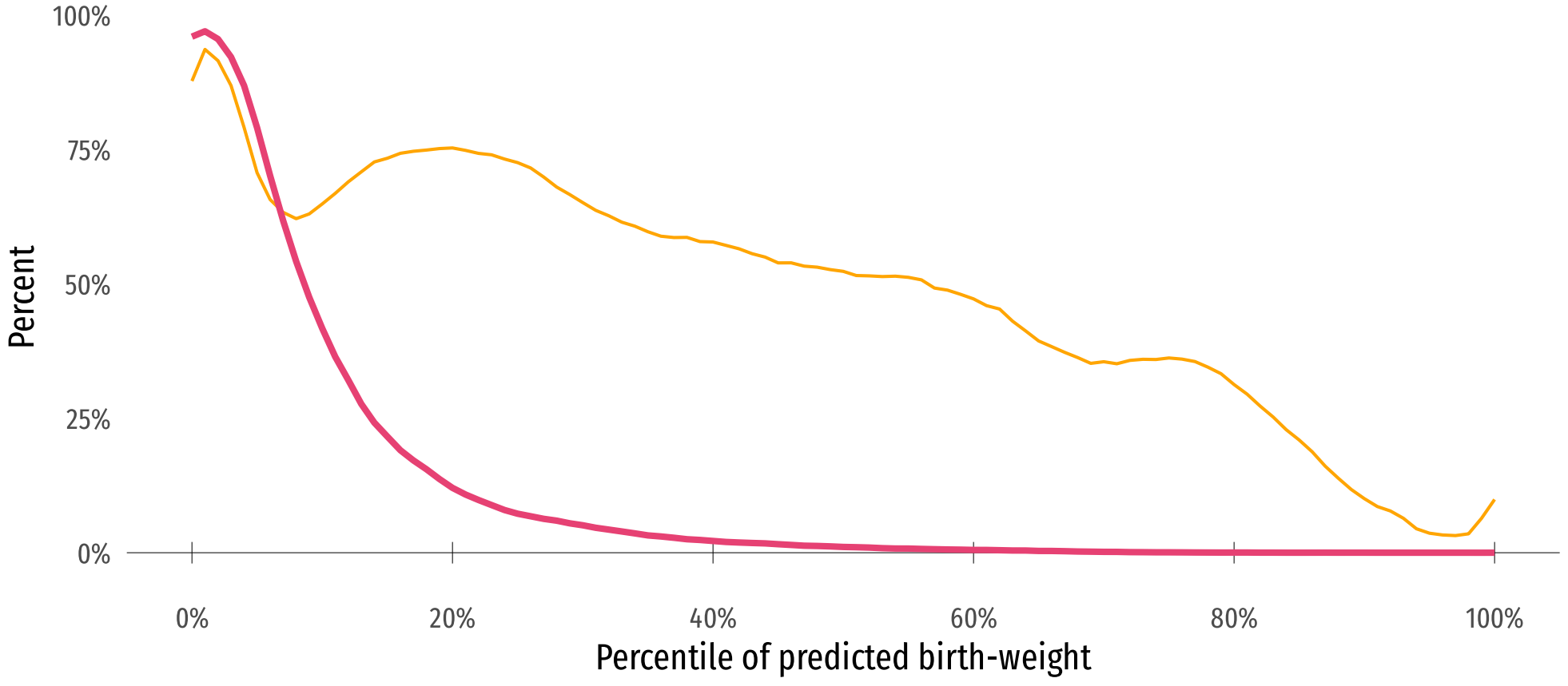
	Full sample	Q_1	Q_2	Q_3	Q_4	Q_5
GLY/km^2	-9.46	−12.98	−9.44	−7.64	−6.46	−4.29
	(3.42)	(2.72)	(1.43)	(1.19)	(1.11)	(0.97)
Controls						
Local pesticides	×	×	×	×	×	×
Unemployment	×	×	×	×	×	×
Family demog.	×	×	×	×	×	×
Fixed effects						
Yr × Mo + Cnty	×	×	×	×	×	×
N (millions)	8.99	1.24	1.73	1.88	2.02	2.14
Implied effect at mean (d)	−1.32	−2.32	−1.70	−1.37	−1.16	−0.77
2012 gestation mean (d)	271.6	270.0	272.2	272.6	272.4	272.5

Who are these predicted low-weight births?

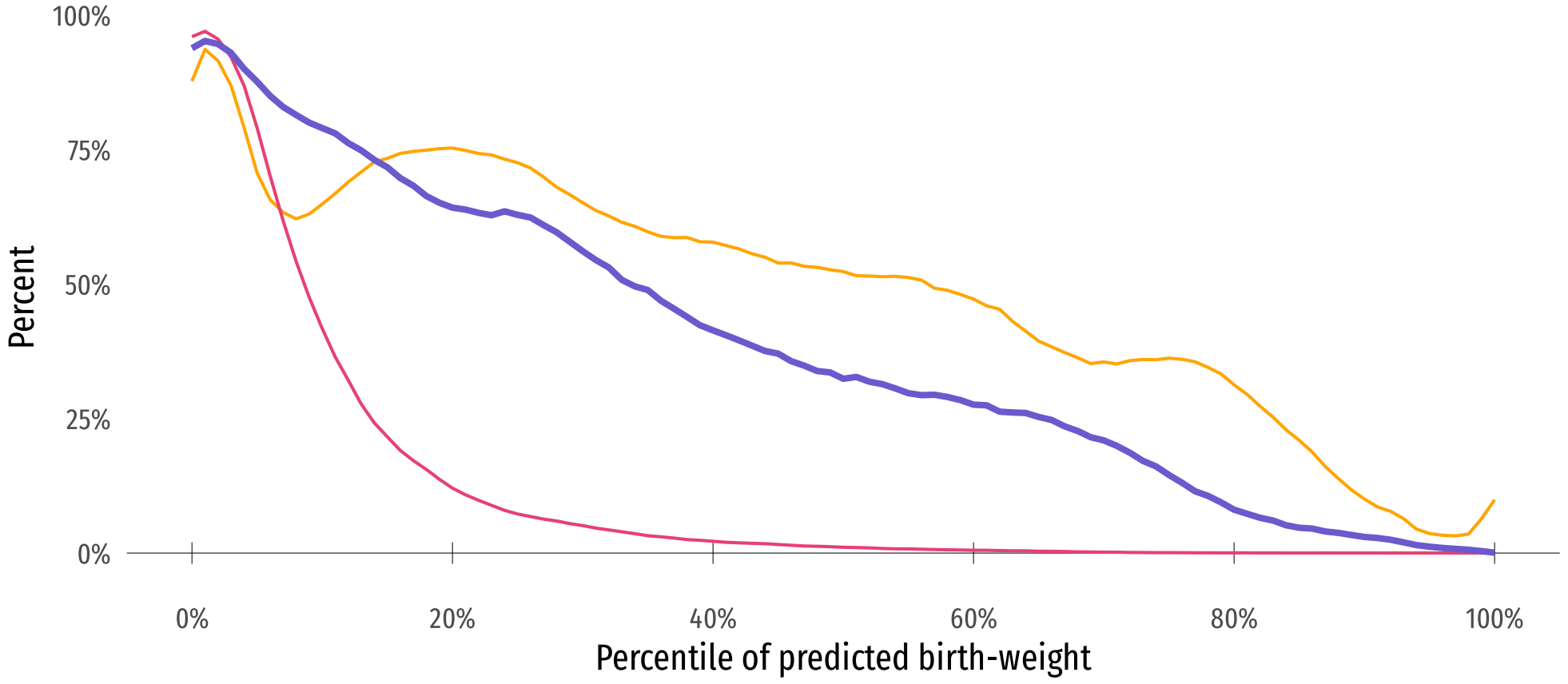
Predicted lower-weight births are more likely female



Predicted lower-weight births are more likely female and/or Black



Predicted lower-weight births are more likely female and/or Black with **unmarried** parents.



Estimated effects

Context and exposure

Presented effects represent ***mean* GLY exposure**.

- $\approx$ BWT effect of Food Stamp Program access (Almond, Hoynes, Schanzenbach; 2011)
- $> 2\times$ BWT effect stnd. dev. increase in late-term CO (Currie, Neidell, Schmieder; 2009)
- $\Delta\mathrm{P}(\mathrm{LBW})$ and $\Delta\mathrm{P}(\mathrm{Preterm}) \approx$ exp. to leaking petro. tanks (Marcus; 2021)

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Effects at the ***90th percentile* of GLY exposure** are $\sim$ 3 times larger:

- BWT loss 62–95 g;
- P(LBW) increases 1–2 pp;
- P(Preterm) increases 4–7 pp.

↳ $\Delta\mathrm{P}(\mathrm{LBW}) \approx$ living < 1 km of a fracking site (Currie, Greenstone, and Meckel, 2017).

Summary

Main findings

Significant evidence that the increase in **GLY exposure** following GM-seed rollout

- **reduced birthweights** and **gestation length**
- yielded an **unequal health burden**

Results account for **27–45% of the BWT decline** in rural counties since 1995.

Rollout of GLY-resistant GM tech drove these changes.

Outstanding questions

Outstanding questions for future work.

Mechanisms?

- What is the mechanism? Water? Dust? Occupation?
- *Water* No evidence of water-based exposure as in Dias, Rocha, and Soares.

Other effects?

- Are there outcomes in adults—cancer or otherwise?
- *Related* Are effects in adults from in-utero or adult exposure?

In the works: Resolving measurement issues and extending to other outcomes.[†]

† Definitely open to ideas and collaboration.

Policy implications

1. GLY: Adverse and unequal **effects for birthweight**.
2. Raises questions about **current regulation**.

> *"No risks of concern to human health from current uses of glyphosate."*
> –US EPA

- Most **water utilities** do not treat for GLY.
- Monsanto registered GLY as an antibiotic and anti-parasite **human treatment**.

3. *Related:* **Who** is steering regulation?

> EPA *"relied mostly on registrant-commissioned, unpublished regulatory studies."*
> –Benbrook (2019) comparing IACR and US EPA reports.

4. Likely need to **revisit** our GM-GLY beliefs/investment—yield, income, health, ecology.

↳ We need better **data** on pesticide exposure and human/ecological health outcomes.

Thank you!

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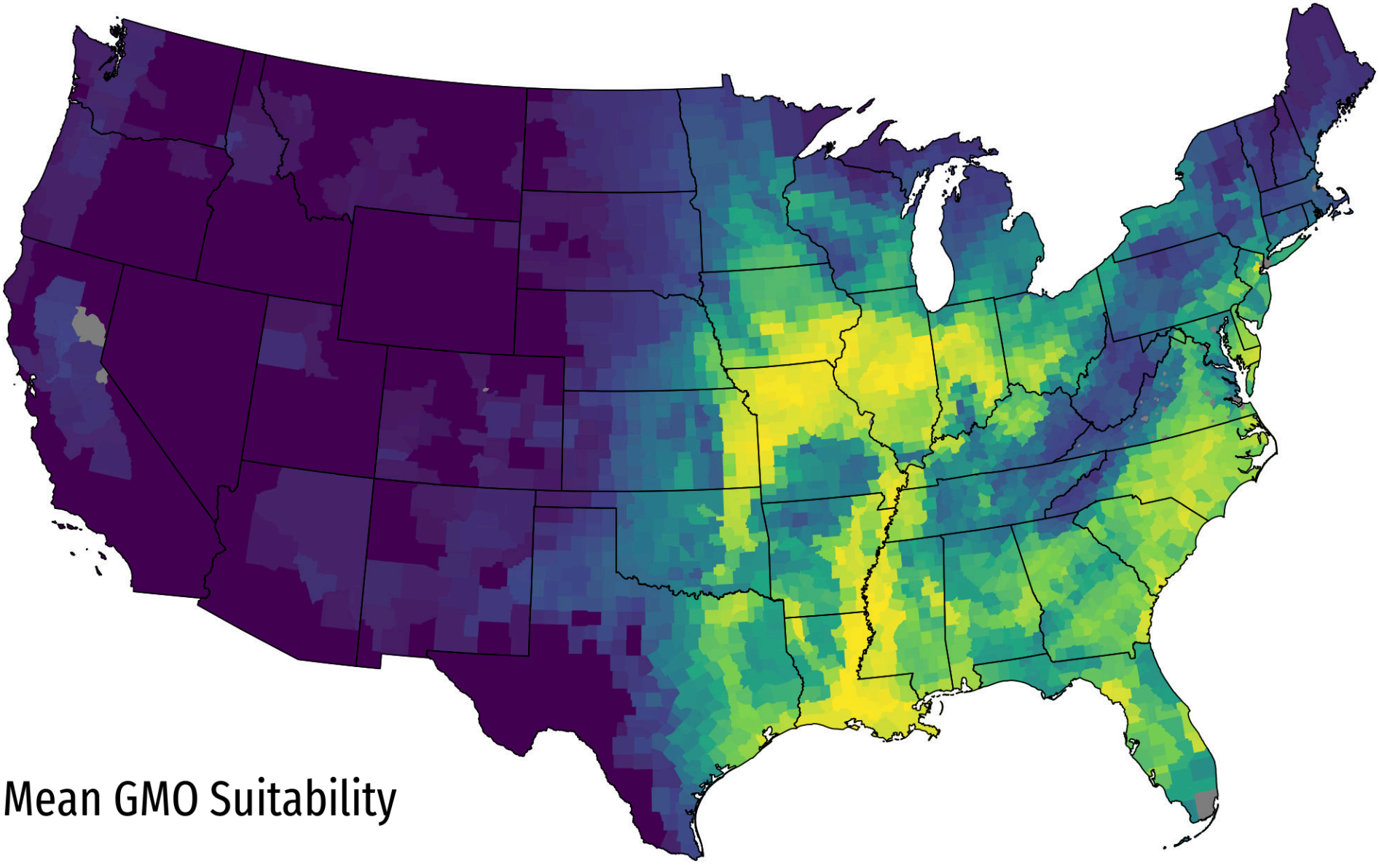
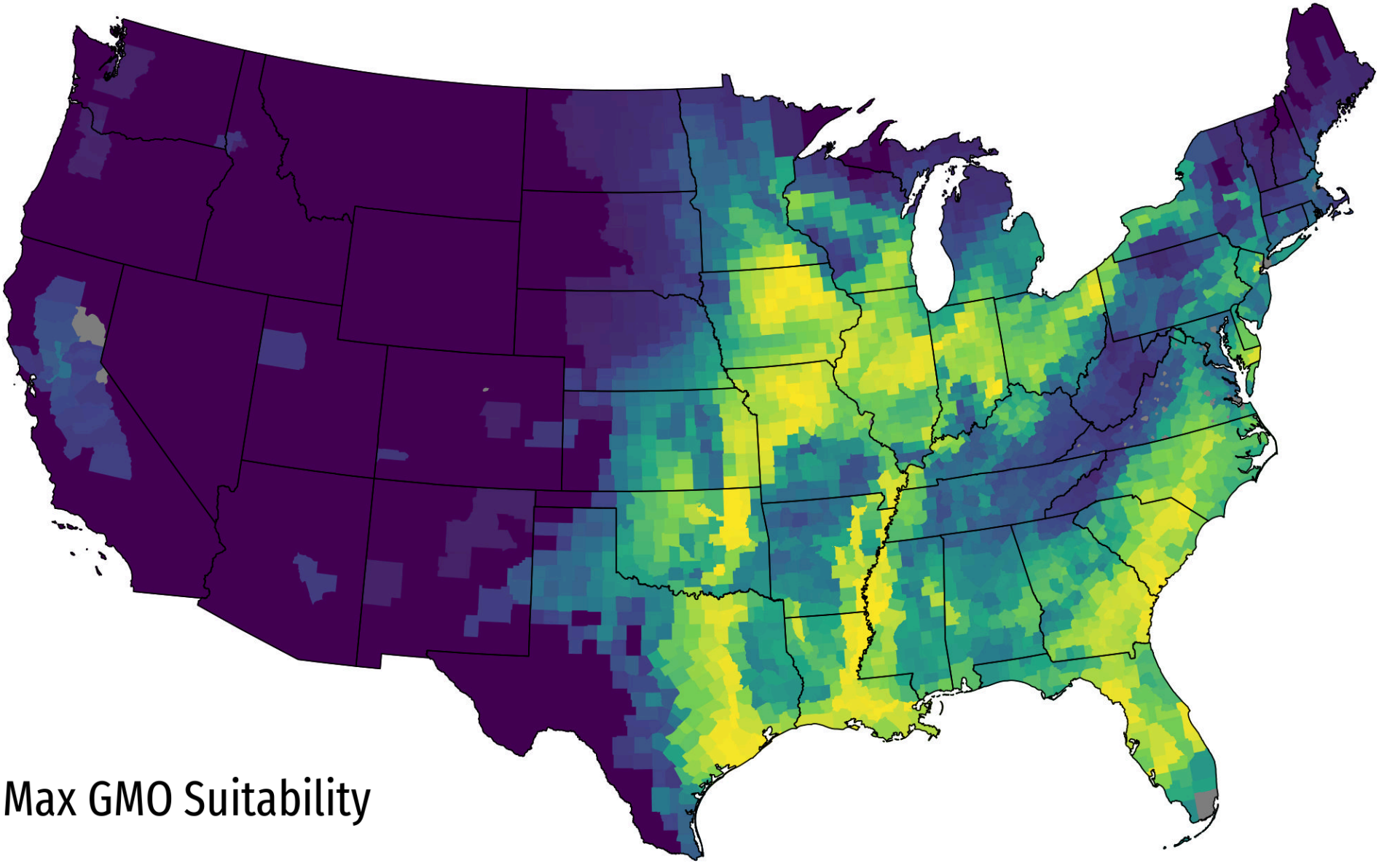
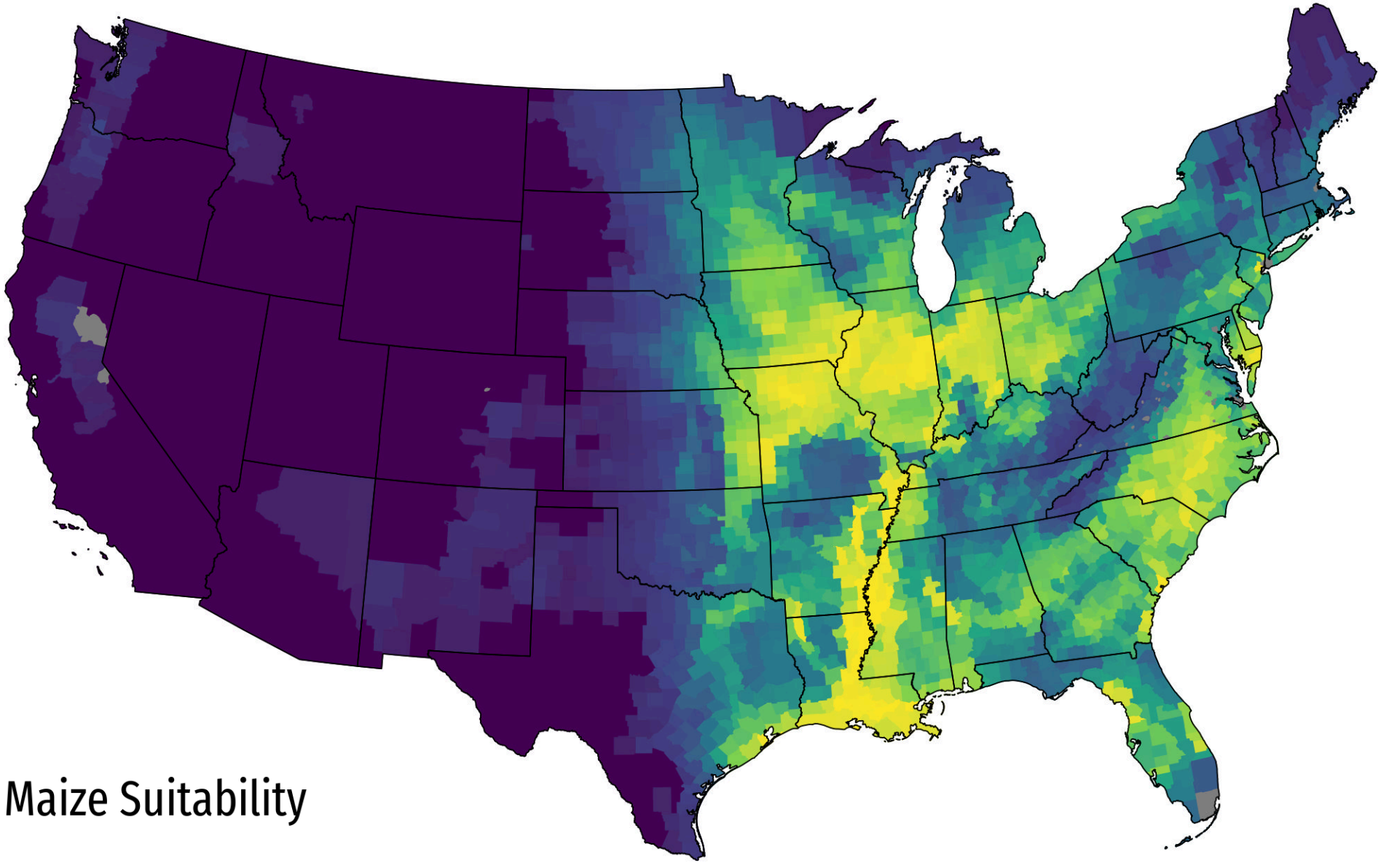
Appendix

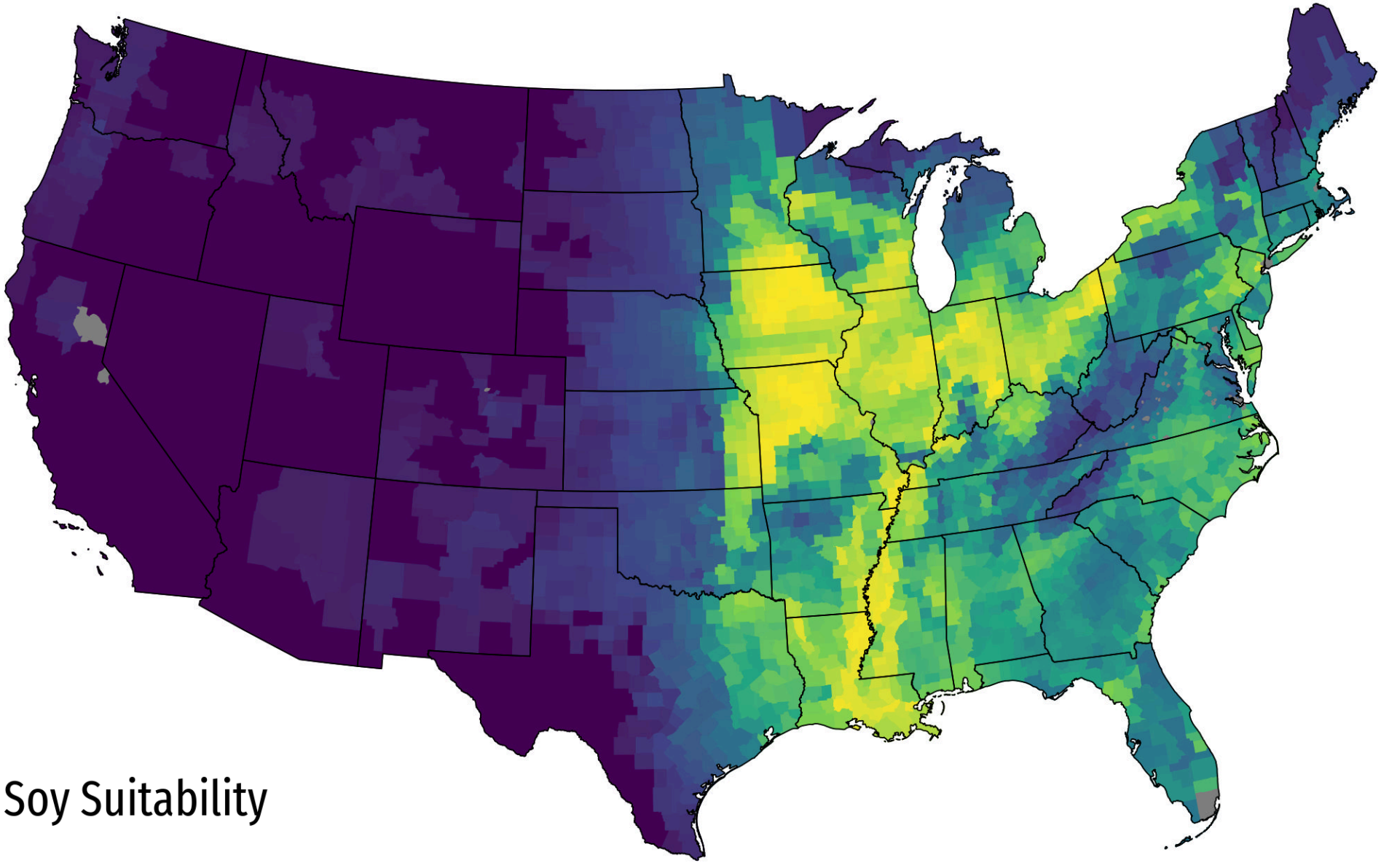
Appendix

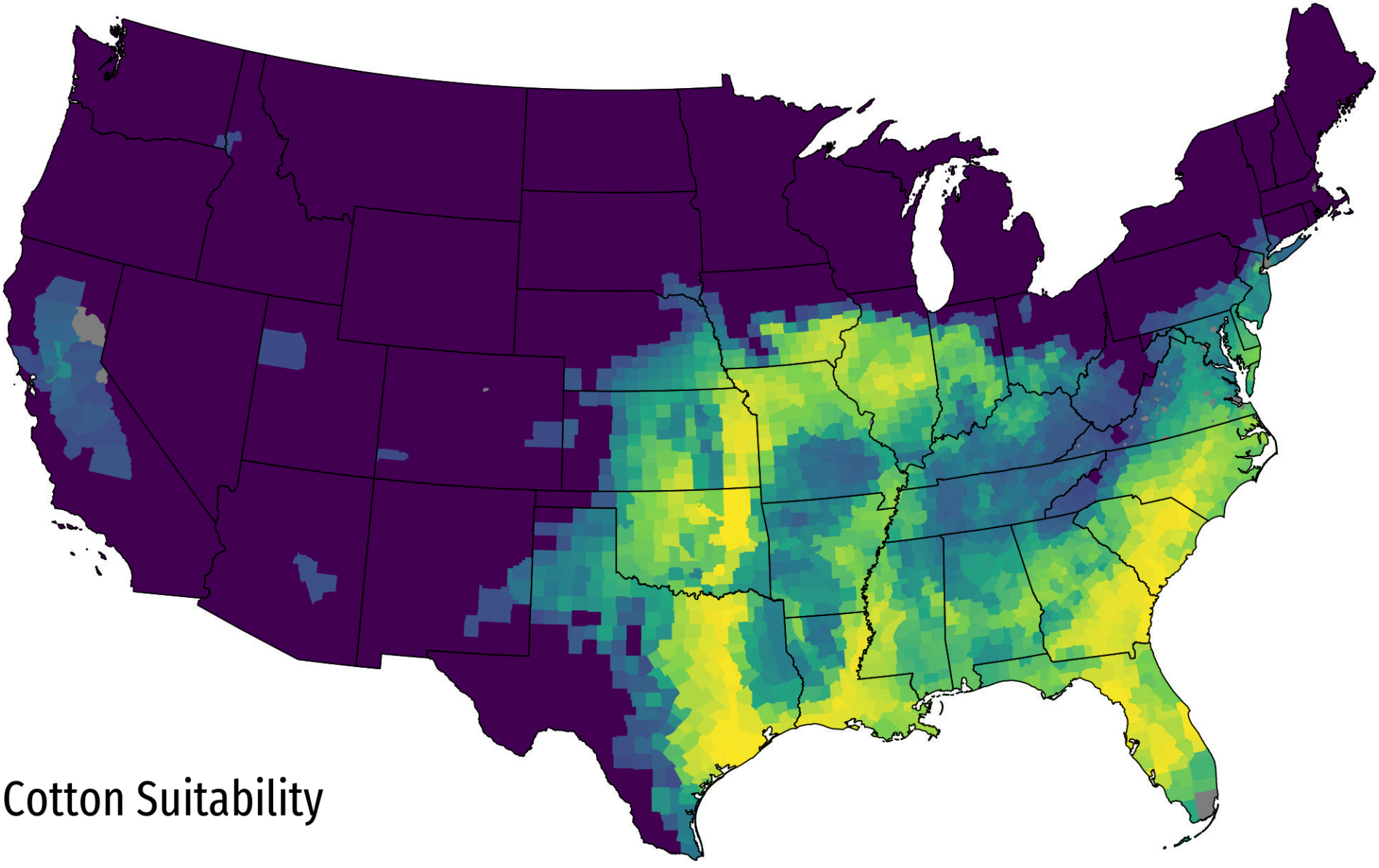
Instrument maps

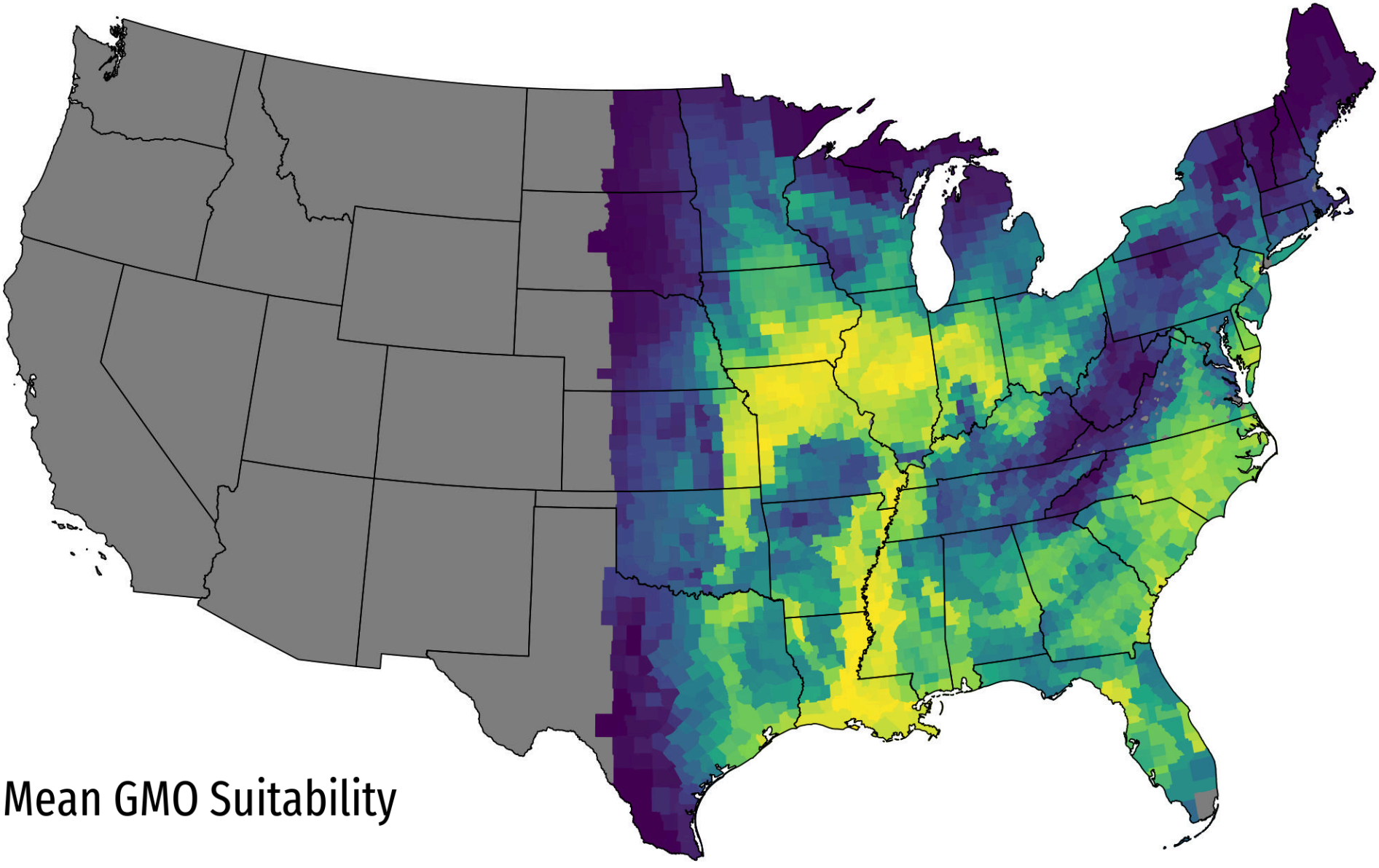

Mean GMO Suitability

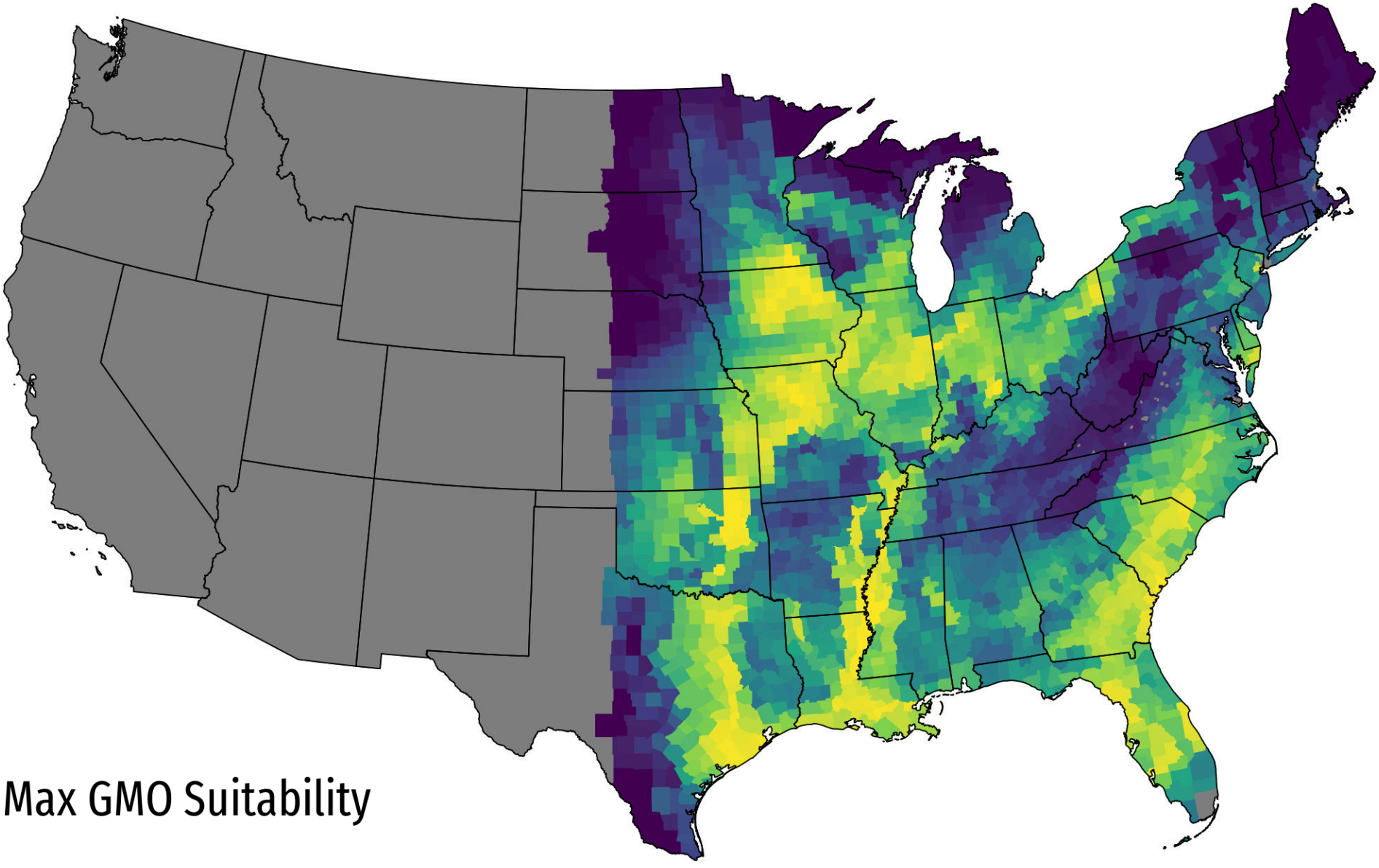

Max GMO Suitability

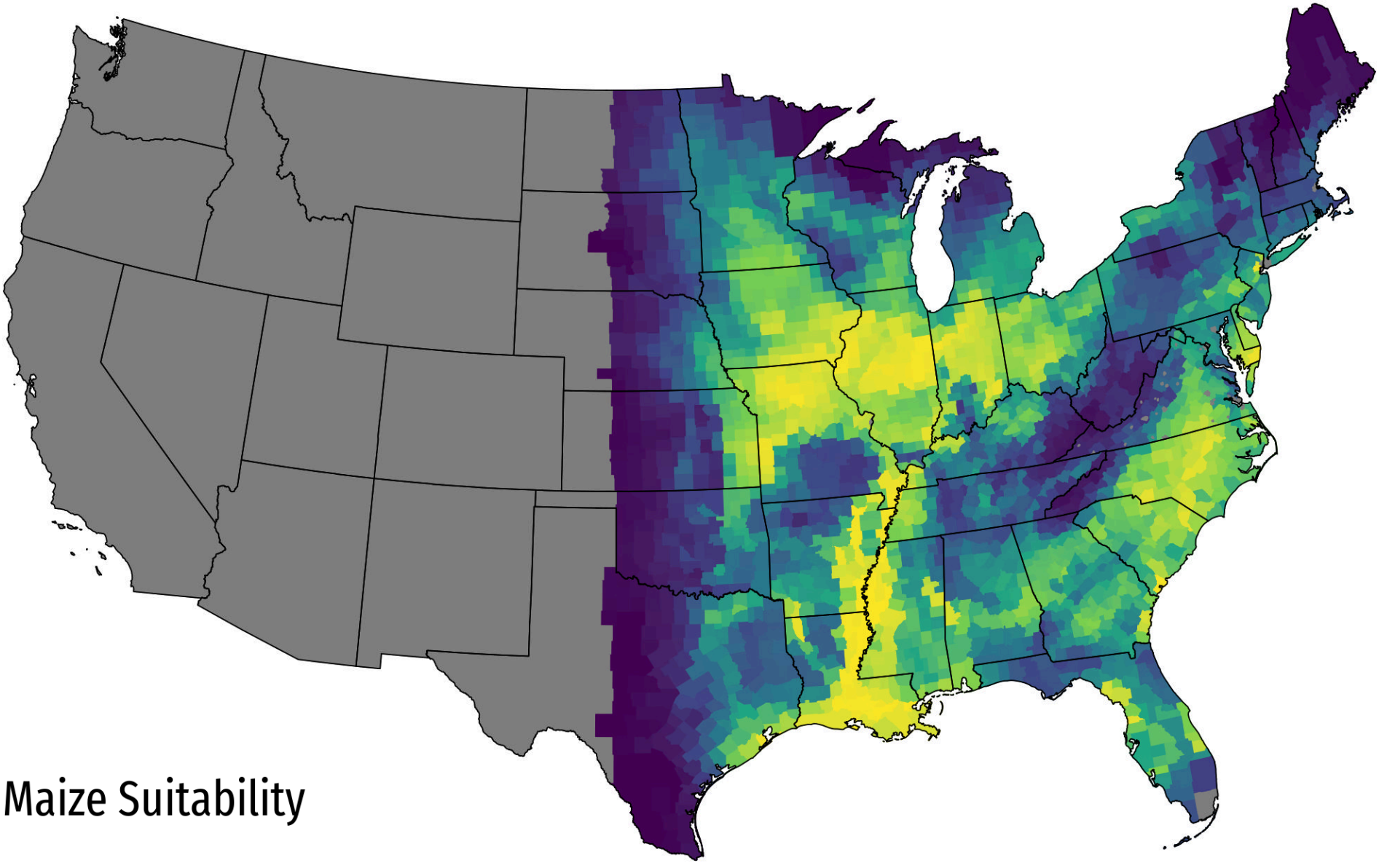

Maize Suitability

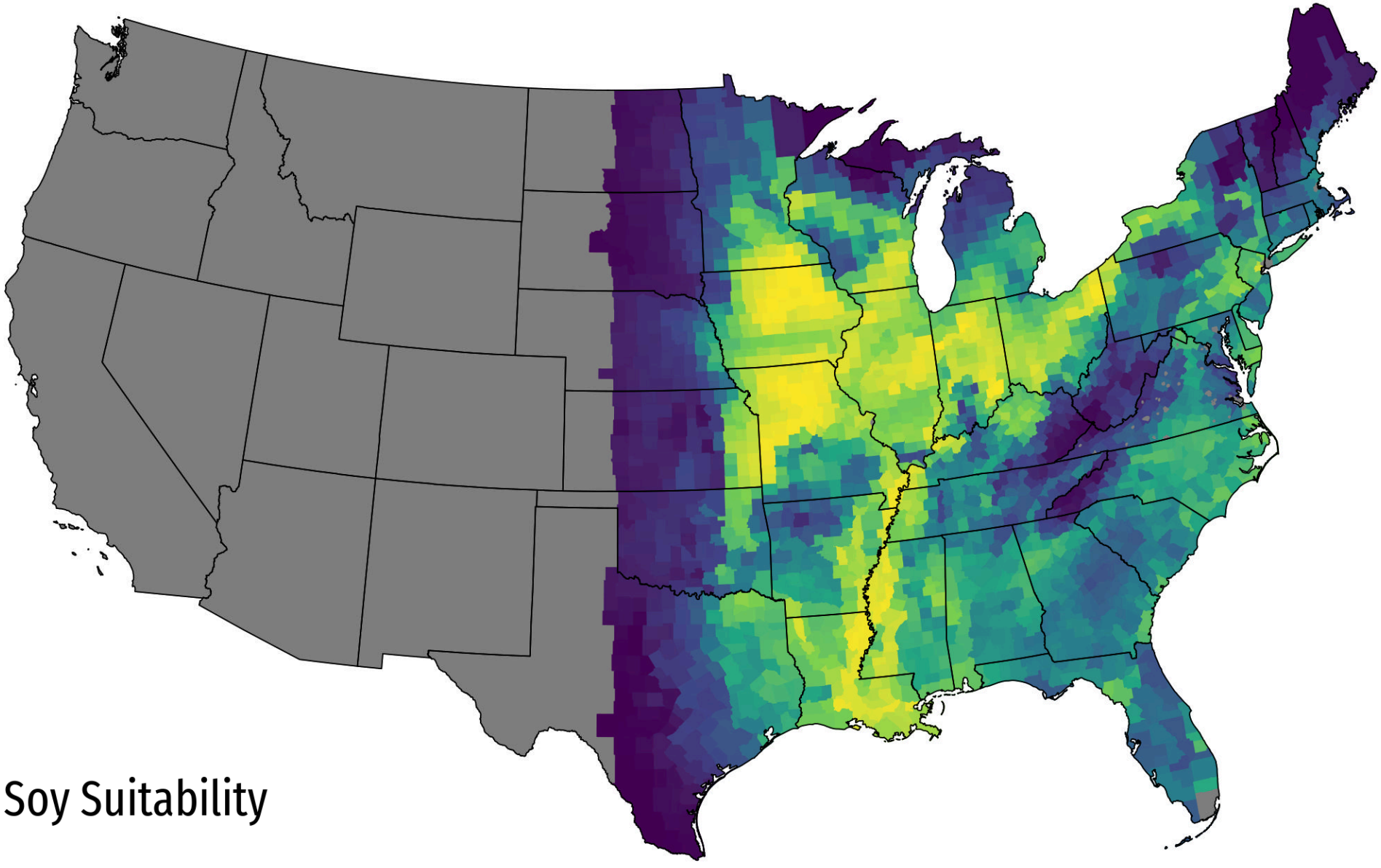

Soy Suitability

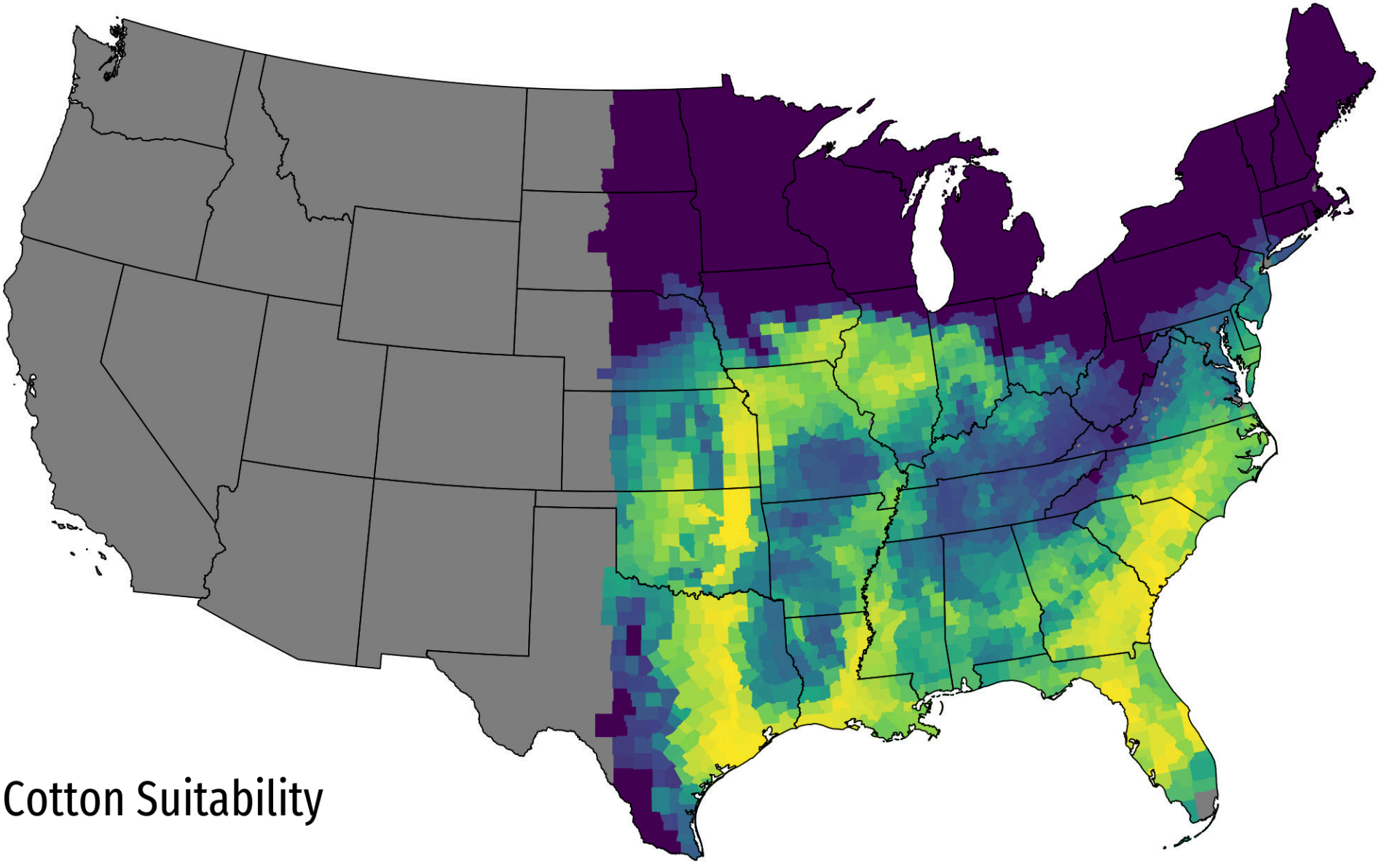

Cotton Suitability


Mean GMO Suitability


Max GMO Suitability


Maize Suitability


Soy Suitability


Cotton Suitability

Appendix

Comparing models

Comparing Estimates 2SLS, shift-share IV, and OLS

	1 *BW (g)*	2 *BW Pctl.*	3 *P(Low BW)*	4 *P(V. Low BW)*	5 *Gest (w)*	6 *P(Preterm)*	7 *P(C-section)*
2SLS results							
GLY/km^2	−1,376.2	−0.698	0.330	0.075	−9.46	0.963	0.474
	(640.7)	(0.322)	(0.148)	(0.033)	(3.42)	(0.442)	(0.344)
S-S results							
GLY/km^2	−870.5	−0.442	0.205	0.049	−5.49	0.622	0.130
	(305.7)	(0.158)	(0.072)	(0.017)	(1.47)	(0.224)	(0.187)
OLS results							
GLY/km^2	54.2	0.021	-0.018	-0.003	−0.355	0.024	-0.001
	(61.1)	(0.030)	(0.021)	(0.006)	(0.305)	(0.043)	(0.065)
Controls							
Local pesticides	×	×	×	×	×	×	×
Unemployment	×	×	×	×	×	×	×
Family demog.	×	×	×	×	×	×	×
Fixed effects							
Yr × Mo + Cnty	×	×	×	×	×	×	×
Sample	US	US	US	US	US	US	US

Setup

1. Motivation
2. Uncertainty
3. Overview

Lit. and contribution

1. General
2. In lab
3. Observational
4. Gerona *et al.*, 2022

Background

1. Glyphosate: Timeline
2. Glyphosate: Chemistry
3. Roundup
4. GM

Empirical strategy

1. Data
2. Estimating equation
3. First stage

Results

1. Reduced-form event studies
2. 2SLS estimates
3. Heterogeneity

Discussion

1. Summary
2. Policy

Appendix

1. Instrument maps
2. Compare models