

Unintended Consequences of the CDC's 2016 “*Guideline for Prescribing Opioids for Chronic Pain*” for Individuals with *Sickle Cell Disease*

Hyeun Ah Kang¹, Bofei Wang², Jamie C. Barner¹, Kenneth I. Ataga³, and Robert C. Mignacca^{1,4}

¹The University of Texas at Austin

²The University of Texas at El Paso

³The University of Tennessee Health Science Center

⁴Children's Blood and Cancer Center at Dell Children's Hospital

Conflict of interest

- Funded by the **American Association of Colleges of Pharmacy (AACCP)**



2021-2022 New Investigator Award

- Conducted independently
- No conflict of interest



Photo obtained from the Facebook page of Sickle Cell Association of Texas Marc Thomas Foundation

Outline

Background

Objectives

Methods

Results

Conclusion

Background

Sickle Cell Disease (SCD) is a *rare*, inherited blood disorder that disproportionately affects *African Americans*.

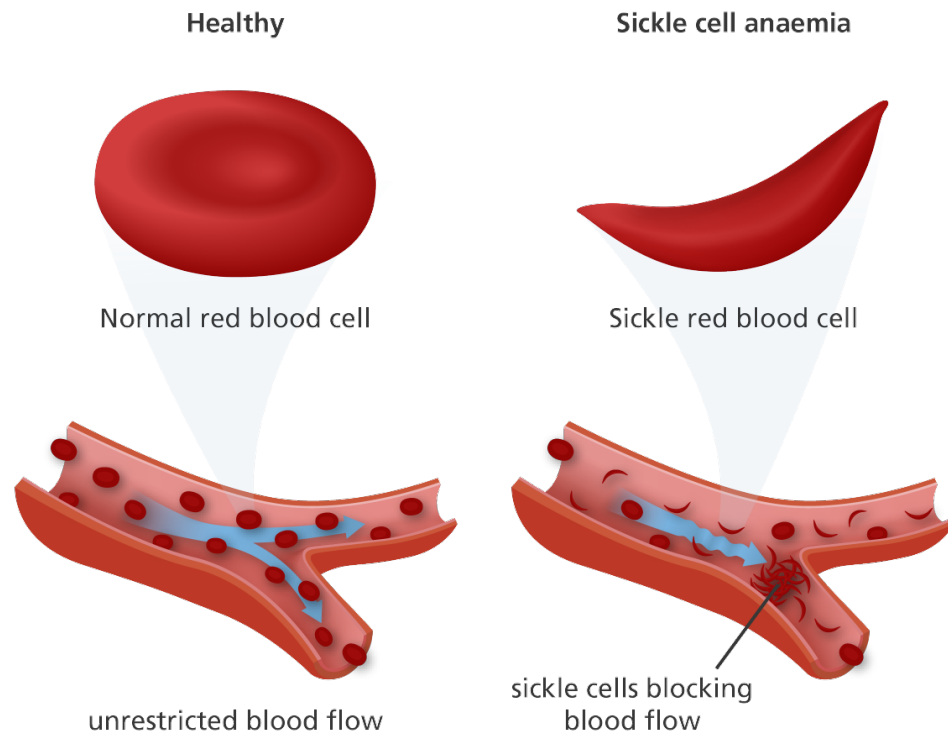


Illustration showing the difference between normal red blood cells and sickle red blood cells.
Image credit: Genome Research Limited

- **Sickle cell disease (SCD)** is characterized by a defect in one of the genes for **hemoglobin** resulting in the production of sickle cell hemoglobin (HbS) in **red blood cells**.¹
- **Symptoms**²
 - Anemia, vaso-occlusive crisis, acute chest syndrome, stroke
- **Prevalence** and **incidence** in the U.S.
 - Approximately 100,000 Americans have SCD³
 - 2,000 infants with SCD are identified each year⁴
 - 90% of patients are African American⁵
- **Mortality**⁶
 - Median survival is 58-66

Inadequate pain management using *prescription opioid* has increased *health inequities* among people living with *SCD*.

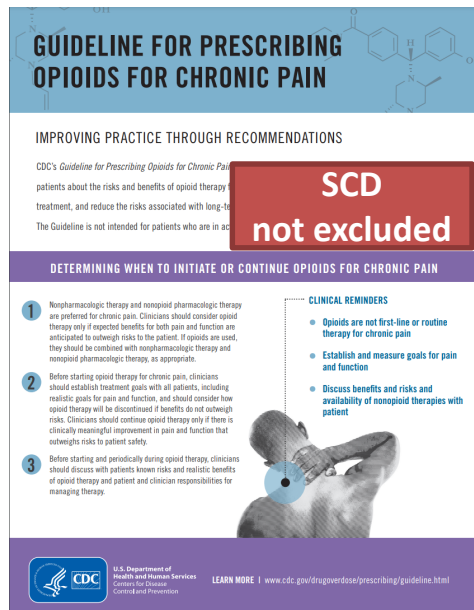
- A hallmark of SCD, *vaso-occlusive crisis (VOC)*
 - 1) 61.5% of SCD patients experience ≥ 1 VOC episode with an average of 2.9/year requiring treatment in the ED or inpatient setting^{7,8}
 - 2) 54-85% of the patients rely on opioid therapy to control VOC pain without other treatment options available^{9,10}
 - 3) Uncontrolled pain can lead to neuropathic pain, lower quality of life, loss of productivity, and increased use of costly ED visits and hospitalizations^{11,12}
 - 4) Economic burden (SCD): \$2.98 billion/year in the U.S.¹³
- Disease-specific guidelines (e.g., NHLBI, ASH) *recommend opioid analgesics* to control VOC pain.¹⁴⁻¹⁷
- Patients with SCD often face *restrictive access to opioid therapy*.^{18,19}



“Opioid epidemic” and subsequent *guidelines* on opioid prescribing may *exacerbate the longstanding barriers* to needed opioid therapy.

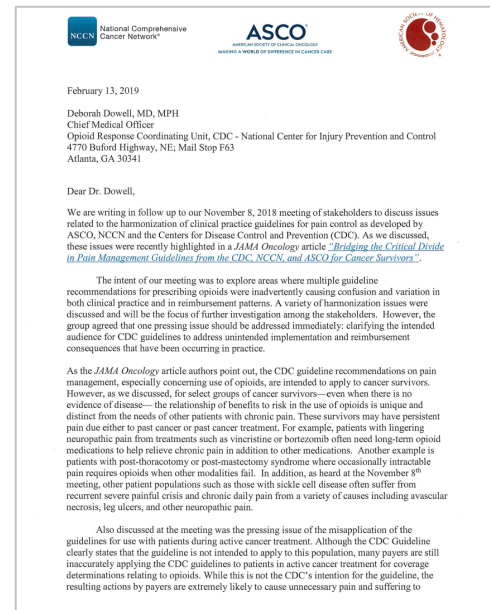
March 2016

CDC “Guideline for Prescribing Opioids for Chronic Pain”²⁰



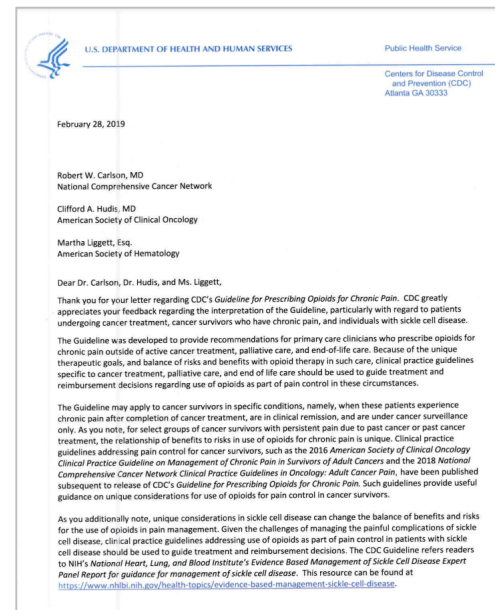
February 2019

Letter of the ASH, ACSO, NCCN to the CDC regarding misapplication²¹



February 2019

CDC’ acknowledgement of SCD as an excluded condition²²



However,

- Misapplication continued
- Concerns from HCP and patients including those with SCD

Medical News & Perspectives

Limits on Opioid Prescribing Leave Patients With Chronic Pain Vulnerable

Rita Rubin, MA

COMMENTARY

Pain Medicine 2020; 21: 229–231
doi: 10.1093/pm/pnz152

The National Imperative to Align Practice and Policy with the Actual CDC Opioid Guideline

Medical leaders: CDC must revise 2016 opioid guideline

CDC’s opioid guideline for chronic pain gets second look

Jeffrey Fudin, PharmD, hears from many chronic pain patients by way of his blog, where he writes about all things having to do with the world of pain.

Working with prescribers
Taking all of this into account, Fudin said it’s more important than ever to

Original Investigation | Hematology

Management of Chronic Pain in Adults Living With Sickle Cell Disease in the Era of the Opioid Epidemic

A Qualitative Study

Cynthia B. Senha, PhD; Nitya Bakshi, MBBS, MS; Diana Ross, RN, MS; Lakshmanan Krishnamurti, MD

The CDC has seeking evaluations of *intended* and *unintended impacts of the guideline* on clinician and patient outcomes.²³ However, evidence on the impact on those with *SCD* is limited.

Intended impacts	Target population	Author, year	Opioid prescribing practice	Pain control outcomes
	All U.S. population	Bohnert, 2018 ²⁴	Decreased	N/A
	Opioid naïve individuals	Jeffrey, 2019 ²⁵	Decreased	N/A
	Patients visiting ED	Dayer, 2019 ²⁶	Decreased	N/A
	Patients at risk for opioid misuse	Scherrer, 2020 ²⁷	Decreased	N/A
	Opioid naïve individuals	Goldstick, 2021 ²⁸	Decreased	N/A
	Adults with chronic or acute pain	Encinosa, 2021 ²⁹	Decreased	N/A
	Individuals with chronic pains	Townsend, 2021 ³⁰	Decreased	N/A

Unintended impacts	Target population	Author, year	Opioid prescribing practice	Pain control outcomes
	Post-operative treatment	Sutherland, 2021 ³¹	Decreased	N/A
	Cancer patients	Chen, 2022 ³²	Decreased	N/A
	<i>Patients with SCD</i>	<i>N/A</i>	<i>N/A</i>	<i>N/A</i>

Objectives

Objectives

The goal was to provide quantitative **real-world evidence** that can help determine if the 2016 CDC guideline resulted in **unintended consequences** for patients with **SCD** and, if so, to what extent.

Specific aim 1: To assess the association of **the release of CDC guideline** with changes in **opioid prescribing level** among patients with SCD.

Specific aim 2: To assess the association of **the release of CDC guideline** with changes in **pain-related health outcomes** among patients with SCD.

Methods

Methods

Data source

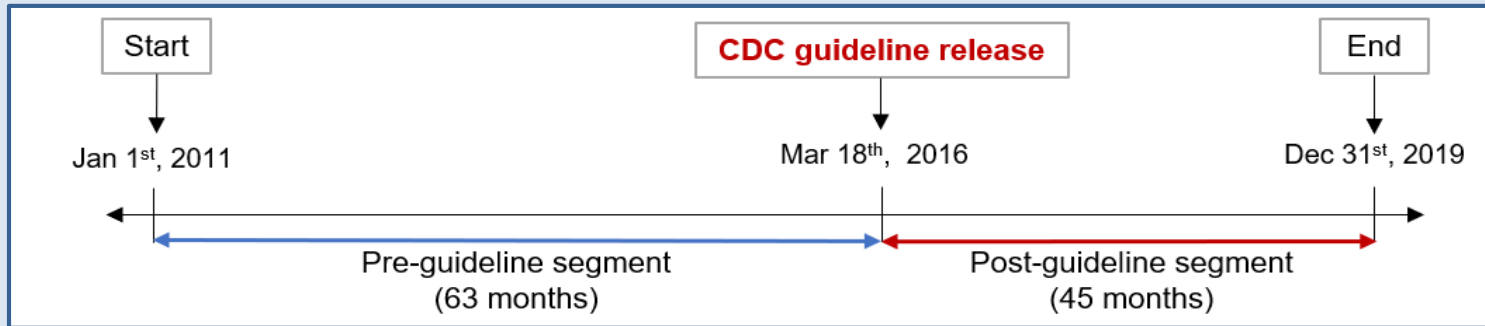
IBM® MarketScan® commercial claims data from 01/01/2011 to 12/31/2019

Inclusion & exclusion criteria

1. ≥ 3 inpatient or outpatient visits with SCD diagnoses within 5 years³³
2. No cancer diagnosis
3. Age ≥ 1 year old

Study design & Analysis

Interrupted time series design with segmented regressions (breakpoint: **March 2016**)



- Coefficients from the regression:
 - β_2 : one-time change immediately at the time of guideline release
 - β_3 : difference in the pre- and post-guideline trends

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + e_t$$

Study outcomes

Specific Aim 1: Opioid prescribing practice

1. Monthly rate of opioid prescriptions dispensed
2. Mean total morphine milligram equivalents (MME) per patient per month
3. Mean daily MME per opioid prescription
4. Mean number of days supplied per opioid prescription

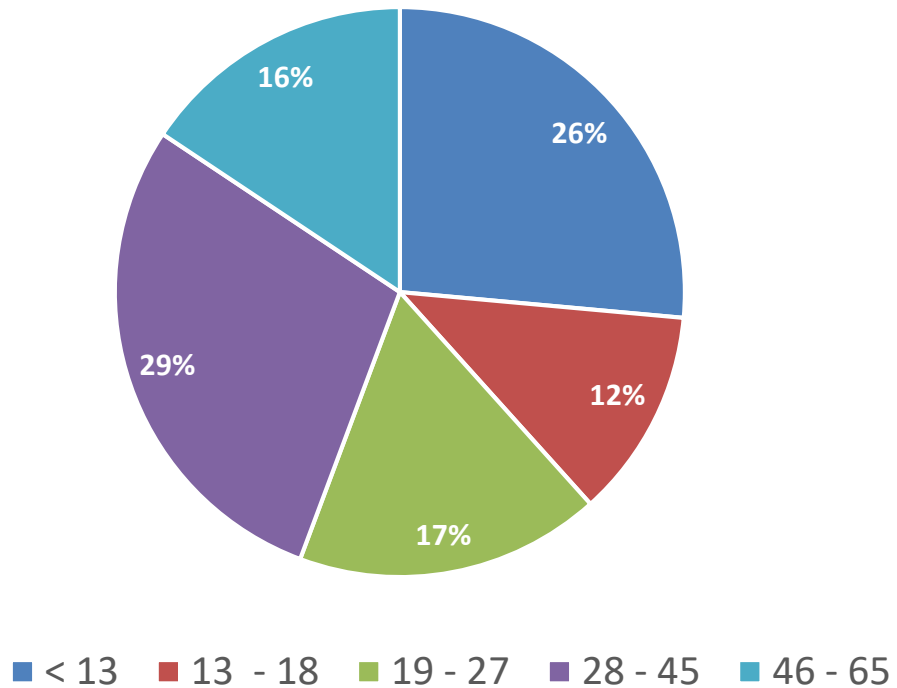
Specific Aim 2: Pain-related health outcomes

1. Monthly rates of VOC-related Emergency Department (ED) visits
2. Monthly rates of VOC-related hospitalizations

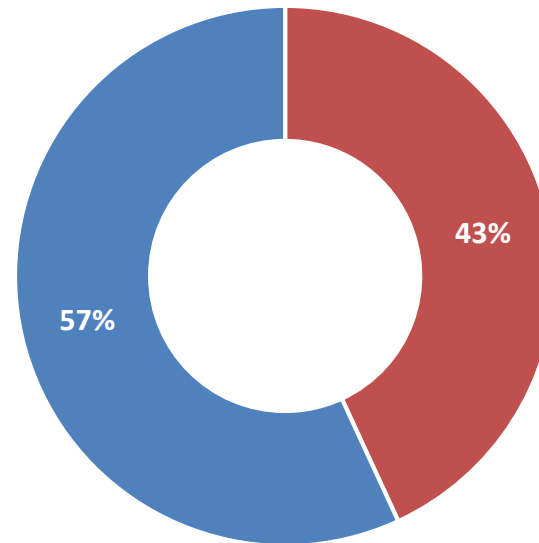
Results

Study population characteristics (N=14,979)

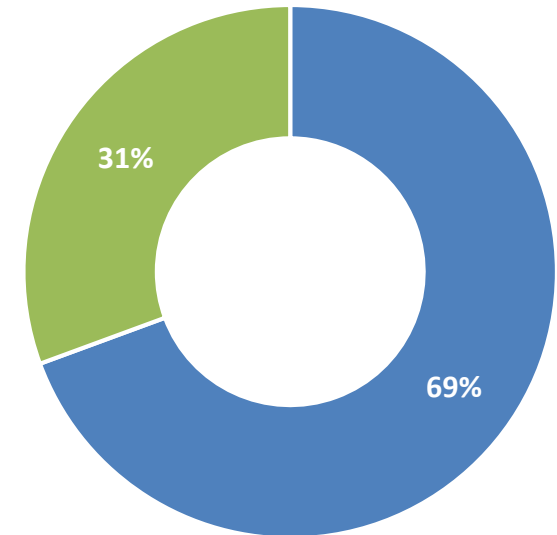
Age = 25.9 (± 16.9)



Gender

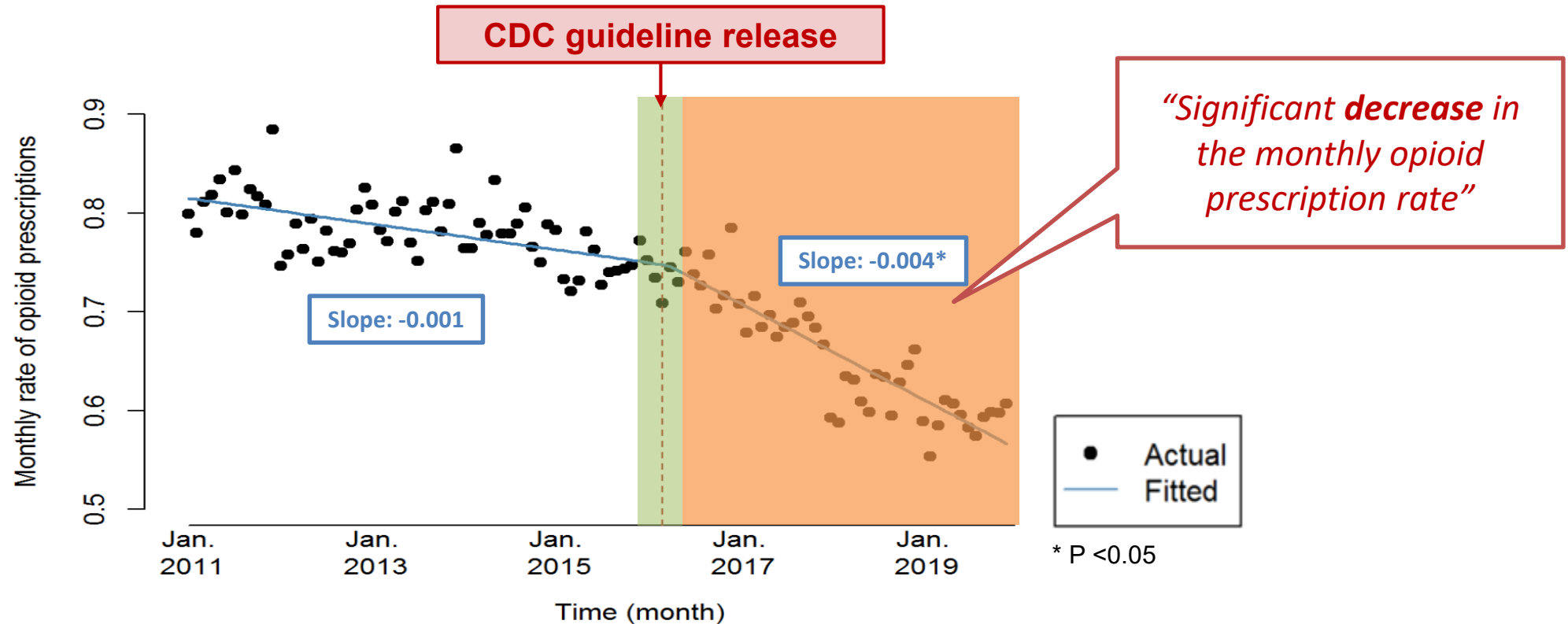


Opioid use



Aim1

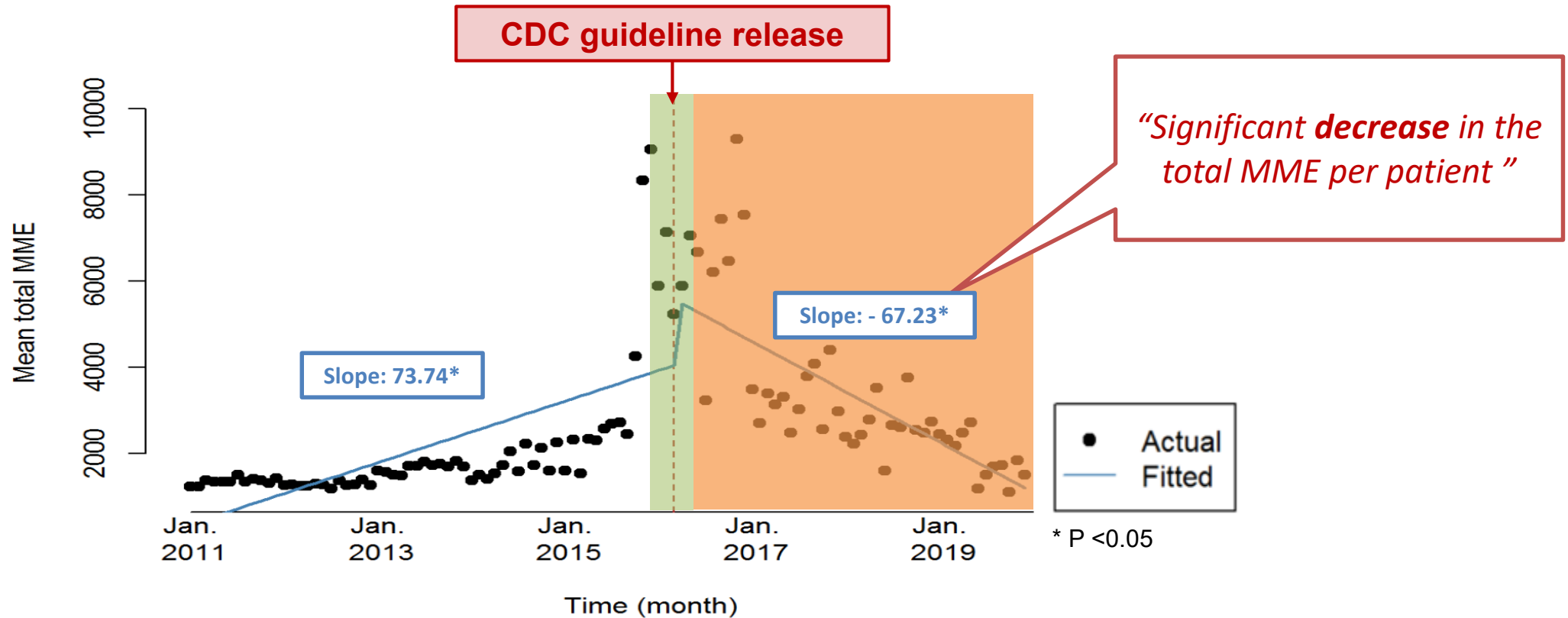
Monthly rate of opioid prescription



Immediate change				Change over time			
β_2	95% CI		P-value	β_3	95% CI		P-value
- 0.008	- 0.035	0.020	0.572	- 0.003	- 0.004	- 0.002	<0.001

Aim1

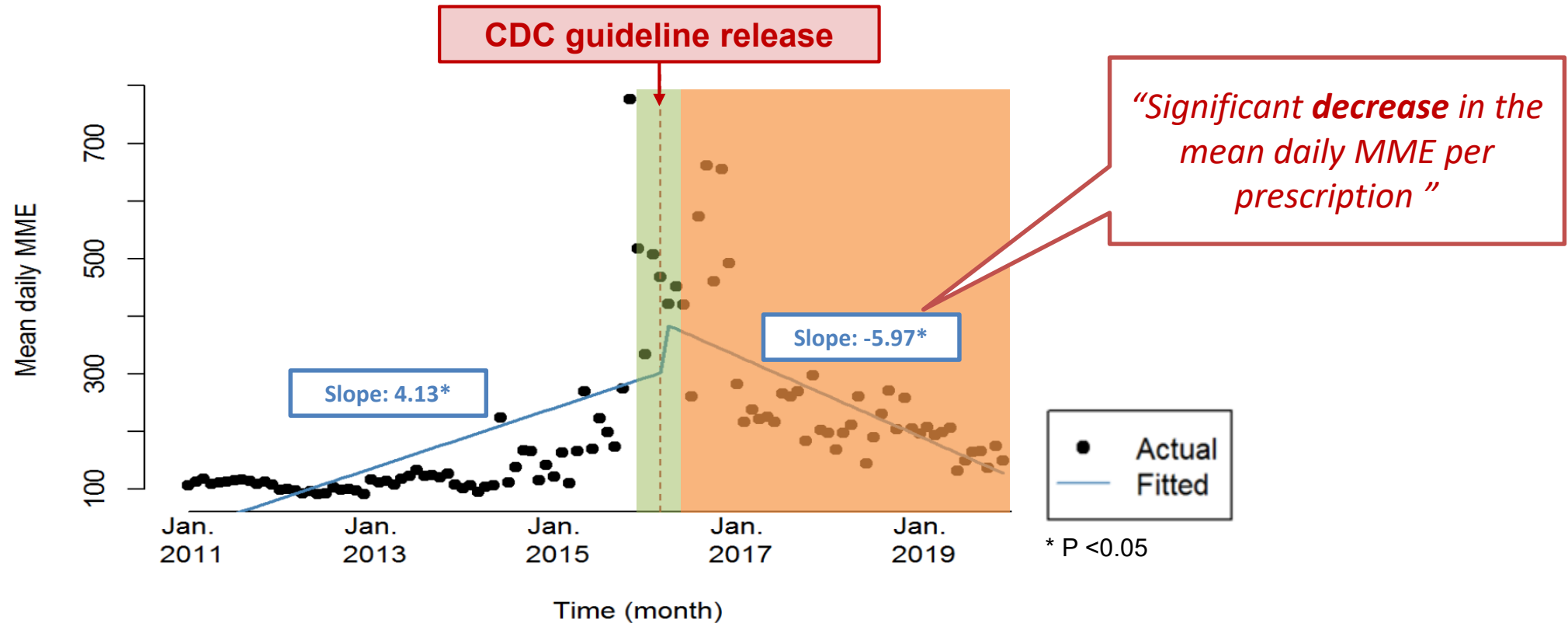
Mean total MME per person



Immediate change				Change over time		
β_2	95% CI		P-value	β_3	95% CI	P-value
- 57.28	-1748.9	1634.3	0.947	- 141.1	- 219.5 - 62.47	0.001

Aim1

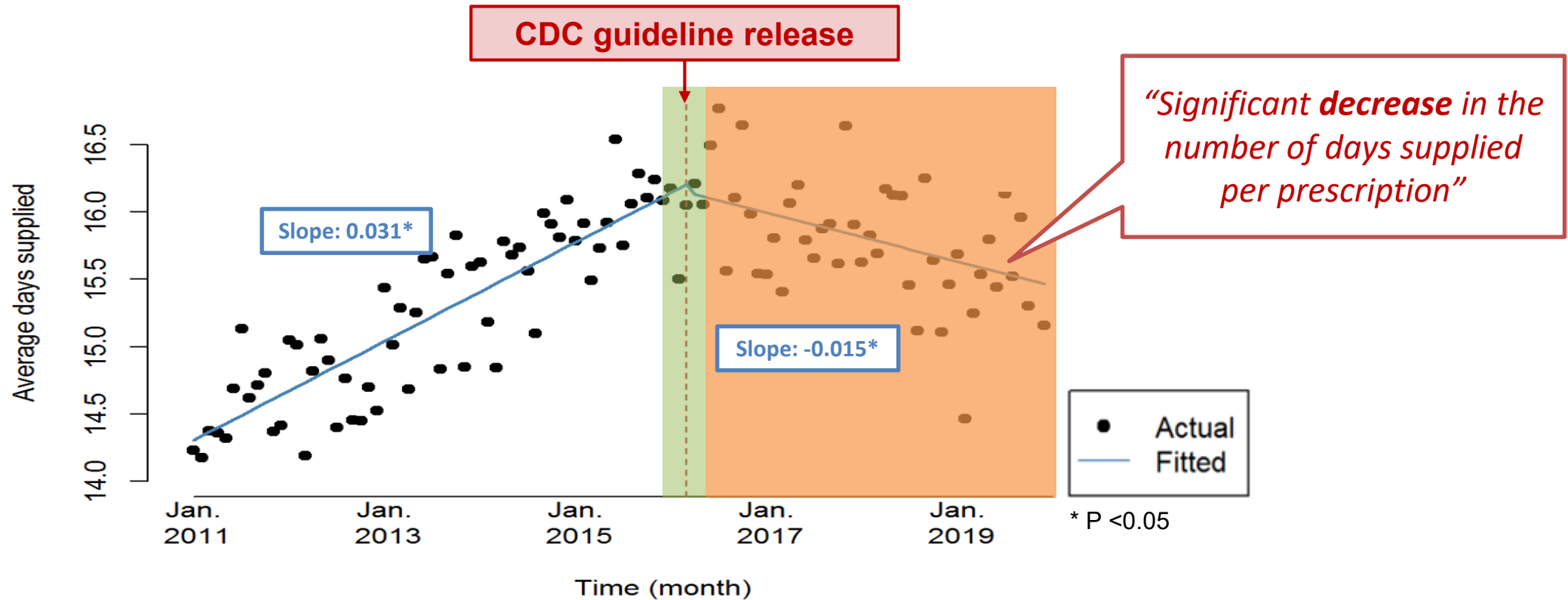
Mean **daily MME** per prescription



Immediate change				Change over time			
β_2	95% CI		P-value	β_3	95% CI		P-value
102.3	- 12.6	217.3	0.080	- 10.1	- 14.59	- 5.615	<0.001

Aim1

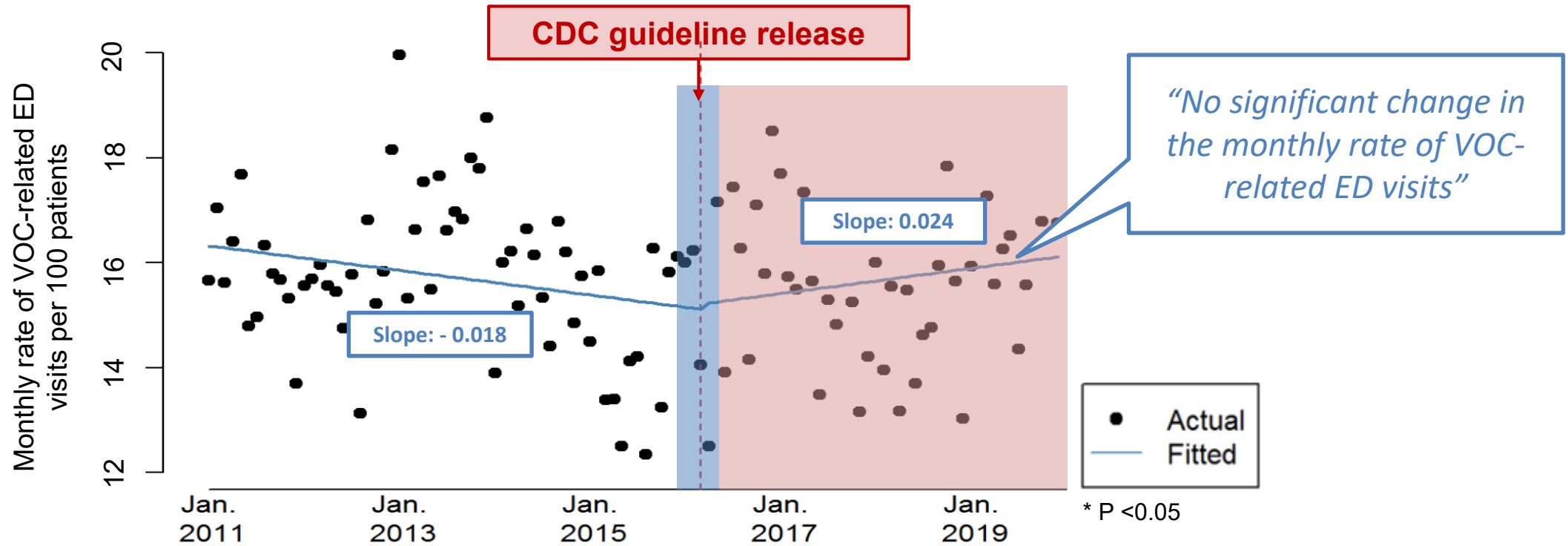
Mean number of **days supplied** per prescription



Immediate change				Change over time			
β_2	95% CI		P-value	β_3	95% CI		P-value
- 0.078	- 0.354	0.199	0.579	- 0.045	- 0.055	- 0.036	<0.001

Aim2

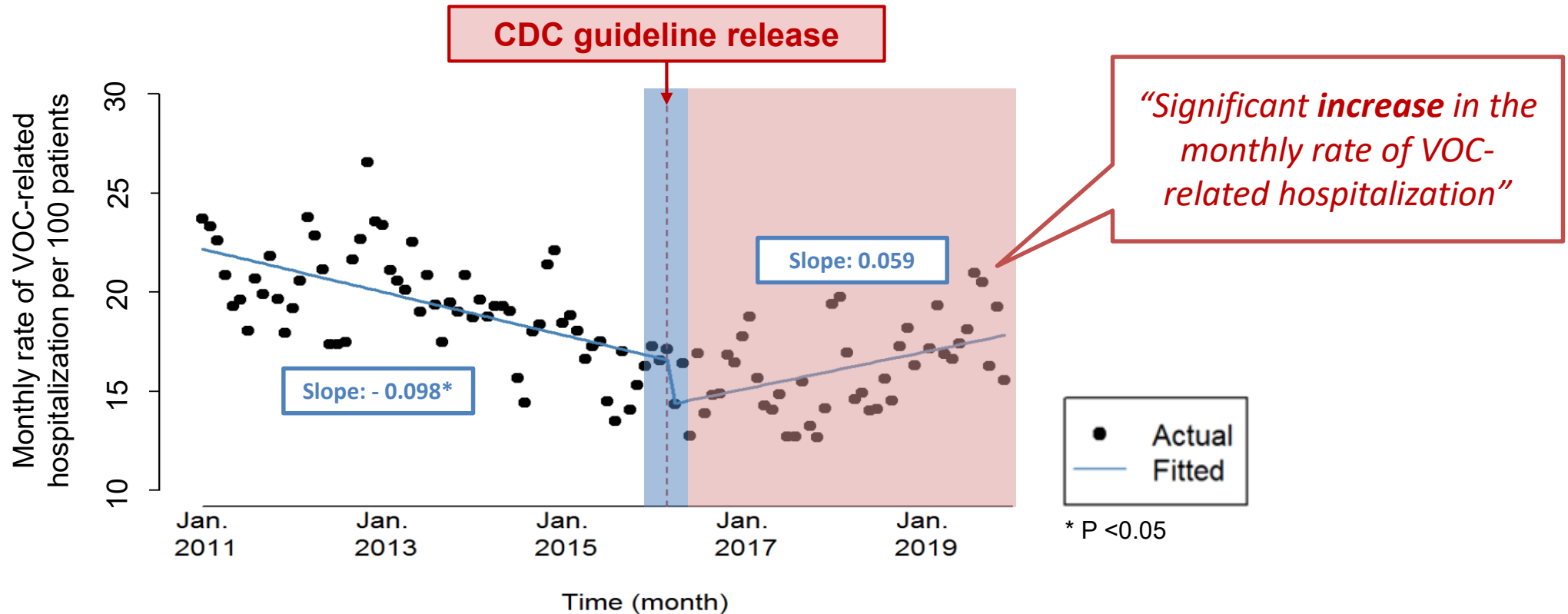
VOC-related ED visits



Time (month)							
Immediate change				Change over time			
β_2	95% CI		P-value	β_3	95% CI		P-value
- 0.087	- 1.438	1.265	0.899	0.041	- 0.005	0.088	0.083

Aim2

VOC-related hospitalizations



Immediate change				Change over time		
β_2	95% CI		P-value	β_3	95% CI	P-value
- 1.343	- 3.731	1.044	0.267	0.156	0.068	0.245
				0.001		

Conclusion

Conclusion

Release of *the CDC guideline* was associated with a decreases in opioid prescribing practices and an increase in the monthly rate of pain-related hospitalizations among patients with SCD.

➤ The guideline may have an unintended negative impact on SCD population.

	Study outcomes	Results
Opioid prescribing practice	1. Monthly rate of opioid prescriptions dispensed	<i>Downward (p<0.001)</i>
	2. Mean total MME per patient	<i>Downward (p=0.001)</i>
	3. Mean daily MME per opioid Rx	<i>Downward (p<0.001)</i>
	4. Mean number of days supplied per opioid Rx	<i>Downward (p<0.001)</i>
Health outcomes	1. Monthly rates of VOC-related ED visits	No sig. change (p=0.083)
	2. Monthly rates of VOC-related hospitalizations	<i>Upward (p=0.001)</i>

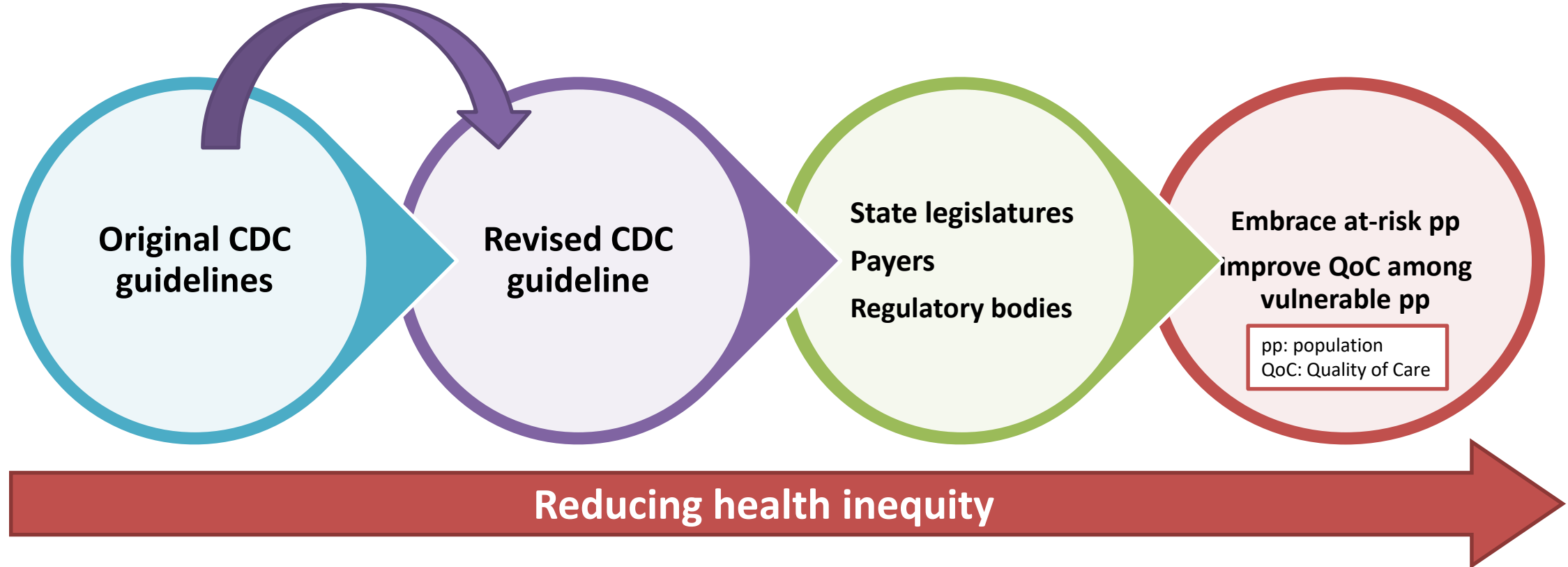
Nationally representative
health insurance claims data

Quantified outcomes
among patients with **SCD**

RWD

RWE

Conclusion



Policymakers:

- 1) Careful consideration of vulnerable populations who can be negatively impacted
- 2) Clear communication regarding the intention and scope of interventions

Study limitations

- Designed as a single group time series because of the absence of a U.S. control group unexposed to the CDC guideline.
 - However, because level and trend of the pre-intervention segment serve as control for the post-intervention segment, it still addresses important threats to interval validity and constitutes a methodologically acceptable design for studying intervention effects.³⁴
- Use of an administrative claims database
 - The scope will be limited by the information collected in the database.
 - The validity of the study results will depend upon the accuracy of records in the database.
- Examined the outcomes in commercially insured patients; study findings may not be generalizable to the patients with SCD who have public (mainly Medicaid) insurance.
- Unable to assess the appropriateness of individual opioid prescribing.

Future direction

- Validation: Advanced analysis (Adjusted interrupted time series)
 - Examine trend changes of study outcomes over time while controlling for preexisting trends as well as temporal changes in population composition
 - Predisposing factors: age, gender, comorbidity index
 - Enabling factors: employment status, census region, rural/urban status
 - Need factors: meteorological seasons, other pain conditions
 - Measure outcomes per person per month
 - Generalized estimating equation (GEE): $g(E(Y_{i,t})) = \beta_0 + \beta_1 T_{i,t} + \beta_2 X_{i,t} + \beta_3 X_{i,t} T_{i,t} + X_{i,t} + e_{i,t}$
- Relative impact of the guideline compared to different populations
 - For example, opioid prescribing in SCD vs. chronic pain vs. cancer vs. general population
- Examine the impacts of revised guidelines on opioid prescribing and health outcomes among SCD population

Reference (1/2)

1. National Organization for Rare Disorders (NORD). *Sickle Cell Disease*. <https://rarediseases.org/rare-diseases/sickle-cell-disease/>
2. Yawn, B.P. et al., Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA*, 2014. 312(10): p. 1033-1048.
3. Brousseau DC, A Panepinto J, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States: National and state estimates. *Am J Hematol*. 2010;85(1):77-78.
4. Tracy M. et al., Sickle Cell Anemia, in *Pharmacotherapy principles & practice*, 3rd edition. 2013, McGraw-Hill Medical: New York. p. 1191-1206.
5. Center for Disease Control and Prevention (CDC). Sickle Cell Disease (SCD). [cited 2018 Apr 25th]; Available from: <https://www.cdc.gov/ncbddd/sicklecell/facts.html>.
6. Chan, C.Y.J. et al., Sickle Cell Disease, in *Pharmacotherapy : A Pathophysiologic Approach*, 7th edition. 2008, McGraw-Hill Medical: New York. p. 1685-1700.
7. Kang HA, Barner JC, Richards K, Bhor M, Paulose J, Kutlar A. Association between vaso-occlusive crises and opioid prescriptions among patients with sickle cell disease: A retrospective claims-based study. *J Health Econ Outcomes Res*. 2020;7(1):94-101.
8. Shah N, Bhor M, Xie L, Paulose J, Yuce H. Sickle cell disease complications: Prevalence and resource utilization. *PLoS One*. 2019;14(7): e0214355.
9. Han J, Saraf SL, Zhang X, et al. Patterns of opioid use in sickle cell disease. *Am J Hematol*. 2016;91(11):1102-1106.
10. Ballas SK, Kanter J, Agodoa I, et al. Opioid utilization patterns in United States patients with sickle cell disease. *Blood*. 2017;130(Suppl 1):130.
11. Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. *Am J Hematol*. 2005;79(1):17-25.
12. Ballas SK. Update on pain management in sickle cell disease. *Hemoglobin*. 2011;35(5-6):520-529.
13. Huo J, Xiao H, Garg M, Shah C, Wilkie DJ, Iii AM. The Economic Burden of Sickle Cell Disease in the United States. *Value in Health*. 2018;21:S108.
<https://doi.org/10.1016/j.jval.2018.07.826>
14. National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: expert panel report, 2014. Accessed April 7, 2022.
https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf
15. Brandow AM, Carroll CP, Creary S, Edwards-Elliott R, Glassberg J, Hurley RW, Kutlar A, Seisa M, Stinson J, Strouse JJ, Yusuf F. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood advances*. 2020;23(4(12)):2656-701.
16. National Institute for Health and Care Excellence. Sickle cell disease: managing acute painful episodes in hospital, June 27, 2012. Accessed April 7, 2022.
<https://www.nice.org.uk/guidance/cg143>.
17. Rees DC, Olujohungbe AD, Parker NE, Stephens AD, Telfer P, Wright J. Guidelines for the management of the acute painful crisis in sickle cell disease. *Br J Haematol*. 2003;120(5):744-752.
18. Sinha CB, Bakshi N, Ross D, Krishnamurti L. Management of chronic pain in adults living with sickle cell disease in the era of the opioid epidemic: A qualitative study. *JAMA Netw Open*. 2019;2(5): e194410.

Reference (2/2)

19. Joynt M, Train MK, Robbins BW, Halterman JS, Caiola E, Fortuna RJ. The impact of neighborhood socioeconomic status and race on the prescribing of opioids in emergency departments throughout the United States. *J Gen Intern Med*. 2013;28(12):1604-1610.
20. Dowell D, Tamara MH, Roger C. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315(15):1624-1645.
21. National Comprehensive Cancer Network, American Society of Clinical Oncology, and American Society of Hematology. Letter to CDC. February 19, 2019. Accessed April 7, 2022. <https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2019-NCCN-ASCO-ASH-Letter-CDC.pdf>
22. Centers for Disease Control and Prevention. CDC Opioid Guideline Clarification Letter. February 28, 2019. Accessed April 7, 2022. <https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2019-CDC-Opioid-Guideline-Clarification-Letter-to-ASCO-ASH-NCCN.pdf>.
23. Dowell D, Haegerich T, Chou R. No shortcuts to safer opioid prescribing. *N Engl J Med*. 2019;380(24):2285-2287.
24. Bohnert ASB, Guy GP Jr, Losby JL. Opioid prescribing in the United States before and after the Centers for Disease Control and Prevention's 2016 Opioid Guideline. *Ann Intern Med*. 2018;169(6):367-375. doi: 10.7326/M18-1243.
25. Jeffery MM, Hooten WM, Jena AB, Ross JS, Shah ND, Karaca-Mandic P. Rates of physician coprescribing of opioids and benzodiazepines after the release of the centers for disease control and prevention guidelines in 2016. *JAMA Netw Open*. 2019;2(8):e198325.
26. Dayer LE, Breckling MN, Kling BS, Lakkad M, McDade ER, Painter JT. Association of the “CDC Guideline for Prescribing Opioids for Chronic Pain” with emergency department opioid prescribing. *J Emerg Med*. 2019;57(5):597-602.
27. Scherrer JF, Tucker J, Salas J, Zhang Z, Grucza R. Comparison of opioids prescribed for patients at risk for opioid misuse before and after publication of the Centers for Disease Control and Prevention’s opioid prescribing guidelines. *JAMA Netw Open*. 2020;3(12):e2027481.
28. Goldstick JE, Guy GP, Losby JL, Baldwin G, Myers M, Bohnert AS. Changes in initial opioid prescribing practices after the 2016 release of the CDC guideline for prescribing opioids for chronic pain. *JAMA Netw Open*. 2021;4(7):e2116860.
29. Encinosa W, Bernard D, Selden TM. Opioid and non-opioid analgesic prescribing before and after the CDC’s 2016 opioid guideline. *Int J Health Econ Manag*. 2021;8;1-52.
30. Townsend T, Cerdá M, Bohnert A, Lagisetty P, Haffajee RL. CDC guideline for opioid prescribing associated with reduced dispensing to certain patients with chronic pain: Study examines impact of CDC guideline for opioid prescribing. *Health Aff*. 2021;40(11):1766-1775.
31. Sutherland TN, Wunsch H, Pinto R, et al. Association of the 2016 US Centers for Disease Control and Prevention opioid prescribing guideline with changes in opioid dispensing after surgery. *JAMA Netw Open*. 2021;4(6):e2111826.
32. Chen Y, Spillane S, Shiels MS, et al. Trends in opioid use among cancer patients in the United States: 2013-2018. *JNCI Cancer Spectr*. 2022;6(1):pkab095.
33. Centers for Medicare & Medicaid Services. CCW Chronic Conditions. Chronic Conditions Data Warehouse. 2021. Assessed February 7, 2022. <https://www2.ccwdata.org/web/guest/condition-categories>.
34. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309.



Thank you for the opportunity to present our work

Questions or potential **collaboration**:

Hyeun Ah Kang, Ph.D.

h.kang@austin.utexas.edu

The University of Texas at Austin
College of Pharmacy
Health Outcomes Division