Doctors, Death, and Drug Money

A Quantitative Analysis of Direct-to-Physician Pharmaceutical Marketing and Mortality

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Tiivistelmä/Referat – Abstract

This thesis examines direct-to-physician pharmaceutical marketing in the United States of America. In 2013, about 78 opioid prescriptions were being written for every 100 people, and 17,000 people in the United States died from an opioid overdose. This study asks, what is the relationship, if any, between contemporary direct-to-physician pharmaceutical marketing practices and opioid mortality in the United States? Contained within an expansive piece of U.S. federal legislation, the Patient Protection and Affordable Care Act of 2010 is a provision which mandates pharmaceutical manufacturers to report marketing payments made to physicians, hospitals, and other relevant healthcare providers. By connecting marketing payments to mortality data at several geospatial levels, the study finds that there is a plausible relationship between the direct-to-physician pharmaceutical marketing and mortality.

Avainsanat – Nyckelord – Keywords
drug marketing, opioids, mortality, United States of America, Open Payments

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Preface and Acknowledgements

I wrote the better part of the thesis between 2014 and 2016, my time divided between Helsinki and New York City. Despite my best efforts, the original findings were frustratingly inconclusive. The project was delayed and from the fall of 2017 until the spring of 2020, it was left mostly untouched. Today, reflecting on my own words, I am surprised by the study's intense positivism, and the relentless appeal to fact and objective knowledge. My use of 'theory' is probably the most glaring example of this naiveté. The study involves an odd pairing of vulgar, methodologically nationalist, Marxism with an analytically complex quantitative and computational approach. Though the thesis might be fitting for a graduate program in public health or social epidemiology, it is hardly sociology in the European sense of the discipline. The thesis does, however, constitute a proper contribution to contemporary American sociology. And for that, perhaps I should apologize.

This work is made possible by SmartyStreets. SmartyStreets donated access to a geocoding service which was used to aggregate the data used in this study. Thank you to my friends and family, most especially my grandparents who supported my graduate studies at the University of Helsinki. Thank you to my sister, Kaitlyn Leamy, who proofread the final draft. Thank you Ryan Schroeder, Daniel Weinstein, and Gwinyai P. Muzorewa. My appreciation is also extended to Liisa Myyry, Tuomas Martikainen, Aino Sinnemäki, Juha Luukkonen, and Karri Silventoinen for guiding me through the research and writing process. An extra special thanks to Ilkka Arminen and Marianne Järveläinen for always going the extra mile. Thank you Ajaye, Karla, and all of the Louisville CREW for your formative friendship. Thank you Islam Faress, for sharing your thoughts, humour, sexy chicken, and pharmaceutical expertise. Thank you to all the folks who contributed to this project in the REMS and ERI seminars, Anu Lehtiö, Visa Rantanen, Alina Thimm, Nuriiar Safarov, Valeria Rabito, Ulla-Kaisa Pihlaja, Sara Mahonen, and Maria Seppanen. Thank you Yasemin Ozer for your friendship. Thank you K.K. Rebecca Lai, without you this project would have never been finished. Most

importantly, this paper is for my friends who are no longer with us, Sam Rathnow and Tiffany Carlysle.

1.0 INTRODUCTION

This study is an exploration of a peculiar American marketing practice. During a period of market de-regulation in the 1980's and 1990's, marketing campaigns by pharmaceutical companies began directly targeting patients. As the marketing strategy developed pharmaceutical companies redirected their campaigns towards physicians. In 2013, 3% of U.S. adults were regularly receiving opioid prescriptions to treat non-cancerous medical conditions, 1 in 3 U.S. adults received a prescription opioid, about 78 opioid prescriptions were being written for every 100 people, and 17,000 people in the United States died from an opioid overdose.[1] Of those using non-prescription opioids like heroin, about 4 in 5 developed an opioid addiction while taking a prescription opioid.[2] Around this time I began to explore a possible connection between the practice of marketing drugs directly to doctors and the public health crisis. The exploration began as a broad attempt to evidence relationships between public health outcomes and direct-to-physician pharmaceutical marketing before being distilled into an examination of direct-to-physician opioid marketing and drug-related mortality.

My central research question can be summarized as follows: What is the relationship, if any, between contemporary direct-to-physician pharmaceutical marketing practices and opioid mortality in the United States? More specifically, what can uniquely large datasets and the methods associated with them tell us about this possible relationship? Primarily, this is a quantitative endeavour that operationalizes marketing by way of physician-industry financial interactions, and opioid mortality by way of public health statistics.

1.1 THE PHARMACEUTICAL INDUSTRY IN THE UNITED STATES

[1] K.M. Dunn, K.W. Saunders, C.M. Rutter, et al., "Overdose and prescribed opioids: Associations among chronic non-cancer pain patients," *Annals of Internal Medicine* 152, no. 2 (2010): 85-92.; Center for Disease Control, "Opioid Prescribing Rate Maps," (2013).

[2] National Institute on Drug Abuse Prescription. "Opioid Use is a Risk Factor for Heroin Use," (2018).

The practices of the pharmaceutical industry have a substantial and well-documented impact on global health. In the United States, the pharmaceutical industry maintains networks of financial relationships with regulatory bodies, public policy makers, drug prescribers, and consumers. As such, public policy makers have taken a particular interest in collaboration and regulation with the pharmaceutical industry. In the late 1990's, one of these regulatory bodies, the United States' Food and Drug Administration (FDA), issued informal guidelines that encouraged the emergence of contemporary direct-to-consumer pharmaceutical advertising strategies.[3] Henceforth, the marketing practices of the global pharmaceutical industry have become the subject of increasing examination in public health, medical, and sociological inquiry. Among these marketing practices is a practice which I refer to as direct-to-physician pharmaceutical marketing. Direct-to-physician pharmaceutical marketing is the giving of money, goods, gifts, and services by pharmaceutical companies directly to doctors. In the United States this form of marketing is a nearly ubiquitous practice in the pharmaceutical industry and almost all physicians report some financial relationship with the pharmaceutical industry.[4] Examples of prevalent forms of direct-to-physician pharmaceutical marketing include cash payments, vacations, and dinners at high-end restaurants.

Recently, national level healthcare regulators in the United States have sought to address the marketing phenomenon. Contained within an expansive piece of U.S. federal legislation, the Patient Protection and Affordable Care Act of 2010 (ACA) or Obamacare, is a provision which mandates pharmaceutical manufacturers to report marketing payments made to physicians, hospitals, and other relevant healthcare providers.[5] These financial-relationship and marketing data are gathered by a program within the Centers for Medicare and Medicaid Services (CMS), a large U.S. government body which facilitates medical care for qualifying U.S. residents. This data gathering

[3] J.A. Greene and D. Herzberg, "Hidden in plain sight: Marketing prescription drugs to consumers in the twentieth century," *American Journal of Public Health* 100 no.5 (2010): 793–803.
[4] Eric G. Campbell, Russell L. Gruen, James Mountford, Lawrence G. Miller, Paul D. Cleary, and David Blumenthal. "A National Survey of Physician–Industry Relationships." *New England Journal of Medicine* 356, no. 17 (2007): 1742-750.
[5] Patient Protection and Affordable Care Act, 42 U.S.C. § 18001 et seq. Section 6002. (2010).

program is referred to as the Open Payments Program of the Centers for Medicare and Medicaid (OPP).

The OPP has agglomerated and published data concerning the financial relationships between drug companies and doctors. The data, also referred to as Open Payments Data, affords significant research opportunities because it is the first publicly accessible, nationally representative, and systematically collected dataset which documents the financial relationships between physicians and the pharmaceutical industry in the United States. The dataset has some significant shortcomings. Unlike health outcomes data in some Nordic states that are available at the individual level, this sort of individual-level health outcomes data is often unavailable in the U.S. and is not employed in this study. Therefore, I linked Open Payments data to other nationally representative datasets in order to make it useful for this study. Following the data collectors' own words, I maintain that the thinking and policy that led to the creation of the Open Payments dataset was driven by a desire to control healthcare costs in the public sector.[6] This project, a sociological and public health project, is an attempt to reappropriate the cost-controlling efforts of healthcare economists and policymakers to better understand the origins or development of the "opioid crisis" by interrogating the relationships between doctors and drug makers.

A central assumption of this study is that direct-to-physician marketing, within the context of a global capitalism, is employed by pharmaceutical firms because it augments their sales, revenues and aggregate profitability. Following Karl Marx's framework in *Capital Vol. I*, I conceive of direct-to-physician marketing as a form of constant capital, an input cost or investment with the aim of generating surplus capital.[7] The thinking, for better or worse, follows a rigid sort of economic determinism. That is not to say that Marx himself is an economic determinist, but my reading and application of *Capital* is quite deterministic.

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[6] U.S. General Services Administration. "Open Payments Apps Help Healthcare Professionals Track Reporting On The Go". March 2014.

[7] Karl Marx, *Capital, Vol I.*, translated by Samuel Moore and Edward Aveling, (New York: International Publishers 1972 [1867]) Chapter 8: Constant Capital and Variable Capital. 199-212

Drawing substantially on Open Payments Data, the U.S. Census Bureau's demographic and small area health coverage estimates (SAHIE), and state and regional mortality data, a hypothesized relationship between direct-to-physician marketing and opioid mortality is examined. Analytically, this is accomplished by compiling correlation matrices to explore potential relationships among and between marketers, physicians, mortality, and other relevant factors. Following this preliminary examination, multivariate linear regression and Poisson regression are utilized to assess drug related mortality nationwide via county-level analysis, and in 100 densely populated urban areas where more complete and robust data are available. Finally, logarithmic transformation of key variables is employed in order to normalize the data.

1.2 THE POLITICS OF HEALTHCARE CORPORATIONS: THEIR REGULATORS AND OTHER MACROECONOMIC CONDITIONS

Macroeconomic conditions have well-documented relationships to health outcomes. Some measures of public health tied to human development might *necessarily* reflect macroeconomic conditions. However, in this study, larger questions which concern both political economy and orthodox macroeconomics are largely neglected. Instead, I situate questions of politics and economy firmly within settler-colonial, racial capitalism, the modern nation state and so forth. Even within the classically liberal public health discourse, a vast network of interlocking directorates, corruption, and bribery are noted as defining characteristics of the U.S pharmaceutical and regulatory institutions.[8] These administrative and fiscal relationships, largely characterised by monetary transactions and in-kind goods and services, are safeguarded by a human rights discourse. More specifically, these financial relationships constitute a form of "free speech." In addition to the implicit protection afforded by a discourse of fiscal relationships constituting a form of free speech, special and explicit legal protection and approval is afforded to private sector entities, including pharmaceutical companies. This is exemplified by a 2010 U.S. Supreme Court ruling concerned with constitutional law, in which the court

[8] Leadership roles in multiple, legally separate corporations or entities. Here the term is used broadly and also refers to conflicting leadership roles spanning public, regulatory bodies, and private, profit-seeking firms. *See* John Scott, *Corporate Business and Capitalist Classes. Big Business and Corporate Power* (Oxford: *Oxford University Press*, 1997): 7 and John Braithwaite *Corporate Crime in the Pharmaceutical Industry* (*Routledge,* 1984).

ruled that the U.S. federal government may not impose restrictions on monetary transactions in the form of anonymous 'donations' to politicians and political campaigns.[9] That is to say, *corporate entities in the United States have the legal right to finance politicians, anonymously and without monetary limit,* and to restrict this practice would be a violation of the most fundamental human rights. Transposing this liberal legal construct on the pharmaceutical sector, by exercising their constitutionally guaranteed right, it is clear that *for-profit pharmaceutical corporations finance the political campaigns and projects of the elected and appointed officials who are charged with the regulation of the pharmaceutical corporations.* Of course, there are laws against bribery and other sorts of collusion. Nonetheless, pharmaceutical companies are paying their regulators even if it is via indirect means.

In addition to the systematic, industry-wide, financial collusion between pharmaceutical regulatory bodies and pharmaceutical manufacturers, those serving in leadership roles often revolve between government regulatory bodies, the Drug Enforcement Administration, and for-profit healthcare companies.[10] This is commonly referred to as a "revolving door". For example, during the period examined in this study, the director of the CDC Washington Office, a position "which serves as a critical link between CDC and the Washington policy community", had assumed the role after leaving their position as Senior Vice President of a major lobbying firm which works to assist pharmaceutical and healthcare firms "address regulatory and operational issues such as the Stark Act, Anti-Kickback Statute and FDA guidelines."[11] In a similar vein, the highest ranking member of the United States government body responsible for collecting the Open Payments Data, came to the position after being appointed by the President of the United States, leaving his most recent role as Executive Vice President

[9] Citizens United v. Federal Election Commission, No. 08-205, 558 U.S. 310 (2010)
[10] Dave Davies, "Tales Of Corporate Painkiller Pushing: 'The Death Rates Just Soared'" National Public Radio, 22 August 2019, Accessed 24 March 2020.
[11]"Director, CDC Washington Office". September 23, 2015, accessed May 26, 2016, http://www.cdc.gov/about/leadership/new-leaders/cdcwashington.html.; LLP, Faegre Baker Daniels. "Health Care - the Law Firm of Faegre Baker Daniels." 2000. Accessed May 26, 2016. http://www.faegrebd.com/Health-Care.

of Optum, a major healthcare subsidiary of the largest healthcare corporation in the United States.[12]

These examples, while anecdotal, are indicative of the structure and function of the broader healthcare and pharmaceutical industries in the United States. Writing from within the conflict paradigm, the power structure of U.S. American public-private collusion has been systematically documented by the critical theorist and sociologist G. William Domhoff in his works on class dynamics and the so-called power elite, notably in his book *Who Rules America?*.[13] Domhoff's tools for network analysis are publicly available and can be used to evidence the interlocking structure between pharmaceutical firms and note conflicts of interest.[14] Public service announcements openly evidence the same collusion.[15] Drawing a parallel to the infamous military-industrial complex, physician Arnold S. Relman offers an account of the 'medical-industrial complex.[16] Published in 1980 in the *New England Journal of Medicine*, Relman notes the dominance of pharmaceutical manufacturers in the healthcare industry and expresses concern about the breadth of privatization and role of regulation.[17]

1.3 MARKETING AS A DETERMINANT OF HEALTH OUTCOMES

This study frames direct-to-physician pharmaceutical and opioid marketing as constituting a social determinant of health within the broader context of the pharmaceutical-industrial complex. Mortality is employed as the key outcome measure.

Existing literature documents the importance of industry payments to physicians. A 2016 study of physicians' prescribing patterns in the state of Massachusetts found that

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[12] "CMS Leadership." Centers for Medicare and Medicaid Services. Accessed June 22, 2016. https://www.cms.gov/About-CMS/leadership/.
[13] G. William Domhoff, *Who Rules America?,* 7th ed. 2014.
[14] G. William Domhoff, "Who Rules America: Search a Database of the Power Elite." 2012. Accessed June 1, 2016. http://www2.ucsc.edu/whorulesamerica/power_elite/search.html.
[15] Regulatory Affairs Professionals Society. "FDA Seeks Industry Representation on 17 of Its Drug Advisory Committees." 2016. Accessed November 1, 2016. http://www.raps.org/Regulatory-Focus/News/2015/04/15/21977/FDA-Seeks-Industry-Representation-on-17-of-its-Drug-Advisory-Committees/.
[16] Arnold S. Relman, "The New Medical-Industrial Complex," New England Journal of Medicine 303, no. 17, (1980): 963.
[17] Ibid. 963-970.

industry payments have a significant impact, the authors writing, "Payments for educational training were associated with a 4.8% increase in the rate of brand-name prescribing."[18]

While pharmaceutical advertising to consumers is a matter of significant sociological interest as it relates to health outcomes, the current study concerns itself chiefly with the role of direct-to-physician marketing. This is because of the physicians' pivotal role in prescription drug sales and consumption. For most U.S. American prescription drug consumers, physicians serve as gatekeepers and advisors. Very few prescription-only drugs are obtained without prior facilitation by a physician or other healthcare professional (eg. nurse practitioner). Moreover, within the current methodological framework, one which relies on the county as the unit of analysis, assessing direct-to-consumer advertising presents analytical difficulties because the advertising is not well-documented at the county-level. The absence of direct-to-consumer advertising as a covariate is an important shortcoming of the study.

2.0 HEALTH OUTCOMES AND DIRECT-TO-PHYSICIAN MARKETING

Another relevant factor is public policy and the interplay between illicit and prescription opioid abuse, as well as non-opioid drugs used for ostensibly non-medical purposes. Public health researchers contend that efforts to criminalize and prosecute prescription drug addiction, normative social values dependent on drug status and perceived legitimacy, and the quality and purity of prescription drugs relative to those manufactured outside of legal regulation, have notable effects in rising prescription drug use, illicit drug use, and their interplay.[19,20,21] Conversely, in the Commonwealth of Kentucky, increased regulation, police action, and prosecution and criminalization of

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[18] J.S. Yeh, J.M. Franklin, J. Avorn, J. Landon, et. al. "Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts" *JAMA Internal Medicine* 176, no. 6 (2016): 763-768.

[19] T.J. Cicero, E.H. Adams, A. Geller, J.A. Inciardi, et. al. "A post-marketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States." *Drug Alcohol Dependence* 57, (1999): 7–22.

[20] E.C. Senay. "Clinical experience with T's & B's." *Drug Alcohol Dependence* 14 (1985): 305–311.

[21] G.E. Woody, E.C. Senay, A. Geller, E.H. Adams, et. al. "An independent assessment of MEDWatch reporting for abuse/dependence and withdrawal from Ultram (tramadol hydrochloride)." *Drug Alcohol Dependence* 72, (2003): 163–168.

prescription drugs has very likely resulted in an increase in illicit opioid use. Kentucky's Office of Drug Control Policy publically claims, "A key driver behind the uptick in heroin abuse was the reformulation of two widely abused prescription pain drugs, making them harder to crush and snort. Drug manufacturers reformulated OxyContin in 2010 and Opana in 2011."[22] Policy variation as it concerns illicit and prescription drug regulation and their availability might account for some of the variation in mortality. Unfortunately, this variation is not operationalized in the current study.

2.1 INTERSECTIONAL PARADIGMS AND HEALTH COMPLEXITY THEORY

Noting the exemplary health inequalities in the United States, especially access to healthcare, the supposed impact of pharmaceutical marketing practices is likely to vary across social groupings. The intersections of masculinity, class, and white supremacy are documented as playing a significant role as it concerns opioid abuse and mortality.[23] However, due to a lack of accessible and relevant data that is compatible via inferential statistics with the key measures of mortality, and the methodological limitations of this study, the impact of direct-to-physician opioid marketing on mortality across social groups is rendered relatively ambiguous.

Drawing on Elizabeth McGibbon and Charmaine McPherson's arguments in *Applying Intersectionality & Complexity Theory to Address the Social Determinants of Women's Health*, the current study seeks to incorporate some of these concerns into the analytical design. McGibbon and McPherson suggest that "feminist intersectionality theory can be applied in tandem with complexity theory to support the amelioration of inequities in the social determinants of women's health."[24]

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[22] Kentucky Office of Drug Control Policy, "The Heroin Epidemic." Retrieved February 29, 2016, from http://odcp.ky.gov/Pages/The-Heroin-Epidemic.aspx

[23] Anne Case and Angus Deaton. "Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century." *PNAS* 112 no. 49 (2015).

[24] Elizabeth McGibben and Charmaine McPherson. "Applying Intersectionality & Complexity Theory to Address the Social Determinants of Women's Health." Accessed 29 February 2016. https://tspace.library.utoronto.ca/bitstream/1807/27217/1/10.1_mcgibbon_mcpherson.pdf.

Interestingly, health researchers have found that, "Native Americans and Asians, had 32% lower odds of having a visit where an opioid was prescribed."[25] This finding is consistent with Anne Case's and Angus Deaton's findings concerning a rise in white-middle class mortality, and with theories of whiteness which contend that normative understandings of white folks, would suggest that they are more trustworthy, thus less likely to abuse medications, and they are more sensitive to pain than people of color who are often seen as not-fully-human, animalistic, and thus more tolerant of physical pain.[26] Additionally, this manifestation of white supremacy is empirically evidenced by biologists studying public health.[27]

The CDC analyzed data from the 2012 National Health Interview survey finding severe disparities in access to coverage by race.[28] According to the CDC's Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2012, "Among adults under age 65, 49% who were uninsured had no visits to a doctor or other health professional in the past 12 months compared with 17% having private health care coverage and 14% with Medicaid."[29] The report also finds that white men visit physicians more frequently than men in any other gender and racial demographic.[30] Thus, it seems reasonable to postulate that white men might use prescription drugs with greater frequency. The role of mass incarceration, as it disproportionately affects men of color, and systemically inhibits said men from access to healthcare, is unknown. In short, the existing sociological theory and circumstantial evidence suggests that people with greater and more frequent contact with health professionals, are more likely to die from drug poisoning or its consequences, than their less medically attended peers.

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[25] Yngvild Olsen, Gail L. Daumit, and Daniel E. Ford. "Opioid Prescriptions by U.S. Primary Care Physicians From 1992 to 2001." *The Journal of Pain* 7, no. 4 (2006): 225-35.
[26] Case and Deaton.
[27] White supremacy in sociological literature has specific meanings which are distinct from popular and reductive uses of the term. For more on this, see Charles Mills' *The Racial Contract*, Paul Gilroy's *The Black Atlantic*, Barnor Hesse's concept *Raceocracy*, and Patricia Hill Collins *Black Feminist Thought*; Alessio Avenanti, Angela Sirigu, and Salvatore M. Aglioti. "Racial bias reduces empathic sensorimotor resonance with other-race pain." *Current Biology* 20, no. 11 (2010): 1018-1022.
[28] CDC National Center for Health Statistics. "NCHS Data on Racial and Ethnic Disparities." July 2014. http://www.cdc.gov/nchs/data/factsheets/factsheet_disparities.pdf
[29] CDC National Center for Health Statistics. "Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2012." Vital and Health Statistics. Vol. 10. Issue. 260. February 2014. http://www.cdc.gov/nchs/data/series/sr_10/sr10_260.pdf
[30] Ibid.

2.2 DIRECT-TO-PHYSICIAN PHARMACEUTICAL MARKETING: EFFECTS IN THE PUBLIC HEALTH LITERATURE

In the 1970's U.S. American sociologists first made explicit the interlocking directorates found within the pharmaceutical and banking sectors.[31] Moreover, the conflicts of interest existing within the U.S. Food and Drug Administration (FDA) —the regulatory body charged with the study and approval of all prescription drugs in the U.S— and the pharmaceutical industry are extensive according to several of FDA reports and spokespersons who have admitted to hiding evidence of fraud in medical research trials. Given what amounts to a pervasive and systemic collusion of interests between state regulatory agencies and private entities, the data provided via CMS must be treated with great skepticism if they should be used in scientific inquiry.

In *The Effects of Pharmaceutical Firm Enticements on Physician Prescribing Patterns* researchers summarize the work concisely in their abstract writing:

> "We examined the impact on physician prescribing patterns of pharmaceutical firms offering all-expenses-paid trips to popular sunbelt vacation sites to attend symposia sponsored by a pharmaceutical company. The impact was assessed by tracking the pharmacy inventory usage reports for two drugs before and after the symposia... A significant increase in the prescribing pattern of both drugs occurred following the symposia. The usage of drug A increased from a mean of 81 +/- 44 units before the symposium to a mean of 272 +/- 117 after the symposium ($p < 0.001$). The usage of drug B changed from 34 +/- 30 units before the symposium to 87 +/- 24 units ($p < 0.001$) after the symposium. These changed prescribing patterns were also significantly different from the national usage patterns... These alterations in prescribing patterns occurred even though the majority of physicians who attended the symposia believed that such enticements would not alter their prescribing patterns."[32]

The United States is unique among developed states in that it permits direct-to-physician pharmaceutical marketing.[33] The private influence on state-run regulatory bodies is well-documented, but the public health effects consequent of these

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[31] Ned Mccraine and Martin J. Murray. "The Pharmaceutical Industry: A Further Study in Corporate Power." *International Journal of Health Services* 8, no. 4 (1978): 573-88.

[32] James P. Orlowski and Leon Wateska. "The Effects of Pharmaceutical Firm Enticements on Physician Prescribing Patterns." *Chest* 102, no. 1 (July 1992): 270–73.

[33] "Developed states," "Global North," "1st World," and so on, are signifiers for states which are located —in Wallersteinian terms— as closer to the "core." See *World Systems Theory Vol. 1*. The term "developed states" does not capture how states have come to be developed.

public-private relationships are far from understood particularly as it concerns collusion in the institution of pharmacy. During the period from 1999 to 2012, prescription opioid consumption in the United States was at an unprecedented high.[34] However, the rhetoric of the pharmaceutical industry and lobby at large suggests that increased spending in the form of direct-to-physician pharmaceutical marketing and physician education should yield an improvement in public health outcomes. By examining the relationships among and between pharmaceutical marketing, prescribing behaviors, and health outcomes, this study explores possible consequences of direct-to-physician pharmaceutical marketing.

The marketing methods of the pharmaceutical industry are observable via the data at hand, the details of their approach and reasoning however, remain unexplained, it demands historical and qualitative explanation. To be clear, we can see how industry conducts direct-to-physician pharmaceutical marketing in monetary and tangible terms, what is not ostensibly clear by the data, is their collective logic and processes which result in direct-to-physician marketing as we observe it in relatively conventional fiscal terms.

Unequal public trust in physicians, across class and race groups especially, is of theoretical relevance. Among U.S. medical sociologists and public health researchers it is common knowledge that throughout the 19th and 20th century, western healthcare providers both in the private and public sectors, routinely neglected to actively practice informed consent with respect to medical research conducted on those seen as inferior on the basis of their identities. This phenomenon is particularly apparent and pronounced in incidents like the Tuskegee syphilis experiments, the legacy of which has far reaching and devastating effects.[35] Other incidents implicate Harvard and John Hopkins universities, where researchers conducted unanesthetized gynecological

[34] E.D. Kantor, C.D. Rehm, J.S. Haas, A.T. Chan, et. al. "Trends in Prescription Drug Use among Adults in the United States from 1999-2012." *JAMA* 314 no.17 (2015): 1818-31.
[35] S.B. Thomas and S.C. Quinn. "The Tuskegee Syphilis Study, 1932 to 1972: implications for HIV education and AIDS risk education programs in the black community." *American Journal of Public Health* 81, no. 11 (November 1991): 1498-1505.

experiments conducted on females of color deemed pain adept due to their race.[36] Similarly, physicians engaged in infanticide, forced reproductive sterilization, and the military testing of chemical weapons on mostly Black folks living in public housing in St. Louis, Missouri.[37] This public mistrust, especially among the marginalized, of the medical community continues to exhibit consequences across stratified racial and class lines. As such, the pharmaceutical industry might target these communities and their physicians accordingly. Moreover, these already marginalized groups are less likely to have access to healthcare and are more likely to forgo or even avoid medical treatment altogether.

2.3 PRESCRIBING PATTERNS

Another central assumption of this project is that physician behaviors have an impact on health outcomes. Among these physician behaviors is a pattern of drug prescribing. It is important to note that substantial sociological, anthropological, and public health literature suggests that by comparison to healthcare systems, socioeconomic determinants of health have a greater explanatory capacity as it concerns various health outcomes.[38] Nonetheless, there is substantial evidence indicating harmful effects of prescribing patterns on health outcomes. For example, a 2015 longitudinal cohort study of adults (n=2848) in the U.S. who had experienced a nonfatal opioid overdose found that 91% of them were subsequently represcribed opioids, and those that were represcribed opioids were found to be disproportionately prone to recurrent overdose.[39]

In short, if direct-to-physician marketing did not have an impact on physicians' prescribing patterns, and in turn pharmaceutical sales and revenues, the pharmaceutical industry, which is conceived of as a self-interested, profit-driven actor, would not engage in the practice. Given the documented impact of opioid prescribing patterns on

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[36] Harriet A. Washington, *Medical Apartheid: The Dark History of Medical Experimentation on Black Americans from Colonial Times to the Present*. New York, NY: Knopf Doubleday Publishing Group, 2008.
[37] Ibid.
[38] M. G. Marmot and Richard G. Wilkinson. *Social Determinants of Health*. Oxford: Oxford University Press, 2006.
[39] Marc R. Larochelle, Jane M. Liebschutz, Fang Zhang, Dennis Ross-Degnan, et. al. "Opioid Prescribing After Nonfatal Overdose and Association With Repeated Overdose." *Annals of Internal Medicine* 164, no. 1 (2015): 1.

the incidence of overdose, and subsequent opioid related mortality, it seems sociologically reasonable and socially important to explore the possibility that direct-to-physician marketing also has an impact on indicators of social well being.

3.0 EXISTING LITERATURE: PROPUBLICA

Physicians' attitudes concerning pharmaceutical representatives and marketing practices have been examined extensively in survey research and in systematic reviews of pharmaceutical marketing literature.[40] Findings by Propublica, a 'big data' and media firm, suggest that physician prescribing patterns are directly correlated with pharmaceutical marketing expenditures by the amount expended and by the type of expenditure, specifically noting that physicians who received remittances from the pharmaceutical industry for speaking at a conference or event were more likely to prescribe drugs produced or sold by the paying company.[41] This analysis was accomplished by linking address and name data across datasets and integrating the 2014 Open Payments data with data from another U.S. prescription drug program called Medicare Part D. Record attrition as a consequence of unmatched links was minimal, Propublica reported that the methods allowed for more than 99.7% of physicians to be linked across datasets. This finding supports the central assumption of this study, that pharmaceutical marketing has an impact, or at the very least is related to, prescription patterns.

Existing literature concerning Open Payments Data is generally concerned with (1) the data's application within a given medical subfield, (2) the data's composition, and (3) the implementation and legislative processes concerning the Open Payments Program. Some significant variance in payments to physicians in at least one specialty and census region (in frequency and total reported amount) was demonstrated in early assessments of the data.[42] Further examination has revealed significant variation in payment amounts

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[40] Puneet Manchanda and Elisabeth Honka. "The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review." *Yale Journal of Health Policy, Law, and Ethics* 5 no. 2. (March 2013).

[41] Ryann Grochowski Jones and Charles Ornstein. "Matching Industry Payments to Medicare Prescribing Patterns: An Analysis." *ProPublica.* (March 2016).

[42] V.K. Rathi, A.M. Samuel, and S. Mehra, "Industry ties in otolaryngology: initial insights from the physician payment sunshine act." *Otolaryngology - Head Neck Surgery* (June 2015).

across medical specialties and subspecialties.[43] These findings provide an empirical basis on which the current study builds by investigating payments across all reported specialties.

3.1 OPEN PAYMENTS LITERATURE

The current study relies on established conventions in public health, sociological, and epidemiological literature to guide the construction of crude mortality rates. Among the studies with such a coding procedure, D.K. Wysowski's study contained a procedure for coding prescription drug-related mortality, and it provides a basis for this study.[44] It also serves to provide a process for selecting particularly relevant ICD-10-CM codes by setting a $n \geq 1000$ limitation on causes listed as underlying or multiple on death certificates.[45] A dramatic increase in methadone, amphetamine, and psychostimulant-related mortality is noted, as well as mortality related to anticoagulants.

A research team at Northwestern University employed the Open Payments data to evaluate the potential conflict of interest between neurosurgeons and osteopathic surgeons, finding that physicians that received payments from pharmaceutical companies and other medical device companies were no more likely to have complications associated with their surgeries than their united counterparts who received no industry payments.[46]

As a matter of understanding how Open Payments are reported, what limitations there are to the financial data, and what the risks and opportunities for MPCs are, it behooves

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[43] Andre M. Samuel, , Matthew L. Webb, Adam M. Lukasiewicz, Daniel D. Bohl, et. al. "Orthopaedic Surgeons Receive the Most Industry Payments to Physicians but Large Disparities Are Seen in Sunshine Act Data." *Clinical Orthopaedics and Related Research* 473, no. 10 (June 2015): 3297-3306.
[44] D.K. Wysowski, "Surveillance of Prescription Drug-related Mortality Using Death Certificate Data" *Drug Safety* 30 no. 6 (2007): 533-40.
[45] Ibid.
[46] R.W. Cook, J.A. Weiner, M.S. Schallmo, D.S. Chun, et, al. "Conflicts of Interest in Spine Surgeons: An Analysis of the Effects of Industry Payments on Practice Patterns and Complication Rates in Spine Surgery." *Spine Journal* 16 no. 10 (2016): 347-348.

us to review the legal literature on the subject. Christian Dingler's Opening Pandora's Box: The Open Payments Reporting Requirements develops the discussion on compliance with this component of the ACA.[47] The so-called loopholes in the program are further discussed by Paul Lichter in Implications of the Sunshine Act: Revelations, Loopholes, and Impact which finds that it is permissible for unrestricted grants to be documented and categorized as research payments.[48] Grants of this nature include salaries for physicians involved, but the nature of the work and compensation amount are not required to be reported in the open payments data.[49]

The problem of industry-physician conflicts of interests is not limited to study by sociologists and public health researchers. In an article written in 2010 by medical professionals, there is a call for a centralized system of accountability due to what they call "rife" conflicts of interests within academic medical centers.[50]

3.2 THE OPEN PAYMENTS DATA: REPORTING AND LIMITATIONS

In and of itself, the OPP data is useful and holds significant research potential as is evidenced by a number of studies that use it descriptively.[51] However, standing alone it is not suitable to address the subject of the research question: What is the nature of the relationship, if any, between contemporary direct-to-physician pharmaceutical marketing practices and opioid mortality in the United States of America since the marketing practice emerged in the late 1990's? In order to address this question, the data had to be reconfigured. This is the reason for the county-level aggregation and integration with demographic data.

The guide to reporting payments explicitly references 18 U.S. Code § 1030 - Fraud and related activity in connection with computers in an effort to protect the data's integrity

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[47] Christian Dingler, "Opening Pandora's Box: The Open Payments Reporting Requirements" *Health Law Litigation* (June 2014).
[48]Paul R. Lichter. "Implications of the Sunshine Act: Revelations, Loopholes, and Impact" *American Academy of Ophthalmology* (2015): 653-655.
[49]Ibid.
[50] B.A. Liang and T. Mackey, "Confronting conflict: addressing institutional conflicts of interest in academic medical centers" *American Journal of Law and Medicine* 36 (2010): 136–187.
[51]CDC Open Payments Program,. "Open Payments User Guide" Accessed May 3, 2016. https://www.cms.gov/OpenPayments/Downloads/Open-Payments-User-Guide.pdf.

and the integrity of the reporting entities. The Open Payments Program allows third parties to report the data, and requires that specific individuals —not firms— be named in the reporting process to be held liable. The language of the legislation allows anyone with the legal authority to represent an applicable manufacturer or provider in the position of 'officer' to legally attest to the quality of the data.

CMS reports that it has been able to verify the identity of 98.8% of payment recipients, but notes that unverified recipients' payments are excluded from the data.[52] The Open Payments data, however, does not extend to nurse practitioners or physician assistants, both of which are legally permitted to prescribe medication.

The American Medical Association (AMA) criticizes the OPP claiming that it has an "overly complex registration process and [provides] inadequate opportunity for physicians to review their individual data."[53] This criticism seems to question the integrity of the data. While the medical and academic rhetoric regarding the data's accuracy seems to concern itself with perceptions of individual physicians and patient misinformation, it does little to put forth concern regarding the data's integrity on a structural level.

The collection and gathering of Open Payments data is the legal responsibility of pharmaceutical firms. In addition to data-reliability concerns stemming from this process —a process in which the regulated industry guides the regulation process— there are other limitations to the data. The data excludes payments to nurses, nurse practitioners, and physicians in residency. The Open Payments data is limited to payments pertaining to prescription drugs covered under Medicare and Medicaid. Drugs not covered by a federal payer may be marketed differently, this creates a fundamental limitation, a bias in the study with largely unknown consequences. "patients with Medicaid (OR 2.09 [95% CI 1.82-2.40]) or Medicare (OR 2.00 [95% CI 1.68-2.39]) had

[52] Thomas Sullivan, "Physician Payments Sunshine Act: CMS posts 2014 Open Payments Data Totaling $6.49 Billion" *Policy and Medicine* (May 2018).
[53] American Medical Association, "Media Guide for Reporting Open Payments Data" Web. (2014) Updated June 2015.
https://www.ama-assn.org/press-center/press-releases/ama-guide-media-reporting-open-payments-data-release-0

significantly higher odds of having a visit where an opiate was prescribed compared to patients in private fee-for-service plans."[54]

The marketing strategies of the pharmaceutical industry, particularly multinational pharmaceutical companies, have been criticized by social researchers and policymakers alike. As a component of the Affordable Care Act (ACA) the Centers for Medicaid and Medicare (CMS) began a program in which payments from pharmaceutical companies to physicians and teaching hospitals are documented. The data is voluminous and comprises 6 unique datasets. This data includes all applicable manufacturers and group purchasing organizations who are in acting accordance with the federal regulation. Mounting criticism of the OPP is readily found in a search of academic databases which yields article titles like, "Open Payments': Has CMS gone too far?", "Open payments may help drive malpractice claims", and "'Open Payments' moves forward despite snags."[55]

3.3 A REVIEW OF DIRECT-TO-PHYSICIAN PHARMACEUTICAL MARKETING LITERATURE

Prior to the implementation of the Open Payments Program, in 2007, a nationwide survey of physicians in the United States (n = 3,167) found that of the 58% of physicians that responded, 94% reported some financial relationship with the pharmaceutical industry.[56] The relationships of interest are quite similar to those documented in the Open Payments data. They include consulting fees, payments for various "professional activities", and free lunches.[57] Also, a history of regulatory attempts at sub-national-levels is documented in a work entitled The Physician Payment Sunshine Act.[58]

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[54] N.D. Volkow, T.A. McLellan, J.H. Cotto, M. Karithanam, et. al., "Characteristics of Opioid Prescriptions in 2009." *JAMA* 305 no. 13 (April 2011): 1299-1301.
[55] Bob Gatty, "Open Payments': Has CMS gone too far?" *Urology Times.* (January 2014).; Bob Gatty. "'Open Payments' moves forward despite snags." *Urology Times* (September 2014).; Alicia Gallegos, "Open Payments may help drive malpractice claims" *CHEST Physician* (September 2014).
[56] E.G. Campbell, R.L. Gruen, J. Mountford, L.G. Miller LG et. al., "A National Survey of Physician–Industry Relationships." *New England Journal of Medicine 357, no. 5* (August 2007): 507–508.
[57] Ibid.
[58]Sachin Santhakumar and Eli Y. Adashi. "The Physician Payment Sunshine Act." *JAMA* 313, no. 1 (January 2015): 23.

Underpinning specific theoretical assumptions and analytical direction put forth in the current study, is a Norwegian study concerned with the sale of prescription drugs. The study provides a methodological precedent for aggregating financial data concerning prescription drugs at the individual and county-levels, and more importantly, finds sales of drugs with abuse potential predicts rates of drug abuse even in spite of relatively strict regulatory measures.[59]

Of the findings in *Industry Financial Relationships in Orthopaedic Surgery* the distribution of total dollars received by individual physicians — most notably orthopedic surgeons— is especially relevant to the current study.[60] The researchers find that the total dollars received are concentrated among a small group of physicians, namely orthopedic surgeons. Making up less than 1% of all those practicing, they nonetheless received nearly 70% of the total monetary value.[61] Additionally, the study puts forth a procedure for linking Open Payments data at the geographical level, as well as methods for normalizing payments data across subspecialties.[62]

An additional mediating factor in direct-to-physician pharmaceutical advertising is the role of direct-to-consumer advertising. This strategy affects physicians in two clearly distinguishable ways. Direct-to-consumer advertising is commonplace in the national media. Physicians are exposed to it directly while listening to the radio or watching television. Importantly, these advertisements often encourage consumers to "ask your doctor about [given drug]". Thus, there is not only the initial direct effect, but a secondary effect that takes place during physician-patient interactions. "Direct-to-Consumer Pharmaceutical Advertising: Therapeutic or Toxic" outlines the

[59] I. Rossow and J.G. Bramness, "The total sale of prescription drugs with an abuse potential predicts the number of excessive users: a national prescription database study" *Biomed Central Public Health* 25 no. 15 (March 2015): 288.
[60]G. L. Cvetanovich, P. N. Chalmers, and B. R. Bach. "Industry Financial Relationships in Orthopaedic Surgery: Analysis of the Sunshine Act Open Payments Database and Comparison with Other Surgical Subspecialties." *The Journal of Bone & Joint Surgery* 97, no. 15 (August 2015): 1288–1295.
[61] Ibid.
[62] Ibid.

structure and consequences of this strategy.[63] "The Role of Direct-to-Consumer Pharmaceutical Advertising in Patient Consumerism" provides a concise and helpful summary of this phenomenon.[64] This mediating factor is not included in this study's models. Similarly, the purchasing power at the county-level is not examined. To be clear, neither the impact of direct-to-consumer advertising nor the ability of consumers to purchase drugs is fully captured by the aggregate variables (eg. median income) included in the current analysis.

4.0 VISUALIZING VARIABLES AND WRANGLING DATA

Mortality, drug marketing, and demographic variables make up the core of this analysis. There are several measures of mortality that are considered here. Each form is a distinct way of measuring death from drug poisoning. Drug marketing is categorized according to the types of drugs being marketed. And demographic variables are included in order to paint a picture of mortality and marketing across social groups. All of the relevant variables are aggregated at the county-level. Of course, counties themselves do not die or advertise the latest painkiller. In the absence of individual-level data on prescribing patterns, drug sales, and drug consumption, the county serves as a bridge between marketing and death. For the county-level comparison to be meaningful, counties must be heterogeneous, and in many ways they are heterogeneous. Nonetheless, the aggregation presents analytical difficulties.

In order to operationalize the relationship between drug marketing and drug mortality, I first turned to the OPP 2013 records. The 2013 records are comprised of payments or gifts from a pharmaceutical company to a physician made between July and December of 2013. Each record, among other variables about the transaction, contains an address which includes a state. By aggregating this data to the state-level (N=51, includes Washington D.C.), it was integrated with several state-level mortality datasets from CDC WONDER Multiple Cause of Death, 1999-2013 requests.

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[63] C.L. Ventola. "Direct-to-consumer pharmaceutical advertising: therapeutic or toxic?" *Pharmacy and Therapeutics* 36 no. 10 (2011):669-684.

[64] B. Wang and A.S. Kesselheim, "The role of direct-to-consumer pharmaceutical advertising in patient consumerism." *Virtual Mentor* 15 no. 11 (2013): 960–965.

4.1 INCOME INEQUALITY

The relationships between social capital, income inequality, and mortality are well-documented in public health literature. Irrespective of gross income and wealth, economic inequality has been found to be strongly correlated with mortality in the United States and elsewhere. By utilizing the Robin Hood Index, a measure of income inequality which examines the distribution of income by calculating a perfect redistribution from those living above mean income to those below, a Harvard School of Public Health study found that, "income inequality leads to an increase in mortality via a divestment in social capital."[65] More recently, comprehensive reviews of the income-inequality-mortality literature have been compiled; one such review in Social Epidemiology, includes three distinct and sociological theories and a substantial body of evidence linking the two.[66]

In the current study, income inequality is operationalized as a county-level Gini coefficient and included as a covariate in the regression analysis. Gini measures of inequality have been subject to methodological criticism for glossing over the structure of inequality, reducing it to a single measure. Alternatively, measures of income inequality examining deciles or the aforementioned Robin Hood Index have been developed. They are not employed here. Moreover, a measure of wealth is not included as a covariate. Importantly, wealth in the United States reveals greater discrepancies in economic inequality, especially along racial lines, due to a long history of economic, social, and political disenfranchisement.

4.2 HEALTH COVERAGE: SMALL AREA HEALTH INSURANCE ESTIMATES

Relying on U.S. Census Bureau's Small Area Health Insurance Estimates (SAHIE) data, which is comprised of hierarchical, Bayesian modified, estimates of health insurance coverage across demographic groupings, the current analysis provides a series of Pearson product-moment correlations and multiple regressions to better understand the

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[65] Ichirō Kawachi, B.P. Kennedy, K. Lochner, and D. Prothrow-Stith, "Social Capital, Income Inequality, and Mortality." *American Journal of Public Health* 87 no. 9 (September 1997):1491-8.
[66] Lisa F. Berkman, Ichirō Kawachi, and M. Maria, *Social Epidemiology.* 2nd ed. New York: Oxford University Press (2014): Pages 126-147.

relationship between healthcare and drug-related mortality. The U.S. Census maintains the data, "can be used to analyze geographic variation in health insurance coverage, as well as disparities in coverage by race/ethnicity, sex, age and income levels that reflect thresholds for state and federal assistance programs."[67]

The insurance data includes the following sociologically relevant demographic descriptors: (1) age is provided in 5 categories, under 65, 18-64, 40-64, 50-64, and under 19, (2) race is given categorically as follows: all races, white alone, black alone, hispanic, (3) sex is provided as: both sexes, male, and female, (4) income is listed relative to the poverty line at rates of 138%, 200%, 250%, 400%, and between 138% and 400%.[68]

4.3 OPIOID AND PRESCRIPTION DRUG MORTALITY

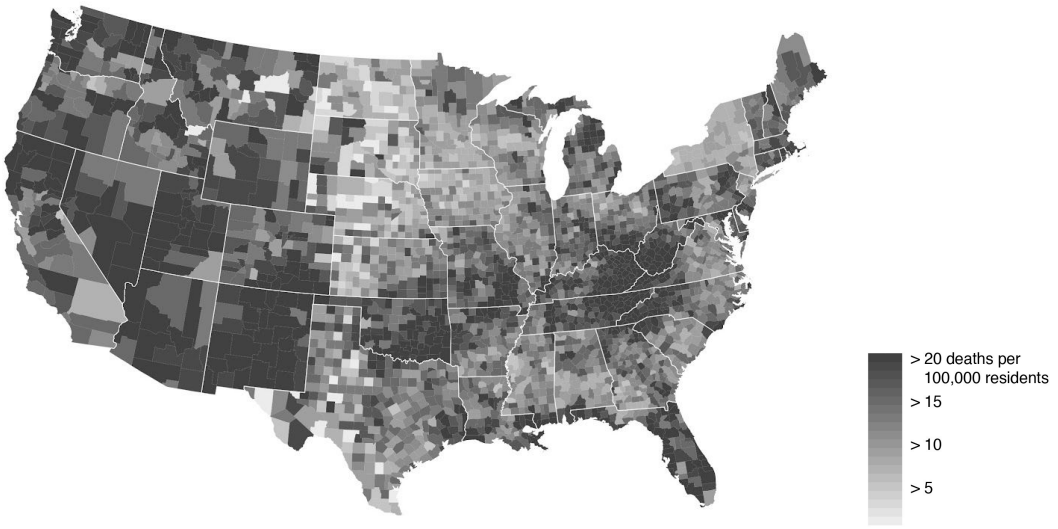
Data from a CDC WONDER Multiple Cause of Death, 1999-2014 Request provides the basis for the preliminary state-level analysis as well as the subsequent county-level analysis. The OPP data contains 1,809 unique entries in 2013 for marketed drugs or medical devices and 2,698 uniques in 2014 and a total of 3,398 unique entries between the years. Each drug or device was individually assessed to determine its risk for abuse.

2013 & 2014 CDC Drug Poisoning Mortality Per 100,000 Residents[69]

[67]United States CDC. "Drug Poisoning Mortality: United States, 1999–2014. NCHS Data Visualization Pilot". Accessed June 7, 2016. http://blogs.cdc.gov/nchs-data-visualization/drug-poisoning-mortality/.

[68] U.S. Census Bureau, "Small Area Health Insurance Estimates. 2013 & 2014" Accessed March 1, 2016. http://www.census.gov/did/www/sahie/ [citing full paragraph]

[69] United States CDC. "Drug Poisoning Mortality: United States, 1999–2014. NCHS Data Visualization Pilot". Accessed June 7, 2016. http://blogs.cdc.gov/nchs-data-visualization/drug-poisoning-mortality/.



Each of the 3,398 unique entries were searched in the U.S. National Library of Medicine PubMed database made available by The National Center for Biotechnology Information and classified according to its documented potential for abuse.[70] Drugs were assigned risk abuse status in the following categories: Risk Not Identified, Other, Medical Device or Non-Pharmaceutical Medical Product, Low Risk/Interest, Moderate Risk/Interest, Opioids, Barbiturates, Benzodiazepines, Stimulants. Drugs with abuse potential that are used in the treatment of serious disease and illness like cancer and HIV/AIDS are categorized as Low Risk in order to avoid misleading effects on mortality.

Other studies concerned with prescription, illicit, and alcohol related mortality have included indirect causes in mortality count and rate calculations; for example, cirrhosis of the liver, a condition associated with extensive and prolonged alcohol use, has been included in studies of alcohol related mortality.[71] This analysis excludes these additional causes. This is because the pharmacological and ischemic (restriction of blood supply) preconditioning of distal and peripheral organs is an observed consequence of prolonged opioid use in other mammals, meaning that while habitual opioid users may be more inclined to overdose, they might be comparatively

[70] U.S. National Library of Medicine PubMed. Web. https://www.ncbi.nlm.nih.gov/pubmed; Documentation of drug schedules/classifications available to researchers on request.
[71] Anne Case and Angus Deaton, "Rising Morbidity and Mortality in Midlife among White Non-Hispanic Americans in the 21st Century." *Proceedings of the National Academy of Sciences* 112, no. 49 (2015): 15078-15083.

physiologically resistant to organ failure (ie. heart attack).[72] By excluding these additional causes of mortality the dependent mortality measure might more precisely and accurately account for prescription drug related mortality, but this precision comes at the expense of statistical power given the reduction of cases included. However, some nonexclusive-opioid causes of mortality are included. Due to the strong relationship between opioid and other prescription drug use and marketing, and the need for statistically significant mortality counts, all prescription drug related mortality is included in the operationalization of the dependent, mortality variable.

A limitation of aggregating opioid marketing into a single category is that such a procedure does not account for the potential mitigating impact that drugs like methadone, an opioid substituted for heroin by many recovering heroin addicts, have on other types of opioid mortality. A 2015 study conducted across the Republic of Ireland —the occupied territory in the North excluded— indicates that taken as a whole, the effect methadone is a decrease in mortality.[73] In this study, methadone is not included in the marketing data, but other opioids that could have a similar impact are included because when the study was conducted, no existing research which evidences this effect in other opioids.

On a relevant note, it is important to mention that the death certificates, from which mortality records are assembled, do not typically include the specific drug associated with death. Additionally, county-level mortality records are based on the county of residency at the time of death, not the place in which death was pronounced. This could present biases in areas where those using prescription opioids are likely to travel frequently or in association with drug use.

Opioid identification poses methodological difficulties because determining what constitutes an opioid is not limited to molecular structure, botanical origin, or

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[72] Takayuki Miki, Michael V. Cohen, and James M. Downey. "Opioid Receptor Contributes to Ischemic Preconditioning through Protein Kinase C Activation in Rabbits." *Myocardial Ischemia and Reperfusion* (1998): 3-12.

[73] Gráinne Cousins, Fiona Boland, Brenda Courtney, Joseph Barry, Suzi Lyons, and Tom Fahey. "Risk of Mortality on and off Methadone Substitution Treatment in Primary Care: A National Cohort Study." *Addiction* 111, no. 1 (2015): 73-82.

biochemical function alone. In a brief telephone interview with a representative of the United States' Food and Drug Administration, the representative claimed that no comprehensive list of prescription opioids is made publically available. Moreover, they suggested that if such information was of interest, one might be able to obtain it through a legal request colloquially referred to as a Freedom of Information Act (FOIA) request and that the processing time would be dependent on the amount of information that would need to be redacted.

County and state mortality rates labeled as 'unreliable' in the data obtained via CDC WONDER requests were included in the regression analysis for two reasons. The 'unreliable' labeling is an automatic procedure which is based on assumptions about the application of the data. Their 'unreliable' label is dependent on the population of the county in which they occurred. While mortality rates in low population, rural, counties are subject to greater error variance, taken as a whole their relationship to prescription drug marketing is not inherently negligible. The lack of reliability is specific to the predictive capacity of the mortality rate data in longitudinal applications. The current study employs a cross-sectional approach. Moreover, there is no reason to suspect the reporting of these deaths is procedurally unreliable. Omitting these deaths from the analysis would create an urban bias. These data are not statistically inferred, but represent actual reported deaths.

4.4 GEOCODING, LINKAGE, AND AGGREGATION OF DATA

The initial dealings with the Open Payments were concerned with linking the data to geospatial, socially, and politically defined areas. This geocoding process was performed with the intent of producing a helpful county-level dataset linked to county-level health outcomes. Simply, each record of a financial transaction between a doctor and a pharmaceutical company has an associated address, but this information does not include a county. Counties have both names and identification numbers. An effort was made to assign both name and identification number to each financial record. To do this a latitude and a longitude was assigned to each record, and then that coordinate was located within the boundaries of the relevant space.

Moreover, some of the financial records have incorrect or incompatible geospatial information concerning an address, location, city, or state. For example, in a given financial record, a street address might not exist in the city or state named in that record. In the 2013 general payments data, there were 5,484 records in which the address provided did not match any address existing in the state provided. These records have been omitted from the study. In the 2014 general payments data 1,588 records were subject to omission on the same grounds. All together, 7,072 records were omitted from the study for this reason. Four of these omitted records document the marketing of opioids.

Given the size of the data and technological limitations, initially the geocoding efforts were conducted via a webtool yielding no matches utilizing two random samples (n = 1,000) of addresses from the general payments 2013 dataset. Subsequent geocoding attempts resulted in significant attrition in usable records due to their returning of "no-match" (missing values) for latitude and longitude. The missing values occurred due to a limitation in the functionality of an application programing interface which was unable to process superfluous address-related information included in queries. By restructuring address data, the number of results missing records was reduced to 41 in both samples (n = 1,000).

In an effort to produce greater usable records the addresses were further recoded. This was accomplished by selecting the address variable to be geocoded by the first appearing numeric value. In other words, the address variable selected for geocoding was selected dependent on the value type of the first character in its field. This recoding resulted in missing values of 33 and 27 from the two aforementioned cohort-style samples (n = 1,000). Additional measures were taken, including recoding informed by United States Postal Service's (USPS) complete list of street types, and the removal of "STE" and "Suite" from the addresses. The USPS-informed measures produced greater missing values (NA = 58 & 47) and the "STE" correction measures produced a relatively small change (NA = 32 & 28) accompanied by further complications. Thus, the original, value-based recode method was selected for application to the larger data

set. For the purpose of reproducibility, the complete R script, commentary, and statistical analysis is published online.[74]

The missing address data is treated as missing at random (MAR), though it should be noted that causal explanations for missingness are plausible. The 'no-match' returns tended towards longer addresses with greater complexity. Cursory observations of missing addresses suggest addresses containing "P.O box" and "STE", in addition to misspellings and incidental typing mistakes are to account for the majority of missing addresses. Given the large volume of data and minimal attrition of records, imputation methods are deemed unnecessary as it pertains to record loss. The attrition of payment cases, consequent the aforementioned imperfect geocoding process and assumed to be MAR, totals an approximate $595,529,141 in expenditures, 6.077% of the total reported amount of approximately $9.92 billion.

4.5 PHARMACEUTICAL ABUSE-POTENTIAL CLASSIFICATION PROCEDURE

Narrowing the scope of the study to high-risk and abuse-heavy pharmaceuticals required that the drugs being marketed in the 2013 and 2014 Open Payments data be identified. This was accomplished by writing an R-script that identified all unique values listed in the general payments data under the five categories containing drug names. According to this procedure 1,809 unique entries in 2013 and 2,698 unique entries in 2014 were observed. Between the two datasets 3,398 unique entries were observed. It is important to note, 'unique entries' is to mean exactly that, unique strings of data. For example, the drug Jentadueto may appear multiple times in the data as "Jentadueto", "JENTADUETO", and "Linagliptin / Metformin".

These 3,398 drugs, medical devices, medical procedures, and other entries were classified primarily according to their opioid status. Opiate derivatives, opiate synthetics, and other abuse prone pharmaceuticals like barbiturates and amphetamines comprised the minority of entries by unique value. The majority of the entries by unique value were not for pharmaceuticals at all, but instead medical procedures and sometimes ambiguous subjects with seemingly little medical relevance. These are classified as not

[74] GitHub.

identified, in clinical trial, topical and dermatological, over-the-counter (non-prescription), or medical device or procedure. Another category, other, was used for other biological materials like blood, and abstract entries like ‘education’ and ‘default’, and plants. An additional category comprised of ‘low-risk’ for abuse pharmaceuticals contains a range of drugs including: all cancer specific drugs, HIV drugs, vaccinations, Hepatitis B medications, Multiple Sclerosis medications, other antivirals, drugs for hypertension, drugs for asthma, blood disorders, cholesterol medications, antibacterials and antifungals, drugs to prevent organ and limb rejection, local anesthetics like lidocaine, drugs primarily used for contraceptive purposes, most NSAIDs, end-stage of life drugs, smoking cessation medications, some atypical antipsychotics, and ophthalmic solutions. Even drugs with relatively high abuse potential are included here if they are primarily used in people with serious and fatal medical conditions.

Drug categories of comparatively greater interest include one labeled, ‘Moderate or Possible Risk’ which contains some antipsychotics, synthetic testosterone, some sedatives, and some sleep aids. Additional high risk categories are stimulants, opiates, benzodiazepines, barbiturates, and —a possible mediating category— drugs used in opiate addiction treatment. One additional category, ‘unknown’, was used throughout the categorization process for drugs that were not readily classified according to their abuse potential. Each drug was manually checked via a Google application against databases made available by the United States Food and Drug Administration, the U.S. National Library of Medicine, U.S. National Institutes of Health, U.S. National Cancer Institute, U.S. Centers for Disease Control and Prevention, the World Health Organization and ClinicalTrials.gov. Drugs and medical devices not found in these databases were classified according to information made available by the manufacturer or classified as unidentified. No pharmaceuticals without substantial supporting evidence were included in any of the ‘high risk’ categories (ie. opiates, barbiturates, benzodiazepines). However, due to possible researcher error, drugs with high-risk for abuse may have been improperly classified as low-risk. Drugs which were not found in the aforementioned databases were identified according to pharmacologic composition. In other words, the data are organized so it is very unlikely to infer a connection

between drug marketing and mortality that has no empirical or ontological basis, but an existing connection could be easily missed.

This classification procedure presents a significant limitation to the study because the pharmacokinetics of the respective pharmacological substances are not central to the study. Drugs which might be correlated with abuse and act on opiate receptors might have been unintentionally excluded from the current study. Some antiepileptic drugs, selective serotonin reuptake inhibitors, certain antidepressants, and other pharmaceuticals with known risks are excluded from moderate and high risk classification despite their clinically observed association with high risk behavior and suicide. This also presents a significant limitation to the study.

4.6 DESCRIPTIVE STATISTICS

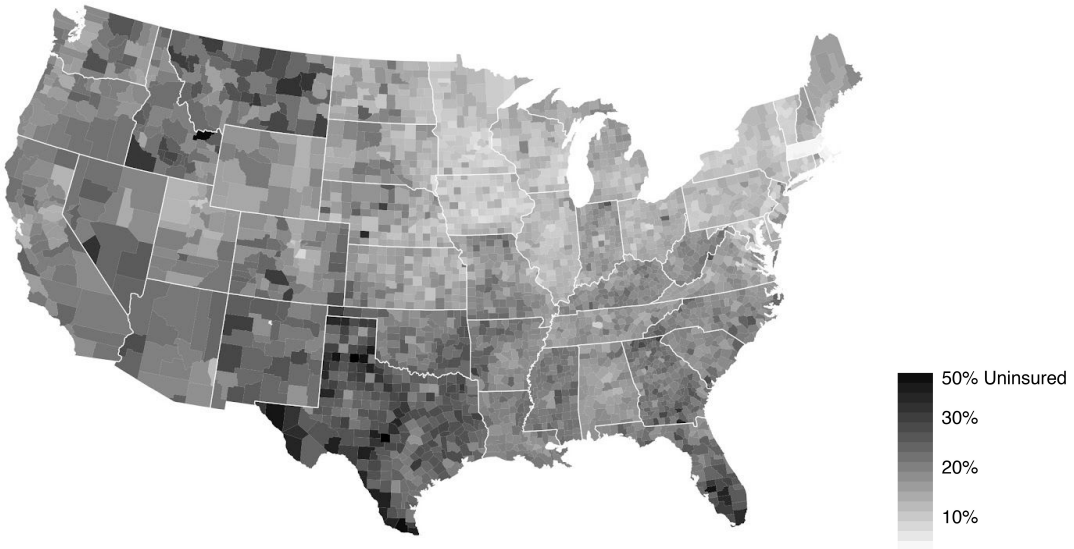
Before discussing opioid marketing data, it will be helpful to give a brief overview of relevant socioeconomic factors. These data come mostly from national censusing. In the United States, health uninsurance and unemployment rates are mostly consistent across highly populated and less populated areas, varying by only a few percentage points. That is to say, whether one lives in a city or a rural environment is not a great indicator of employment or health insurance status. Of course, there is variation within types of paid work performed by city dwellers relative to their counterparts working in less populated settings.

Median income, however, is much higher in urban centers. American households in highly populated urban areas report about $14,000 more in annual income than the national mean. Income inequality as measured by a Gini coefficient, is somewhat higher in highly populated areas.

The descriptive statistics contain important characteristics. For example, there are more than twice as many doctors in highly urbanized counties relative to their less urbanized counter-parts. In 2013 and 2014, for every one prescription opioid death in an urban population there were nearly two deaths in the general population. Yet, when all types of drug deaths are examined, the ratio is closer to 1:1. Also, the stratification of formal

educational attainment is apparent. This stratification appears across and within urban and non-urban settings.

2013 Uninsured Rates[75]



[75]United States CDC SAHIE uninsured aggregate 2013 and 2014 data mapped in RStudio with ggplot. Some county codes are inconsistent with the original data source and must be manually corrected for county-level mapping. They are (1) St. Martin, Louisiana (2) Currituck, North Carolina (3) Okaloosa, Florida (4) Galveston, Texas (5) Accomack, Virginia (6) Pierce, Washington (7) San Juan, Washington

Physicians Per 100,00 Residents

Descriptive Statistics By Variable and Level

	Counties							Urban Centers (Top 100 Counties)						
	Mean	Median	SD	Skew	Kurtosis	Obs	Missing	Mean	Median	SD	Skew	Kurtosis	Obs	Missing
Controls														
Uninsurance Rates	.1748	.1721	.05459	.4969	.4242	3141	1	.1649	.1635	.06297	.4809	.7379	100	0
%Unemployment	6.268	6	2.304	1.242	4.49	3141	1	6.199	6	1.517	1.03	1.446	100	0
Median Income	47125	45229	12105	1.389	3.558	3141	1	61822	56872	16381	.7105	-.2001	100	0
Gini Income	.4378	.4356	.03476	.3531	.4682	3142	0	.4691	.4681	.03419	.4364	1.139	100	0
% <High school	15.45	14.1	6.913	.877	.886	3142	0	13.54	12.3	5.506	1.657	3.632	100	0
% High school only	34.88	35.2	7.009	-.2948	.1553	3142	0	23.91	24.35	4.687	-.3412	-.5634	100	0
% Some college	29.92	30	5.255	.0347	.003042	3142	0	27.7	28.45	4.637	-.2885	-.1803	100	0
% ≥Bachelor degree	19.76	17.6	8.828	1.531	3.1	3142	0	34.84	33.3	9.629	.2974	-.3491	100	0
% White	83.67	90.11	16.64	-1.71	2.845	3142	0	65.48	68.31	14.48	-.9542	.7778	100	0
Physician Per 100,000	55.45	47.82	44.57	3.004	24.51	3142	0	118.8	112.5	44.14	.7783	.7113	100	0
Marketing Payments														
All Payments	1173204	12447	10722925	34	1465	2968	174	24917823	11566319	52901293	6.976	56.79	100	0
Opioid, per cap	.01264	.004867	.06872	26.55	798.4	1916	1226	.04768	.01615	.2268	9.518	90.65	100	0
Opioid, per doc	20.72	9.165	96.41	26.12	851.2	1904	1238	35.11	14.08	135.3	9.361	88.59	100	0
LR, per cap	.936	.2201	1.962	6.041	58.27	2929	213	4.688	3.557	4.466	3.335	13.68	100	0
LR, per doc	1397	619.1	2466	6.818	77.65	2813	329	3732	3343	2549	3.664	20.65	100	0
MR, per cap	.1508	.04021	.3481	7.536	101.9	2591	551	.5947	.4379	.8305	6.307	47.06	100	0
MR, per doc	248.2	92.55	970.9	25.84	829.3	2537	605	464.8	424.4	367.3	3.769	19.53	100	0
HR, per cap	.02198	.005813	.09906	22.82	691.6	1970	1172	.09429	.04739	.3331	9.336	88.29	100	0
HR, per doc	31.89	11.55	118.8	17.26	407.3	1956	1186	73.42	41.15	199.6	8.957	83.38	100	0
Mortality Measures														
Mortality	1055	1059	270.1	.1335	.4299	3063	79	722.2	693.6	166.9	.5303	-.09454	100	0
Drug Mortality	13.78	13.05	4.937	-.3415	-.7999	3137	5	14.97	15.05	4.526	-.4938	-.9528	100	0
Prescription Mortality	14.91	11.51	12.6	3.359	16.57	588	2554	8.593	8.057	4.481	.8205	.1083	100	0
Prescription Opioid Morality	12.01	8.745	12.22	3.795	19.24	469	2673	6.1	5.153	3.585	.9547	.3524	98	2

The pharmaceutical marketing dataset used in this study only includes drugs, devices, biologicals, and medical supplies covered by some form of Medicare or Medicaid. In other words, some form of the U.S. national government's health insurance scheme must cover the drug in order for it to appear in this study. There certainly are drugs that fall outside of the scope of these public insurance programs. And there is every reason to expect that pharmaceutical companies market these drugs to physicians and consumers. However, the bias presented by this is not accounted for by analytical procedures.

As it concerns specific causes of mortality at the county level, tabulations or counts of less than 10 are omitted in order to maintain anonymity of deceased persons, their families, associates, etc. For example, if 2 people in Absaroka County, Wyoming were trampled to death by giraffes, this data would be omitted from the dataset because it would be easy to identify the trampled persons. Therefore, subgroup analysis at the county-level would be difficult using this dataset. However, subgroup analysis of the data at the state-level, in high population counties, and in large metropolitan areas remains statistically powerful because these regions are not subject to the aforementioned suppression. Here subgroup is intended to refer to any coherent social group other than the general population of an area.

Of the total 240,868 cases of research payments recorded in the 2013 Open Payments data, 197,547 were payments made to non-covered entities. In these cases, the non-covered entity has some association with a covered entity or covered doctor. Of the reported 2013 payments, less than .002% (n=346) of payments were made outside of the United States. Given the multinational nature of the marketers in question, this data is not likely to help paint a picture of their international payments at large.

The 2013 general payments includes 1,314 unique payers totaling $971,973,670 (applicable manufacturers or group purchasing organizations), almost all of these payments were made in the United States or its 'territories'. In Puerto Rico, which was not included in this study, 2013 general payments totaled $3,209,688. In sum —payments in *de facto* colonies eg. American Samoa and Guam— $3,214,070 in

payments are excluded in addition to $6,069 that remain unaccounted for at the state-level. Notably, in the 2013 general payments 4,055,634 transactions were recorded and though these are not employed directly in my analysis, they are used in other similar studies as independent variables.[76] The 2013 research payments total $1,552,650,054 made by 527 unique payers. In the 2013 ownership and research payments, all payments were accounted for at the state-level. Given the values of these payments relative to total expenditures, these missing values are of minimal concern. Notably, no ownership payments were observed in Hawaii or Alaska. The research payments data contains $2,976,836 in expenditures in Puerto Rico which were excluded.

4.7 VARIABLE AND DATA SUMMARY

Mortality data (noted as *mortalityA*, see appendix *1)* is derived from a CDC WONDER Multiple Cause of Death, 1999-2013 request provides the basis for the preliminary state-level analysis. The data used in the current analysis is public-use data, however, it should be noted that restricted-use forms are available and contain more comprehensive county-level measures.

In sum, 35 variables, some as aggregates (eg. drug name and NDC), across all datasets (6) provided via the OPP and through the U.S. Center for Disease Control's data system the Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) requests, are used in the analysis. The CDC WONDER data are composed of mortality figures grouped according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM, U.S. American Revision) coding system and by county or county-equivalent geospatial region. In short, the data are composed of variables concerning how pharmaceuticals are marketed, where they are marketed, and the health outcomes of populations in the aforementioned areas. Unfortunately, when this study was originally conducted, the nationally representative data concerning health outcomes (eg. hospitalization) only extended through 2013, so these could not be used as reliable dependent variables. The marketing data in question were only captured

[76]Scott E. Hadland, Ariadne Rivera-Aguirre, Brandon D. L. Marshall, and Magdalena Cerdá, "Association of Pharmaceutical Industry Marketing of Opioid Products With Mortality From Opioid-Related Overdoses." *JAMA Network Open* 2 no. 1 (January 2019).

during 2013 and 2014. The mortality data comes from the same period, from 2013 and 2014. The analysis does not lag mortality which is an important limitation of the study. No longitudinal analysis of the data which might attempt to establish causality between health outcomes and marketing was performed.

5.0 ANALYSIS

In the initial exploratory analysis, state and county-level per capita direct-to-physician marketing expenditures were calculated using population data from the 2010 U.S. Census Regional and Demographic Data and treating the 2013 and 2014 OPP data as cross-sectional by grouping ownership, research, and general payments from 2013, with their respective counterparts in 2014. Thus, the calculated product is indicative of per capita expenditures by county for a 17 month period beginning in August of 2013 and extending to December of 2014. Given that the population data used during this preliminary and exploratory analysis is from the 2010 U.S. Census, population change between these periods (2010 and 2014) is unaccounted for using this procedure. Subsequent analyses in this study employ population estimates for 2014 as given by the U.S. Census.

Public health researchers in the United States employ a number of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) coding procedures to account for prescription drug related mortality. Generally, these procedures include categorizations for intentional and unintentional overdoses, adverse effects, and assaults involving drugs. Additionally, coding procedures often incorporate the use of illicit (non-prescription) drug use. The ICD-10-CM[77] procedure was used in the coding of prescription drug-related death. *(see appendix I)*

Per capita expenditures for 2013 general payments, ownership payments, and research payments were calculated using the US Census 2013 state estimates. Pearson's correlations between per capita expenditures and prescription drug related mortality per 100,000 were performed yielding no statistically significant effects for general

[77] Prescription Drug Overdose Team, CDC. "Prescription Drug Overdose Data & Statistics: Guide to ICD-9-CM AND ICD-10-CM Codes Related to Poisoning and Pain"(12 August 2013).

payments or open payments, and a moderately high inverse correlation between research payments and crude mortality ($r = -.334$, $p < 0.05$, $N=51$).

Correlation matrices were constructed and significant relationships were observed. Taken causally, they suggest direct-to-physician marketing yields improved health outcomes (i.e. life expectancy). While theoretical implications were considered, notably the notion that marketing prescription drugs to physicians constitutes a form of continuing professional education and improves physician performance, this explanation might be an inadequate simplification. Alternatively, a spurious relationship between direct-to-physician pharmaceutical marketing, income, and health outcomes was postulated. After further examination of the data in the form of a multiple regression, it was determined that median household income, when included in the regression, accounts for much of the variance in mortality at the state-level.

Though these analyses are telling, they do not insufficiently address the core questions of this research project. In order to address the shortcomings, a multiple Poisson regression and a log-transformed regression were used. Moreover, marketing payments for non-opioid drugs were subsequently excluded, and instead only marketing payments for selected opioid drugs were included. The state-level analysis was eliminated and a county-level analysis was conducted.

These exploratory analyses rely on the assumption that the data at hand is normally distributed. Most variables are normally distributed, however, they are not all normally distributed. In particular, per capita payments were examined for normality and it was determined that they are non-parametrically distributed according to a graphical plot and a Shapiro-Wilk test. Therefore, the exploratory findings should be approached with caution. Additionally, West Virginia appears as an outlier with an illicit and prescription drug poisoning crude mortality rate of 48 per 100,000 inhabitants, well over twice the median rate. Nonetheless, it is included in the analysis.

Normality testing and visual examination of graphical representations of some of the control variables (eg. education variables, median household income, rates of

(un)insurance, etc.) indicates relative normality of the data. The distribution of payments and mortality data, however, creates cause for concern as it pertains to the assumption of normality.

The state-level expenditures were calculated with post-attrition data by using Federal Information Processing Standard Publication (FIPS) codes contained within previously constructed county-level aggregate expenditures. Notably, an approximate 6% of cases and at least $52 million in payments, were excluded from the analysis. These missing cases were treated as MAR. Given the nonparametric distribution of these data further analysis is required.

The inverse correlation found between research payments and mortality might be explained by a consequence of error, the MAR assumption, or difficulties that occurred in the data aggregation process. It might also be attributable to a spurious factor accounted for by median income or wealth. Additionally, it might be due to a beneficial public health effect spurring from private investment in pharmaceutical research. These explanations suggest a need for thorough evaluation of the structuring and analytical process, and potentially the incorporation of mediating factors.

In summary, the following three findings are particularly helpful for further examination of the data:

1. The state-level aggregation of the data is not wholly sufficient for the purposes of this study because too much heterogeneity is lost. Therefore, county-level analysis is needed.
2. The assumption of MAR might be wrong. Missing records could be a consequence of systematic bias.
3. Measures of income, wealth, and/or other socioeconomic data might be needed to explain the observed correlation and mediate for spurious relationships.

Nonetheless, the state-level payments were aggregated from the original Open Payments files and Pearson's correlations were performed using the 2013 general payments,

research payments, and ownership payments as they relate to crude mortality rates as defined by the aforementioned coding procedure.

State-Level Drug Poisoning Mortality and Aggregate Industry-Physician Payments Correlations		
	r	p-value
General Payments	-0.2744	0.0513
Research Payments	-0.3405	0.0145
Ownership Payments	-.0536	.7147

Due to differences in prescribing patterns across physician types, payments to physicians were aggregated by type and correlated via the Pearson product-moment method with mortality. None of the correlations were found to be statistically significant in accordance with the (.05) convention.

Six (6) physician types were identified in the dataset. Medical doctors, ostephathists, chiropractic, dentistry, optometry, podiatry. $236,673,912 in payments were not assigned to physicians, but instead to teaching hospitals.

State-Level Payments by Physician Type and Mortality by Drug Poisoning Correlations				
Physician Type	Total Payment	% payments	r	p-value
Other (Teaching Hospital)	$236,723,298	0.2436	-0.2636	0.0617
Chiropractor	$77,774	0.00008	0.15611	0.3002
Doctor of Dentistry	$27,684,117	0.02848	-0.0357	0.8035
Doctor of Optometry	$9,214,477	0.0095	0.0716	0.6177
Doctor of Osteopathy	$22,164,911	0.0228	0.1547	0.2785
Doctor of Podiatric Medicine	$5,611,244	0.0058	-0.2039	0.1512
Medical Doctor	$670,497,848	0.6898	-0.2494	0.0775

For each physician type and for teaching hospitals, per capita expenditures by state were computed. Subsequently, a Pearson's correlation was performed. No physician type was found to be correlated with crude *mortalityA* at a statistically significant level. Three "Covered Recipient Types" were observed in the research payments dataset. "Covered Recipient Physician", "Covered Teaching Hospital", and "Non-covered Recipients entities".

Covered Recipient Types and Mortality by Drug Poisoning Correlations				
	N	**%**	**r**	**p-value**
Covered Recipient Physician	15967	0.06629	-0.1357	0.3473
Covered Recipient Teaching Hospital	27354	0.11356	-0.2120	0.1395
Non-covered Recipient Entity	197547	0.82015	-0.3111	0.0279

Only non-covered recipient entities were found to be correlated with *mortalityA* at the chosen significance level (CI=95%). Mostly, "non-covered recipient entities" are private health clinics and research organizations. One explanation for this relationship is that private healthcare organizations are most likely to target patients covered by insurance, with financial resources, and exist in close physical proximity to the target populations, which happen to have generally better health outcomes. As a matter of understanding this relationship, further investigation into factors relating to *mortalityA* is needed.

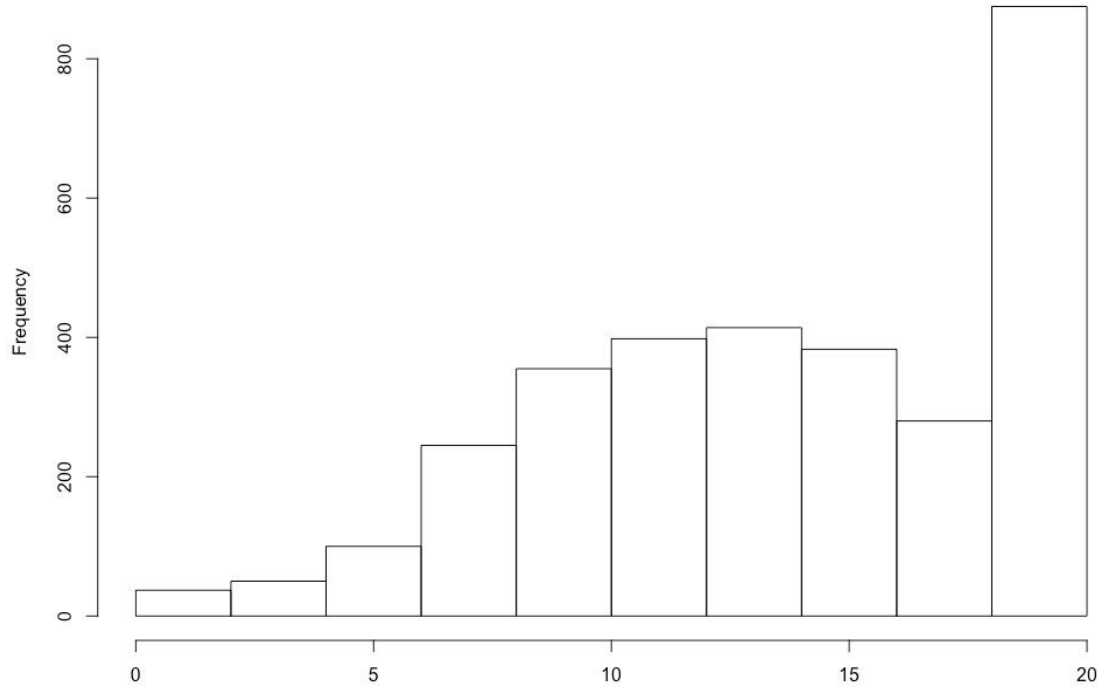
5.1 DISTRIBUTION AND OVERDISPERSION OF KEY VARIABLES

Linearity, statistical independence, homoscedasticity, and normality of data are required if the inferences made from the multivariate linear regression are to be valid. The overdispersion of opioid payments at the county-level threatens the required assumptions for modeling the data according to conventional multivariate linear regression. Given that the outcome measure used in this study is mortality, a form of count, rate, or event data, Poisson regression, a generalized linear model, was selected

due to its appropriateness in analyzing data in count and rate form. In this case, that count and rate data takes the form of incidents of mortality which are independently observed and follow a Poisson distribution. The types of both the dependent and independent variables here are compatible with Poisson regression. However, in order to employ Poisson regression, the distribution of the data must not be overly dispersed where the observed variance is significantly greater than expected variance. Unlike standard linear regression, in which estimated variance is determined from a parameter which is independent of the mean, in generalized linear models like Poisson regression, the variance and mean are interrelated based on the model's structure. Thus, certain assumption tests are required. The data's dispersion was determined by calculating the mean, observed and expected variance, and a Kolmogorov–Smirnov statistic as a means of testing the parametric/nonparametric distribution of each of the CDC WONDER sets of rate/count mortality data.

A more expansive, but less precise, mortality dataset comprised of intervals of mortality rates was treated initially as an ordinal dependent variable and analyzed via ordinal regression models. However, this approach does not account for uncertainty pertaining to the variation within a given interval, instead relying on a midpoint. Provided by the CDC, the data has undergone both left and right censoring as well as interval censoring and thus requires analysis with interval regression.

County-Level, Age-Adjusted, Drug Poisoning Deaths Per 100,000



The most complete drug poisoning data made publically available is truncated, with deaths of greater than 20 per 100,000 being grouped into a single category. Therefore, as seen in the histogram above, there is a heavy right skew.

Population-estimated error margins for Gini index estimates, uninsurance rate estimates, and demographic estimates are unaccounted for in the regression analyses. The explanatory variables' variance errors are assumed to be uncorrelated and orthogonal relative to the error variance assumed by the model.

Top 100 Counties Pearson's r Correlation Matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1 Uninsured Rates																							
2 Unemployment	0.24*																						
3 Median Income	-0.52***	-0.51***																					
4 Gini income	0.10	0.09	-0.25*																				
5 % <High School	0.62***	0.61***	-0.52***	0.21*																			
6 % High School Only	0.11	0.39***	-0.59***	-0.11	0.19																		
7 % Some College	0.23*	0.16	-0.34***	-0.56***	-0.04	0.26**																	
8 % Bachelor Degree	-0.51***	-0.61***	0.75***	0.20*	-0.64***	-0.72***	-0.59***																
9 % White	0.00	-0.23*	0.04	-0.18	-0.23*	0.06	0.25*	-0.02															
10 Physician per 100,000	-0.48***	-0.28**	0.28**	0.57***	-0.29**	-0.31**	-0.63***	0.62***	-0.12														
11 All Payments	0.09	0.09	-0.09	0.30**	0.21*	-0.14	-0.15	0.03	-0.13	0.23*													
12 Opioid, per cap	0.02	-0.10	-0.04	0.14	-0.01	-0.12	-0.09	0.11	0.07	0.14	0.03												
13 Opioid, per dr.	0.05	-0.10	-0.05	0.13	-0.01	-0.11	-0.06	0.09	0.08	0.10	0.02	1.00***											
14 LR, per cap	-0.13	-0.04	-0.11	0.55***	0.05	-0.10	-0.39***	0.21*	-0.17	0.60***	0.73***	0.28**	0.27**										
15 LR, per dr.	0.12	0.06	-0.28**	0.42***	0.17	0.05	-0.16	-0.04	-0.13	0.23*	0.82***	0.26*	0.26**	0.87***									
16 MR, per cap	-0.22*	-0.13	-0.07	0.37***	-0.03	-0.08	-0.30**	0.20*	-0.05	0.52***	0.24*	0.39***	0.38***	0.74***	0.47***								
17 MR, per dr.	-0.08	-0.12	-0.18	0.29**	-0.02	0.01	-0.14	0.07	0.03	0.27**	0.18	0.49***	0.49***	0.63***	0.50***	0.91***							
18 HR, per cap	0.02	-0.10	-0.06	0.16	-0.01	-0.09	-0.10	0.10	0.06	0.16	0.05	0.99***	0.99***	0.32**	0.29**	0.42***	0.52***						
19 HR, per dr.	0.06	-0.08	-0.09	0.13	0.00	-0.05	-0.05	0.05	0.08	0.08	0.03	0.98***	0.99***	0.28**	0.29**	0.39***	0.53***	0.99***					
20 All Mortality	-0.22*	0.15	-0.39***	0.17	-0.20*	0.65***	0.19	-0.29**	0.21*	0.14	-0.11	-0.01	-0.01	0.09	0.11	0.03	0.07	0.01	0.02				
21 Drug Mortality	-0.02	0.19	-0.44***	0.18	-0.01	0.34***	0.28**	-0.30**	0.13	-0.01	0.11	0.12	0.13	0.22*	0.27**	0.17	0.20*	0.14	0.15	0.47***			
22 Prescription Mortality	-0.31**	-0.10	-0.18	0.04	-0.28**	0.28**	0.15	-0.05	0.23*	0.21*	-0.10	0.15	0.16	0.15	0.08	0.22*	0.26**	0.17	0.17	0.52***	0.55***		
23 Prescription Opioid Mortality	-0.24*	-0.05	-0.24*	0.01	-0.18	0.29**	0.17	-0.14	0.29**	0.13	-0.11	0.12	0.12	0.11	0.05	0.21*	0.25*	0.13	0.12	0.48***	0.53***	0.98***	
24 Opioid Claims (Part D)	0.02	0.02	-0.47***	0.16	-0.15	0.29**	0.31**	-0.20*	0.22*	0.10	-0.05	0.20*	0.21*	0.23*	0.26*	0.21*	0.27**	0.22*	0.22*	0.62***	0.46***	0.51***	0.49***

Top 100 Counties Spearman's rho (ρ) Correlation Matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1 Uninsured Rates																							
2 Unemployment	0.24*																						
3 Median Income	-0.53***	-0.49***																					
4 Gini income	0.12	0.11	-0.34***																				
5 % <High School	0.62***	0.49***	-0.55***	0.29**																			
6 % High School Only	0.07	0.42***	-0.56***	-0.02	0.20*																		
7 % Some College	0.31**	0.17	-0.32**	-0.49***	0.05	0.21*																	
8 % Bachelor Degree	-0.54***	-0.56***	0.75***	0.10	-0.63***	-0.67***	-0.57***																
9 % White	-0.13	-0.20*	0.06	-0.24*	-0.38***	0.10	0.25*	-0.03															
10 Physician per 100,000	-0.53***	-0.25*	0.24*	0.47***	-0.29**	-0.24*	-0.59***	0.60***	-0.15														
11 All Payments	0.00	-0.13	-0.16	0.51***	0.14	-0.10	-0.25*	0.13	-0.21*	0.50***													
12 Opioid, per cap	-0.01	-0.14	0.07	0.33***	-0.14	0.00	-0.16	0.22*	0.04	0.34***	0.38***												
13 Opioid, per dr.	0.17	-0.06	0.00	0.10	-0.10	0.11	0.11	-0.01	0.14	-0.06	0.17	0.90***											
14 LR, per cap	-0.15	-0.12	-0.16	0.61***	-0.02	0.03	-0.37***	0.22*	-0.18	0.66***	0.78***	0.58***	0.32**										
15 LR, per dr.	0.15	0.03	-0.37***	0.47***	0.18	0.20*	-0.07	-0.10	-0.14	0.17	0.66***	0.51***	0.46***	0.83***									
16 MR, per cap	-0.17	-0.16	-0.06	0.50***	-0.09	-0.04	-0.31**	0.30**	-0.11	0.53***	0.59***	0.50***	0.28**	0.83***	0.71***								
17 MR, per dr.	0.07	-0.05	-0.20*	0.32**	0.04	0.10	-0.02	0.01	0.00	0.03	0.37***	0.35***	0.36***	0.55***	0.74***	0.84***							
18 HR, per cap	0.02	-0.06	-0.09	0.38***	-0.01	0.08	-0.15	0.11	-0.05	0.31**	0.46***	0.78***	0.69***	0.62***	0.61***	0.61***	0.53***						
19 HR, per dr.	0.21*	0.03	-0.18	0.20*	0.07	0.17	0.09	-0.10	0.02	-0.04	0.30**	0.70***	0.78***	0.40***	0.57***	0.43***	0.53***	0.92***					
20 All Mortality	-0.25*	0.21*	-0.38***	0.19	-0.13	0.66***	0.18	-0.29**	0.25*	0.22*	0.07	0.24*	0.18	0.33***	0.27**	0.25*	0.17	0.21*	0.15				
21 Drug Mortality	0.09	0.16	-0.42***	0.18	0.13	0.36***	0.30**	-0.34***	0.17	-0.05	0.16	0.21*	0.23*	0.20	0.33***	0.12	0.21*	0.28**	0.31**	0.48***			
22 Prescription Mortality	-0.30**	-0.08	-0.16	0.04	-0.22*	0.32**	0.13	-0.01	0.22*	0.23*	0.09	0.28**	0.21*	0.29**	0.25*	0.31**	0.24*	0.30**	0.22*	0.55***	0.58***		
23 Prescription Opioid Mortality	-0.24*	-0.04	-0.24*	0.03	-0.16	0.32**	0.15	-0.11	0.28**	0.15	-0.01	0.20	0.15	0.21*	0.19	0.23*	0.21*	0.23*	0.17	0.51***	0.56***	0.98***	
24 Opioid Claims (Part D)	0.12	0.10	-0.54***	0.15	-0.04	0.32**	0.41***	-0.28**	0.20*	0.04	0.19	0.24*	0.27**	0.35***	0.45***	0.28**	0.32**	0.28**	0.29**	0.59***	0.55***	0.46***	0.45***

Examining the Pearson's correlation matrix, it can be seen that in the most populated 100 counties, all forms of mortality included in the data set —that is mortality from prescription drug overdoses, mortality from all prescription drugs, and mortality from all drugs— are significantly ($p < .05$) correlated with the amount of money spent per doctor on opioid marketing. However, the correlation is low to moderate (about .20 to .30) and it is specific to more common opioid products and not especially potent ones. Other significant correlations can be observed which might be expected. For example, all drug mortality is significantly correlated with the level of education at all levels included in the study; a county's rate of high school completion or completion of "some college" only, both being positively correlated with all drug mortality, and rate of college completion being inversely related to all drug mortality. This finding is consistent with existing literature on overdose mortality in the U.S.[78]

6.0 RESULTS

In the simple multivariate regression models, the lack of health insurance is a reliable predictor of drug-related mortality both at the nationwide county and the urban level. However, these models suggest that uninsurance appears to have opposite effects at the county and urban levels. Whereas uninsurance is associated with a significant increase in drug mortality at the county-level, uninsurance is associated with a significant decrease in drug mortality in major urban areas. To give a problematic and overly simplified example which corresponds to these models, if you are living in a major U.S. city and have health insurance, you are about 20% less likely to die from a drug overdose relative to the "average" person in the same setting. However, generally speaking, if you are living in the U.S. and have health insurance, you are more likely to die from a drug overdose. One possible explanation for the latter phenomenon is that people with health insurance are more likely to have access to drugs. Similarly, unemployment rates are good predictors of drug mortality at the county-level. Greater unemployment is closely and significantly associated with greater drug mortality.

[78] For example, see "The impact of opioid use disorder on levels of educational attainment: Perceived benefits and consequences" by Matthew S. Ellis et. al. in *Drug and Alcohol Dependence*. (January 2020).

County-Level Multivariate Linear Regression Models Summary, Drug Mortality

	Model1	Model2	Model3	Model4	Model5	Model6
Uninsurance Rates	.206 (.01968)***	.2931 (.02688)***	.2953 (.02703)***	.3165 (.02099)***	.2068 (.01968)***	.305 (.02695)***
%Unemployment	.7982 (.04437)***	.64 (.05888)***	.6456 (.05919)***	.7224 (.04548)***	.7942 (.04442)***	.6307 (.05894)***
Median Income	-.00002253 (.00001146)*	.000009934 (.00001379)	.00001022 (.00001382)	-.00001443 (.00001144)	-.00002169 (.00001147)	.00001696 (.00001381)
Gini*100	.03219 (.03015)	.1237 (.04251)**	.1251 (.04294)**	.0339 (.03182)	.03 (.03017)	.1144 (.04276)**
% <High school	.4971 (1.374)	-1.596 (1.59)	-1.7 (1.594)	-.1658 (1.323)	.5261 (1.373)	-1.583 (1.585)
% High school only	.5894 (1.373)	-1.45 (1.59)	-1.55 (1.594)	-.03224 (1.323)	.6188 (1.373)	-1.423 (1.585)
% Some college	.5379 (1.374)	-1.489 (1.591)	-1.59 (1.595)	-.07652 (1.323)	.5683 (1.373)	-1.456 (1.586)
% ≥Bachelor degree	.5604 (1.373)	-1.531 (1.59)	-1.63 (1.593)	-.06509 (1.323)	.5911 (1.373)	-1.5 (1.585)
% White	.07967 (.005851)***	.08968 (.007478)***	.08868 (.007505)***	.09011 (.005909)***	.07863 (.005881)***	.0826 (.007572)***
Physician Per 100,000	.01637 (.00227)***	.01216 (.002635)***	.01262 (.002654)***	.0103 (.002289)***	.01631 (.00227)***	.01178 (.002645)***
Opioid, per cap		3.539 (1.353)**				
Opioid, per doc			.001951 (.0009622)*			.001828 (.0009571)
LR, per doc				.0002057 (.00003219)***		
Opioid Claims (Part D)					.2001 (.1172)	.9894 (.2085)***
R square	.1785	.1917	.1909	.2181	.1792	.2004
Adjusted R square	.1759	.1871	.1862	.215	.1764	.1954
Obs.	3136	1916	1904	2813	3136	1904
Missing	6	1226	1238	329	6	1238

Urban Districts Multivariate Linear Regression Models Summary, Drug Mortality

	Model1	Model2	Model3	Model4	Model5	Model6
Uninsurance Rates	-.204 (.09999)*	-.2028 (.09957)*	-.2044 (.09949)*	-.2059 (.09872)*	-.204 (.1)*	-.2043 (.09978)*
%Unemployment	.0532 (.3681)	.08774 (.3675)	.08945 (.3672)	.1157 (.365)	.06017 (.3683)	.09074 (.3683)
Median Income	-.00008646 (.00004733)	-.00007786 (.00004758)	-.00007789 (.0000475)	-.00007488 (.00004716)	-.00006579 (.00005202)	-.00006355 (.00005193)
Gini*100	.5227 (.1952)**	.5258 (.1944)**	.5224 (.1943)**	.4645 (.1954)*	.5124 (.1956)*	.5148 (.1951)**
% <High school	8.657 (6.589)	8.752 (6.562)	8.758 (6.557)	8.258 (6.509)	7.952 (6.633)	8.227 (6.62)
% High school only	8.83 (6.58)	8.947 (6.553)	8.95 (6.547)	8.441 (6.5)	8.092 (6.627)	8.392 (6.616)
% Some college	9.146 (6.614)	9.252 (6.587)	9.255 (6.582)	8.751 (6.534)	8.371 (6.667)	8.672 (6.655)
% ≥Bachelor degree	8.717 (6.594)	8.812 (6.567)	8.816 (6.561)	8.329 (6.513)	7.979 (6.641)	8.261 (6.629)
% White	.0257 (.02793)	.02227 (.02793)	.02221 (.0279)	.02967 (.02766)	.0207 (.02842)	.0189 (.02839)
Physician Per 100,000	.001177 (.01533)	.0002956 (.01528)	.0007409 (.01526)	-.001639 (.01521)	-.003047 (.01596)	-.002329 (.01593)
Opioid, per cap		2.235 (1.69)				
Opioid, per doc			.003884 (.002821)			.003471 (.002891)
LR, per doc				.000298 (.0001639)		
Opioid Claims (Part D)					5.218 (5.439)	3.849 (5.544)
R square	.4	.4117	.4126	.4217	.4062	.4159
Adjusted R square	.3326	.3381	.3392	.3494	.332	.3353
Obs.	100	100	100	100	100	100
Missing	0	0	0	0	0	0

However, in the multivariate regressions and most of the other models, median income is not significantly associated with drug-related mortality. Interestingly, this finding is consistent with existing public health literature concerning drug mortality.[79] Whereas other economic measures of individual and household wellbeing, like house value and income inequality are associated with drug mortality, median household income is not.[80] My analysis also finds that income inequality captured according to a Gini coefficient, however, is a significant predictor of drug mortality, but the best evidence for income inequality is at the urban level. In other words, the multivariate regressions suggest that income inequality is a good predictor of mortality, but this is mostly limited to densely populated areas. Educational variables, which have been reliable predictors of opioid mortality in other studies, were not found to be a significant predictor of drug mortality in these simple multivariate regressions.[81] In the correlation tables, the presence of physicians relative to the general population reveals a significant and positive correlation to prescription drug mortality ($r = .21$, $p < .05$). Similarly, in the multiple regression, there is a statistically significant relationship between physicians per 100,000 and drug mortality, however, with the other variables introduced into the model, the observed relationship is very small.

Controlling for demographic factors, the simple multivariate regressions suggest that the marketing dollar amount spent both per capita and per doctor are statistically significant predictors of overdose mortality at the county-level. More specifically, for every additional dollar spent on opioid marketing *per capita* at the county level, *model 2* predicts an increase in drug-related mortality of about 3.5 people per 100,000. However, that finding should be read cautiously because the mean spending *per capita* is only about $.01, so an increase of opioid marketing expenditures to $1 per capita would represent a 100 fold increase in opioid marketing expenditures. Nonetheless, because of

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[79] James R. Langabeer, Kimberly A. Chambers, Marylou Cardenas-Turanzas, and Tiffany Champagne-Langabeer, "County-level factors underlying opioid mortality in the United States" *Substance Abuse.* (March 2020).

[80] Ibid.

[81] These studies use comparatively nuanced methods for looking at educational attainment across social groupings, breaking up the educational attainment according to groupings like Spanish language speakers, men with a bachelor's degree over time, etc. For an example, see Jessica Y. Ho's 2017 article "The Contribution of Drug Overdose to Educational Gradients in Life Expectancy in the United States, 1992–2011" in *Demography*.

the considerable variation in direct-to-physician opioid marketing across counties —the standard deviation is about 6 times the mean— the model suggests an important but small association between population-adjusted, opioid marketing expenditures and mortality from all drugs. Notably, these marketing predictors are not statistically significant in the simple multivariate regression models which examine urban districts alone. These findings might be cause to reject the null hypothesis, and claim that opioid marketing does, afterall, have an effect on opioid mortality, however, it is important to remember that these models are concerned with general drug mortality. When the dependent variable is changed to mortality coded for exclusively prescription drugs or opioids, statistical significance can no longer be found. Here, it is important to recall that the mortality data for prescription and drug overdose is poor. And, because of the non-normal distribution of the data, the validity of the multivariate models is questionable.

County-Level Multivariate Quasipoisson Regression Models Summary, Drug Mortality

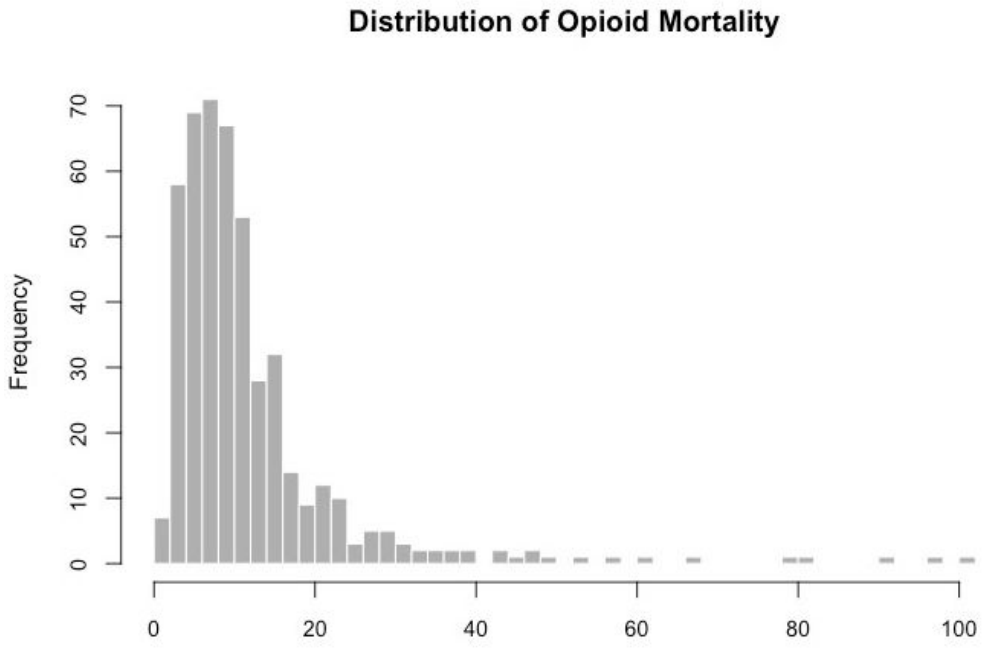
	Model1	Model2	Model3	Model4	Model5	Model6
Uninsurance Rates	.01467 (.001429)***	.02031 (.001881)***	.02044 (.001891)***	.02222 (.001496)***	.01475 (.00143)***	.02124 (.001895)***
%Unemployment	.05359 (.003062)***	.04151 (.003933)***	.04181 (.003949)***	.04774 (.003108)***	.05338 (.003065)***	.04116 (.003956)***
Median Income	-.000002166 (.0000008707)*	.0000003651 (.000001003)	.0000003725 (.000001005)	-.00000152 (.0000008532)	-.000002097 (.0000008709)*	.0000008436 (.000001007)
Gini*100	.00244 (.002243)	.009127 (.003007)**	.009236 (.003036)**	.002532 (.002313)	.002279 (.002243)	.008467 (.003031)**
% <High school	.01966 (.1012)	-.1221 (.1129)	-.1283 (.1131)	-.02802 (.09583)	.02128 (.1012)	-.1228 (.1128)
% High school only	.027 (.1012)	-.1113 (.1129)	-.1173 (.1131)	-.01788 (.0958)	.02865 (.1012)	-.111 (.1128)
% Some college	.02278 (.1012)	-.1142 (.1129)	-.1202 (.1132)	-.02139 (.09582)	.0245 (.1012)	-.1135 (.1128)
% >=Bachelor degree	.02476 (.1012)	-.1174 (.1128)	-.1234 (.1131)	-.02049 (.09581)	.02652 (.1012)	-.1168 (.1127)
% White	.005557 (.0004286)***	.006181 (.0005373)***	.006117 (.0005395)***	.006212 (.00043)***	.005485 (.0004305)***	.005725 (.0005449)***
Physician Per 100,000	.001147 (.0001572)***	.0008205 (.0001787)***	.0008482 (.0001792)***	.0007238 (.0001604)***	.001139 (.0001569)***	.0007863 (.0001778)***
Opioid, per cap		.2216 (.08188)**				
Opioid, per doc			.0001313 (.00006202)*			.0001243 (.00006236)*
LR, per doc				.00001343 (.000002067)***		
Opioid Claims (Part D)					.01397 (.008157)	.06103 (.0134)***
Obs.	3136	1916	1904	2813	3136	1904
Missing	6	1226	1238	329	6	1238

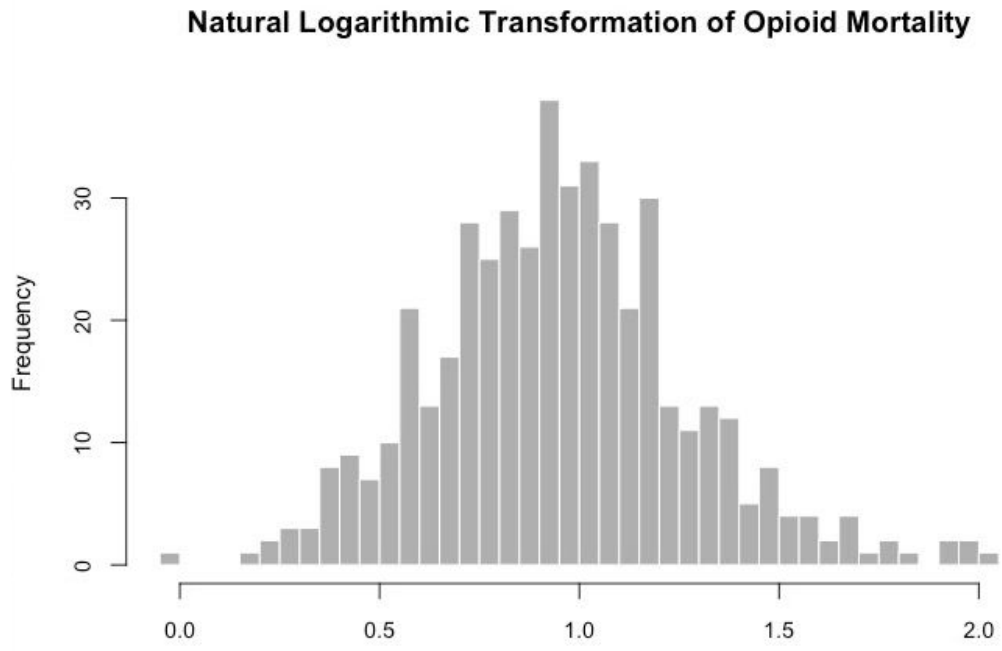
Urban Districts Multivariate Quasipoisson Regression Models Summary, Drug Mortality

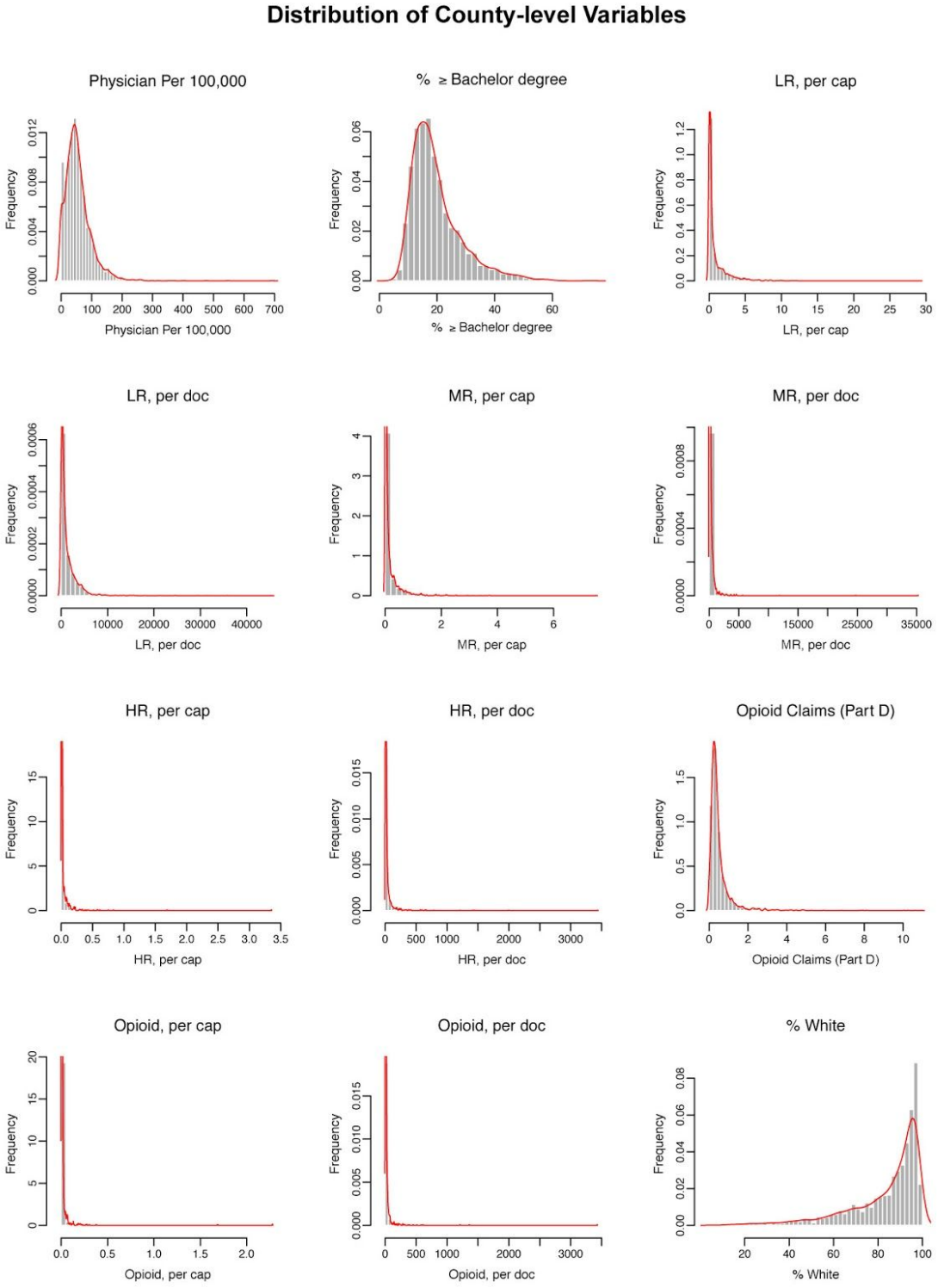
	Model1	Model2	Model3	Model4	Model5	Model6
Uninsurance Rates	-.01495 (.006766)*	-.01491 (.00677)*	-.015 (.006765)*	-.01499 (.006782)*	-.01492 (.00683)*	-.01499 (.00682)*
%Unemployment	.002746 (.02465)	.004894 (.02468)	.005036 (.02466)	.007284 (.02459)	.003259 (.02477)	.005202 (.0248)
Median Income	-.000005928 (.000003309)	-.000005302 (.000003335)	-.000005301 (.00000333)	-.000005177 (.000003319)	-.000005083 (.000003618)	-.00000453 (.000003619)
Gini*100	.04037 (.01383)**	.04067 (.01381)**	.04048 (.0138)**	.03667 (.01394)*	.03975 (.01393)**	.04014 (.01392)**
% <High school	.611 (.4409)	.6238 (.4408)	.6247 (.4405)	.5796 (.4376)	.5765 (.4471)	.6046 (.4474)
% High school only	.6221 (.4403)	.6365 (.4403)	.6372 (.44)	.5917 (.437)	.5861 (.4469)	.6162 (.4473)
% Some college	.6459 (.4427)	.6598 (.4427)	.6604 (.4424)	.6151 (.4395)	.6084 (.4496)	.6386 (.45)
% ≥Bachelor degree	.6139 (.4412)	.6267 (.4411)	.6274 (.4408)	.5836 (.4379)	.5781 (.4477)	.6066 (.448)
% White	.002012 (.001964)	.001747 (.001969)	.001742 (.001967)	.002271 (.001972)	.001844 (.001996)	.001658 (.001996)
Physician Per 100,000	.000003488 (.001044)	-.00004331 (.001046)	-.00001665 (.001044)	-.0002005 (.00105)	-.0001825 (.001098)	-.0001205 (.001099)
Opioid, per cap		.1382 (.1008)				
Opioid, per doc			.0002393 (.0001677)			.0002269 (.0001728)
LR, per doc				.00001887 (.00001049)		
Opioid Claims (Part D)					.2069 (.3468)	.1166 (.3553)
Obs.	100	100	100	100	100	100
Missing	0	0	0	0	0	0

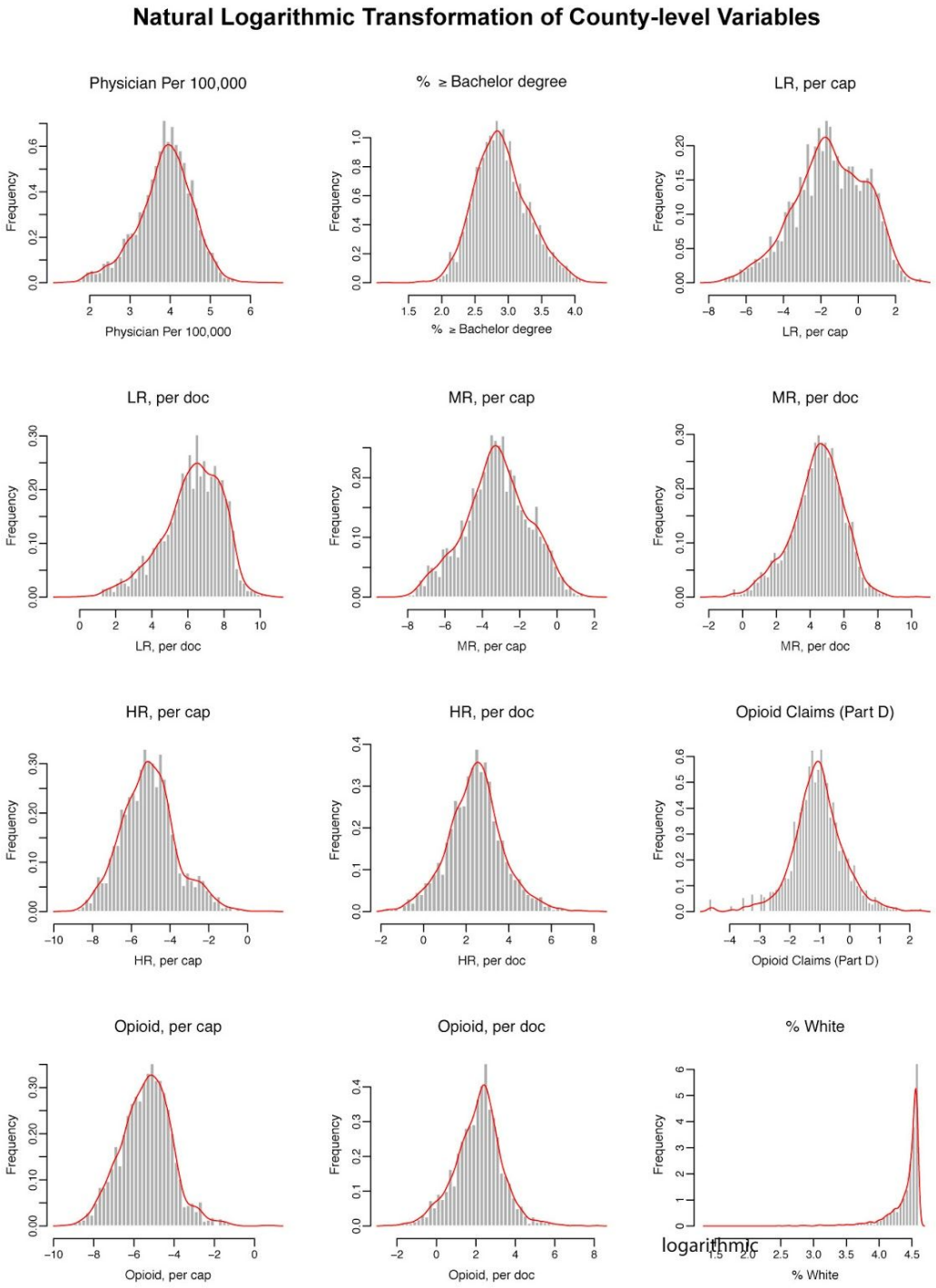
The Poisson regression can be interpreted very much like a standard, multivariate, linear regression. Most modeling software uses natural logarithmic log-link function and provides an exponentiated β in the output tables. If there is a change of "1" in the explanatory variable, the change in the variable being explained can be understood by the given coefficient provided that all other variables in the model remain constant. However, the change in the dependent variable must be understood not simply as a change in the count or rate of mortality, but a change in the log of the count or rate of mortality. Unlike multivariate, linear, regression, there is no reliable measure of model fit like R2 or Adjusted R2; a pseudo-R2 has been developed, but one is not included here because it is unreliable and mostly irrelevant for the purposes of this study. Though Poisson regression is most often used for modeling count data, it can also be used for modeling rate data, in this case various forms and rates of mortality at the county and urban levels. For example, looking at *Model 4* in the regression summary labeled *County-Level Multivariate Quasipossion*, for every one 1% increase in a county's rate of uninsurance, the county's drug overdose mortality *log rate* can be expected to increase by .022 per 100,000 people. Looking at the same model, it is also clear, for example, that an 1% increase in the whiteness of a county predicts the log rate of drug mortality will increase by about .06 per 100,000 people. In this case, the drug mortality variable is a measure of deaths with a specific medical inclusion criteria (see *Appendix I)* per 100,000 at the county-level. Other covariates in this model can be interpreted following this reasoning. Notably, several covariates in the model do not qualify as statistically significant according to the .05 convention.

The opioid marketing variables have a statistically significant effect on drug mortality. On average (mean), pharmaceutical companies spent about $20 marketing opioids to each doctor in a given county. Though statistically significant, the effect of marketing on all drug mortality is inconsequential however it is measured. Here, the controls are far better predictors of mortality.


Distribution of Opioid Mortality
Frequency
0
10
20
30
40
50
60
70
0
20
40
60
80
100


Natural Logarithmic Transformation of Opioid Mortality
Frequency
0
10
20
30
0.0
0.5
1.0
1.5
2.0


Distribution of County-level Variables
Physician Per 100,000
Frequency
0.000
0.004
0.008
0.012
0 100 200 300 400 500 600 700
Physician Per 100,000
% ≥ Bachelor degree
Frequency
0.00
0.02
0.04
0.06
0 20 40 60
% ≥ Bachelor degree
LR, per cap
Frequency
0.0 0.2 0.4 0.6 0.8 1.0 1.2
0 5 10 15 20 25 30
LR, per cap
LR, per doc
Frequency
0.0000 0.0002 0.0004 0.0006
0 10000 20000 30000 40000
LR, per doc
MR, per cap
Frequency
0 1 2 3 4
0 2 4 6
MR, per cap
MR, per doc
Frequency
0.0000 0.0004 0.0008
0 5000 15000 25000 35000
MR, per doc
HR, per cap
Frequency
0 5 10 15
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5
HR, per cap
HR, per doc
Frequency
0.000 0.005 0.010 0.015
0 500 1000 2000 3000
HR, per doc
Opioid Claims (Part D)
Frequency
0.0 0.5 1.0 1.5
0 2 4 6 8 10
Opioid Claims (Part D)
Opioid, per cap
Frequency
0 5 10 15 20
0.0 0.5 1.0 1.5 2.0
Opioid, per cap
Opioid, per doc
Frequency
0.000 0.005 0.010 0.015
0 500 1000 2000 3000
Opioid, per doc
% White
Frequency
0.00 0.02 0.04 0.06 0.08
20 40 60 80 100
% White


Natural Logarithmic Transformation of County-level Variables
Physician Per 100,000
% ≥ Bachelor degree
LR, per cap
LR, per doc
MR, per cap
MR, per doc
HR, per cap
HR, per doc
Opioid Claims (Part D)
Opioid, per cap
Opioid, per doc
% White
Frequency
logarithmic

Due to the heavy skewness of these predictors and requirement for normality in linear models, these regressors (see distributions above) were transformed by taking their natural log and regressing them on mortality variables. Both opioid mortality and prescription mortality were logarithmically transformed, but all drug mortality was not. The results of the models which examined both opioid and prescription mortality are not reported here, but can be found in the appendix. These results lack statistical significance and suggest, like the correlation matrix, some technical error in the construction of these variables in the database or register. This is the case for both models that both examine the log-transformed and standard forms of opioid and prescription mortality.

However, following the logarithmic transformation of the independent variables, models were built which examined all drug mortality— the data for which is the most complete mortality data available in this study— and these models produced revealing and statistically significant results. Interpreting coefficients in a logarithmically transformed model is very much like reading a standard regression model, however, the interpretation depends on how the log-transformation was conducted. In this case, only the independent variables were log-transformed. Therefore, when reading the regression table, independent variables should be thought of in terms of a percentage change for every 1 unit increase in all drug mortality per 100,000. For example, in the log transformed regression below the coefficient in Model1 associated with uninsurance is .2854. This should be divided by 100 (0.2854/100 = 0.002854). Therefore, Model1 suggests that for every 1 unit increase, —in this case that is a 1% increase— in uninsurance, all drug mortality increases by about .0029 per 100,000 ($p < .001$). Coefficients throughout the table can be interpreted by following this procedure. Interestingly, and perhaps this is the most relevant finding which addresses my central research question, in all of the models at the county-level, all measures of direct-to-physician opioid marketing are significantly related to mortality, though the effect size is small. For example, a 100% increase in opioid marketing at the county level predicts an increase in drug mortality per 100,000 of about 0.4 or 0.5 ($p <. 001$).

County-Level Multivariate Linear Regression Models Summary, Drug Mortality, Log

	Model1	Model2	Model3	Model4	Model5	Model6
Uninsurance Rates	0.2854 (0.02032)***	0.2942 (0.02678)***	0.2942 (0.02678)***	0.3344 (0.02099)***	0.3011 (0.02053)***	0.3045 (0.02678)***
%Unemployment	0.7138 (0.04512)***	0.6035 (0.05878)***	0.6035 (0.05878)***	0.6576 (0.04569)***	0.7036 (0.04504)***	0.5985 (0.05853)***
Median Income	-0.00002188 (0.00001139)	-0.000000101 (0.00001371)	-0.0000001009 (0.00001371)	-0.00002555 (0.0000114)*	-0.00000962 (0.00001165)	0.00001413 (0.00001406)
Gini*100	0.04821 (0.03123)	0.09429 (0.04277)*	0.09429 (0.04277)*	0.01983 (0.03166)	0.0428 (0.03125)	0.07858 (0.04274)
% <High school	-0.2772 (0.04554)***	-0.1967 (0.05474)***	-0.1967 (0.05474)***	-0.2953 (0.04499)***	-0.2723 (0.04541)***	-0.185 (0.05458)***
% High school only	-0.1247 (0.03946)**	-0.04302 (0.04563)	-0.04302 (0.04563)	-0.1294 (0.03855)***	-0.1214 (0.03933)**	-0.03333 (0.04548)
% Some college	-0.1543 (0.03724)***	-0.06653 (0.04336)	-0.06653 (0.04336)	-0.1479 (0.03629)***	-0.1456 (0.03715)***	-0.05201 (0.04331)
% >=Bachelor degree	-3.553 (0.8716)***	-3.167 (1.065)**	-3.167 (1.065)**	-4.085 (0.8595)***	-3.419 (0.8691)***	-2.736 (1.065)*
% White	0.0803 (0.005818)***	0.08894 (0.00748)***	0.08894 (0.00748)***	0.08865 (0.005872)***	0.07677 (0.005858)***	0.08312 (0.007574)***
Physician Per 100,000	0.5475 (0.1432)***	0.6412 (0.1861)***	1.184 (0.193)***	0.6741 (0.1414)***	0.5179 (0.1433)***	1.107 (0.193)***
Opioid, per cap		0.5426 (0.07887)***				
Opioid, per doc			0.5426 (0.07887)***			0.5024 (0.0791)***
LR, per doc				0.4388 (0.04945)***		
Opioid Claims (Part D)					0.5015 (0.1053)***	0.6553 (0.1556)***
R square	0.1938	0.2081	0.2081	0.2302	0.2006	0.2154
Adjusted R square	0.191	0.2035	0.2035	0.2272	0.1975	0.2104
Obs.	2907	1904	1904	2813	2896	1904
Missing	235	1238	1238	329	246	1238

Urban Districts Multivariate Linear Regression Models Summary, Drug Mortality, Log

	Model1	Model2	Model3	Model4	Model5	Model6
Uninsurance Rates	-0.2126 (0.1003)*	-0.2742 (0.101)**	-0.2742 (0.101)**	-0.216 (0.09945)*	-0.2223 (0.09953)*	-0.2744 (0.1008)**
%Unemployment	-0.06968 (0.4027)	-0.1244 (0.3929)	-0.1244 (0.3929)	-0.02516 (0.4003)	-0.09081 (0.3992)	-0.1334 (0.3922)
Median Income	-0.00008672 (0.00004785)	-0.0001064 (0.00004733)*	-0.0001064 (0.00004733)*	-0.00007088 (0.00004849)	-0.00004966 (0.00005258)	-0.00007785 (0.00005332)
Gini*100	0.5651 (0.1949)**	0.4415 (0.1967)*	0.4415 (0.1967)*	0.4845 (0.1998)*	0.5182 (0.1953)**	0.4216 (0.1971)*
% <High school	-0.2135 (0.3463)	-0.1971 (0.3374)	-0.1971 (0.3374)	-0.2419 (0.3438)	-0.07016 (0.3542)	-0.09689 (0.3478)
% High school only	0.01059 (0.2676)	-0.07909 (0.2633)	-0.07909 (0.2633)	-0.03688 (0.267)	0.06982 (0.2676)	-0.02712 (0.2666)
% Some college	0.2682 (0.2909)	0.1906 (0.2851)	0.1906 (0.2851)	0.2371 (0.2891)	0.242 (0.2886)	0.1804 (0.2848)
% >=Bachelor degree	-4.692 (9.85)	-6.305 (9.618)	-6.305 (9.618)	-6.073 (9.805)	-2.536 (9.849)	-4.594 (9.714)
% White	0.02259 (0.02915)	0.01546 (0.02855)	0.01546 (0.02855)	0.02556 (0.02897)	0.004948 (0.03084)	0.003684 (0.03027)
Physician Per 100,000	-0.434 (1.817)	-1.121 (1.793)	-0.1721 (1.773)	-0.5036 (1.802)	-1.336 (1.883)	-0.8427 (1.863)
Opioid, per cap		0.9484 (0.3939)*				
Opioid, per doc			0.9484 (0.3939)*			0.8448 (0.4033)*
LR, per doc				1.381 (0.8695)		
Opioid Claims (Part D)					2.149 (1.318)	1.53 (1.327)
R square	0.3904	0.4281	0.4281	0.4074	0.4083	0.4367
Adjusted R square	0.3219	0.3566	0.3566	0.3334	0.3343	0.359
Obs.	100	100	100	100	100	100
Missing	0	0	0	0	0	0

However, little statistical significance can be found in the log-transformed models which examine, exclusively, highly populated urban areas. In even the most robust of these models (see model 3 and model 6) only 3 or 4 of the 11 predictors reach significance ($p < .05$).

The results of my analysis point to a plausible relationship between the key variables, but these findings are preliminary and do not lend themselves to clear and definite conclusions. Many of the models lack statistical significance, both at the county and urban levels. The lack of statistical significance could be due to a "true" null hypothesis, that marketing does not have an effect on mortality at the county-level. However, the "true" null hypothesis scenario does not make sense concerning demographic covariates like education which have a well-documented relationship to mortality at the county and urban level. The log-transformed model which examines drug mortality in all counties provides the best evidence for a relationship between direct-to-physician marketing and drug related death. There are probably several reasons for these shortcomings, and thanks to a more recent study published by public health researchers and physicians, we now have the results of a study which addresses most of this study's important shortcomings.

7.0 Discussion

Several years after the data in the current study were compiled and analyzed, Scott E. Hadland, Ariadne Rivera-Aguirre, and Brandon D. L. Marshall —respectively, a public health professor and physician at Boston University, a public health researcher at New York University, and a public health professor at Brown University— produced a very similar study which addresses many of the limitations mentioned in my original analysis. The study was published in January of 2019 in Substance Use and Addiction and is titled *Association of Pharmaceutical Industry Marketing of Opioid Products With Mortality From Opioid-Related Overdoses*.[82]

[82] Scott E. Hadland, Ariadne Rivera-Aguirre, and Brandon D. L. Marshall, "Association of Pharmaceutical Industry Marketing of Opioid Products With Mortality From Opioid-Related Overdoses" *Substance Use and Addiction* 2 no. 1 (January 2019).

Relying on most of the same data sources and linking procedures as this study, their study also investigated county-level overdose mortality and pharmaceutical marketing. There are several important differences between the analytical procedures they employed, and the ones I employed here. First, they used overdose mortality data with a 1-year lag, the assumption being it takes time for the impact of marketing to take effect. Again, the mortality data employed in my study are partially lagged, but only by a period of 6 months, and include 6 months which run concurrent to the marketing data. Hadland et. al. also had access to restricted use mortality data which is more complete, but which is unavailable to researchers affiliated exclusively with non-U.S. universities. Second, they used negative binomial regression to address the over-dispersion of the data, a procedure I had tried and failed to employ. Third, they accounted for prescribing patterns and used prescribing patterns as a mediating variable. When I originally conducted the analysis and compiled the data in this study, the prescribing data was not readily available and getting access to it was made prohibitively difficult due to time constraints, but more importantly, the most robust forms of this data are prohibitively expensive and are mostly sold to pharmaceutical companies. Fourth, in addition to examining the population-adjusted payments to doctors as a total dollar amount, they examined the gross number and frequency of payments to physicians. The impact of prolonged and repeated exposure to marketing efforts were not captured by my model and are only discussed in passing in the theoretical section of this paper. Fifth, and this is very important, Hadland et. al. included marketing payments for *fentanyl* in their analysis. At the time I was conducting the original analysis, the widespread "abuse" of fentanyl was just beginning to receive attention, and I had excluded it from my analysis because it was also being used to treat addiction to other opioids. Finally, the way Hadland et. al. employed controls, demographic covariates, etc. ensured greater heterogeneity among the covariates. For example, they did not reduce "race" to a single continuous category which I call "whiteness."

Hadland et. al. found a significant association between prescription opioid overdoses and opioid marketing at the county-level. They write that the, "greatest effect size was observed for the number of payments per capita, and the smallest effect size was

observed for the marketing value in dollars per capita." Moreover, they found that overdose mortality was also significantly associated with all county-level covariates, excluding one age variable, a finding that is not consistent with my analysis, which of course, uses a different and less-robust set of procedures. The mediation analysis, which examined the effects of prescribing rates on overdose mortality, found that prescribing rates could account for 3% to 26% of the observed overdose mortality. By looking at the total dollar amount spent on marketing only 3% of the overdose mortality is "explained", but by looking at the number of physicians actually receiving payments, up to 26% of the overdose mortality can be explained. The researchers conclude by arguing that policymakers should consider regulating opioid marketing and pharmaceutical companies should consider voluntarily stopping the practice.

7.1 ADDITIONAL CONSIDERATIONS

There are possible systematic biases in the Open Payments reporting processes. The reporting process relies on the marketing (pharmaceutical) organizations to accurately, precisely, and earnestly report their activity. Due to possible financial consequences, marketing organizations might be hesitant to accurately report their activity. This is further substantiated by the broad opposition to the Open Payments Program by physicians, many of whom have objected to supposed pharma claims that they received payments.

Opioids, including opioid analgesics, are thought to be helpful in the preconditioning of major bodily organs in such a way that might minimize the trauma caused by a major medical difficulty. In other words, the bodily effect of opioid analgesics might prepare the body for traumatic events (ie. organ failure). This phenomenon is important both in theoretical applications, but also in considering the current quantitative methodology which relies on mortality as a dependent outcome variable at the county-level. If the hypothesis that direct-to-physician opioid analgesic advertising results in greater consumption of opioid analgesics, and opioid analgesics have the capacity to improve longevity in long-term users that do not die from overdose, this presents some methodological challenges. In other words, it is entirely possible that greater opioid

analgesic consumption can conditionally improve life-expectancy while concurrently producing an increase in overall mortality due to overdose.

8.0 CONCLUSIONS AND SUGGESTIONS FOR FURTHER RESEARCH

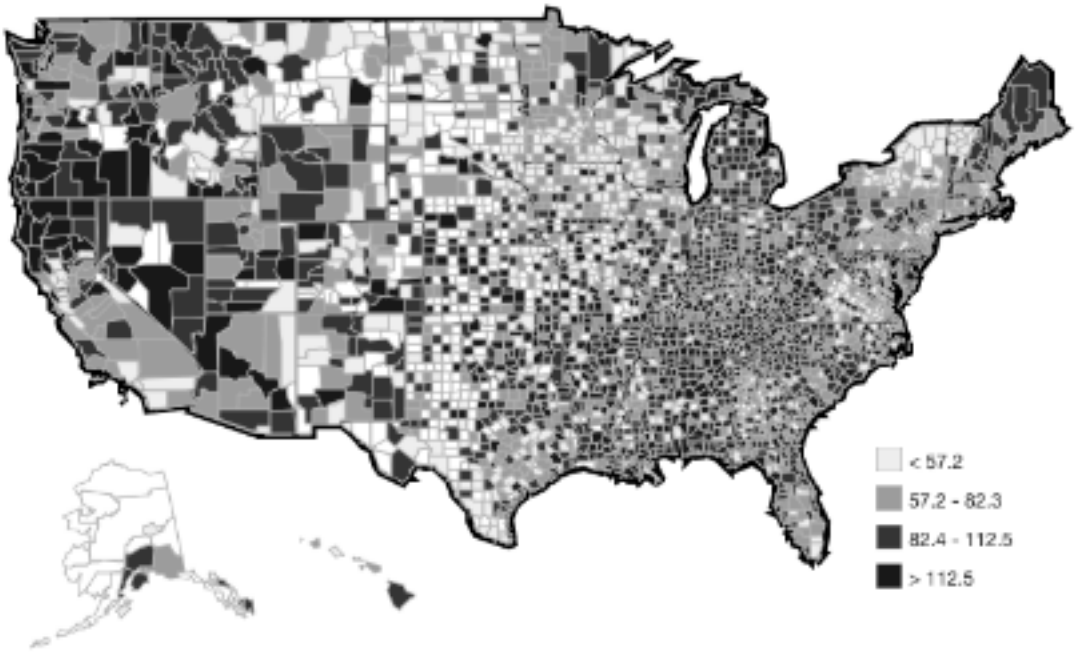
This study has uncovered significant, but weak evidence supporting the association between direct-to-physician marketing and drug mortality. This evidence comes both from the original analysis, as well as more robust studies which have set out to address the same research questions since the analysis was conducted. On the whole, though the association is quite uncertain, it nonetheless suggests some relationship between opioid marketing and general drug mortality. One reason the data reveal no clear and definite relationship between marketing and mortality is because there are significant limitations in the analyses and the coding procedures, namely, prescribing patterns are included in the quantitative analysis. Fortunately, more comprehensive studies have included prescribing patterns and provide a strong case for a link between opioid mortality and direct-to-physician opioid marketing.

Further research into direct-to-physician opioid and pharmaceutical marketing on public health and mortality can build from the findings of this project via several routes. First, future research can employ the reappropriated and alternative applications of existing, cleaned, pharma-financial data and methods presented in this study.[83] Second, additional research in this vein can build on the historical and interpretive findings by interrogating the effects of increased prescription opioid regulation and policy prior to the collection of the Open Payments data. Third, further research could improve on the analytical procedure employed in this study by calculating Bayesian estimates of age-adjusted mortality for the opioid and prescription drug mortality. Fourth, additional research might consider other nonparametric, log-transforming procedures, and negative binomial regression.

[83] See *Appendix III* or link below:
https://docs.google.com/spreadsheets/d/1l2KisqcIMbxibydlSy99Fha97r3y_tLxipxOeUchYLM/edit?usp=sharing

Another important consideration which this study mentions —but does not address analytically— is the commercial, legal, and illicit opioid distribution networks which are not restricted to county or state boundaries. These networks are an important mediating factor that is not accounted for in the models. For example, one pharmacy in Kermit, West Virginia, a remote town of about 400 people which sits on the state border with Kentucky, dispensed about 9,000,000 doses of hydrocodone during the study period.[84]

A CDC Map of County-Level Prescriptions Per 100 Persons in 2013 [85]



Of course, it is quite improbable that all of these opioids are being consumed by the population of Kermit, and it is likely that they are being used in Kentucky, surrounding counties, and elsewhere. The models used in this study do not even account for prescribing patterns, much less the illicit redistribution of opioids and other drugs.

Now that the CDC has made prescribing data available, responsible researchers addressing the questions at the core of this project should consider using it. Notably, a

[84] Chris McGreal, "Why were millions of opioid pills sent to a West Virginia town of 3,000?" *The Guardian* (October 2019).
[85] CDC. *U.S. County Prescribing Rates*, (2013). https://www.cdc.gov/drugoverdose/maps/rxcounty2013.html

quick visual examination of the opioid prescribing patterns of the CDC's county-level, population adjusted, rate map shows obvious similarities to the maps produced in my analysis (see page 24) which shows mortality from prescription drug overdose.

Prescription drug-related mortality and harm data for large metropolitan areas, where medical facilities, industry-physician relationships, and documented health visits are concentrated might prove to be of greater use than the most populous county-level data used here. City identifiers exist within the Open Payments data in its original form as released by CMS, thus, aggregating financial data across cities is a relatively simple procedure. Additionally, theory in the urban studies paradigm, which has long addressed drug use and abuse, might be well-suited to address the consequences of direct-to-physician marketing on public health.

Given the variation in toxicity of opioids, a measure of the opioid equivalence —typically given in equivalent units of morphine— might be used in future studies. Methodologically, marketing expenditures on more potent opioids could be weighted to reflect their potential for abuse and mortality. More specifically, this would mean identifying opioids according to measures of both their toxicity and marketing.

The statistical modeling procedures used in this study do not employ estimated error margins provided by the various agencies who collect and structure the data. In future research, researchers might include error margins for explanatory and control variables in the analysis by performing an error weighted regression. This could be accomplished by performing an ordinary least squares fit and comparing it to a weighted least squares (WLS) fit, the latter of which would utilize the margin of error estimates. WLS regression has the advantage of being able to include these error margins.

Additional injury-related and health outcomes data could be employed. Outcome variables like hospitalization or Narcan use should be more sensitive indicators of the public health effects of over-prescribing and direct-to-physician marketing. Also, now that data over a longer period of time is available, as well as data concerning prescribing patterns, these data could be used to make a more complete and longitudinal model.

Additionally, longitudinal studies can account for the continued effects of direct-to-physician marketing over time, examining the compounding or weakening influence of payments over a number of years.

Obviously, understandings of opioid mortality cannot always be constructed on the basis of coefficients, p-values, regressions, and positivism. Social scientists concerned with direct-to-physician opioid marketing and mortality might consider alternative methodological approaches like ethnographic study, interviewing, legal-archival work, and discourse analysis. During the course of this project I benefited from informal discussions, or rather, interviews with a handful of researchers and doctors who have experiential knowledge about these practices, and without this "data" the study could not have been completed.

Finally, this study was guided by a positivist, technocratic, "data-driven" approach. In other words, the study was driven by a hegemonic epistemological paradigm and its assumptions about the proper application of data. There are always normative and political assumptions embedded in even the most "data-oriented" and supposedly neutral approaches. Unsurprisingly then, the conclusions of the study have implications for public policy, but do not contribute to pressing theoretical debates in sociology. For example, the study could have taken direct-to-physician pharmaceutical marketing as a unique faucet of biopolitical governmentality under late capitalism which facilitates the dispossession of indigenous lands in a settler colony, but instead the study uncritically embraces a vague humanitarian ethic which regards mortality as an indicator for social well-being.

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Appendix I

Category	Underlying Cause	Contributing Cause (Multiple Cause)
Illicit drug poisoning	X40 X41 X42 X43 X44 X60 X61 X62 X63 X64 X85 Y10 Y11 Y12 Y13 Y14	T40.1 T40.5 T40.7 T40.8 T40.9 T43.6
Pharmaceutical poisoning	X40 X41 X42 X43 X44 X60 X61 X62 X63 X64 X85 Y10 Y11 Y12 Y13 Y14	T36 T37 T38 T39 T40.2 T40.3 T40.4 T41 T42 T43.0 T43.1 T43.2. T43.3 T43.4 T43.5 T43.8 T43.9 T44 T45 T46 T47 T48 T49 T50.0 T50.1 T50.2 T50.3 T50.4 T50.5 T50.6 T50.7 T50.8
Prescription opioid poisoning	X40 X41 X42 X43 X44 X60 X61 X62 X63 X64 X85 Y10 Y11 Y12 Y13 Y14	T40.2 T40.3 T40.4
Other pharmaceutical poisoning	X40 X41 X42 X43 X44 X60 X61 X62 X63 X64 X85 Y10 Y11 Y12 Y13 Y14	T36 T37 T38 T39 T41 T42 T43.0 T43.1 T43.2. T43.3 T43.4 T43.5 T43.8 T43.9 T44 T45 T46 T47 T48 T49 T50.0 T50.1 T50.2 T50.3 T50.4 T50.5 T50.6 T50.7 T50.8
Illicit opioid poisoning (opium and heroin)	X40 X41 X42 X43 X44 X60 X61 X62 X63 X64 X85 Y10 Y11 Y12 Y13 Y14	T40.0 T40.1
All opioid poisoning (illicit and prescription)	X40 X41 X42 X43 X44 X60 X61 X62 X63 X64 X85 Y10 Y11 Y12 Y13 Y14	T40.0 T40.1 T40.2 T40.3 T40.4

See Appendix II for Coding Detail. The state-level data in the current study includes deaths coded as T50.9.

Appendix II: Mortality Schedule (*MortalityA*) Coding and CDC Classification Detail

Underlying Causes:

X40 (Accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics)

X41 (Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified)

X42 (Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified)

X43 (Accidental poisoning by and exposure to other drugs acting on the autonomic nervous system)

X44 (Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances)

X60 (Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics)

X61 (Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified)
X62 (Intentional self-poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified)
X63 (Intentional self-poisoning by and exposure to other drugs acting on the autonomic nervous system)
X64 (Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances)
X85 (Assault by drugs, medicaments and biological substances)
Y10 (Poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent)
Y11 (Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified, undetermined intent)
Y12 (Poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified, undetermined intent)
Y13 (Poisoning by and exposure to other drugs acting on the autonomic nervous system, undetermined intent)
Y14 (Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent)
Contributing Causes:
T36 Poisoning by, adverse effect of and underdosing of systemic antibiotics
T37 Poisoning by, adverse effect of and underdosing of other systemic anti- infectives and antiparasitics
T38 Poisoning by, adverse effect of and underdosing of hormones and their synthetic substitutes and antagonists, not elsewhere classified
T39 Poisoning by, adverse effect of and underdosing of nonopioid analgesics, antipyretics and antirheumatics
T40 Poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics [hallucinogens]
T41 Poisoning by, adverse effect of and underdosing of anesthetics and therapeutic gases
T42 Poisoning by, adverse effect of and underdosing of antiepileptic, sedative-hypnotic and antiparkinsonism drugs
T43 Poisoning by, adverse effect of and underdosing of psychotropic drugs, not elsewhere classified
T44 Poisoning by, adverse effect of and underdosing of drugs primarily affecting the autonomic nervous system
T45 Poisoning by, adverse effect of and underdosing of primarily systemic and hematological agents, not elsewhere classified
T46 Poisoning by, adverse effect of and underdosing of agents primarily affecting the cardiovascular system
T47 Poisoning by, adverse effect of and underdosing of agents primarily affecting the gastrointestinal system
T48 Poisoning by, adverse effect of and underdosing of agents primarily acting on smooth and skeletal muscles and the respiratory system
T49 Poisoning by, adverse effect of and underdosing of topical agents primarily affecting skin and mucous membrane and by ophthalmological, otorhinolaryngological and dental drugs

T50 Poisoning by, adverse effect of and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances

Documentation of the drug schedules/classifications used in this study are available to researchers on request (leamy@newschool.edu)

Appendix III: Variable and Source Table

Variable	Source	Source Location
ID	Assignment	
County	United States Census Bureau	http://www2.census.gov/geo/docs/reference/codes/files/national_county.txt
County_FIPS	United States Census Bureau	http://www2.census.gov/geo/docs/reference/codes/files/national_county.txt
CountyPopulation2013	United States Census Bureau	http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk
CountyPopulation2014	United States Census Bureau	http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk
All_Cause_ Mortality_Count	CDC Wonder Multiple Cause 2014	http://wonder.cdc.gov/
All_Cause_ Mortality_Rate	CDC Wonder / Calculated	http://wonder.cdc.gov/
Age_Adjusted_Mortality	CDC Wonder	http://wonder.cdc.gov/
All_Drug_Mortality_Count	CDC Wonder (X40-X44, X60-X64, X85, Y10-Y14) AllCauseMortality 2014	http://wonder.cdc.gov/
All_Drug_Mortality_Rate	(X40-X44, X60-X64, X85, Y10-Y14)/CountyPopulation AllCauseMortality 2014	http://wonder.cdc.gov/
Prescription_Drug_Mortality_Count	CDC WONDER (T36-T39, T40.2-T40.4, T41-T43.5, T43.7 -T50.8)	http://wonder.cdc.gov/
Prescription_Drug_Mortality_Rate	(T36-T39, T40.2-T40.4, T41-T43.5, and T43.7 -T50.8)/CountyPopulation	http://wonder.cdc.gov/
Opioid_Analgesic_Mortality_Count	CDC WONDER (T40.2-T40.4)	http://wonder.cdc.gov/
Opioid_Analgesic_Mortality_Rate	(T40.2-T40.4)/CountyPopulation	http://wonder.cdc.gov/
Uninsured_Count	Small Area Health Insurance Estimates (SAHIE)	https://www.census.gov/did/www/sahie/
Uninsured_MOE_Count	Small Area Health Insurance Estimates (SAHIE)	https://www.census.gov/did/www/sahie/
Uninsured_Rate	Small Area Health Insurance Estimates (SAHIE)	https://www.census.gov/did/www/sahie/
Uninsured_MOE_Rate	Small Area Health Insurance Estimates (SAHIE)	https://www.census.gov/did/www/sahie/

Insured_Count	Small Area Health Insurance Estimates (SAHIE)	https://www.census.gov/did/www/sahie/
Insured_MOE_Count	Small Area Health Insurance Estimates (SAHIE)	https://www.census.gov/did/www/sahie/
Insured_Rate	Small Area Health Insurance Estimates (SAHIE)	https://www.census.gov/did/www/sahie/
Insured_MOE_Rate	Small Area Health Insurance Estimates (SAHIE)	https://www.census.gov/did/www/sahie/
Drug Poisoning Mortality	American Medical Association Master File 2012	http://www.healthindicators.gov/Indicators/Primary-care-providers-per-100000_25/Profile/Data
Estimate_Gini_Index	American Community Survey 2013 - 5 Year Estimates	https://www.census.gov/content/dam/Census/library/publications/2014/acs/acsbr13-02.pdf
Margin_of_Error_Gini_Index	American Community Survey 2013 - 5 Year Estimates	https://www.census.gov/content/dam/Census/library/publications/2014/acs/acsbr13-02.pdf
Household_Income	American Community Survey 2013 - 5 Year Estimates	https://www.census.gov/content/dam/Census/library/publications/2014/acs/acsbr13-02.pdf
Demographics	United States Census Bureau 2014 Estimates	https://www.census.gov/popest/data/counties/asrh/2014/files/CC-EST2014-ALLDATA.csv
Unemployment	United States Department of Agriculture - Economic Research Service (ACS)	http://www.ers.usda.gov/data-products/county-level-data-sets/download-data.aspx
Education	United States Department of Agriculture - Economic Research Service (ACS)	http://www.ers.usda.gov/data-products/county-level-data-sets/download-data.aspx
CDC Interval Prescription Drug Mortality	NYT and Centers for Disease Control and Prevention	
Drug Poisoning Mortality	CDC / NCHS	http://blogs.cdc.gov/nchs-data-visualization/drug-poisoning-mortality/
Race	American Community Survey 2014 - 5 Year Estimates	https://www.census.gov/content/dam/Census/library/publications/2014/acs/acsbr13-02.pdf