Contemporary Issues in Population Health: Disability, Pain Management, and Opioid Overdose in the United States

by

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Dedication

This dissertation is dedicated to the countless health care workers who work to provide safety and solace in our most difficult, vulnerable moments, and particularly amid the current pandemic. You have made an indelible mark on my life and on that of so many others.

Acknowledgements

Despite my use of "I" throughout this dissertation, it is most definitely a product of "us". First and foremost, I want to thank my coauthors and mentors on each of the three papers. Big thanks to Neil Mehta, coauthor on Paper 1 and my committee co-chair, for his training and mentorship on that paper and throughout the PhD process. I am grateful for the many ways in which my skills and style have been shaped by his guidance, and I look forward to my future collaborations. Magda Cerdá, Rebecca Haffajee, Amy Bohnert, and Pooja Lagisetty are coauthors on Paper 2, and each have imbued me with insights that are key to that paper and to my training more broadly. I especially want to thank Magda for her incredible generosity and mentorship following my move to New York, and Rebecca for helping to launch and hone my use of claims data. Paper 3 was actually the first I completed and published, and thus entailed the most growth as a scholar and colleague. Thanks to each of my coauthors on that paper: David Hutton, Freida Blostein, Tran Doan, Sammie Madson-Olson, and Paige Galecki. I am especially indebted to David, whose deep commitment to mentorship was reflected in many hours of one-on-one meetings, practice conference presentations, and countless late-night emails. I hope to emulate his generosity, patience, and didactic acuity in my own mentorship.

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Abstract

This dissertation addresses several contemporary health challenges affecting the US population, drawing on methods and perspectives from health services research, social demography, and medical sociology. Paper 1 examines the pathways from educational attainment to difficulty with activities of daily living (ADLs) and instrumental activities of daily living (IADLs), helping to elucidate the means by which education shapes health outcomes throughout life. Less educated individuals experience higher rates of disability than those with higher educational attainment, and this disparity appears to be growing at both middle and older ages. Yet the mechanisms underlying it are not well understood. In this study, I use nationally representative data from the Panel Study of Income Dynamics to estimate the contributions of three mediators—excess body mass index (BMI), cigarette smoking, and manual labor—to educational disparities in ADL/IADL disability incidence. Disparities are evident in both younger and older adults (33-64 years, 65-96 years) and larger in women. At younger ages, these factors account for an estimated 60-70% of disparities in disability incidence between the most and least educated. Among women ages 65 and over, they account for nearly 40% of that disparity. Estimates in older men are more variable, suggesting an explanatory power of 20 to 60%.

Papers 2 and 3 speak to the US opioid crisis, which resulted in nearly 47,000 deaths in 2018. Paper 2 centers on unequal treatment in pain management. Research has shown that black and Hispanic chronic pain patients are less likely than their white counterparts to receive opioid

prescriptions, and there is evidence that provider bias contributes to this disparity. Using Optum healthcare claims data, I investigate whether the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain influenced seven measures of opioid prescribing—and, if so, whether these changes varied by patient race/ethnicity, thereby influencing preexisting disparities. Across racial/ethnic groups, the guideline is associated with a gradual decline in the frequency of opioid prescribing, the average daily dose prescribed, and the frequency of high-dose prescribing. However, point estimates suggest these declines may have tended to be sharper in black and Hispanic patients, potentially amplifying black/white and Hispanic/white disparities in prescribing. While the guideline aimed to provide clinicians an evidence-based framework to inform opioid prescribing decisions, its emphasis on providers' use of personal judgment to determine each patient's prescribing needs may have increased reliance on racial stereotypes and bias amid clinical uncertainty.

Finally, Paper 3 asks how the scarce resources available to reduce opioid-related deaths can be allocated for maximum health benefit. Distribution of naloxone for reversing opioid-related overdose reduces mortality, but it is not known whether distribution remains cost-effective in the context of rising naloxone prices and fentanyl-related overdose rates. Moreover, it is unclear whether distribution to people likely to witness or experience overdose ("laypeople"), police and firefighters, or emergency medical services (EMS)—as well as combinations of these—are equally cost-effective strategies. I conduct a cost-effectiveness analysis examining these questions and find that high distribution to all three target groups minimized overdose deaths, averting 21% of fatalities compared to "bare minimum" distribution. This strategy is highly cost-effective from a health sector perspective, cost-saving from a societal perspective, and robust to hypothetical moral hazard. The results suggest that communities with

insufficient resources for distributing to all three groups should prioritize distribution to laypeople and EMS.

Chapter 1 - Introduction

In recent years, surveillance studies have documented alarming trends in the health status of the U.S. population. A long secular decline in age-adjusted disability prevalence during the 1980s and 1990s appeared to end in the early 2000s (Choi et al., 2016; Freedman et al., 2002, 2004, 2012, 2013; Lakdawalla et al., 2004; Manton et al., 2006; Martin et al., 2010b; R. F. Schoeni et al., 2008; Seeman et al., 2010) and, after rising for more than fifty years, U.S. life expectancy fell each year between 2014 and 2017 (Woolf & Schoomaker, 2019).

Americans in midlife have been particularly affected by these adverse developments. Trends in disability prevalence have flattened among those at older ages, while they have been rising among Americans under age 70 (Choi et al., 2016; Freedman et al., 2012, 2013; Lakdawalla et al., 2004; Martin et al., 2010b; Seeman et al., 2010). And, over the past decade, all-cause mortality among those ages 25-64 increased from 328.5 deaths per 100,000 population to 348.2 per 100,000 (Woolf & Schoomaker, 2019). A sharp rise in rates of fatal overdose, driven in large part by opioid-related overdose, has been a key contributor to these worsening mortality trends (Scholl et al., 2018; Woolf & Schoomaker, 2019).

This dissertation draws on methods and perspectives from health services research, social demography, and medical sociology to investigate three aspects of these contemporary health challenges, with an emphasis on their sociodemographic dimensions. Paper 1 examines the pathways to educational disparities in U.S. disability, while Papers 2 and 3 center on two

elements of the 21st century opioid crisis: racial disparities in opioid prescribing amid efforts to reduce unsafe prescribing (Paper 2) and the allocation of scarce resources to ensure naloxone distribution enables the greatest gains for population health (Paper 3).

Paper 1 - Pathways to educational disparities in disability incidence: The contributions of excess BMI, smoking, and manual labor involvement

In Paper 1, I work to elucidate the pathways that make less educated Americans more likely to experience difficulty conducting activities of daily living (ADLs) and instrumental activities of daily living (Iezzoni et al., 2014; Robert F. Schoeni et al., 2005). ADLs and IADLs include everyday behaviors like bathing, walking, using the toilet, preparing meals, and conducting housework, and reporting difficulty with at least one of these activities is often used as an indicator of disability (LaPlante, 2010; Palmer & Harley, 2012). The educational gradient in difficulty with ADLs and IADLs appears to be growing among adults at both older and middle ages (Montez et al., 2017; Robert F. Schoeni et al., 2005; Zajacova & Lawrence, 2018), yet the mechanisms producing it have received limited attention in the academic literature (Iezzoni et al., 2014).

Educational attainment shapes health throughout the life course via a complex set of pathways (Link & Phelan, 1995; Phelan et al., 2010; Zajacova et al., 2012; Zajacova & Lawrence, 2018). Higher educational attainment enables greater access to flexible resources, such as knowledge, power, money, and advantageous social connections, that can be deployed in any setting for the benefit of health (Link & Phelan, 1995). These resources operate at both the individual and contextual levels, influencing the individual behaviors that shape health, such as diet, exercise,

and smoking, as well as the contexts an individual occupies, such as work environment—all of which can in turn influence the risk of experiencing difficulty with ADLs and IADLs (Phelan et al., 2010; Zajacova & Lawrence, 2018).

This study estimates the contributions of excess BMI, cigarette smoking, and manual labor involvement to educational disparities in the incidence of difficulty with activities of daily living (ADLs) and instrumental activities of daily living (IADLs). While the majority of studies on trends and disparities in ADL/IADL difficulty rely on prevalence as a main outcome, I take advantage of longitudinal nationally representative data from the Panel Study of Income Dynamics (PSID) to study incidence—thereby overcoming several methodological challenges associated with the study of prevalence.

In addition to ADL/IADL difficulty in later life, this study sheds light on that arising among adults at middle ages, which has received comparatively little attention in the literature. I thus estimate the population-level proportion of disparities attributable to each mediator for four separate groups: women under age 65 years, men under age 65, women ages 65 and over, and men ages 65 and over. This allows me to account for variation by age, cohort, and gender in the educational disparities of interest and the processes contributing to them. Finally, I take advantage of earlier-life measures to more accurately characterize the causal pathways among the measures of interest: to account for likely confounding of the education-ADL/IADL difficulty relationship, I control for childhood socioeconomic status; and, to measure excess BMI and manual labor involvement more completely than in many prior studies, I use earlier-life BMI and occupation data in addition to contemporaneous data.

Paper 2 – Racial/ethnic disparities in opioid prescribing to chronic pain patients: The role of the 2016 CDC Guideline to reduce unsafe prescribing

Nearly 48,000 Americans died of opioid overdose in 2017, reflecting a steady increase in opioid-related mortality from 2.9 deaths per 100,000 population in 1999 to 14.9 deaths per 100,000 in 2017 (Kaiser Family Foundation, 2019; Scholl et al., 2018). This public health crisis was accompanied by and has often been attributed to increases in rates of opioid prescribing for pain management, which reached a peak of 81.3 opioid prescriptions per 100 population in 2012 before beginning a consistent decline (Centers for Disease Control and Prevention, 2020). Indeed, prescription opioid use increases the risk of non-medical opioid use and opioid-related mortality, particularly at higher doses and number of days supplied (Bohnert et al., 2011; Edlund et al., 2013).(Edlund et al., 2007; Mason, 2017) In 2006, for example, prescription opioid misuse accounted for an estimated 37 percent of all poisoning deaths (Warner et al., 2009). And while opioid prescribing decreased after 2012, the "second wave" of the opioid epidemic—beginning in earnest in 2010 and characterized by a sharp rise in heroin-related overdose—has been attributed in large part to a transition from prescription opioids to heroin (Centers for Disease Control and Prevention, 2020; Ciccarone, 2019).

In an effort to stem the flow of people developing dependence on or addiction to opioids, much of the policy response to the present opioid crisis has centered on opioid prescribing. In March 2016, for example, the U.S. Centers for Diseases Control and Prevention (CDC) released the Guideline for Prescribing Opioids for Chronic Pain. This document offered a series of

recommendations regarding the initiation, titration, and termination of opioid prescribing to chronic pain patients, and emphasizes the clinician's role in tailoring pain management to each patient's specific circumstances. Early research suggests that the guideline accelerated the ongoing decline in opioid prescribing at the national level (Bohnert et al., 2018; Dayer et al., 2019), but there is evidence that it has at times been misapplied, potentially resulting in the undertreatment of pain and/or unsafe discontinuation of prescribing for some patients (Dowell et al., 2019).

Black and Hispanic chronic pain patients are at particularly high risk of such misapplication, given the well-documented racial/ethnic disparities in pain management—especially for pain that is less easily observed and measured (Cleeland, 1997; Meghani et al., 2012; Ng et al., 1996; Todd et al., 1993, 2000; Won et al., 1999). Clinicians may be disproportionately likely to suspect black and Hispanic patients of so-called drug-seeking behavior, and to in turn prescribe fewer opioids, take more precautionary measures such as urinalysis, and reduce prescribed doses despite a lack of clinical indication (Becker & Turner, 2011; Buonora et al., 2018; Gaither et al., 2018; Meghani et al., 2012; Moskowitz et al., 2011).

Using a large repository of administrative health care data, this study examines whether the CDC Guideline's estimated effect on prescribing patterns varied by race/ethnicity, in turn exacerbating or ameliorating preexisting disparities in opioid prescribing for chronic pain patients. By providing a framework for deciding when to prescribe opioids, in what dose, and over what time period—as well as guidance for avoiding high-risk co-prescribing with other medications—the guideline may have reduced clinical uncertainty. The provision of these clinical guideposts may

have mitigated clinicians' tendency to rely on racist or race-specific priors in decision-making about opioid prescribing, resulting in larger declines in prescribing intensity among white patients compared to black and/or Hispanic patients—and in turn lessening racial/ethnic disparities in pain management.

Alternatively, the guideline could have contributed to a widening of racial/ethnic disparities in prescribing. In stressing the dangers of unsafe prescribing while emphasizing provider discretion in evaluating the risks and benefits for each patient, it may have actually increased clinical uncertainty, prompting greater reliance on racist priors to assess a patient's "legitimate" need for prescription opioids. That is, the guideline may have led clinicians to decrease prescribing intensity more strongly in black and/or Hispanic patients compared to white patients, in turn exacerbating existing disparities in opioid receipt.

This address this question, I examine the association of passage of the CDC guideline with rates and levels of opioid prescribing, as well as benzodiazepine co-prescribing, in chronic, non-cancer pain patients with osteoarthritis and fibromyalgia. To study trajectories and disparities in prescribing in a large sample of individuals from all fifty states, and to enable association of chronic pain diagnoses with subsequent prescription receipt, I use health care claims data from OptumInsight's Clinformatics Data Mart. In an effort to assess disparities arising from provider decision-making rather than issues of socioeconomic status, access, or pain prevalence, I examine prescribing outcomes of clinical encounters with patients who are insured and have received diagnoses that meet my criteria for chronic, non-cancer pain.

Paper 3 - Cost-effectiveness analysis of alternative naloxone distribution strategies: First responder and lay distribution in the United States

While Paper 2 focuses on policies to address initiation of nonmedical opioid use, Paper 3 addresses a different dimension of the opioid crisis: efforts to reduce mortality among people already at risk of opioid-related overdose. Ensuring access to naloxone, a safe and effective opioid antagonist, is a key component of such work. If administered in time and in sufficient dosage, naloxone can reverse opioid-related overdose, extending a person's life and providing additional opportunity to pursue treatment for opioid use disorder.

Prior research has shown distribution of naloxone to people using opioids to be highly cost-effective—i.e., to provide substantial health benefits at a low cost to the health care system and society (Coffin & Sullivan, 2013a). However, it is not clear how this strategy of distribution to laypeople (those likely to witness or experience overdose) compares to first responder distribution. Law enforcement officers, firefighters, and emergency medical services (EMS) are increasingly equipped with naloxone, enabling earlier administration than when the medication is first available at the emergency department—and thus potentially saving more lives (Belz et al., 2006; C. S. Davis, Ruiz, et al., 2014; Gulec et al., 2018).

However, resources to address the opioid crisis are scarce, and a number of factors may increase or diminish the cost-effectiveness of naloxone distribution to each of the three potential target groups: laypeople, police and fire, and EMS. In many rural areas, for example, police and fire may arrive to an overdose scene considerably earlier than an ambulance, saving precious time if these first responders are equipped with naloxone (C. S. Davis, Ruiz, et al., 2014). Yet many

overdose witnesses do not call 911 out of fear of legal or other repercussions, potentially

reducing the effectiveness of distribution to first responders (Galea et al., 2006). While family

and friends of an overdose victim are often the "true" first responders—and despite a body of

evidence to the contrary—many policymakers fear that lay naloxone distribution results in moral

hazard, increasing opioid use and in turn worsening health outcomes at the population level.

In the context of these intertwining forces, I estimate and compares the cost-effectiveness of

naloxone distribution to each of three target groups, both individually and in combination. To do

so, I use a mathematical modeling approach that is robust to the limitations in data regarding

people who use opioids, particularly in the context of a rapidly evolving crisis. This enables

extensive sensitivity analyses that speak to a range of real-life circumstances, providing the

means to make evidence-based policy decisions in the face of incomplete data and urgent human

need.

Chapter 2 - Pathways to Educational Disparities in Disability Incidence: The Contributions of Excess BMI, Smoking, and Manual Labor Involvement

INTRODUCTION

In the United States, difficulty with activities of daily living (ADLs) and instrumental activities of daily living (IADLs) is starkly patterned by education (Iezzoni et al., 2014; Robert F. Schoeni et al., 2005). ADLs and IADLs include everyday behaviors like bathing, walking, using the toilet, preparing meals, and conducting housework. Reported difficulty conducting at least one of these activities independently is frequently used as an indicator of disability (Burkhauser et al., 2006; Iezzoni et al., 2014; LaPlante, 2010; Martin & Schoeni, 2014; Palmer & Harley, 2012). Disability is defined here as one's ability, due to a combination of physical, cognitive, environmental, and societal attitudinal factors, to carry out everyday life activities (Palmer & Harley, 2012; Verbrugge & Jette, 1994).

In a nationally representative study of adults ages 45 to 89, 21.5% of those without a high school degree reported experiencing ADL difficulty, compared to just 4.9% of those with a college degree or more (Montez et al., 2017). This gradient seems to be growing in adults at both older and middle ages (Montez et al., 2017; Robert F. Schoeni et al., 2005; Zajacova & Lawrence, 2018), yet the mechanisms producing it are not well understood (Iezzoni et al., 2014). Compared to disparities in mortality, educational disparities in disability have received little attention. In

particular, few empirical studies have examined potential mediators of the relationship between education and disability and their respective contributions to disparities.

Educational attainment shapes health throughout the life course via a multifarious and complex set of pathways (Link & Phelan, 1995; Phelan et al., 2010; Zajacova et al., 2012; Zajacova & Lawrence, 2018). Higher educational attainment enables greater access to flexible resources, such as knowledge, power, money, and advantageous social connections, which can be deployed in any setting for the benefit of health (Link & Phelan, 1995). These resources operate at both the individual and contextual levels, influencing the individual behaviors that shape health, such as diet, exercise, and smoking, as well as the contexts an individual occupies, such as work environment—all of which can in turn influence disability risk (Phelan et al., 2010; Zajacova & Lawrence, 2018).

While there is evidence that excess BMI and smoking partially mediate the education-disability relationship (Cutler & Lleras-Muney, 2010; Sainio et al., 2007), such research is scarce and has a number of important limitations. First, a third mediator and likely confounder, involvement in manual labor (defined here as working as an operative or laborer), has received little attention (Cutler & Lleras-Muney, 2010). Manual labor can increase disability risk through repetitive stress and other mechanisms (Bang & Kim, 2001; Leigh & Fries, 1992; Marmot et al., 1997).

Second, prior research has focused predominantly on older adults, overlooking disparities in disability at middle ages. Yet these groups may exhibit important differences in the trends and consequences of disability. Disability can have a range of adverse consequences for individual

well-being, influencing mental health, everyday task independence, role fulfillment, social relationships, finances, and other outcomes (Carr, 1999; Darling, 1987). Its occurrence among those under retirement age may be of particular concern, interfering with the ability to work, take care of children and aging parents, save for retirement, and engage in other activities important in middle life. Moreover, trends in earlier-life disability may differ in direction and magnitude from those in older adults (Martin & Schoeni, 2014; Robert F. Schoeni et al., 2008). Between 1997 and 2010, for example, ADL/IADL disability prevalence increased among adults under age 65, while decreasing among those ages 65 and over (Iezzoni et al., 2014; Martin & Schoeni, 2014). A more thorough understanding of the trends in and processes underlying earlier-life disability is needed.

Moreover, the respective roles of excess BMI, smoking, and manual labor in explaining educational disparities in disability incidence likely vary by age, cohort, and gender—due to variation both in the prevalence of the mediators by group, and in the associations among education, the mediators, and disability. For example, smoking prevalence among women and educational disparities in smoking are greater in more recent cohorts (Escobedo & Peddicord, 1996; Link & Phelan, 2009; Pampel, 2009). In addition, the association between education and BMI is more pronounced in women (Brunello et al., 2013; Y.-J. Kim, 2016), and we might expect the effects of manual labor on disability to manifest predominantly during working ages. These variations suggest that age-gender groups will differ in the pathways underlying educational disparities.

Finally, by examining disability prevalence rather than incidence, existing research raises the specters of Neyman bias and reverse causation (Grimes & Schulz, 2002; Mehta, 2015). In Neyman bias, for example, smoking-related mortality results in a healthier observed population of smokers, reducing smoking's estimated effect on disability (Grimes & Schulz, 2002). In reverse causation, disability may lead to reductions in excess BMI or manual labor involvement, making these mediators appear protective in prevalence studies (Mehta, 2015). In addition, related research has typically estimated only mediation percentages, rather than accounting for the mediators' prevalence in the population and, in turn, estimating the percent of disparities they explain at the population level.

To address these gaps in the literature, this study uses the Panel Study of Income Dynamics (PSID) to estimate the contributions of excess BMI, smoking, and manual labor to disparities in incident ADL/IADL difficulty at the population level, stratifying by age and gender. In doing so, I take advantage of life course factors including childhood socioeconomic status, earlier-life BMI, and historical occupation data.

Educational disparities in disability

Education influences health-related outcomes like disability via a variety of biomedical, environmental, and social pathways, including economic circumstances, social support and influence, health behaviors, stress, environmental exposures, and health care access (Link & Phelan, 1995; Zajacova & Lawrence, 2018). The association between education and self-rated health appears stronger among women, who also experience higher rates of disability overall (Montez et al., 2017; Zajacova & Montez, 2017).

Measures of ADL/IADL difficulty suggest that educational disparities in disability prevalence may be growing. While the prevalence of ADL/IADL difficulty among adults ages 70 and older fell for all educational groups during the 1980s and 1990s, the least educated experienced the smallest decline (Robert F. Schoeni et al., 2005). Between 2000 and 2015, prevalence of ADL/IADL difficulty among those ages 45-64 stabilized among the most educated and increased among other educational groups (Zajacova & Montez, 2017).

Education, excess BMI, and disability

A strong association between educational attainment and BMI, particularly among women, is well-documented (Brunello et al., 2013; Y.-J. Kim, 2016). Using sibling data, for example, Kim (2016) finds that those with a college degree have an estimated 0.7-unit lower body mass index (BMI) than high school graduates with no college attendance (Y.-J. Kim, 2016). Less educated groups gain weight more rapidly during adulthood, such that educational disparities in BMI widen throughout much of the life course (Clarke et al., 2009). There is also evidence that BMI can influence educational attainment (Karnehed et al., 2006).

Mediators between education and BMI include health literacy and resources for deploying it, exposure to norms and social support, and stress related to social status, sense of control, and socioeconomic security, among others (for an overview, see Zajacova & Lawrence, 2018). Health conditions mediating the excess BMI-disability relationship include higher risk of diabetes, coronary artery disease, and osteoarthritis—all of which can undermine mobility and independence (Samper-Ternent & Al Snih, 2012). The rising prevalence and duration of obesity

in the U.S. population may partly explain rising rates of ADL/IADL difficulty, particularly in recent cohorts (Iezzoni et al., 2014; Martin & Schoeni, 2014).

Reverse causation, in which illness causes weight loss, can mask the BMI-disability relationship by making higher BMI look protective—particularly in older age, when health declines are more common (Stokes & Preston, 2016). Measurement of BMI at multiple points in the life course may therefore help capture the effects of excess BMI on health (Abdullah et al., 2011; Mehta, 2015).

Education, smoking, and disability

More educated groups may have more economic, cognitive, social, and cultural resources to avoid or quit smoking (Link & Phelan, 1995; Pampel, 2009). While smoking was not clearly patterned by educational status in the 1950s, an educational gradient emerged in the wake of the Surgeon General's Report on Smoking and Health and subsequent attention to smoking's adverse effects. Educational disparities grew as smoking rates declined earlier and more rapidly among the more educated (Escobedo & Peddicord, 1996; Link & Phelan, 2009; Pampel, 2009).

The strong educational gradient in smoking may be due in part to effects of educational attainment on smoking, and in part to common causes such as early-life exposures. Net of familial factors, however, individuals with less than a high school degree appear to make fewer quit attempts and be less likely to quit smoking (Gilman et al., 2008).

Disability rates in more recent cohorts would likely have risen more sharply absent declines in smoking in those groups (Martin & Schoeni, 2014). Smoking predicts disability via greater incidence of musculoskeletal injury (Altarac, 2000), higher probability of progression from injury to disability (Lincoln et al., 2003), contribution to cardiovascular and respiratory diseases (Murray & Lopez, 1997), and other pathways (Manouchehrinia et al., 2013). There is evidence of a dose-response relationship between smoking and disability incidence (Claessen et al., 2010), and evidence that cessation can reverse or diminish some adverse health consequences (Lincoln et al., 2003; Manouchehrinia et al., 2013). In addition to the causal effects of smoking on disability, these factors may have common causes, such as health consciousness and underlying mental health (Claessen et al., 2010).

Education, manual labor, and disability

Manual labor involvement may be a third key mediator of the education-disability relationship (Cutler & Lleras-Muney, 2010). Occupation is starkly patterned by education: less educated individuals have fewer career options and are disproportionately likely to be unemployed or conduct manual labor (Leigh & Fries, 1992). In addition to the likely causal effect of educational attainment on manual labor involvement, these factors may be influenced by common causes such as family socioeconomic status and structural factors that channel educational groups into distinct vocations.

Manual laborers experience higher rates of disability than their counterparts, although research in U.S. populations is limited (Abdullah et al., 2011; Cutler & Lleras-Muney, 2010; Leigh & Fries, 1992; Li, 2000; Mansson, 1998). In the U.S., for example, disability is most common among

machine operators, farm workers, and laborers (Cutler & Lleras-Muney, 2010; Leigh & Fries, 1992). Manual labor often entails more occupational hazards and repetitive movements than other work, contributing to musculoskeletal injuries and disability (Leigh & Fries, 1992). Some forms of manual labor may also entail limited job control, which can contribute to disability by increasing stress, a risk factor for cardiovascular disease (Marmot et al., 1997; Rahkonen et al., 2006; Warren et al., 2004). Manual labor may also increase disability risk by perpetuating low socioeconomic status: lower wages and status may impede individuals' ability to invest in their health and to transition to a more health-conducive job.

The pathways between manual labor and disability may also include interactions with excess BMI and smoking. Smoking prevalence is higher in manual labor and related jobs (Bang & Kim, 2001), likely reflecting social network effects among other factors (Christakis & Fowler, 2008). Conversely, the physical activity involved in manual labor may promote lower BMI and prevent other adverse effects of more sedentary lifestyles (Rydwik et al., 2013).

Aims

I examine the proportion of educational disparities in the incidence of ADL/IADL difficulty ("incidence") explained by excess BMI, smoking, and manual labor, independently and jointly. I use nationally representative, longitudinal data with up to seven waves of follow-up, and take advantage of earlier-life measures of socioeconomic status, body mass index (BMI), and occupation. I compare actual disparities in incidence to their estimated counterfactuals in the absence of excess BMI, smoking, and manual labor, enabling estimation of the percentage of disparities explained by each mediator of interest.

I address several important gaps in the literature. To my knowledge, this is the first study to estimate the population-level contributions of three key mediators underlying the relationship between education and difficulty with ADLs and /IADLs. To account for distinct processes in men and women at middle versus older ages, I stratify by gender and age at exposure to the mediators. Third, whereas prior studies have examined predictors of ADL/IADL prevalence, I study incidence, reducing the risks of Neyman bias and reverse causation.

METHODS

Study population

The PSID is a nationally representative survey that followed participants and their descendants annually from 1968-1997 and biennially thereafter (Appendix A-1). Individuals were eligible for the analytic sample if they participated in PSID in 1986 (the earliest wave in which height and weight were reported) and at least two consecutive waves between 2003 and 2015.

Measures

In line with existing literature and PSID recommendations, ADL/IADL difficulty was defined as difficulty with at least one ADL or IADL (Burkhauser et al., 2006; Cutler & Lleras-Muney, 2010; Iezzoni et al., 2014; Laditka & Laditka, 2016; Martin et al., 2010a; Martin & Schoeni, 2014; Robert F. Schoeni et al., 2005). Since 2003, PSID has asked about difficulty conducting a standard set of ADLs and IADLs without assistance or special equipment. The assessed ADLs include: difficulty bathing or showering; dressing; eating; getting in or out of a bed or a chair; walking; getting outside; and using or getting to the toilet. The assessed IADLs include:

difficulty preparing meals; shopping for toiletries or medicines; managing money; using the telephone; doing heavy housework; and doing light housework. Incidence with ADL/IADL difficulty was defined as a switch from no difficulty in wave t-1 to any difficulty in wave t (Appendix A-2).

Excess BMI was measured using two continuous indicators, calculated using self-reported height and weight: 1986 ("earlier-life") BMI and time-varying ("contemporaneous") BMI between 2003 and 2015. To examine associations between excess BMI and incident ADL/IADL difficulty, these were equal to absolute BMI minus 25 (Mehta et al., 2014; Preston et al., 2013) (Appendix A-3). Smoking history (never, former, current smoker) was time-varying. The manual labor variable was binary and indicated ever having been an "operative" or "laborer" between 1968 and 2001. Appendix A-4 details construction of this variable and discusses the associations between each type of manual labor and incidence.

Because people may obtain education between waves, this variable was time-varying (less than high school, high school degree, college degree). Obtaining a GED, attending some college, receiving non-academic training after high school, and obtaining an Associate's degree were coded as "high school degree". Appendix A-5 details the reasoning behind this categorization.

I controlled for sociodemographic factors likely to be independently related to education, ADL/IADL difficulty, and the mediators: age (continuous), gender, childhood socioeconomic circumstances ("Were your parents poor when you were growing up, pretty well off, or what?":

"poor", "average/it varied", "pretty well off"), race/ethnicity (non-Hispanic white, black, Hispanic non-black, and non-Hispanic other), and year (categorical) (Appendix A-5).

Statistical analysis

Regression models

Analyses were conducted in Stata 15.0. Logistic regressions, stratified by gender and age at exposure to the time-varying predictors (under 65 years old vs. 65 and above), predicted incidence of ADL/IADL difficulty for up to seven waves of follow-up, between 2003 and 2015 (Appendix A-6). Waves in which a respondent was at risk for incident ADL/IADL difficulty (i.e., did not currently report any difficulty) were included in regression analyses, with an indicator of whether incidence occurred in the following wave. Individuals could experience incidence multiple times. 950 observations were excluded due to covariate missingness or extreme values of BMI (less than 15 and greater than or equal to 50), driven predominantly by missing mediator data (Appendix A-5). To alleviate reverse causation, all time-varying predictors were lagged one wave. Appendix A-7 discusses and tests the assumption, implicit in these regression models, that the associations between the mediators and incident ADL/IADL difficulty do not vary by educational attainment.

Percent of disparities explained by mediators

Following regression, I calculated predictive margins and educational disparities by age-gender group, using the observed distribution of covariates to estimate incident ADL/IADL difficulty in each age-gender-educational category. Educational comparisons included college versus no high school degree; high school versus no high school degree; and college versus high school degree.

I used the same approach to estimate incidence and disparities in each subgroup under four counterfactual scenarios: (a) no excess BMI in the population, in 1986 or contemporaneously; (b) no smoking; (c) no involvement in manual labor; and (d) none of the three risk factors in the population. That is, I set the indicator of the corresponding mediator(s) to zero for the entire sample and calculated the corresponding predictive margins, holding the values of all other covariates as observed. I compared the observed and counterfactual disparities to estimate the percentage of observed disparities explained by the mediators, individually and jointly. Confidence intervals were calculated using the delta method (Oehlert, 1992; Phillips & Park, 1988). These methods were only able to approximate the causal processes of interest and assume no unobserved confounding. For clarity, I use the terms "explained" and "contributed" to describe the estimated proportion of disparities attributable to a given mediator, but these cannot be interpreted to be true causal effects.

Supplementary analyses

I conducted a number of supplementary analyses. First, I examined sedentariness in year of study entry (more than 10 minutes of heavy exercise per week, or not) as a potential mediator in the regressions and re-estimated percentages of disparities explained (Appendix A-8). Concerns about reverse causation precluded its inclusion in the main analysis. In a second supplementary analysis, I examined the ADL and IADL with which participants most often had difficulty— walking and heavy housework. The higher frequency of difficulty with these activities could suggest that distinct processes underlie the ability to conduct them. Third, I examined persistent difficulty, i.e., ADL/IADL difficulty lasting at least two consecutive waves. Appendix A-8 outlines the frequency of persistent difficulty by age-gender group. Fourth, I examined difficulty

with ADLs and IADLs separately. Fifth, I used a method of mediation analysis recently developed by Karlson, Holm, and Breen to examine whether the association between manual labor and incident ADL/IADL difficulty in younger men was mediated by excess BMI and smoking, given that manual labor involvement may influence each of these via effects on physical activity, social exposure, and workplace smoking policies (Karlson et al., 2012). Finally, I examined whether the association of each mediator with incidence varied by educational group (Appendix A-7).

RESULTS

Descriptive statistics

Table 2-1 displays weighted sample characteristics. Incident ADL/IADL difficulty (i.e., a switch from no difficulty to any difficulty in the subsequent wave) was evaluated for 3,129 individuals at risk for incident difficulty for an average of 4-5 waves. There were 1,398 cases of incidence. Incidence was greater in women (younger women: 4.4 cases per 100 person-years; younger men: 3.0 per 100 person-years; older women: 9.8 per 100 person-years; older men: 8.3 per 100 person-years). The sample was predominantly white and most had attained only a high school degree. Men were more likely than women to have completed college.

BMI was lower in women than men in 1986 (younger women: 23.0; younger men: 25.2; older women: 24.0; older men: 26.1) and at study entry (i.e., the first wave, 2003-2015, present in the analytic sample; younger women: 26.6; younger men: 27.7 women; older women: 25.6; older men: 27.1). BMI increased between 1986 and study entry. Among older individuals, women

were less likely than men to have ever smoked (40% vs. 67%); this difference was less pronounced in younger individuals (56% vs. 53%). Across age groups, 29-35% had ever participated in manual labor.

Walking was the most prevalent ADL difficulty and performing heavy housework was the most prevalent IADL difficulty (Appendix A-9). Others were clustered with similar prevalence. Except in women 65 and over, education was positively associated with ever having smoked (Table 5-1; Figure 5-2). In women, education was negatively associated with excess BMI; it was positively associated with excess BMI in older men. Across groups, education was negatively associated with ever participating in manual labor.

Regressions

Estimated associations between predictors and incident ADL/IADL difficulty varied by age-gender group (Table 2-2). Age was positively associated with incidence in all groups and being black (vs. non-Hispanic white) was associated with incidence in men. With the exception of older men, higher education was associated with lower incidence, though estimates were not always statistically significant at the p=0.05 level. Similarly, higher childhood socioeconomic status was associated with lower incidence in all but older women, but estimates were imprecise. Higher 1986 and contemporaneous BMI, as well as smoking, tended to be positively associated with incidence. Manual labor was associated with higher odds of incidence in younger men (OR = 1.50, 95% CI: 1.08-2.10).

Disparities in incident ADL/IADL difficulty and estimated percent explained

Educational disparities in incident ADL/IADL difficulty were evident in both men and women (Figure 2-1). With the exception of older men, for whom it was highest among those with a high school degree, incidence decreased with greater educational attainment. Larger disparities were observed among women than men, and this gender difference was most pronounced among the least educated.

Overall, excess BMI, smoking, and manual labor were estimated to explain a greater percentage of disparities in younger compared to older adults (younger women: 58-62%; younger men: 65-72%; younger men; older women: 38-39%; older men: 20-60%), although estimates did not reach statistical significance at the $p=0.05$ level in older men (Table 2-3). In younger women, smoking and excess BMI appeared to be the main contributors to disparities (smoking: 21-30%; excess BMI: 36-39%), while in younger men the main contributors appeared to be smoking and manual labor (smoking: 23-35%; manual labor: 33-38%). In older women, excess BMI appeared to be the main contributor to disparities (30%). While estimates for older men were noisy, smoking appeared to be the main contributor to disparities. In this group, higher BMI appeared to suppress educational disparities, reflecting lower average BMI among the least compared to more educated older men.

Tables 5-2 through 5-7 and appendix text provide results of the supplementary analyses.

DISCUSSION

In this study, I estimated population-level contributions of three key mediators of educational disparities in incident ADL/IADL difficulty among both younger and older women and men. I

took advantage of seven waves of nationally representative, longitudinal data on ADL/IADL difficulty, combined with information on life course factors including childhood socioeconomic circumstances, earlier-life BMI, and occupational history. Educational disparities in ADL/IADL difficulty were evident among both younger and older adults (under 65, 65 and over) and larger in women. Together, excess BMI, smoking history, and manual labor involvement appeared to account for roughly 60-70% of disparities in incident ADL/IADL difficulty between the most and least educated under age 65. Among women aged 65 and over, these factors tended to account for nearly 40% of that disparity. Estimates in older men were more variable, but the models indicated an explanatory power of 20-60%.

The stronger contribution of smoking to disparities in younger compared to older women likely reflects the growing prevalence and educational gradient in smoking in recent decades (Escobedo & Peddicord, 1996; Link & Phelan, 2009; Pampel, 2009). Smoking also appeared to explain more of the educational disparity in ADL/IADL difficulty among men, a product of the starker educational gradient in smoking among men compared to women.

Conversely, excess BMI appeared to contribute more to educational disparities among women. This finding was related to the more consistent relationship between education and BMI among women. Indeed, contemporaneous BMI was higher among men with a high school degree than among their more and less educated counterparts. This is consistent with prior research (Brunello et al., 2013; Y.-J. Kim, 2016), and may relate to findings that education predicts exercise and employment more strongly in women, factors inversely related to excess BMI (Brunello et al., 2013). Moreover, larger educational disparities in smoking—which is inversely related to

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weight—among men may suppress an educational gradient in BMI in this group (Rydwik et al., 2013).

Ever conducting manual labor appeared to be a key driver of disparities in young men. While estimates were imprecise, it appeared to contribute less in older adults. The apparent differential by age may suggest that manual labor's effect on ADL/IADL difficulty is most pronounced during working ages, although my study is not conclusive in this regard. While prevalence of and educational disparities in manual labor involvement were considerable in younger women, manual labor's estimated contribution to disparities in incident ADL/IADL difficulty was not significantly different from zero. This may suggest that women and men coded as "laborers" or "operatives" conduct substantively distinct types of work, with differential consequences for difficulty with ADLs and IADLs. More research on the contribution of manual labor to ADL/IADL difficulty by gender and throughout the life course is warranted.

The three mediators of interest appeared to explain less of the disparities in the older group than in the younger group. Differential ability to manage biological frailty may serve as an additional mediator, explaining residual disparities at older ages: more educated individuals, who on average have more financial and other resources, may be better able to adapt to growing frailty at older ages—e.g., installing home infrastructure to prevent falls and, when a fall does occur, obtaining support to reduce the risk of developing ADL/IADL difficulty. Because each age group comprised individuals from different birth cohorts, both age and cohort effects are likely combining to produce the patterns observed here. Research examining multiple birth cohorts as they age is needed to untangle these effects.

Reflecting the unique disadvantage of not obtaining a high school degree, disparities between the most and least educated were largest, followed by those between the middle and least educated. Moreover, despite strong associations between education and the mediators, substantial disparities were left unexplained after accounting for them—a product of the myriad pathways by which limited education can influence health, and which I was unable to account for. These might include persistent stress, environmental exposures, neighborhood resources, social influence, unstable housing, unemployment, unstable employment, and others (Bambra & Eikemo, 2008; Baum et al., 1999; Burgard et al., 2012; Christakis & Fowler, 2008; Glass et al., 2006). Therefore, while successful behavioral interventions may reduce disparities in disability, they alone are not sufficient. Broad-based policies that improve access to quality education are also needed (Link & Phelan, 1995).

Separate examination of ADLs, IADLs, and the two most common manifestations of ADL/IADL difficulty (difficulty walking and conducting heavy housework) did not meaningfully change my conclusions. In a supplementary analysis of persistent difficulty, defined as ADL/IADL difficulty lasting at least two waves, the estimated percentage of disparities explained in women grew, driven in younger women by a larger estimated contribution of manual labor. Exposure to manual labor may be associated with musculoskeletal injuries that contribute to earlier-life and prolonged spells of difficulty with ADLs and IADLs. Finally, supplementary examination of potential additive interactions between education and the mediators revealed that education is a likely effect modifier of the association between smoking and ADL/IADL difficulty, particularly in women. Further research is needed to confirm these findings and to elucidate both the

mechanisms underlying them and their consequences for the pathways to educational disparities in ADL/IADL difficulty.

This study has limitations. First, comparisons of percent of disparities explained between mediators and across age-gender groups were complicated by imprecise estimates, particularly in older adults. I reported apparent trends between groups or mediators, but was often unable to reject the null hypothesis of no difference at an alpha of 0.05. Despite the strengths afforded by my longitudinal data and earlier-life measures, reverse causation remains a challenge. I attempted to address this by including 1986 BMI in addition to contemporaneous BMI, providing a measure less related to concomitant health decline. As my analyses reflected, earlier-in-life BMI predicts health outcomes independent of baseline or contemporaneous BMI (Abdullah et al., 2011; Mehta et al., 2014). To further address reverse causation, I lagged BMI and smoking by one wave (two years), and fixed the measure of ever having participated in manual labor to 2001, the wave prior to initiation of analysis. Reverse causation concerns precluded inclusion of one potential mediator of disparities: unemployment. Unemployment is strongly related to disability (Leigh & Fries, 1992; Mansson, 1998), but much of this relationship may be due to the effects of disability on unemployment.

In addition, the links between education and my mediators may in part be explained by common causes such as early-life exposures and personality factors, rather than reflecting a pure causal effect of education on smoking behavior, excess BMI, and manual labor participation (Claessen et al., 2010; Gilman et al., 2008). As a result, the mediators I examined may mediate not only the relationship between education and difficulty with ADLs and IADLs, but also the relationship

between these common causes and disability. I attempted to minimize this bias by controlling for childhood socioeconomic status, but data limitations precluded controlling for other early-life exposures or individual traits. Nonetheless, my findings help elucidate the extent to which educational disparities in incident ADL/IADL difficulty would shrink if the mediators were eliminated in the population.

My measure of whether the participant had ever conducted manual labor was imperfect. I likely underestimated manual labor involvement among the older group due to incomplete data on their working years: when PSID began in 1968, individuals in the older group were already 30-58 years old, so some manual labor involvement was likely missed. Second, my measure of manual labor involvement does not capture physically demanding domestic labor. This could lead to underestimation of ADL/IADL difficulty related to manual labor, particularly in women (Leigh & Fries, 1992). Third, missingness in the occupation variable may have resulted in misclassification of some individuals as "never manual"; this would also result in conservative estimates of manual labor's contribution to disparities.

While evidence suggests excess BMI can itself contribute directly to difficulty with ADLs and IADLs (Samper-Ternent & Al Snih, 2012), it may also function as a proxy for other important risk factors such as exercise. However, in the supplementary analysis in which sedentariness in the year of study entry was included as a potential mediator, the estimated contribution of excess BMI to disparities fell by only 0-4 percentage points, suggesting my main estimates for excess BMI are not merely capturing the effects of sedentariness on ADL/IADL difficulty.

This study examined disparities in difficulty with at least one of 13 standard ADLs and IADLs, a measure frequently used as an indicator of disability (Iezzoni et al., 2014; Martin & Schoeni, 2014; Palmer & Harley, 2012; Samper-Ternent & Al Snih, 2012). A social-relational model of disability acknowledges that disability results from an interaction between physical impairment and social and environmental conditions—i.e., that the consequences of physical impairment for one's ability to carry out everyday life activities are shaped by the environmental structures and resources available to the person (Reindal, 2008). As a result, disability may often be ameliorated by contextual changes—such as ramps, Braille signage, health aides, and many others—without change to the body itself.

Within this context, ADL and IADL measures are useful indicators of disability in that they assess one's ability to conduct higher-order activity, which is the product of both biomedical and socioenvironmental processes. However, because PSID's ADL and IADL measures ask about trouble conducting the activity without assistance or special equipment, their specificity as measures of disability is likely constrained. That is, they may be prone to false positives, in which individuals with physical impairment who report ADL/IADL difficulty are able to make use of adaptive measures and consequently do not actually experience disability. Because access to such adaptive measures is likely greater among more educated people, my estimates of disparities in ADL/IADL difficulty probably underestimate disparities in disability as defined in the social-relational model. Longitudinal data evaluating ADL/IADL difficulty both with and without adaptive measures are needed.

Against a backdrop of population aging and widening educational disparities in disability, this study provides important insight into the mechanisms underlying those gaps. My findings suggest that excess BMI, smoking, and manual labor explain 20-70% of disparities in incident ADL/IADL difficulty, and that the mediators driving them vary by age-gender group. Further research is needed to account for the proportion of disparities left unexplained, and to better characterize the ways in which the mediators of interest translate into health conditions and, ultimately, difficulty conducting activities core to everyday life.

Table 2-1. Sample characteristics by age group and gender

	Under 65				65 and older			
	Women		Men		Women		Men	
	Est.	95% C.I..	Est.	95% C.I..	Est.	95% C.I..	Est.	95% C.I..
Unique individuals	1,352	--	1,106	--	382	--	289	--
Waves at risk for disability, mean	4.0	--	4.2	--	4.5	--	5.1	--
Incidence, cases	492	--	300	--	354	--	252	--
Incidence, per 100 person-years	4.4	(3.9 to 4.9)	3.0	(2.6 to 3.5)	9.8	(8.7 to 11.0)	8.3	(7.1 to 9.4)
Characteristics at study entry								
Age, mean, years	50.2	(49.7 to 50.6)	50.4	(49.9 to 50.8)	73.9	(73.2 to 74.6)	72.5	(71.8 to 73.2)
Body mass index (BMI) in 1986, kg/m^2								
Mean	23.0	(22.8 to 23.3)	25.2	(25.0 to 25.5)	24.0	(23.6 to 24.5)	26.1	(25.7 to 26.6)
Overweight or obese, %	23.0	(20.5 to 25.7)	48.6	(45.3 to 51.9)	30.1	(25.3 to 35.3)	60.1	(54.1 to 65.8)
Obese, %	7.3	(5.8 to 9.1)	9.5	(7.7 to 11.6)	7.0	(4.7 to 10.2)	11.5	(8.2 to 15.8)
BMI at study entry kg/m^2								
Mean	26.6	(26.3 to 27.0)	27.7	(27.5 to 28.0)	25.6	(25.1 to 26.1)	27.1	(26.6 to 27.5)
Overweight or obese, % (BMI $\geq$ 25.0)	52.7	(49.6 to 55.8)	76.0	(73.1 to 78.7)	47.0	(41.6 to 52.5)	66.2	(60.4 to 71.6)
Obese, %	23.4	(20.9 to 26.1)	24.8	(22.1 to 27.7)	13.3	(10.0 to 17.4)	19.2	(14.8 to 24.5)
Smoking, %								
Never	54.2	(51.0 to 57.3)	47.2	(43.9 to 50.5)	59.8	(54.3 to 65.1)	32.5	(27.2 to 38.4)
Former	26.4	(23.7 to 29.3)	28.9	(26.1 to 32.0)	31.6	(26.7 to 37.0)	61.6	(55.7 to 67.3)
Current	19.4	(17.1 to 22.1)	23.9	(21.2 to 26.8)	8.5	(5.9 to 12.2)	5.8	(3.6 to 9.2)
Manual labor, %	32.4	(29.5 to 35.4)	35.3	(32.3 to 38.5)	28.9	(24.2 to 34.1)	25.2	(20.4 to 30.6)
Race/ethnicity, %								
Non-Hispanic white	79.9	(77.3 to 82.2)	88.7	(86.5 to 90.5)	85.1	(80.6 to 88.7)	88.7	(83.9 to 92.2)
Black	13.9	(12.0 to 16.0)	7.6	(6.2 to 9.2)	9.7	(6.9 to 13.3)	4.0	(2.2 to 7.1)
Hispanic non-black	4.2	(3.0 to 5.9)	2.1	(1.2 to 3.5)	3.0	(1.5 to 6.0)	3.1	(1.5 to 6.2)

Non-Hispanic other	2.0	(1.3 to 3.2)	1.7	(0.9 to 3.2)	2.2	(0.9 to 5.3)	4.3	(2.1 to 8.3)
Educational attainment, %								
Less than high school	8.2	(6.7 to 10.0)	7.3	(5.9 to 9.1)	17.4	(13.5 to 22.1)	16.8	(12.9 to 21.7)
High school degree	66.3	(63.3 to 69.2)	59.2	(55.9 to 62.3)	63.6	(58.1 to 68.8)	54.0	(48.0 to 59.8)
College degree	25.5	(22.8 to 28.3)	33.5	(30.5 to 36.7)	19.0	(15.0 to 23.7)	29.2	(24.1 to 35.0)
Childhood SES								
Poor	28.8	(26.1 to 31.7)	19.5	(17.1 to 22.2)	47.0	(41.5 to 52.5)	46.8	(40.9 to 52.8)
Average/it varied	52.6	(49.5 to 55.7)	49.6	(46.4 to 52.9)	43.0	(37.7 to 48.5)	39.3	(33.6 to 45.2)
Well off	18.6	(16.3 to 21.2)	30.8	(27.9 to 33.9)	10.1	(7.1 to 14.0)	13.9	(10.3 to 18.6)
Calendar year, mean	2003.6	(2003.5 to 2003.7)	2003.3	(2003.2 to 2003.4)	2004.0	(2003.8 to 2004.2)	2003.6	(2003.4 to 2003.8)

Note: Estimates are weighted. Overweight refers to BMI greater than or equal to 25.0 and obese to BMI greater than or equal to 30.0.

Table 2-2. Odds ratios, logistic regressions on disability incidence, age-stratified

	Under 65		65 and older	
	Women	Men	Women	Men
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
BMI, contemporaneous	1.049**	1.028	1.150***	1.02
	(1.017, 1.082)	(0.988, 1.069)	(1.086, 1.217)	(0.952, 1.094)
BMI, 1986	1.077**	1.089***	0.951	1.063
	(1.023, 1.134)	(1.036, 1.144)	(0.874, 1.035)	(0.987, 1.145)
Smoking				
Never	*Ref.*	*Ref.*	*Ref.*	*Ref.*
Former	1.343*	1.096	1.357	1.643**
	(1.001, 1.801)	(0.754, 1.594)	(0.984, 1.871)	(1.143, 2.361)
Current	1.851***	1.638*	1.145	2.015
	(1.307, 2.621)	(1.102, 2.436)	(0.638, 2.056)	(0.923, 4.399)
Manual	1.05	1.504*	1.162	1.111
	(0.784, 1.407)	(1.075, 2.104)	(0.819, 1.647)	(0.734, 1.680)
Age	1.052***	1.042**	1.103***	1.088***
	(1.028, 1.076)	(1.014, 1.071)	(1.076, 1.130)	(1.058, 1.119)
Race/ethnicity				
Non-Hispanic, white	*Ref.*	*Ref.*	*Ref.*	*Ref.*
Black	1.148	1.794**	0.657	3.114**
	(0.833, 1.582)	(1.193, 2.697)	(0.369, 1.170)	(1.355, 7.154)
Hispanic, non-black	1.815	0.304	0.646	1.469
	(0.902, 3.655)	(0.043, 2.156)	(0.202, 2.068)	(0.557, 3.871)
Non-Hispanic, other	0.624	2.189	0.666	0.716
	(0.207, 1.879)	(0.979, 4.894)	(0.243, 1.823)	(0.247, 2.078)
Education				
Less than high school	*Ref.*	*Ref.*	*Ref.*	*Ref.*
High school degree	0.727	0.708	0.753	0.98
	(0.454, 1.165)	(0.400, 1.251)	(0.455, 1.245)	(0.605, 1.588)
College degree	0.565*	0.525*	0.694	1.375

	(0.324, 0.986)	(0.276, 0.997)	(0.385, 1.251)	(0.756, 2.503)
Childhood SES				
Poor	*Ref.*	*Ref.*	*Ref.*	*Ref.*
Average/varied	0.879	0.926	1.004	0.785
	(0.662, 1.167)	(0.641, 1.336)	(0.731, 1.380)	(0.547, 1.126)
Well off	0.746	0.762	1.111	0.460*
	(0.514, 1.082)	(0.471, 1.235)	(0.669, 1.844)	(0.246, 0.859)
Year				
2003	*Ref.*	*Ref.*	*Ref.*	*Ref.*
2005	0.826	1.051	0.776	0.895
	(0.576, 1.184)	(0.656, 1.684)	(0.483, 1.245)	(0.541, 1.482)
2007	0.802	1.046	1.084	0.832
	(0.564, 1.142)	(0.660, 1.657)	(0.693, 1.694)	(0.526, 1.317)
2009	1.014	1.266	0.953	0.793
	(0.712, 1.444)	(0.804, 1.996)	(0.597, 1.522)	(0.478, 1.316)
2011	1.000	1.707*	1.036	0.667
	(0.677, 1.476)	(1.027, 2.838)	(0.649, 1.652)	(0.392, 1.133)
2013	0.850	1.419	0.854	0.915
	(0.538, 1.343)	(0.832, 2.423)	(0.512, 1.424)	(0.552, 1.517)
Constant	0.007***	0.005***	0.000***	0.000***
	(0.002, 0.025)	(0.001, 0.026)	(0.000, 0.001)	(0.000, 0.003)
Observations	5,388	4,615	1,704	1,461

Note: * p<0.05, ** *p*<0.01, *** *p*<0.001. OR=odds ratio.

Figure 2-1. Disability incidence by age, gender, and education
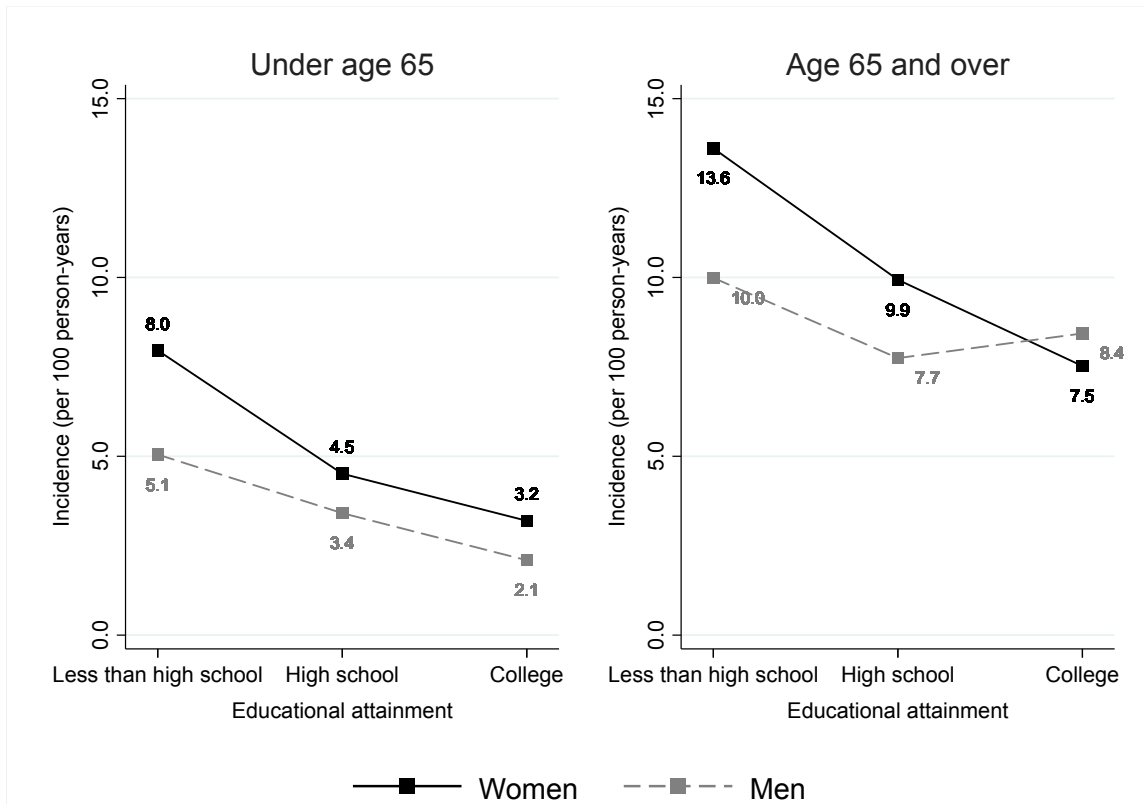
Table 2-3. Percent of educational disparities explained by smoking, excess BMI, and manual labor

Under 65	Women (95% CI)			Men (95% CI)		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	4.8 (1.6, 7.9)	3.5 (0.4, 6.5)	1.3 (0.3, 2.4)	3.0 (0.6, 5.3)	1.7 (-0.7, 4.0)	1.3 (0.5, 2.2)
Percent explained						
Smoking	23.1 (9.3, 36.8)	20.5 (6.2, 34.8)	29.8 (8.9, 50.6)	29.5 (2.3, 56.7)	34.5 (-2.0, 70.9)	23.2 (-2.3, 48.8)
Excess BMI	37.8 (18.3, 57.2)	38.6 (13.6, 63.5)	35.6 (14.4, 56.9)	15.0 (2.0, 28.0)	5.6 (-19.3, 30.6)	26.7 (10.4, 42.9)
Manual	4.0 (-19.5, 27.5)	3.8 (-18.3, 25.9)	4.5 (-22.8, 31.8)	35.1 (5.9, 64.3)	32.7 (1.3, 64.0)	38.2 (4.8, 71.6)
All	**58.2 (33.3, 83.0)**	**56.8 (29.9, 83.8)**	**61.8 (25.2, 98.4)**	**64.7 (36.0, 93.4)**	**68.9 (26.7, 91.0)**	**72.0 (37.6, 106.4)**

65 and over	Women (95% CI)			Men (95% CI)		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	6.1 (1.8, 10.4)	3.7 (-0.4, 7.7)	2.4 (-0.2, 5.0)	1.5 (-2.0, 5.1)	2.3 (-1.1, 5.6)	-0.7 (-3.2, 1.8)
Percent explained						
Smoking	0.0 (-7.2, 7.1)	-2.0 (-13.6, 9.6)	3.0 (-8.1, 14.2)	56.3 (-40.7, 153.2)	20.5 (-2.6, 43.5)	N/A
Excess BMI	29.9 (5.0, 54.8)	30.1 (-6.5, 66.8)	29.5 (1.5, 57.6)	-17.3 (-81.2, 46.6)	13.4 (-52.7, 25.8)	N/A
Manual	10.2 (-14.1, 34.4)	11.7 (-17.7, 41.2)	7.8 (-11.3, 26.9)	27.2 (-93.2, 147.5)	11.2 (-33.5, 55.9)	N/A
All	**38.3 (8.3, 68.3)**	**38.7 (-2.1, 79.6)**	**37.7 (5.8, 69.6)**	**60.4 (-58.0, 178.7)**	**19.9 (-27.5, 67.3)**	**N/A**

Note: PY = person-years

Chapter 3 - Racial/Ethnic Disparities in Opioid Prescribing to Chronic Pain Patients

INTRODUCTION

Unequal medical treatment across racial and ethnic groups that is unexplained by differences in socioeconomic status and access to health care has been extensively documented (Goonesekera et al., 2015; Goyal et al., 2015; Johansen et al., 2015; McKinlay et al., 2012; Rangrass et al., 2014; Schulman et al., 1999; Van Ryn et al., 2006). Differential pain management is one notable manifestation of these disparities: disproportionate undertreatment of pain in non-white and Hispanic patients has been observed, for instance, in emergency departments (Todd et al., 1993, 2000), nursing homes (Won et al., 1999), postoperative settings (Ng et al., 1996), and in management of cancer-related pain (Cleeland, 1997)—despite similar medical conditions across the compared groups. A 2012 meta-analysis found that, while black and Hispanic patients with traumatic, surgical, or non-traumatic/non-surgical pain were as likely to receive non-opioid analgesics as their white counterparts, they were less likely to receive opioids (Meghani et al., 2012). In addition, nonwhite pain patients may be less able to access the pain medications prescribed for them: several studies have found that pharmacies in predominantly non-white neighborhoods are less likely to carry a sufficient supply of opioid analgesics than those in white neighborhoods (C. R. Green et al., 2005; Morrison et al., 2000).

Consequences of disparities in pain management may not only include disproportionate suffering and functional impairment; they may also reduce trust in health care providers, a key factor in

patients' decisions to seek treatment and preventive care and to adhere to medical recommendations (Anderson et al., 2009; Benkert et al., 2006; Boulware et al., 2003; Cintron & Morrison, 2006; Shavers et al., 2010; Williams & Mohammed, 2009).

America's ongoing opioid crisis, which killed nearly 48,000 people in 2017 (Scholl et al., 2018), has brought pain management decisions to the forefront of many clinicians' minds. Unsafe prescribing of opioid analgesics has received much of the blame for the steep rise in opioid-related morbidity and mortality, although more upstream social, economic, and demographic processes are also likely at play (Dasgupta et al., 2018). In March 2016, the U.S. Centers for Disease Control and Prevention (CDC) released the Guideline for Prescribing Opioids for Chronic Pain, offering twelve recommendations to reduce unsafe prescribing while emphasizing the clinician's role in tailoring pain management to each patient's specific circumstances.

Early evidence suggests that, at the US population level, the 2016 guideline accelerated the preexisting decline in opioid prescribing. (Bohnert et al., 2018). However, it is not clear whether this shift was equally distributed across racial/ethnic groups. Instead, it may have widened or narrowed disparities in pain management—for instance by amplifying or reducing clinicians' reliance on racial/ethnic stereotypes in making prescribing decisions. This study thus examines whether publication of the 2016 guideline was associated with subsequent opioid prescribing for two chronic pain conditions and, if so, whether this association varied by race/ethnicity.

Pathways to unequal treatment in healthcare

A number of pathways likely contribute to racial/ethnic disparities in the health care encounter over and above issues of access to care, which are also pervasive (Chen et al., 2016; Waidmann

& Rajan, 2000). Broadly, providers may possess implicit and explicit bias regarding the clinical, behavioral, and social features of a given racial/ethnic group, which may in turn influence their interpretation of the clinical information a patient shares and the medical recommendations they make (Balsa & McGuire, 2003b; van Ryn & Fu, 2003). In addition, both stereotype-driven beliefs and the mere fact of racial/ethnic discordance between provider and patient may influence provider interpersonal behavior (Balsa & McGuire, 2003b; van Ryn & Fu, 2003). This can in turn affect the patient's understanding of their health condition or status, as well as the questions they ask, the follow-up care they pursue, and the treatments they request and/or adhere to (Benkert et al., 2006; Boulware et al., 2003; van Ryn & Fu, 2003; Williams & Mohammed, 2009).

Unequal treatment may be more likely in the context of greater clinical uncertainty: in such cases, providers may turn to more subjective factors to inform their decision-making, including their priors regarding different racial and ethnic groups (Balsa & McGuire, 2003a; Merrill et al., 2002). These stereotype-driven priors may be most likely to be activated when the beliefs map closely onto one or more of the potential health outcomes—such as nonmedical opioid use or development of dependence, in the case of opioid prescribing.

Both clinical uncertainty and racial/ethnic stereotypes may thus play an important role in decisions to prescribe opioids for chronic pain. Pain is a subjective, difficult-to-measure phenomenon, and chronic pain may be more difficult for providers to evaluate than acute traumatic or surgical pain (Meghani et al., 2012; Singhal et al., 2016). This results in clinical uncertainty about a patient's subjective experience and need for pain management. In an effort to reconcile this uncertainty, and amid concern about opioids' potential for misuse and overdose,

clinicians may call on racial and ethnic stereotypes regarding so-called drug-seeking behavior. For example, one study of low-income HIV patients and their primary care providers found that, despite equivalent rates of reported nonmedical drug use across racial/ethnic groups, providers exhibited less trust in non-white patients (Moskowitz et al., 2011).

Trust, in turn, is a key factor in decisions about chronic pain management (Merrill et al., 2002). For example, while Hispanic and non-Hispanic black individuals experience lower rates of prescription opioid overdose than whites (Bohnert et al., 2011; Paulozzi, 2012) and are equally or less likely to report nonmedical opioid use when receiving prescription opioid therapy (Han et al., 2017), they may be more likely to receive urine testing and other precautionary measures (Becker & Turner, 2011; Gaither et al., 2018). In addition, a recent study found that black patients receiving long-term opioid therapy were more likely than their white counterparts to experience a dose reduction during two years of follow-up (Buonora et al., 2018). In contrast, two clinical factors associated with higher risk of addiction and overdose—high baseline dosage and receipt of a concurrent benzodiazepine prescription—were not positively associated with dose reduction in those patients (Buonora et al., 2018). Racial and ethnic stereotypes around patient deception and likelihood of nonmedical use are likely rooted in part in decades of less sympathetic, less humanized representation of nonwhite people who use opioids compared to their white counterparts (Netherland & Hansen, 2016).

Aims

Clinical uncertainty, in combination with stereotype-driven priors, may thus contribute to the persistence of racial/ethnic disparities in opioid prescribing for pain. Indeed, Meghani et al.

(2012) found that racial/ethnic disparities in opioid prescribing were larger when the source of pain was non-traumatic and non-surgical—i.e., when it was less easily identified and appraised (Meghani et al., 2012). The CDC's 2016 Guideline on Opioid Prescribing for Chronic Pain may have reduced clinical uncertainty by providing a framework for deciding when to prescribe opioids, in what dose, and over what time period—as well as how to avoid high-risk co-prescribing with other medications. This framework could thus serve to reduce providers' reliance on priors regarding their patient's race and/or ethnicity, thereby alleviating disparities in opioid prescribing among chronic pain patients.

Alternatively, the guideline could have contributed to a widening of racial/ethnic disparities in prescribing. In stressing the dangers of unsafe prescribing while emphasizing provider discretion in assessing the risks and benefits for each patient, the guideline may have prompted greater reliance on racist priors to assess a patient's "legitimate" need for prescription opioids. A study of benzodiazepine prescribing suggests that such disparate intervention impacts do occur. Examining the effects of a New York State triplicate law, Pearson, Soumerai, Mah, et al. (2006) found that, while patients in predominantly white neighborhoods exhibited the highest rates of overall benzodiazepine use and of potentially problematic use, prescribing decreases attributable to the law were sharpest in predominantly black neighborhoods (Pearson et al., 2006).

I examine whether the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain was associated with an overall change in opioid prescribing for chronic pain and, if so, whether this change varied by racial/ethnic group. It also assesses whether any disparate changes served to narrow or widen existing racial/ethnic disparities. To accomplish this, I examine frequency and

level of opioid prescribing and co-prescribing with benzodiazepines—outcomes directly related to the guideline's recommendations—in two groups: osteoarthritis patients and fibromyalgia patients. Opioids may slightly improve function and reduce pain related to osteoarthritis (Cepeda et al., 2006; da Costa et al., 2014), although recent evidence suggests they are not superior to non-steroidal anti-inflammatory drugs (Krebs et al., 2018). Still, in 2012, the American College of Rheumatology strongly recommended opioids for use in patients with pharmacologic treatment-refractory osteoarthritis who could or would not undergo total joint arthroplasty (Hochberg et al., 2012). In contrast, experts have generally agreed that opioids are not indicated for fibromyalgia, despite being frequently prescribed (Häuser et al., 2017; Macfarlane et al., 2017). I therefore study racial disparities in opioid prescribing for one condition for which opioids were considered appropriate in some patients, and a second for which they were consistently not recommended. If the CDC guideline led prescribers to more critically evaluate their opioid prescribing decisions, then opioid prescribing for fibromyalgia may have declined more sharply than that for osteoarthritis.

I use healthcare claims data from OptumInsight's Clinformatics Data Mart, allowing evaluation of trajectories and disparities in prescribing in a large sample of people with chronic pain from all fifty states. In an effort to assess disparities arising from provider decision-making rather than issues of socioeconomic status, access, or pain prevalence, I examine rates and levels of prescribing during clinical encounters with patients who are insured and have received diagnoses of osteoarthritis or fibromyalgia.

METHODS

Data

Optum administrative healthcare data comprise deidentified outpatient, inpatient, and pharmacy claims for individuals with commercial insurance plans from UnitedHealthcare. These data are similar to the commercially insured population in the United States and enable longitudinal observation of diagnosis and prescription receipt in 12.4 to 14 million unique individuals per year (Jeffery et al., 2018; University of Michigan Institute for Healthcare Policy and Innovation, 2016). The dataset provides information on socioeconomic status and race/ethnicity but does not provide local geographical data such as zip code.

Periods of analysis and cohort inclusion criteria

The CDC Guideline was released in March 2016. The period of analysis comprised a 24-month baseline comparison period (March 2014-November 2015) and an 18-month post-intervention comparison period (July 2016-December 2017;

Figure 3-1). The three months prior to and after guideline implementation were excluded from analysis to account for potential anticipatory and lagged effects of the policy ("implementation period"; December 2015-June 2016). A six-month "washout" period (September 2013-February 2014) was used to establish cohort eligibility, as discussed below.

The analytic cohort consisted of adults ages 18-64 who were continuously enrolled in a UnitedHealthcare insurance plan for 24 months, including the six-month washout period and 18 months of the 24-month baseline comparison period. Included individuals must have received at least one diagnosis of the condition of interest during the first half of the baseline analytic period (March 2014-February 2015). Because the CDC guideline was intended for patients outside of active cancer treatment, palliative care, and end of life care, those who received a cancer

diagnosis or palliative care during any of the three observation periods were excluded from the sample. To capture new opioid prescribing, individuals who filled an opioid prescription prior to their first observed pain-related visit were excluded.

Outcomes

Dispensing data served as a proxy for prescribing. In line with a recent validation study, dispensing was assumed to be prescribed at a visit for the condition of interest if it occurred within 15 days of the visit (Rowan et al., 2017). All outcomes were evaluated at the month level.

The four primary outcomes included: (1) percentage receiving any prescription opioid (binary); (2) average daily morphine-equivalent dose of prescribed opioids (continuous); (3) percentage receiving an average daily morphine-equivalent dose of 90 milligrams or more (binary); and (4) percentage receiving concurrent prescriptions of opioids and benzodiazepines (binary). The first outcome corresponds to the guideline's first and fifth recommendations, which state that alternatives to opioids are preferred for chronic pain and that clinicians should initiate opioid prescribing at the lowest effective dosage. The 90 morphine milligram equivalent (MME) threshold corresponds to the guideline's fifth recommendation, that prescribers "avoid increasing dosage to 90 MME or more per day or carefully justify a decision to titrate dosage to 90 MME or more per day." Assessment of concurrent opioid/benzodiazepine prescribing corresponds to the 11th recommendation, "Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible." The three secondary outcomes, all of which were count variables, included: total days of opioids supplied, total number of opioid fills obtained, and the number of days of concurrent opioid and benzodiazepine prescriptions.

Covariates

Sociodemographic measures

Optum populates sociodemographic data from a combination of sources, including directly from

the patient at the point of care, via imputation from the U.S. Census, and via internal modeling.

All sociodemographic variables except age were modeled as categorical, as provided by Optum.

Race/ethnicity categories included black, white, Hispanic, Asian, and other. "Other" was

excluded from analysis due to insufficient sample and difficulty of interpretation; Asian patients

were included in the analysis, but due to small sample and noisy estimates, the corresponding

results are not discussed here. Age was continuous and ranged from 18 to 64 years. Gender

comprised female and male. Educational attainment categories included high school degree or

less; less than college; and college degree. Household income categories included less than

$40,000 per year; $40,000-$59,999; $60,000-$74,999; $75,000-$99,999; $100,000 or more per

year.

Clinical measures

I included several indicators of clinical circumstances that may influence opioid prescribing

decisions and could vary by race/ethnicity. First, I calculated the monthly number of visits

related to the diagnosis of interest (osteoarthritis or fibromyalgia) and the number of days since

the last such visit. Second, I included an indicator of having received another pain-related

diagnosis in the given month (binary); given its length, the list of ICD codes used to make this

determination is not included here but is available upon request. Third, I included four time-

varying indicators of any diagnosis of the following conditions since cohort entry: substance use

disorder; anxiety disorder or post-traumatic stress disorder; major depression; and psychotic and bipolar disorders. ICD codes used to identify these diagnoses are provided in Table 5-8 (Haffajee et al., 2019; Heslin et al., 2012). Finally, I calculated a longitudinal Elixhauser comorbidity index to obtain the number of distinct comorbidities diagnosed for a given individual in a given month (Elixhauser et al., 1998; Manitoba Centre for Health Policy, 2019).

Time

The secular time trend, ranging from March 2014 through December 2017, with the exception of the implementation period, was continuous and, based on visual inspection of the data, was estimated as linear.

Analytic strategy

Generalized estimating equations (GEEs) were used to estimate racial/ethnic differences in the association between the guideline and opioid prescribing. GEEs extend generalized linear models to data with correlated observations, as in longitudinal data (Wang, 2014). Unlike mixed models, GEEs use a quasi-likelihood function to estimate population-averaged effects of the parameters; this approach is preferred when the overall treatment effect, rather than individual-level effects, is of primary interest (Hubbard et al., 2010; Wang, 2014).

Analyses were conducted at the month level. In each month, observations were only included in the analysis if the individual had at least one encounter related to the pain-related condition of interest (i.e., osteoarthritis or fibromyalgia). This enabled comparison of opioid prescribing rates among individuals who had had the opportunity to receive a prescription. Analysis of all

outcomes except "any opioid receipt" was conditioned on having received any opioid fill in the given month. Analysis of the final outcome, number of days of concurrent opioid and benzodiazepine prescriptions, was conditioned on any concurrent prescription in the given month.

Model specification

Modeling was conducted in two stages: the first stage examined overall associations between guideline release and each outcome, regardless of race/ethnicity; the second stage examined whether these associations differed by race/ethnicity.

The regression models in Stages I and II took the following general forms, respectively:

(1) $g(E(Y_{i,t})) = \beta_0 + \sum_{j=1}^{3} \beta_1 Race_{i,j} + \beta_2 Time_{i,t} + \beta_3 Post_{i,t} + \beta_4 Time_{i,t} Post_{i,t} +$

$X_{i,t} + \varepsilon_{i,t}$; and

(2) $g(E(Y_{i,t})) = \beta_0 + \sum_{j=1}^{3} \beta_1 Race_{i,j} + \beta_2 Time_{i,t} + \sum_{j=1}^{3} \beta_3 Time_{i,t} Race_{i,j} + \beta_4 Post_{i,t} +$

$\sum_{j=1}^{3} \beta_5 Post_{i,t} Race_{i,j} + \beta_6 Post_{i,t} Time_{i,t} + \sum_{j=1}^{3} \beta_7 Time_{i,t} Post_{i,t} Race_{i,j} + X_{i,t} + \varepsilon_{i,t}$;

where *g()* refers to the link function relating the mean of the outcome, *E(Y_{i,t})*, to the predictors. The link function varied by outcome: binary outcome variables were generally modeled using the logit link or (in cases of nonconvergence) the identity link, continuous variables using the identity link, and count variables using the negative binomial link function. In addition, *i,t* denotes individual *i* in month *t,* and *j* indicates time-invariant racial/ethnic group (black, Hispanic, or Asian, with white as the reference group). *Time* denotes time, in months, since the start of the observation period, and the interaction with *Race* allows the background secular trend

to vary by racial/ethnic group. *Post* is a binary variable indicating whether the observation

occurred before or after release of the guideline. The coefficient on *Post* describes an

instantaneous (level) change in the outcome following guideline release in March 2016. The

coefficient on the $Time_{i,t}Post_{i,t}$ interaction term, which indicates the number of months since

guideline release, describes a trend (slope) change in the outcome following release. In the Stage

II models, the interaction terms describe any variation in the level and trend changes by

racial/ethnic group. $X_{i,t}$ is a vector of the sociodemographic and clinical covariates described

above.

For each outcome, Pan's quasi-likelihood information criterion (QIC) was used to select the

structure of correlations among intra-individual observations (Cui, 2007; Pan, 2001).

Unstructured correlation is maximally flexible, allowing the correlation between each pair of

intraindividual observations to vary, while exchangeable structure assumes constant correlation

among intraindividual observations. Autoregressive correlation structures that allow a decay in

correlation with increasing temporal distance were not feasible due to unequally spaced

observations. As long as the mean response is correctly specified, GEE models provide

consistent parameter estimates when the correlation structure is misspecified; however, correct

specification of correlation structure may increase efficiency of the parameter estimates (Cui,

2007; Wang, 2014). The structure associated with the lowest QIC value was selected (Table 5-9).

A structure was disqualified if the corresponding model did not converge. When the model failed

to converge regardless of correlation structure, specification of the link function and

distributional family were amended: for binary outcomes, the link function was changed to

identity and family to Gaussian (Table 5-9). Because the meaning of coefficients varies by link

function, average marginal effects are reported for all models—i.e., the estimated change in the dependent variable associated with a one-unit change in the predictor.

Predicted means and disparities

To examine differences in prescribing associated with the guidelines, I generated predicted means (i.e., average predictive margins) for each outcome variable in the observed (guideline) scenario and in the counterfactual (no guideline) scenario for December 2017, the latest month observed. Predicted means in each scenario were generated using the observed distribution of covariates and were compared in both the full sample (Stage I) and within each racial/ethnic group (Stage II). For outcomes that appeared to be influenced by the guideline by December 2017, I generated predicted racial/ethnic disparities in the observed and counterfactual scenarios in that month, allowing me to examine whether the guideline appeared to widen or narrow disparities in prescribing.

Sensitivity analyses

I conducted three sensitivity analyses. In the first, the implementation period was narrowed to span November 2015, when the draft guideline was first released for public comment, through March 2016, when the final guideline was released. That is, the post-release analytic period began in April, immediately after guideline release, in this analysis. In the second sensitivity analysis, I excluded observations occurring during or after October 2017, when President Trump declared the opioid crisis a public health emergency, to account for the possibility that this national event altered the slope of post-guideline trends. In the third sensitivity analysis, the main analysis was the same, but average predictive margins were generated for October 2017 through

December 2017 (rather than December 2017 alone), in an attempt to reduce noise in those estimates. Each of these analyses was conducted for the four main outcome variables, in both pain conditions, and using the Stage I (non-interacted) models.

RESULTS

Sample characteristics

Complete data on all predictors were available in 65% of observations in the osteoarthritis cohort (1,284,468 observations) and 62% in the fibromyalgia cohort (855,371 observations). Race/ethnicity information was the primary source of missingness (missing for 22% of osteoarthritis observations and 26% of fibromyalgia observations), followed by income (missing for 18% of osteoarthritis observations and 19% of fibromyalgia observations). After excluding observations with incomplete data, the osteoarthritis cohort comprised 87,982 distinct patients with a mean of 18.3 observed months involving osteoarthritis-related visits (Table 3-1). The fibromyalgia cohort comprised 56,299 distinct individuals with a mean of 18.9 months involving fibromyalgia-related visits (Table 3-1). 10,771 individuals appeared in both cohorts (corresponding to 12% of the osteoarthritis cohort and 19% of the fibromyalgia cohort). In both cohorts, there was a mean of 32.9 months between the first and last observed diagnosis of interest.

In both cohorts, individuals were predominantly white, female, and ages 45 years or older, although women comprised a larger proportion of the fibromyalgia cohort (Table 3-1). The majority had attended at least some college. Compared to white patients, black and Hispanic patients tended to be less educated and earn lower household income (Tables 5-10 and 5-11).

Black patients were more likely than their white counterparts to be women, more likely to have received a diagnosis of substance use disorder, and less likely to have received a mental health diagnosis. In the fibromyalgia cohort, black patients had also been diagnosed with more comorbidities on average.

Individuals with missing race/ethnicity data were more likely than their counterparts to be missing education and income data, to have received a mental health diagnosis, to fill an opioid prescription following a pain-related visit, and to receive concurrent opioid/benzodiazepine prescriptions (Table 5-12). They also tended to be younger, have more comorbidities, have more monthly pain-related visits, receive higher opioid dosages, and fill more opioid prescriptions per month.

Overall, patients filled at least one opioid prescription following 15.1% of osteoarthritis-related visits and after 16.3% of fibromyalgia visits (Table 3-1). When at least one opioid prescription was filled, the median daily dosage was 45 MMEs and the mean number of monthly fills was 1.3 for both conditions; the mean number of days supplied per month was 28.0 in the osteoarthritis cohort and 30.7 in the fibromyalgia cohort. The dosage was above 90 MMEs in 22.9% of filled opioid prescriptions for osteoarthritis and 24.4% for fibromyalgia. In the osteoarthritis cohort, a concurrent benzodiazepine prescription was filled in 26.4% of cases in which an opioid prescription had been filled; this occurred in 32.2% of cases in the fibromyalgia cohort. When concurrent opioid and benzodiazepine prescriptions were filled, they overlapped for a mean of 7.5 days in the osteoarthritis cohort and 29.0 days in the fibromyalgia cohort. Figure 3-2 depicts

unadjusted trends in each primary outcome variable by condition for black, Hispanic, and white patients.

Regression results

Stage I. Overall associations of racial/ethnic group and guideline release with prescribing

Tables 5-13 and 5-14 provide estimated marginal effects of the main predictors in Stage I of modeling, which examined overall level and trend changes associated with the guideline. In both osteoarthritis and fibromyalgia, and after controlling for likely confounders, Black and Hispanic patients were less likely than their white counterparts to fill an opioid prescription, received lower doses on average, were less likely to receive a dose of greater than 90 MMEs, received fewer fills, and were less likely to receive concurrent opioid and benzodiazepine prescriptions. All else equal, black osteoarthritis patients were 1.3 percentage points less likely than white patients to fill an opioid prescription (95% CI: -1.70, -0.821) and Hispanic patients were 2.0 percentage points less likely (95% CI: -2.48, -1.58). All else equal, the doses that black and Hispanic osteoarthritis patients received were roughly 10 MMEs lower than those white patients received (black: -9.9; 95% CI: -11.48, -8.36; Hispanic: -10.4; 95% CI: -12.20, -8.62). Black and Hispanic osteoarthritis patients were roughly 4 percentage points less likely to receive high-dose prescriptions (black: -4.2; 95% CI: -5.05, -3.34; Hispanic: -4.2; 95% CI: -5.13, -3.19). Estimates for fibromyalgia were similar but tended to be smaller. Black patients also received fewer days supplied and experienced fewer days of concurrent prescriptions.

Using an alpha of 0.05 as a detection threshold, and for both conditions, negative trend but not level changes associated with the guideline were apparent in three of the four main outcomes.

These included a trend change in the percentage receiving any opioid fill (marginal effect in osteoarthritis: -0.031 percentage points, 95% CI: -0.056, -0.006; fibromyalgia: -0.059 percentage points, 95% CI: -0.090, -0.028), the average daily dose (marginal effect in osteoarthritis: -0.563 MME, 95% CI: -0.716, -0.411; fibromyalgia: -0.569 MME, 95% CI: -0.751, -0.387), and the percentage receiving a high dose (marginal effect in osteoarthritis: -0.229 percentage points, 95% CI: -0.317, -0.140; fibromyalgia: -0.237 percentage points, 95% CI: -0.350, -0.124). In osteoarthritis, a negative trend change in number of fills and number of days supplied was also detected (fills: -0.001, 95% CI: -0.003, -0.0007; days supplied: -0.038, 95% CI: -0.074, -0.002). In fibromyalgia, a positive level change in number of fills was detected (0.019 fills, 95% CI: 0.0001, 0.039).

Table 3-2 presents predicted means for December 2017—the latest post-guideline month observed—in the observed and counterfactual (i.e., no guideline) scenarios, holding all other predictors as observed. In both osteoarthritis and fibromyalgia, the guideline appeared to be associated with a roughly 1 percentage point lower rate of receiving any opioid prescription in December 2017, although the difference was marginally significant given an alpha of 0.05. It was also associated with a lower average dose of roughly 10 MMEs and a roughly 4 percentage point lower rate of high-dose prescriptions among those who received opioids. While point estimates of number of days supplied, number of fills, rate of concurrent opioid-benzodiazepine prescribing, and days of concurrent prescribing were also lower in the observed compared to the counterfactual scenario, the corresponding 95% confidence intervals overlapped (Table 3-2).

Stage II. Changes associated with guideline release by race/ethnicity

In the Stage II models, the background secular trend and the guideline exposure variables were interacted with race/ethnicity. Table 3-3 and Table 3-4 show the estimated marginal effects of race/ethnicity as well as racial/ethnic group-specific marginal effects of the secular trend and guideline exposure variables. Tables 5-15 and 5-16 show marginal effects for the complete set of model predictors. Estimated main effects of race/ethnicity, as well as overall level and trend changes, were highly consistent with Stage I models. In both osteoarthritis and fibromyalgia patients, consistent positive predictors of overall and high-risk opioid prescribing included a history of diagnosis with substance use disorder, diagnosis with at least one other pain condition, number of comorbidities, and number of visits per month related to the condition of interest (Tables 5-15 and 5-16). A history of diagnosis with mental health disorder was often positively associated with prescribing and high-risk prescribing. Women tended to be less likely to receive opioids or high-risk prescriptions, with the exception that they were more likely to receive concurrent opioid and benzodiazepine prescriptions. Patients with higher income tended to be less likely to receive opioids or high-risk prescriptions; those with higher education were less likely to receive any opioid fill; when they did receive a prescription, they received higher average doses, more fills, and fewer days supplied. Secular trends were not consistent across outcomes. In both conditions, the probability of any fill increased throughout the analytic period and the probability of concurrent prescriptions decreased. In fibromyalgia, the average number of days supplied appeared to decrease.

Estimated associations of the guideline with prescribing varied by race/ethnicity, although smaller sample sizes resulted in less precise estimates for black and Hispanic patients. In osteoarthritis, and at an alpha of 0.05, the guideline was associated with a lower percentage

receiving any opioid fill in white patients. In December 2017, 21 months after its release, the guideline was associated with an estimated 1.0 percentage point lower percentage receiving any fill in white patients compared to the counterfactual, "no guideline" scenario (Table 3-5).

Among those who received opioids, the guideline was associated with a lower average dose in white, black, and Hispanic osteoarthritis patients. By December 2017, this corresponded to an estimated difference of 9.5 MME, 11.4 MME, and 23.5 MME, respectively. The guideline was also associated with a decline in the percentage receiving high-dose opioid prescriptions in white and black patients. By December 2017, this corresponded to an estimated difference of 4.0 percentage points in white patients and 5.5 percentage points in black patients. In fibromyalgia patients, the guideline was associated with: a lower percentage receiving any fill in white patients (estimate difference of 1.2 percentage points in December 2017); a lower average dose in white and black patients (estimated difference of 9.8 MME in white patients, 10.9 MME in black patients in December 2017); and a lower percentage receiving high-dose prescriptions in white patients (estimated difference of 3.6 percentage points in December 2017). While associations between guideline release and the main outcome variables were less consistently statistically significant in black and Hispanic patients, point estimates were often similar or larger in size compared to white patients.

Figure 3-3 and Figure 3-4 depict predicted means with and absent the guideline for the three main outcome variables with which guideline release was associated. While the patterns of the predicted means are similar to those for the raw means, the models tend to underestimate the average dose and the average percentage receiving a high dose.

Table 3-6 shows estimated racial/ethnic disparities, both with and without the guideline, in December 2017 for the three main outcomes with which guideline release was associated: percentage receiving any fill, average daily dose, and percentage receiving a high-dose prescription. While there were differences in the observed and counterfactual point estimates, the confidence intervals in the two scenarios consistently overlapped. Point estimates of the Hispanic/white disparity were generally larger in the "guideline" compared to the "no guideline" scenario, and this difference was most marked in the average daily dose among osteoarthritis patients: on average, Hispanic osteoarthritis patients received an estimated 14.67 MME (95% CI: 8.97, 20.37) lower dose than white patients in December 2017; absent the guideline, this difference was estimated to be only 0.68 MME (95% CI: -11.10, 12.45). Similarly, estimated black/white disparities in average dose and percentage receiving high dose were larger in the "guideline" scenario, but differences were small. In contrast, and in both conditions, because the guideline was associated with a (not statistically significant) increase in percentage of black patients receiving any fill in December 2017, the guideline was associated with a widening black/white disparity in which a *larger* percentage of black patients received any opioid fill compared to white patients.

Sensitivity analyses

Changing the implementation period to cover November 2015 through March 2016 (i.e., the period between release of the draft guideline and release of the final guideline) and initiating the post-guideline analytic period in April 2016 did not affect the substantive results (Table 5-17). In the second sensitivity analysis, I shortened the post-guideline analytic period to end in September

2017, prior to President Trump naming the opioid epidemic a public health emergency. In this analysis, the estimated differences in observed and counterfactual predicted means for September 2017 were smaller than those for December 2017 in the main analysis, as expected; in the sensitivity analysis, these differences tended to be 55-85% the size of those in the main analysis (Table 5-18). If President Trump's announcement had had no effect on prescribing, the September estimates would be expected to be 86% of the December estimates, suggesting the guideline's effects may have been slightly smaller than estimated in the main analysis. In the third analysis, generating predicted means for October through December 2017, rather than December 2017 alone, had little influence on estimate precision and did not change the overarching pattern of results (Table 5-19).

DISCUSSION

To my knowledge, this study is the first to examine the association of release of the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain with subsequent overall and high-risk opioid prescribing in the population it targeted: people with chronic, non-cancer pain. In addition, it is the first to assess whether these associations varied by patient race/ethnicity, and if so whether this contributed to a widening or narrowing of racial/ethnic disparities in opioid prescribing for chronic pain. To do this, I took advantage of longitudinal healthcare claims data from all fifty states that are similar to the US commercially insured population and that allow linkage of clinical diagnosis and pharmacy information (Jeffery et al., 2018; University of Michigan Institute for Healthcare Policy and Innovation, 2016).

In two closed cohorts—one comprised of osteoarthritis patients, the other of fibromyalgia patients—the guideline was associated with an overall decline in the percentage of patients receiving opioids and, among those who received opioids, with a decline in average daily dose and the percentage of patients receiving a high dose (>90 morphine milligram equivalents, or MME). These declines manifested not as instantaneous changes following the guideline's release, but as gradual decreases. By December 2017, 21 months after release of the guideline, these apparent effects corresponded to an estimated one percentage point difference in the percent of the sample receiving any opioid prescription each month, a 10 MME difference in average daily dose, and a roughly 4 percentage point difference in the percentage receiving a high dose. In osteoarthritis patients, the guideline was also associated with a small decrease in the number of opioid fills and days supplied per month. While no statistically significant associations between guideline release and concurrent opioid/benzodiazepine prescribing were detected, point estimates tended to be negative. Together, these results are in line with a recent study of opioid prescribing trends at the national level (Bohnert et al., 2018) and another examining rates of prescribing in a single emergency department (Dayer et al., 2019). Overall, my findings did not support the hypothesis that the guideline would more strongly influence opioid prescribing for fibromyalgia, for which opioids are categorically not recommended, compared to osteoarthritis (Häuser et al., 2017; Macfarlane et al., 2017).

In both conditions, associations with the guideline were consistently detectable in white patients at an alpha of 0.05. In addition, statistically significant declines in average daily dose were detected in black and Hispanic patients. And in osteoarthritis, the guideline was associated with reduced high-dose prescribing in black patients and with fewer fills in Hispanic patients.

However, lack of statistical significance corresponding to other outcomes may primarily be due to insufficient power: point estimates suggested that black and Hispanic patients were generally estimated to experience the same or larger declines as white patients. For example, by December 2017, the guideline was estimated to have reduced average daily dose by nearly 10 MME in white patients, compared to more than double that in Hispanic patients. While these differences were never statistically significant, point estimates of racial/ethnic disparities with and absent the guideline suggest it may have contributed to a widening of black/white and Hispanic/white disparities in prescribing (with the exception of the black/white disparity in percentage receiving at least one opioid prescription). To help distinguish the consequences of insufficient power from true null effects on disparities, an extension to this study will examine the same relationships in a pooled cohort of patients with osteoarthritis, chronic back and neck pain, fibromyalgia, and chronic headache.

Despite imprecise estimates, there was little evidence to suggest a narrowing of disparities due to the guideline. This may indicate that, despite providing clinicians a framework for deciding when to prescribe opioids and in what dose, the CDC guideline did not diminish racial/ethnic disparities in prescribing. That is, these findings do not appear to support the hypothesis that the guideline reduced clinical uncertainty and, in turn, the tendency to use racial/ethnic stereotypes or bias to inform prescribing decisions. Instead, the guideline may have affected white, black, and Hispanic pain patients similarly; or it may have disproportionately affected patients of color, and particularly Hispanic patients. The latter scenario could result from an *increase* in clinical uncertainty due to the guideline, in which the recommendations' encouragement that providers

use personal judgment to determine each patient's prescribing needs led to *increased* reliance on stereotypes and bias.

In line with prior studies, I found that, after accounting for an array of likely confounders including socioeconomic status, access to health care, the presence of comorbidities, and the frequency of pain-related clinical encounters, black and Hispanic chronic pain patients received less overall and high-risk opioid prescribing on average than their white counterparts. In contrast with other examples of unequal treatment in health care, some have argued that disparate opioid prescribing has had a protective effect, accounting for the lower rates of opioid-related overdose mortality in black and Hispanic Americans in recent decades (Alexander et al., 2018; Frakt & Monkovic, 2019; Kaiser Family Foundation, 2019). Moreover, the medical consensus that opioids are not indicated for fibromyalgia, along with growing evidence that they are no more effective than lower-risk analgesics in some other conditions, may suggest that patients of color are benefiting from receiving fewer opioids. However, for any problem racial/ethnic discrimination in opioid prescribing avoids, it creates many more. Unequal treatment can reduce trust in health care providers, a key factor in decisions to seek treatment and preventive care and to adhere to medical recommendations (Benkert et al., 2006; Boulware et al., 2003; Williams & Mohammed, 2009). In addition, experiences of discrimination may increase depression and feelings of helplessness, and may even worsen the pain experience (Shavers et al., 2010).

Moreover, racial/ethnic disparities in opioid prescribing may result in disproportionately high rates of untreated pain in black and Hispanic patients. In this study, I was unable to examine whether chronic pain patients not receiving opioids received alternative forms of pain

management—for example, lower-risk analgesics such as acetaminophen, physical therapy, or cognitive behavioral therapy. However, a meta-analysis found that black pain patients were less likely than white patients to receive *any* analgesic, while no difference between Hispanic and white patients was detected (Meghani et al., 2012). That is, black/white disparities in opioid prescribing likely reflect a disparity in medication-based pain management overall. Chronic, unmanaged pain can influence quality of life and mental health, and can interfere with one's ability to work and conduct activities of daily living (Shavers et al., 2010). It may also increase the risk of illicit opioid use for pain management, which could have particularly severe adverse consequences in the context of a growing illicit fentanyl supply (Rothstein, 2017; Zoorob, 2019).

The finding that the CDC guideline influenced prescribing intensity across racial/ethnic groups—and particularly the sizeable decline in average daily dose among those prescribed opioids—suggest that clinical guidelines in which compliance is entirely voluntary may result in clinically significant shifts in prescribing behavior. At the same time, the relatively small decrease in percent receiving at least one opioid fill per month may allay concerns that the guideline led to widespread inappropriate discontinuation of pain management among chronic pain patients in need (Rothstein, 2017). For more clarity on this issue, an extension to this study will examine the association of the guideline's release with the percentage of chronic pain patients on opioid therapy who experience abrupt discontinuation.

In an attempt to examine provider racial/ethnic discrimination in opioid prescribing before and after release of the CDC guideline, I studied a sample of patients who had received an osteoarthritis or fibromyalgia diagnosis, who had health insurance, and who, in a given month, had a pain-related healthcare visit. In this way, I was able to rule out many alternative

explanations for disparate rates of opioid use, such as variations in chronic pain prevalence by race/ethnicity and disparities in rates of insurance and other aspects of access to care.

However, I was unable to fully rule out a demand-side explanation—i.e., that black and Hispanic patients may be less likely to accept any or high-dose opioid prescribing than their white counterparts. For example, one qualitative study found that many black cancer patients chose unmanaged pain over opioids or higher doses of opioids, due to aversion to "masking" the pain, concern about unpleasant side effects or developing dependence on opioids, discomfort with the stigma associated with opioid use, fear of doctors considering their pain illegitimate, and other factors (Meghani & Keane, 2007). Variations in these demand-side processes by race/ethnicity have not, to my knowledge, been studied. However, dissemination of the CDC guideline specifically targeted clinicians, suggesting that disparate effects of the guideline by race/ethnicity are unlikely to be fully attributable to differences in demand.

There may be other unobserved confounders. For example, while claims data by definition allowed us to control for access to a clinician, white patients may have greater access to or be more likely to see pain specialists, who in turn may be more likely to prescribe opioids. However, one study found no association between race/ethnicity and pain specialist use (Meghani & Cho, 2009). Alternatively, because I was only able to observe filled prescriptions, disparities in opioid receipt may result not from discrimination in prescribing but from disparate access to pharmacies that stock prescription opioids (Morrison et al., 2000). However, this would not explain disparities in dose, and it is not in line with research that has observed opioid prescribing directly (Meghani et al., 2012).

The absence of a comparison group in this study raises the possibility that the observed associations were caused by other forces. In late October 2017, President Trump declared the opioid crisis a public health emergency, potentially increasing prescriber awareness of opioid overprescribing (The White House, 2018). Analysis excluding the months following this declaration resulted in slightly lower estimated effects of the guideline than in the main analysis, suggesting that the main results may have marginally overestimated the true effects. I was unable to identify any other co-occurring national policies or events that would be expected to cause the observed trend changes. Major state-level policy changes that influenced opioid prescribing, such as widespread implementation of prescription drug monitoring programs, predominantly occurred prior to the analytic period or prior to guideline release (Prescription Drug Abuse Policy System, 2017).

Optum data reflect the age-sex structure of the commercially insured population, a more educated and higher-income group than the US as a whole (Jeffery et al., 2018; University of Michigan Institute for Healthcare Policy and Innovation, 2016). Racial/ethnic disparities in prescribing and effects of the CDC guideline may differ in the broader population. For example, disparities may be larger in a national population of chronic pain patients if there is an interaction between race/ethnicity and socioeconomic status (SES), resulting in a stronger effect of being black or Hispanic on prescribing among lower-SES patients. This effect modification could, in turn, cause any effect of the guideline on disparities to be larger at the national level. Additional research would be needed to compare the associations found in this study with those in a national population of chronic, non-cancer pain patients.

This study examined whether the CDC Guideline for Prescribing Opioids for Chronic Pain was associated with changes in opioid prescribing in its primary target group—patients with chronic, non-cancer pain—and whether these associations varied by race/ethnicity. Racial/ethnic disparities in opioid prescribing are well-documented and have an array of adverse consequences for black and Hispanic people experiencing chronic pain. By providing additional guidance on how and when to prescribe opioids, the guideline could have reduced providers' reliance on racial/ethnic stereotypes in medical decision-making and in turn reduced disparities in prescribing. Yet while the guideline was associated with overall declines in prescribing and high-dose prescribing for patients with osteoarthritis and fibromyalgia, it did not appear to decrease the effect of race/ethnicity on prescribing decisions. In fact, while estimates were too imprecise to draw solid conclusions, the CDC guideline may have contributed to a widening of racial/ethnic disparities in opioid prescribing for chronic pain.

Figure 3-1. Periods used to establish cohort and compare trends

2013				2014											2015												2016									2017
Sep Oct Nov Dec **Jan** Feb	Mar Apr May Jun Jul Aug Sep Oct Nov Dec	**Jan** Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec **Jan** Feb	**MAR**	Apr May Jun Jul Aug Sep Oct Nov Dec **Jan**-Dec.

1-Sep — Following (52 mos.)
1-Sep — Continuous enrollment (24 mos.) — 31-Aug
1-Sep — Washout (6 mos.) — 28-Feb — 1-Mar — CNCP at least 12 mos. prior to guideline (12 mos.) — 28-Feb
1-Mar — Baseline comparison (24 mos.) — 30-Nov — Impl. (3 mos.) — Guideline — Impl. (3 mos.) — 1-Jul — Post-comparison (18 mos.) — 31-Dec

Note: CNCP refers to chronic, non-cancer pain; sample inclusion required newly observed CNCP during the first twelve months of the baseline comparison period. "Implem." refers to the implementation period, i.e., months excluded from analysis to account for potential anticipatory and lagged effects of the policy. March 2016, the month of policy implementation, was also excluded from analysis.

Table 3-1. Characteristics of sample and filled opioid prescriptions

	Osteoarthritis		Fibromyalgia	
	Estimate	95% CI	Estimate	95% CI
Distinct individuals	87,982		56,299	
Total monthly observations	1,284,468		855,371	
Months with osteoarthritis visits	18.3	(18.23 to 18.38)	18.9	(18.83 to 19.03)
Race/ethnicity (%)				
White	77.9	(77.67 to 78.22)	79.5	(79.17 to 79.84)
Black	11.0	(10.78 to 11.19)	8.4	(8.16 to 8.62)
Hispanic	9.1	(8.94 to 9.32)	9.6	(9.33 to 9.81)
Asian	1.9	(1.85 to 2.03)	2.5	(2.41 to 2.67)
Female (%)	58.6	(58.24 to 58.90)	72.0	(71.60 to 72.34)
Age (%)				
18-25	0.5	(0.50 to 0.59)	3.9	(3.70 to 4.02)
25-34	1.7	(1.63 to 1.80)	8.6	(8.39 to 8.86)
35-44	8.6	(8.39 to 8.76)	20.1	(19.79 to 20.45)
45-54	34.1	(33.79 to 34.41)	34.6	(34.19 to 34.98)
55-64	55.1	(54.73 to 55.39)	32.8	(32.42 to 33.20)
Education (%)				
High school degree or less	30.7	(30.43 to 31.04)	25.4	(25.02 to 25.74)
Less than college	53.5	(53.16 to 53.82)	55.3	(54.91 to 55.73)
College degree	15.8	(15.54 to 16.02)	19.3	(18.97 to 19.62)
Income (%)				
<$40K	20.9	(20.66 to 21.20)	18.6	(18.27 to 18.91)
$40K-$59K	12.2	(12.00 to 12.43)	11.5	(11.20 to 11.72)
$60K-$74K	9.6	(9.45 to 9.84)	9.2	(8.96 to 9.44)
$75K-$99K	17.5	(17.26 to 17.77)	16.6	(16.28 to 16.89)
$100K+	39.7	(39.37 to 40.02)	44.2	(43.75 to 44.57)
Mental health diagnosis, ever				
Anxiety, PTSD	35.3	(35.02 to 35.65)	44.9	(44.51 to 45.33)
Depression	24.5	(24.19 to 24.76)	30.1	(29.76 to 30.52)
Psychosis, schizophrenia, bipolar	6.2	(6.05 to 6.37)	7.8	(7.57 to 8.01)
SUD diagnosis, ever	22.4	(22.13 to 22.68)	23.0	(22.68 to 23.38)
Other pain-related diagnosis	42.1	(41.76 to 42.41)	36.6	(36.24 to 37.04)
Elixhauser score (max per month. mean)	0.9	(0.91 to 0.93)	0.7	(0.73 to 0.75)
Days since last pain visit	43.1	(42.71 to 43.47)	38.3	(37.90 to 38.77)
Pain visits per month	2.9	(2.85 to 2.88)	2.9	(2.92 to 2.96)
Months between first and last pain diagnosis	32.9	(32.79 to 32.94)	32.9	(32.84 to 33.04)
Any opioid fill in month (%)				
Overall	15.1	(15.05 to 15.17)	16.3	(16.23 to 16.39)
First year	14.3	(14.16 to 14.36)	14.9	(14.79 to 15.05)
Second year	15.1	(15.00 to 15.21)	16.3	(16.17 to 16.44)
Third year	16.0	(15.81 to 16.17)	17.9	(17.71 to 18.17)
Fills per month, if any	1.3	(1.25 to 1.25)	1.3	(1.25 to 1.26)
Days supplied per month, if any	28.0	(27.96 to 28.12)	30.7	(30.56 to 30.76)
Morphine-milligram equivalents (MME), if any				
Mean (daily)	74.4	(74.03 to 74.73)	78.2	(77.77 to 78.63)
Median (daily)	45.0	(45.0 to 45.0)	45.0	(45.0 to 45.0)
Receiving > 90 MME (%)	22.9	(22.73 to 23.10)	24.4	(24.18 to 24.63)

Concurrent opioids/benzodiazepines, if any opioid		
Any overlap (%)	26.4 (26.16 to 26.55)	32.2 (31.97 to 32.46)
Days with overlap, if any	28.2 (28.05 to 28.35)	29.0 (28.81 to 29.13)

Note: Sample comprises observations for which there was no missingness on any model predictor. Sociodemographic, Elixhauser, and pain visit estimates refer to the individual's first month in the cohort. Mental health and substance use diagnosis refer to diagnosis obtained any time during the observation period. Prescription fill estimates refer to all analyzed months in which a visit for the relevant condition (osteoarthritis or fibromyalgia) occurred. The Elixhauser comorbidity index indicates the number of distinct comorbidities for which an individual had a visit in the month of interest; 30 standard comorbidities were evaluated.

Figure 3-2. Unadjusted trends in opioid prescribing by pain condition and race/ethnicity

A. Osteoarthritis
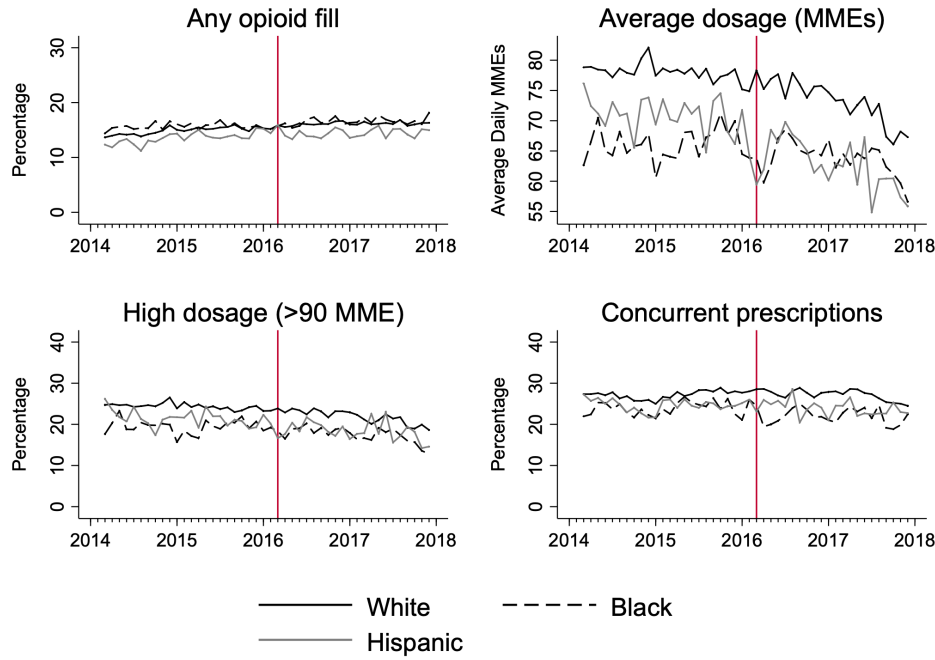
B. Fibromyalgia
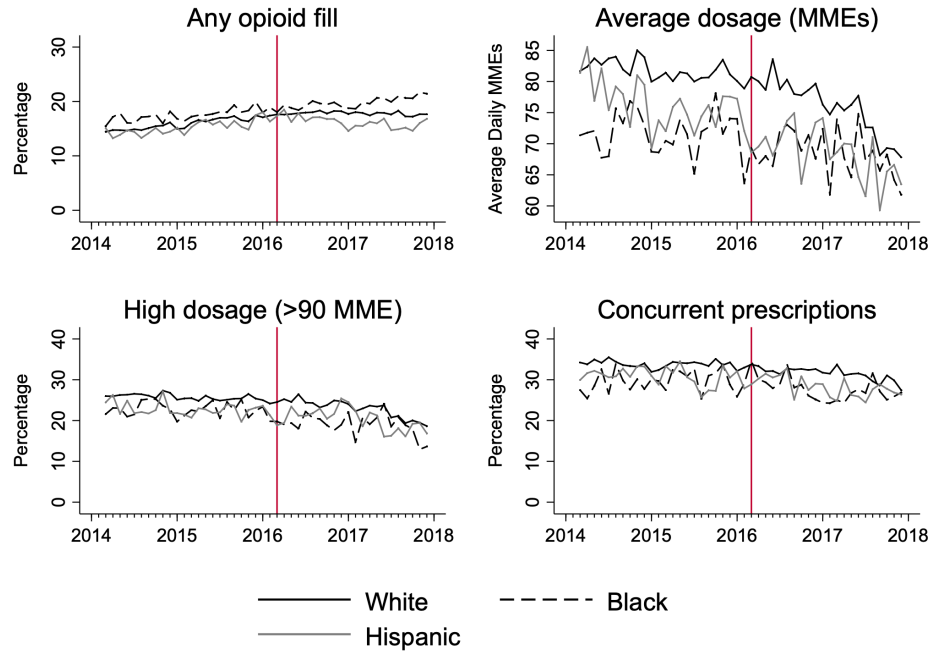
Note: Red line indicates the month of guideline release (March 2016). All outcomes except "any fill" are conditional on having received at least one opioid prescription that month related to the condition of interest.

Table 3-2. Observed and counterfactual predicted means for December 2017, from the Stage I (non-interacted) model

	Any fill (%)	Average dose (MME)	High dose (%)	Concurrent prescriptions (%)	Days supplied	Prescription fills	Days with concurrent prescriptions
Osteoarthritis							
Guideline	14.0 (13.7 - 14.3)	**47.9** **(46.3 - 49.6)**	**11.8** **(10.9 - 12.7)**	18.9 (18.0 - 19.7)	21.0 (20.6 - 21.3)	1.17 (1.16 - 1.18)	25.0 (24.4 - 25.6)
No guideline	14.8 (14.3 - 15.3)	**58.9** **(55.7 - 62.0)**	**16.0** **(14.2 - 17.7)**	19.3 (17.8 - 20.9)	21.6 (20.8 - 22.3)	1.18 (1.16 - 1.21)	25.8 (24.6 - 27.0)
Fibromyalgia							
Guideline	**14.6** **(14.3 - 15.0)**	47.5 (45.5 - 49.4)	**11.8** **(10.8 - 12.9)**	23.6 (22.6 - 24.6)	24.0 (23.6 - 24.5)	1.17 (1.15 - 1.18)	26.4 (25.7 - 27.0)
No guideline	**15.7** **(15.1 - 16.4)**	57.5 (53.8 - 61.1)	**15.4** **(13.4 - 17.4)**	25.4 (23.7 - 27.1)	24.0 (23.1 - 24.8)	1.17 (1.14 - 1.20)	27.4 (26.1 - 28.8)

Note: MME = morphine milligram equivalents. 95% confidence intervals in parentheses. Bold indicates observed and counterfactual estimates with non-overlapping confidence intervals. The counterfactual scenario is that in which the guidelines were not released but all other predictors were as observed.

Table 3-3. Group-specific marginal effects of main predictors from Stage II (interacted) models, osteoarthritis

	Any fill (%)	Average dosage (MMEs)	High dosage (%)	Concurrent prescriptions (%)
Secular trend				
White	0.0348***	0.00216	-0.0248	-0.169***
	(0.0200, 0.0497)	(-0.102, 0.106)	(-0.0800, 0.0304)	(-0.217, -0.122)
Black	-0.014	0.157	0.042	-0.143*
	(-0.0545, 0.0265)	(-0.0461, 0.361)	(-0.0824, 0.167)	(-0.256, -0.0300)
Hispanic	0.0419	0.254	0.0156	-0.261***
	(-0.00103, 0.0848)	(-0.0649, 0.573)	(-0.146, 0.177)	(-0.409, -0.112)
Asian	0.108**	0.627	0.468*	0.197
	(0.0307, 0.186)	(-0.235, 1.490)	(0.0334, 0.902)	(-0.240, 0.635)
Level change				
White	-0.191	1.625	0.876	0.772
	(-0.564, 0.182)	(-0.468, 3.718)	(-0.338, 2.089)	(-0.362, 1.906)
Black	0.323	-0.78	-0.285	-0.331
	(-0.668, 1.313)	(-5.164, 3.604)	(-3.056, 2.486)	(-3.208, 2.545)
Hispanic	-0.955	-3.333	0.0025	2.239
	(-1.978, 0.0689)	(-9.899, 3.233)	(-3.620, 3.625)	(-1.142, 5.620)
Asian	-0.812	-0.996	-3.21	-0.992
	(-2.628, 1.005)	(-15.19, 13.20)	(-10.96, 4.545)	(-11.48, 9.494)
Trend change				
White	-0.0394**	-0.527***	-0.223***	-0.061
	(-0.0677, -0.0111)	(-0.704, -0.351)	(-0.325, -0.121)	(-0.151, 0.0292)
Black	0.0251	-0.506**	-0.246*	-0.0162
	(-0.0515, 0.102)	(-0.871, -0.141)	(-0.475, -0.0182)	(-0.218, 0.186)
Hispanic	-0.0168	-0.958***	-0.226	-0.027
	(-0.0974, 0.0639)	(-1.447, -0.469)	(-0.521, 0.0682)	(-0.289, 0.235)
Asian	-0.0859	-1.032	-0.567	-0.563
	(-0.229, 0.0570)	(-2.689, 0.624)	(-1.437, 0.304)	(-1.366, 0.240)
Race/ethnicity				
White	*Ref.*	*Ref.*	*Ref.*	*Ref.*
Black	-1.323***	-9.778***	-4.274***	-4.696***
	(-1.765, -0.880)	(-11.337, -8.219)	(-5.146, -3.401)	(-5.676, -3.717)
Hispanic	-2.054***	-10.539***	-4.248***	-2.973***
	(-2.507, -1.601)	(-12.324, -8.754)	(-5.244, -3.252)	(-4.074, -1.871)
Asian	-3.680***	-4.639	-1.989	-6.716***
	(-4.443, -2.918)	(-9.551, 0.273)	(-4.679, 0.702)	(-8.988, -4.445)
Observations	1,284,468	191,970	194,045	194,045

Note: *** p<0.001, ** p<0.01, * p<0.05. MME = morphine milligram equivalents. 95% confidence intervals in parentheses. Estimates are racial/ethnic group specific and can be interpreted as a unit change in the outcome variable associated with a unit change in the variable of interest for the group of interest. In contrast with the other predictors, marginal effects of race/ethnicity are in reference to white patients.

Table 3-4. Group-specific marginal effects of main predictors from Stage II (interacted) models, fibromyalgia

	Any fill (%)	Average dosage (MME)	High dosage (%)	Concurrent prescriptions (%)
Secular trend				
White	-0.035	-0.0967	-0.035	-0.191***
	(-0.0971, 0.0271)	(-0.217, 0.0234)	(-0.0971, 0.0271)	(-0.250, -0.132)
Black	-0.0352	0.0152	-0.0352	-0.250**
	(-0.202, 0.132)	(-0.266, 0.296)	(-0.202, 0.132)	(-0.417, -0.0838)
Hispanic	-0.011	-0.125	-0.011	-0.281***
	(-0.210, 0.188)	(-0.513, 0.263)	(-0.210, 0.188)	(-0.448, -0.115)
Asian	0.11	0.271	0.11	-0.545*
	(-0.395, 0.615)	(-0.730, 1.273)	(-0.395, 0.615)	(-0.989, -0.100)
Level change				
White	1.093	2.415	1.093	-0.435
	(-0.360, 2.545)	(-0.0372, 4.866)	(-0.360, 2.545)	(-1.797, 0.926)
Black	-1.108	-0.56	-1.108	0.394
	(-4.880, 2.664)	(-6.672, 5.551)	(-4.880, 2.664)	(-3.629, 4.418)
Hispanic	1.998	1.473	1.998	-0.0963
	(-2.086, 6.082)	(-5.324, 8.270)	(-2.086, 6.082)	(-4.085, 3.892)
Asian	-1.004	-5.307	-1.004	0.895
	(-11.03, 9.018)	(-28.71, 18.10)	(-11.03, 9.018)	(-8.065, 9.854)
Trend change				
White	-0.241***	-0.581***	-0.241***	-0.0937
	(-0.367, -0.115)	(-0.787, -0.375)	(-0.367, -0.115)	(-0.200, 0.0129)
Black	-0.157	-0.495*	-0.157	-0.0499
	(-0.505, 0.190)	(-0.989, -0.000199)	(-0.505, 0.190)	(-0.347, 0.247)
Hispanic	-0.268	-0.538	-0.268	-0.0485
	(-0.689, 0.153)	(-1.165, 0.0883)	(-0.689, 0.153)	(-0.355, 0.258)
Asian	-0.413	-0.787	-0.413	0.698
	(-1.557, 0.732)	(-2.336, 0.761)	(-1.557, 0.732)	(-0.109, 1.505)
Race/ethnicity				
White	*Ref.*	*Ref.*	*Ref.*	*Ref.*
Black	-1.150***	-9.184***	-2.677***	-4.812***
	(-1.815, -0.486)	(-11.413, -6.956)	(-4.053, -1.302)	(-6.316, -3.307)
Hispanic	-1.865***	-7.421***	-3.419***	-3.587***
	(-2.455, -1.275)	(-9.922, -4.920)	(-4.806, -2.032)	(-5.090, -2.083)
Asian	-3.850***	-2.936	-1.844	-7.991***
	(-4.725, -2.974)	(-10.174, 4.301)	(-5.475, 1.788)	(-11.408, -4.574)
Observations	855,371	137,984	137,984	139,484

Note: *** $p<0.001$, ** $p<0.01$, * $p<0.05$. MME = morphine milligram equivalents. 95% confidence intervals in parentheses. Estimates are racial/ethnic group specific and can be interpreted as a unit change in the outcome variable associated with a unit change in the variable of interest for the group of interest. In contrast with the other predictors, marginal effects of race/ethnicity are in reference to white patients.

Table 3-5. Observed and counterfactual predicted means for December 2017, from the Stage II (interacted) model

	Any fill (%)		Average dose (MME)		High dose (%)		Concurrent prescriptions (%)	
	Guideline	No guideline	Guideline	No guideline	Guideline	No guideline	Guideline	No guideline
Osteoarthritis								
White	**14.1**	**15.1**	**50.0**	**59.5**	**12.6**	**16.4**	19.5	20.0
	(13.76, 14.39)	**(14.54, 15.65)**	**(48.12, 51.87)**	**(55.87, 63.03)**	**(11.54, 13.69)**	**(14.46, 18.37)**	(18.51, 20.50)	(18.30, 21.73)
Black	14.9	14.0	**43.4**	**54.8**	8.8	14.3	17.3	18.0
	(14.04, 15.69)	(12.51, 15.52)	**(39.56, 47.15)**	**(47.51, 62.01)**	(6.582, 11.06)	(9.793, 18.77)	(15.28, 19.40)	(13.88, 22.14)
Hispanic	12.9	14.2	**35.3**	**58.8**	8.4	13.1	16.0	14.4
	(12.05, 13.80)	(12.64, 15.83)	**(29.90, 40.76)**	**(47.50, 70.04)**	(5.221, 11.53)	(7.346, 18.92)	(13.38, 18.69)	(9.034, 19.69)
Asian	8.9	11.5	47.4	70.0	12.1	27.2	11.0	23.8
	(7.293, 10.47)	(8.550, 14.44)	(30.95, 63.78)	(39.37, 100.7)	(2.698, 21.41)	(11.61, 42.71)	(1.723, 20.28)	(7.994, 39.63)
Fibromyalgia								
White	**14.6**	**15.8**	**48.6**	**58.4**	**12.3**	**15.9**	24.8	27.2
	(14.23, 15.02)	**(15.14, 16.52)**	**(46.37, 50.86)**	**(54.28, 62.53)**	**(11.16, 13.50)**	**(13.66, 18.06)**	(23.66, 25.97)	(25.10, 29.33)
Black	18.1	17.8	44.3	55.2	10.2	14.1	20.9	21.5
	(16.80, 19.33)	(15.59, 20.00)	(38.90, 49.63)	(45.38, 65.06)	(7.250, 13.19)	(8.031, 20.12)	(17.87, 23.85)	(15.47, 27.56)
Hispanic	12.8	14.3	41.2	51.0	9.6	12.8	20.5	21.6
	(11.71, 13.79)	(12.36, 16.20)	(34.79, 47.61)	(37.57, 64.49)	(6.079, 13.05)	(5.599, 20.03)	(17.20, 23.83)	(15.56, 27.70)
Asian	7.8	8.2	42.9	64.7	8.7	18.2	19.7	4.1
	(5.979, 9.666)	(5.005, 11.48)	(26.61, 59.14)	(26.18, 103.2)	(-1.103, 18.53)	(-6.965, 43.42)	(11.80, 27.56)	(-11.95, 20.22)

Note: Bold indicates observed (guideline) and counterfactual (no guideline) estimates with non-overlapping confidence intervals. MME = milligram morphine equivalents. The counterfactual scenario is that in which the guidelines were not released but all other predictors were as observed. High dose refers to over 90 MME.

Table 3-6. Observed and counterfactual predicted disparities for December 2017, from the Stage II (interacted) model

	Any fill (%)		Average dose (MME)		High dose (%)	
	Guideline	No guideline	Guideline	No guideline	Guideline	No guideline
Osteoarthritis						
Black vs. white	0.8 (-0.08, 1.67)	-1.1 (-2.67, 0.52)	**-6.64 (-10.86, -2.42)**	-4.68 (-12.72, 3.35)	**-3.8 (-6.27, -1.31)**	-2.1 (-7.01, 2.75)
Hispanic vs. white	**-1.2 (-2.08, -0.22)**	-0.9 (-2.54, 0.82)	**-14.67 (-20.37, -8.97)**	-0.68 (-12.45, 11.10)	**-4.2 (-7.57, -0.91)**	-3.3 (-9.38, 2.81)
Asian vs. white	**-5.2 (-6.81, -3.58)**	-3.6 (-6.59, -0.60)	-2.63 (-19.16, 13.89)	10.59 (-20.29, 41.47)	**-0.6 (-9.98, 8.86)**	10.8 (-4.92, 26.42)
Fibromyalgia						
Black vs. white	**3.44 (2.12, 4.77)**	1.96 (-0.34, 4.27)	-4.35 (-10.13, 1.44)	-3.19 (-13.82, 7.45)	-2.11 (-5.31, 1.09)	-1.78 (-8.20, 4.63)
Hispanic vs. white	**-1.87 (-2.98, -0.77)**	-1.55 (-3.59, 0.49)	**-7.41 (-14.19, -0.64)**	-7.37 (-21.43, 6.69)	-2.76 (-6.44, 0.91)	-3.05 (-10.59, 4.49)
Asian vs. white	**-6.8 (-8.68, -4.92)**	-7.59 (-10.89, -4.28)	-5.74 (-22.16, 10.68)	6.3 (-32.42, 45.03)	-3.62 (-13.51, 6.27)	2.37 (-22.92, 27.65)

Note: 95% confidence intervals in parentheses. MME = milligram morphine equivalents. High dose refers to over 90 MME. A black/white disparity of -1.1% in "any fill" indicates that black patients are an estimated 1.1 percentage points less likely to receive an opioid prescription than their white counterparts. Bold indicates an estimated disparity with a 95% confidence interval that does not overlap with zero.

Figure 3-3. Osteoarthritis: predicted means with and without the guideline, by race/ethnicity
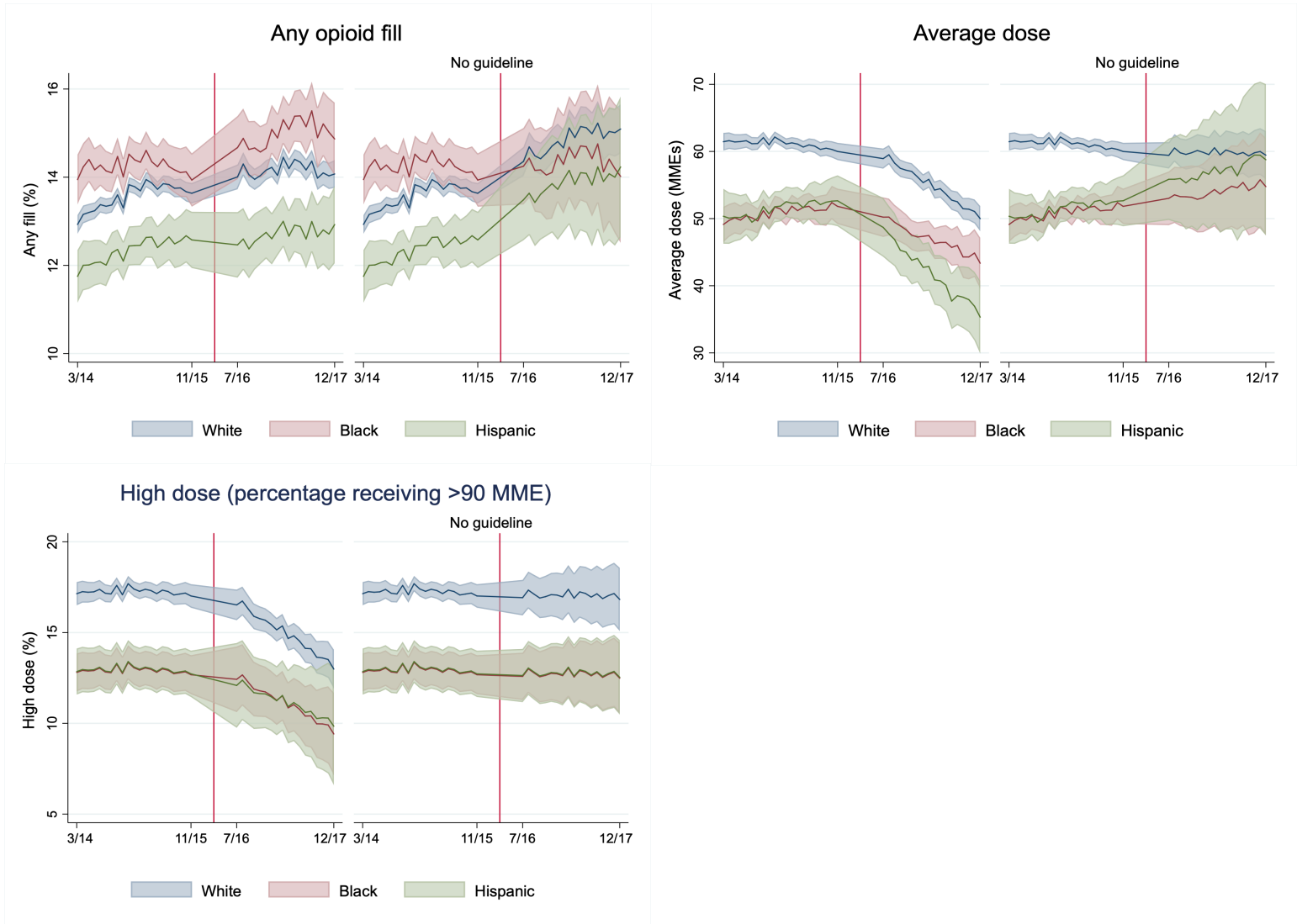
Note: Left panel shows predicted means with the guideline, right panel absent the guideline (counterfactual). Ranges are 95% confidence intervals. Predicted means were not calculated for the implementation period (November 2015-July 2016). Vertical line indicates month of guideline release.

Figure 3-4. Fibromyalgia: predicted means with and without the guideline, by race/ethnicity
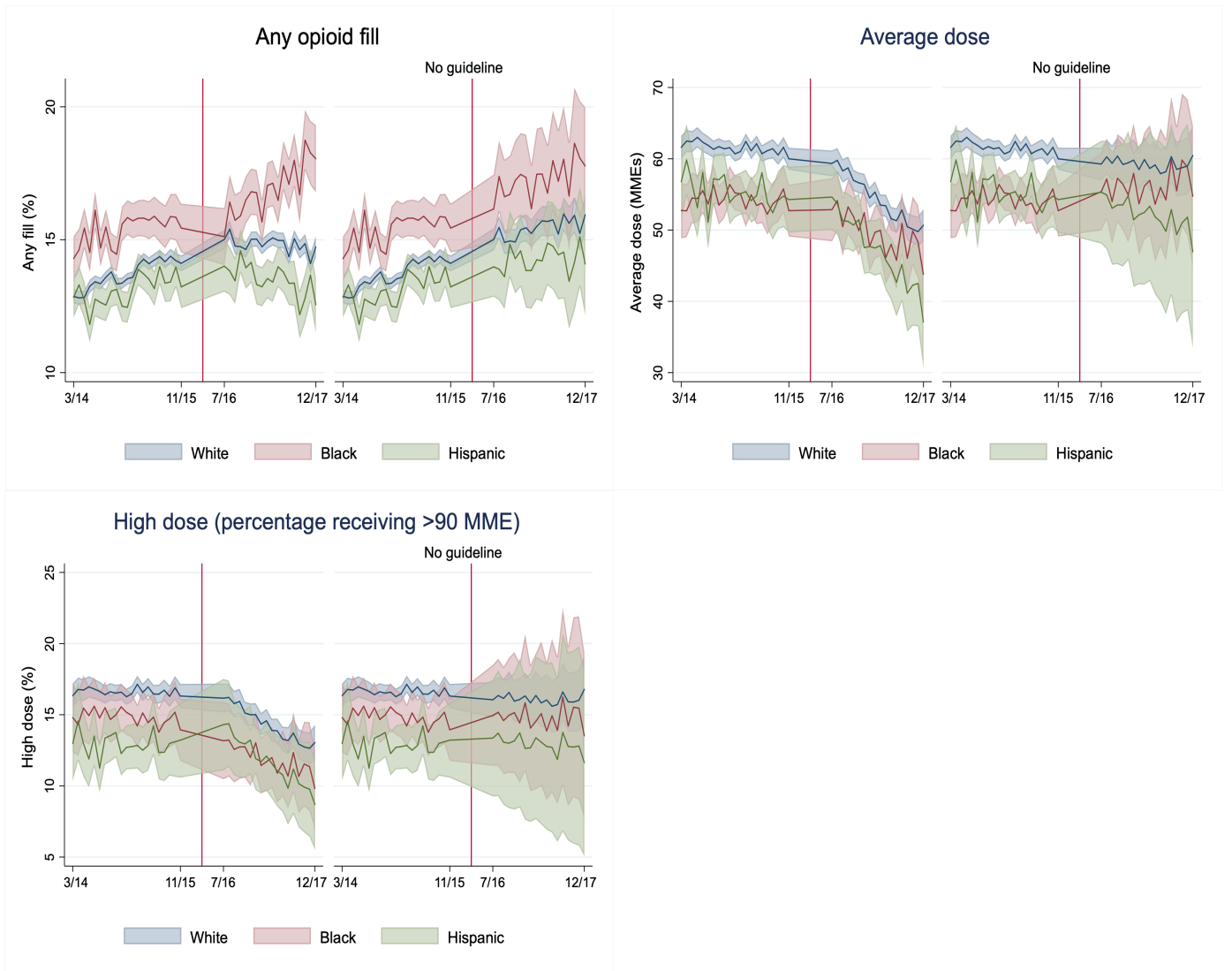
Note: Left panel shows predicted means with the guideline, right panel absent the guideline (counterfactual). Ranges are 95% confidence intervals. Predicted means were not calculated for the implementation period (November 2015-July 2016). Vertical line indicates month of guideline release.

Chapter 4 - Cost-Effectiveness Analysis of Alternative Naloxone Distribution Strategies:

First Responder and Lay Distribution in the United States

INTRODUCTION

In the United States, there were an estimated 48,000 opioid-related overdose deaths in 2017

(Scholl et al., 2018). While the surge of opioid use disorder (OUD) and overdose has been

especially severe in the U.S., opioid-related overdose fatalities have been increasing in a number

of countries, including Canada, Scotland, Wales, and Australia. (National Records of Scotland,

2018; Roxburgh et al., 2018; Special Advisory Committee on the Epidemic of Opioid Overdoses,

2019; Substance Misuse Programme, 2017) Ensuring access to naloxone, a safe and effective

opioid antagonist, is crucial to reducing mortality from opioid overdose (Bird et al., 2016; D.

Kim et al., 2009; Pitt et al., 2018; A. Y. Walley et al., 2013). A recent cost-effectiveness analysis

found that increasing naloxone availability may be one of a few cost-effective interventions to

reduce overdose deaths without causing harm (Pitt et al., 2018). However, prior studies have not

examined whether cost-effectiveness varies by the group targeted for naloxone distribution.

Target groups of naloxone distribution & distribution prevalence

Emergency medical services (EMS), police and fire, and laypeople comprise key target groups

for naloxone distribution. There are potential advantages and disadvantages of distribution to

each of these groups.

EMS distribution

In many communities, EMS are equipped with naloxone (C. S. Davis, Southwell, et al., 2014). This enables administration at the scene of overdose rather than at the hospital, saving precious time (Belz et al., 2006). However, in some communities, EMS consists predominantly of emergency medical technicians (EMTs) and emergency medical responders—together termed basic life support, or BLS, and distinguished from advanced life support (ALS) personnel such as paramedics. BLS personnel lack authorization to administer naloxone in many states (C. S. Davis, Southwell, et al., 2014). This is the case in many rural areas, lowering the likelihood that individuals in these areas will receive naloxone at the scene of an overdose (Faul et al., 2015). EMS distribution could be increased by authorizing naloxone administration by BLS personnel. Evidence from states that allow this indicates that BLS personnel administer naloxone effectively (Belz et al., 2006; C. S. Davis, Southwell, et al., 2014; Gulec et al., 2018); one study found that enabling administration by EMTs could reduce time to administration by 6-10 minutes (Belz et al., 2006).

Police and fire distribution

Naloxone can also be administered by nonmedical emergency responders such as law enforcement officers and firefighters. Because police and fire are more numerous than EMS in many communities, the former may arrive first at an overdose scene (C. S. Davis, Ruiz, et al., 2014). As a result, distribution to police and/or firefighters ("police and fire") may further reduce time to administration, and thus the likelihood of death or severe hypoxia due to insufficient cerebral oxygenation. Distribution to police and fire may be particularly valuable in rural

communities, where ambulances may take longer to arrive or EMS may consist of primarily BLS.

In the U.S., naloxone distribution to EMS, police, and firefighters has risen significantly (Belz et al., 2006; C. S. Davis, Ruiz, et al., 2014; Gulec et al., 2018; North Carolina Harm Reduction Coalition, 2018), and overdose reversals by these groups receive considerable media attention (Depompei, 2016; Wade, 2018; Zendehnam, 2018). However, the cost-effectiveness of first responder distribution strategies has not been studied, and some policymakers have expressed concern about their costs (Wootson Jr., 2017; WOWK-TV, 2018). Additionally, there are constraints on the effectiveness of naloxone distribution to either of these first responder groups. While the majority of overdose events are witnessed (D. Kim et al., 2009; Sherman et al., 2007; Strang et al., 1999), many witnesses do not call 911, often fearing legal repercussions due to the presence of illicit opioids (Galea et al., 2006). Good Samaritan Laws aim to ameliorate this fear, but expansive immunity is not yet universal and initial research is mixed on these laws' effectiveness (Koester et al., 2017; McClellan et al., 2018; National Conference of State Legislatures, 2017; Rees et al., 2017; Zadoretzky et al., 2017).

Lay distribution

A third strategy is to distribute naloxone to laypeople, and in particular those likely to experience or witness an overdose. Distributing directly to laypeople may benefit overdose victims whose witness will not call 911. Moreover, when the witness does call 911, lay distribution may still reduce time to naloxone administration. Naloxone can be distributed to laypeople by community-based organizations, pharmacies, health care facilities, and other sources to individuals likely to

experience or witness overdose (Wheeler et al., 2015). Evidence indicates that trained laypeople recognize overdose and administer naloxone effectively (T. C. Green et al., 2013), and that lay distribution and training programs have successfully reduced overdose mortality (McClellan et al., 2018; McDonald & Strang, 2016).

Lay distribution may also have disadvantages. Because a layperson will likely encounter fewer overdoses than a first responder, a naloxone kit distributed to a layperson may be less likely to be used than one distributed to a first responder, reducing the cost-effectiveness of lay distribution compared to first responder distribution. Some worry that lay naloxone distribution provides an overdose safety net, leading individuals to use opioids more intensively and overdose more frequently (T. C. Green et al., 2013). This increased risk-taking is known as "moral hazard" in the economics literature. Empirical evidence for this hypothesis is lacking: a systematic review of 22 observational studies found no evidence that take-home naloxone programs increased heroin use (McDonald & Strang, 2016), and a recent econometric analysis found no significant association between naloxone access laws and non-medical opioid use (McClellan et al., 2018). Indeed, some studies suggest a decline in opioid use following naloxone training (McDonald & Strang, 2016; Seal et al., 2005). Nonetheless, because some policymakers and health providers continue to cite moral hazard as a concern, it is important to analyze the potential effects of the moral hazard hypothesis on cost effectiveness (T. C. Green et al., 2013; Seelye, 2017).

The size and number of lay distribution programs have grown, as community-based programs have increasingly offered naloxone and states have issued standing orders for provision by pharmacists without individual prescriptions (C. S. Davis et al., 2015; Wheeler et al., 2015).

Nonetheless, a recent study found that only 13% of the counties with the highest opioid overdose rates had naloxone distribution programs for laypeople (Lambdin et al., 2018). One reason may be that lay distribution remains highly controversial (Bachhuber et al., 2015; Blendon & Benson, 2018).

With the rapid evolution of the opioid crisis, the cost-effectiveness of naloxone distribution to all target groups may be shifting. For example, rising prevalence of highly potent opioids like fentanyl has increased risk of death due to overdose, requiring earlier naloxone administration and/or higher doses, and potentially reducing its cost-effectiveness (Frank & Pollack, 2017). Sharply rising naloxone prices have also raised concern (Gupta et al., 2016). Given these changing circumstances, the variation in advantages and disadvantages across strategies, and the scarcity of resources available to address the crisis, a cost-effectiveness analysis of each distribution strategy, both independently and in combination, is needed.

Aims

I conduct a cost-effectiveness analysis to compare eight strategies that encompass all combinations of low and high distribution to laypeople, police and fire, and EMS: low levels of distribution to all groups ("minimum distribution"); high distribution to all groups ("maximum distribution"); and all other combinations of high and low distribution to the three groups (all eight combinations are listed in Table 4-2). Because laypeople likely to experience or witness overdose—people with OUD and their friends and family—are more likely than the average person to benefit from obtaining naloxone, I specifically consider laypeople likely to witness or experience an overdose (henceforth "laypeople").

I examine police and fire separately from EMS for several reasons. First, police and/or fire often arrive to an overdose scene before EMS, such that overdose victims can receive naloxone from police and fire as well as EMS—i.e., they can function as two separate interventions. Second, increasing naloxone distribution to police and fire departments is conceptually distinct from authorizing naloxone administration by BLS, a primary means by which EMS naloxone levels could be increased. I examine police distribution and fire distribution as one strategy, however, because both groups serve a similar function as nonmedical first responders, costs of distribution and training to the two groups are similar, there is great heterogeneity in which party arrives first at an overdose scene, and because data on any differences in frequency and effectiveness of naloxone administration are insufficient to parameterize separate strategies.

METHODS

I developed a decision analytic model in TreeAge Pro 2018. Outcomes of interest included (a) strategy ranking, determined by net monetary benefit, (b) cost-effectiveness, expressed in incremental costs per quality-adjusted life year (QALY) gained, and (c) the number of fatal overdoses (and percent of fatal overdoses averted compared to the worst-case scenario, or minimum, strategy). Net monetary benefit is equal to effectiveness (QALYs) times willingness-to-pay per QALY, minus cost. A strategy is "preferred" if it maximizes net monetary benefit. I used a lifetime time horizon in order to account for both up-front costs of distribution and long-term benefits (such as less lost productivity) of averted deaths. I employed two reference case perspectives: a societal perspective that incorporated productivity and criminal justice system costs, and a health sector perspective that did not (Neumann, Sanders, Russell, Siegel, & Ganiats,

2016). Costs included the cost of naloxone kits themselves, the cost of training recipients to recognize overdose and administer naloxone, the cost of ambulance rides and emergency department visits, and (in the societal analysis) the time costs of lay naloxone training, productivity costs of OUD and overdose (less consumption), and costs to the criminal justice system (Table 5-20; appendix text). Effectiveness is accrued via (a) reductions in mortality and (b) improvements in quality of life due to less hypoxia and reduction in misuse, which is associated with lower health-related quality of life (Nosyk et al., 2010; Pyne et al., 2011; Vanagas et al., 2010).

I modeled a closed cohort of hypothetical individuals with OUD. The average age of first use/misuse of heroin and prescription pain relievers is the average age of first use/misuse of heroin and prescription pain relievers (Lipari et al., 2017), and the average length of heroin use has been found to be about 10 years (Best et al., 2008). Assuming a symmetrical age distribution of misuse, I approximated a cross-section of the population with OUD who enter the model at age 35 (i.e., at the median age of use). Costs and QALYs were scaled to a hypothetical population of 50,000 people in which OUD prevalence is 0.8%, following the 2016 National Survey on Drug Use and Health (Center for Behavioral Health Statistics and Quality, 2016). My cohort thus comprised 400 individuals with OUD (50,000 x 0.8%). Hypothetical individuals in the model could be currently misusing opioids, not currently misusing, or dead. Because prior overdose is a strong predictor of future overdose and mortality (Darke et al., 2007), these health states were further divided as shown in Figure 4-1. Individuals who survived an overdose could suffer from long-term effects of hypoxia. Individuals could transition between states annually, via pathways depicted in Figure 4-1.

Figure 4-2 is a simplified tree of potential events for individuals in a "misusing" health state (the complete model is available upon request). In a given year, an individual with OUD may experience an overdose, which carries a risk of mortality and a risk of severe hypoxia; these probabilities vary depending on the interventions an individual receives. If an overdose occurs, there is some probability that it is witnessed, and some probability that a layperson at the scene (the victim or a witness) has obtained naloxone—e.g., from a pharmacy or community-based program. This parameter varies across strategies. If they have obtained naloxone, whether the witness actually administers it depends on a number of factors: whether the witness recognizes the event as an overdose, whether the witness is aware of the naloxone (if it belongs to the victim), whether the naloxone is at the scene (i.e., not lost or left elsewhere), and whether the witness is willing and able to administer. Lay administration of naloxone reduces the risk of mortality and severe hypoxia.

Regardless of whether the witness administers naloxone, they may choose to call 911. If 911 is called, and if police or fire arrive to the scene before EMS, they may be equipped with naloxone (varying across strategies) and may administer it. If not, they may still reduce average mortality and hypoxia risk via rescue breathing or ventilation by bag-valve. If police and fire do have and then administer naloxone, the reduction in average mortality is larger than if they arrive first but do not have naloxone. There is a given probability that EMS arriving on the scene have naloxone (varying by strategy). There is an additional probability the EMS administer the naloxone. To reflect the capability of EMS to manage breathing and cardiac conditions during an overdose, the arrival of EMS on scene results in a reduction in mortality and hypoxia risk regardless of

naloxone administration. However, the administration of naloxone by EMS garners further risk reduction. If none of the first responders have naloxone, the individual will receive naloxone at the hospital. This delay results in a smaller reduction in mortality and hypoxia risk.

In the minimum distribution strategy, the hypothetical community is assumed to have equipped no laypeople and no police and fire with naloxone (Table 4-1). The probability that EMS arriving at the scene are equipped with naloxone was set to 0.5. This models a community in which 50% of 911 calls are responded to by EMS authorized to administer and equipped with naloxone; in the other 50% of 911 calls, BLS or other personnel not equipped with naloxone arrive. This selection was somewhat arbitrary, but reflects the fact that advanced life support personnel or other responders authorized to administer and equipped with naloxone, will comprise some proportion of EMS in any given community. In the "high police and fire" and "high EMS" strategies, the percentage of each first responder group equipped with naloxone was increased to 100%. In the "high layperson" strategy, the percentage of overdoses at which a layperson (whether victim or witness) has obtained naloxone is increased to 75%; I set the "high layperson" value to less than 100% to reflect the challenge of disseminating naloxone to all individuals likely to experience or witness overdose.

As an example, the "high layperson, low police and fire, low EMS" strategy would model a community in which 75% of individuals likely to witness or experience overdose have obtained naloxone, no police and fire who arrive at an overdose scene are equipped with naloxone, and 50% of 911 calls are responded to by EMS authorized to administer and equipped with naloxone.

To gain insight into the optimal target levels of naloxone distribution, sensitivity analyses examined variation in the precise definition of the levels for each intervention.

Table 5-21 provides parameter point estimates, ranges, and rationales. Selection of input parameters was based on nationally representative data and synthesis of one-off studies. To account for the uncertainty inherent in estimates regarding opioid use and overdose events, I selected a range within which each parameter value was expected to fall and used these ranges to conduct sensitivity analyses. The size of the range reflected the level of uncertainty in the parameter. Model calibration was conducted to ensure the model produced results similar to those observed in the literature and is described in the appendix text and Table 5-23.

I conducted a tornado analysis to examine the effects of varying each parameter individually on model outcomes. For a set of particularly uncertain or potentially influential parameters, I conducted threshold analyses to examine whether any value of the parameter (ranging from zero to one) would change the model's conclusions. For example, given uncertainty in the probability of overdose death in the presence of each intervention, the corresponding mortality parameters were varied from relative risks of zero (no mortality with the given intervention) to one (no reduction in mortality compared to receiving no intervention). Sensitivity analysis on mortality parameters also enabled examination of the impact of increasing use of highly potent fentanyl-like products on cost-effectiveness, as this shift may result in greater mortality at traditional naloxone doses, and/or entail higher costs when multiple doses are required. I also conducted threshold analyses on rising naloxone prices, the effectiveness of subsequent doses of naloxone when multiple doses are administered, and hypothetical moral hazard.

In a probabilistic sensitivity analysis, I simultaneously varied all parameters in 10,000 iterations of a Monte Carlo simulation. This allowed us to evaluate the probability that each strategy would be cost-effective compared to the alternatives, given overall, combined parameter uncertainty. Table 5-22 details the assumptions about the distribution of each parameter.

I used the Consumer Price Index to adjust costs to 2017 US dollars. I used a 3% discount rate applied to both costs and health outcomes (Sanders et al., 2016). I used a threshold for cost-effectiveness of $50,000 (Ubel et al., 2003). For some comparisons, I compared strategies in terms of net monetary benefit, a measure that combines costs and QALYs into a single value measure, by valuing QALYs at $50,000 each.

RESULTS

Results of base case analysis (societal perspective)

High levels of distribution to all three groups maximized net monetary benefit and minimized the number of overdose deaths, while low levels of distribution to all groups entailed the reverse outcomes (Table 4-2). For example, maximum distribution entailed 107 overdose deaths, compared to 136 in the minimum strategy (21% averted compared to the minimum). This strategy would cost a community of 50,000 approximately $40,000 in naloxone training and kits in the first year of distribution, and about $100,000 over five years. The top four strategies (ranked by net monetary benefit) involved high lay distribution, while the bottom four involved low lay distribution.

Table 4-3 disaggregates the costs and savings accrued in each strategy. In strategies with higher rank, criminal justice system costs and costs due to health care not related to overdose were higher because people were kept alive longer; training and kit costs were higher because more naloxone was distributed; costs related to overdose also increased as people were kept alive longer and had additional opportunities to overdose. However, the increased overall costs of naloxone distribution, training, and the societal health and criminal justice costs of individuals with OUD living longer were considerably smaller than the productivity gained by averting deaths. Every strategy was cost-saving compared to its next-best alternative, and cost savings were greatest in the maximum distribution strategy because it minimized deaths (and maximized effectiveness).

The second highest-ranking strategy involved high distribution to laypeople and EMS, but low distribution to police and fire; there were four more overdose deaths in this strategy. The third highest-ranking strategy involved high distribution to laypeople and police and fire, but low distribution to EMS, involving five more overdose deaths than in maximum distribution.

Results of health sector analysis

The results of the health care sector analysis were similar to those from the societal analysis (Table 4-2 and Figure 4-3). Rankings based on net monetary benefit of each strategy were the same, although some strategies were dominated by extended dominance—i.e., there was a more effective strategy with a lower cost-effectiveness ratio (Cantor, 1994). Maximum distribution to all groups remained the preferred strategy and undominated; high distribution to laypeople and EMS (but not police and fire) remained second most preferred and was undominated. Because

societal costs were excluded from this analysis, strategies were no longer cost-saving. However, the incremental cost-effectiveness ratio of all undominated strategies fell below $20,000 per QALY gained.

Sensitivity analysis

Societal analysis

Results were highly robust to uncertainty in the model parameters. For all but one parameter in the tornado analysis—the probability that police and fire arrive before EMS—wide variation in the parameter estimate did not affect strategy ranking. For example, variation in the probability that an overdose is witnessed, the probability that a witness would administer naloxone if obtained, and the probability that a witness would call 911 did not influence which strategy was preferred. Results also were not sensitive to how "low" distribution levels were defined—i.e., to status quo levels in the community—or to variation in training duration, naloxone kit costs (within a reasonable range), or trainer/trainee wages. When police and fire arrived first less than 3.0% of the time 911 was called, high distribution to all groups was no longer preferred; under these circumstances, high distribution only to laypeople and EMS maximized net monetary benefit (Table 5-24).

Threshold analyses identified thresholds in nine additional parameters: the probability an overdose is witnessed, naloxone kit costs, hypothetical moral hazard (represented as an increase in the annual probability of overdose associated with lay naloxone distribution), and the reduction in mortality associated with each possible intervention (Table 5-24). These thresholds occurred at extreme values of each parameter. For example, maximum distribution maximized

net monetary benefit as long as naloxone cost less than $1,432 per kit. In the analysis of

hypothetical moral hazard, high distribution to police/fire and EMS (but not laypeople) was only

preferred to the maximum strategy if lay distribution increased the probability of overdose by at

least 23%.

A two-way sensitivity analysis of the effectiveness of subsequent naloxone doses (e.g.,

administered by EMS following administration by police and fire) revealed that maximum

distribution maximized net benefit even if subsequent doses reduced mortality by as little as

0.01%. Strategy rankings also did not depend on the effectiveness of subsequent doses.

Appendix text further details the results of sensitivity analyses.

Figure 4-4 displays results of the probabilistic sensitivity analysis in cost-effectiveness

acceptability curves, which display the probability that an intervention is preferred to its

alternatives at a given willingness-to-pay (WTP) (Fenwick et al., 2001). Maximum distribution

was consistently most likely to be cost-effective; this probability is larger than 0.8 when

willingness-to-pay is $50,000 or above per QALY. All other strategies were consistently less

than 20% likely to be preferred to the alternatives.

Health sector analysis

As in the societal analysis, variation in only one parameter in the health sector tornado analysis

influenced strategy rankings. If police and fire arrived before EMS less than 7.3% of the time,

then maximum distribution no longer maximized net monetary benefit; instead, high distribution

to laypeople and EMS (but not police and fire) was preferred. Threshold analysis indicated that,

from this perspective, maximum distribution was preferred as long as a naloxone kit cost less than $570; above that, high distribution to laypeople and EMS (but not police and fire) is preferred until a kit reaches $2,210. In addition, high distribution to police/fire and EMS (but not laypeople) was only preferred to the maximum strategy if hypothetical moral hazard increased the probability of overdose rose by at least 20%.

DISCUSSION

This study is the first to evaluate the cost-effectiveness of naloxone distribution to first responder groups individually and in combination with laypeople. The target groups of interest included laypeople likely to witness or experience overdose, police and/or firefighters ("police and fire"), and EMS personnel not currently equipped, such as basic life support personnel who in many states are not authorized to administer naloxone. In both the societal and health sector analyses, high distribution to all three target groups minimized overdose deaths and maximized net monetary benefit, a measure that takes into account both costs and health gains. Compared to a worst-case scenario of minimum distribution to all groups, this strategy averted 21% of overdose deaths. High distribution to laypeople and EMS (but not police and fire) ranked second, while high distribution to laypeople and police and fire (but not EMS) ranked third. Compared to the minimum strategy, these strategies each averted roughly 18% of overdose deaths.

Strategies involving low distribution to laypeople always ranked last. The majority of mortality reduction would result from increased lay distribution, because it could benefit a population not accessible to first responders: overdose victims whose witness does not call 911. In contrast, first responder naloxone benefits victims likely to receive naloxone eventually—if not by first

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responders equipped with naloxone at the scene (police and fire and/or EMS), then once transported to the hospital. The marginal value of lay distribution is thus greater than that of first responder distribution. For a similar reason, increased police and fire distribution reduces mortality less than EMS distribution. Police and fire can administer naloxone and potentially avert fatal overdose when they arrive on scene before EMS. However, because administration by police and fire is always followed by EMS care, its benefit relative to the alternative—EMS treatment alone—is smaller than the benefit of administration by either of the other groups.

In the societal analysis, which took into account productivity and criminal justice system costs, all strategies were cost-saving because the productivity losses averted by keeping a person alive longer far outweighed the societal costs of doing so (e.g., added costs to the criminal justice and health care systems). In the narrower health sector analysis, undominated strategies were highly cost-effective: for example, high distribution to all groups corresponded to an incremental cost-effectiveness ratio of $15,950 per QALY gained, considerably below a threshold of $50,000.

The cost of naloxone is low compared to many life-saving medications. Even amid rising naloxone prices, maximum distribution remained the preferred strategy as long as naloxone kits remained below $1,430 in the societal analysis and $570 in the health sector analysis. As rising naloxone prices risk making naloxone unaffordable to some individuals, organizations, and local governments (Gupta et al., 2016; Wheeler et al., 2015), the medication's cost-effectiveness justifies subsidies or other support to ensure availability. This finding also suggests that, even if rising prevalence of synthetic opioid overdose increases the number of doses needed for

successful reversal, the corresponding increase in cost per reversal is unlikely to undermine naloxone's cost-effectiveness.

While my results suggest that maximum distribution would be highly cost-effective (health sector analysis) or even pay for itself (societal analysis), affordability of up-front costs may influence a community's decision. A community of 50,000 would spend about $40,000 on naloxone training and kits in the first year of high distribution to all groups, and about $100,000 over five years.

The results were remarkably robust to sensitivity analysis. Even in threshold analyses (within the societal analysis) in which I extended parameter ranges beyond what the literature suggests is reasonable, I only saw thresholds at extreme values. In addition, the findings were robust to probabilistic sensitivity analysis, and were comparable with results of related studies of lay distribution (Coffin & Sullivan, 2013a; Langham et al., 2018; Uyei et al., 2017b).

These findings were not sensitive to large increases in the probability of overdose death and to greater need for multiple doses of naloxone—further evidence that, in the context of increased use of highly potent opioids such as fentanyl, naloxone distribution will remain cost-effective.

While empirical evidence indicates otherwise (McClellan et al., 2018; McDonald & Strang, 2016), some decision makers worry that distributing lay naloxone will lead individuals to use opioids more intensively, thereby undermining the health benefits of distribution (Seelye, 2017). my results suggest that, even if moral hazard were to occur, maximum distribution to all groups

would very likely remain preferred. Moral hazard would need to increase the annual probability of overdose by 23% in the societal analysis (20% in the health sector analysis) in order for high distribution to police/fire and EMS—but not laypeople—to be preferred. Such manifestations of moral hazard are inconsistent with prior research (McClellan et al., 2018; McDonald & Strang, 2016), suggesting that this common concern is not a realistic threat to the value of lay naloxone distribution.

This study has limitations. Incomplete and imperfect data produce uncertainty in the parameter estimates in my model. Much existing research is limited to individuals using heroin, who may differ from individuals who misuse other opioids (Darke et al., 2007; Sumner et al., 2016). Studies of overdose witness behavior typically rely on self-reports, raising concern about social desirability bias. I use a combination of national statistics and data from smaller-scale studies, many of which have occurred in urban areas; more research is needed for greater national representativeness. Nonetheless, informed policy decisions are needed now. Given these challenges, I selected a mathematical modelling approach that allows for considerable uncertainty. Extensive deterministic and probabilistic sensitivity analyses examining wide ranges of possible values for each parameter revealed my results to be remarkably robust. Analyses such as this one provide means to make evidenced-based, cost-effective policy decisions in the face of incomplete or low-quality data.

Community-level heterogeneity may necessitate different distribution approaches in different communities. For example, rural and urban areas likely differ in important ways (Faul et al., 2015; Gonzalez et al., 2009; Kerensky & Walley, 2017; Wunsch et al., 2009). However,

insufficient data on rural opioid use and overdose precluded the development of two separate models; this is an area for future research. In the meantime, the robustness of my results to sensitivity analysis suggests that the highest-ranked strategies are likely to remain cost-saving and effective under a wide range of circumstances. Similarly, insufficient data on the frequency and effectiveness of naloxone distribution by police officers and firefighters precluded examination of distribution to these target groups separately. More empirical research on the mortality and morbidity benefits of different forms of first responder naloxone distribution is needed.

I defined "high lay distribution" such that, at 75% of overdose events, either the victim or a witness would have at some point obtained naloxone (though they may not have or administer it at the scene of overdose). I chose this conservative upper bound to reflect the difficulty of reaching all individuals likely to experience or witness overdose.

However, I am unable to estimate the proportion of target laypeople who should receive naloxone in order to ensure that, at 75% of overdose events, someone has obtained naloxone. First, there is some amount of positive spillover of lay distribution, in which a given kit may be administered to someone other than the original recipient (Keane et al., 2018). Second, nonrandom distribution of naloxone among target laypeople may lead to a nonlinear relationship between number of kits distributed and effectiveness. For example, two people at a single overdose event may have obtained naloxone (e.g., if they both live near a distribution site or if one learned about naloxone from the other), while at another event no one may have obtained it—rendering the second layperson kit less able to confer health benefits than if distribution were

homogeneous. The data needed to explicitly model these forces are lacking, limiting my ability to recommend precise target percentages for lay distribution. Nonetheless, my findings support a concerted increase in naloxone distribution to laypeople as well as first responders.

Because naloxone is not randomly distributed among target laypeople, the cost of ensuring that naloxone has been obtained by at least one person at 75% of overdose events is likely higher than that of distributing naloxone to 75% of laypeople. This may be compounded by a related phenomenon, in which, at higher levels of distribution, the remaining laypeople become harder and thus more expensive to reach. Insufficient prior research precluded explicit modeling of these nonlinearities, potentially resulting in underestimation of lay distribution costs and, in turn, overestimation of cost-effectiveness. However, sensitivity analyses demonstrated my key findings to be robust to large increases in the costs of lay distribution (Appendix C-6). Still, my inability to model these nonlinearities likely renders my precise cost estimates imperfect. Further research is needed to better characterize the social networks of individuals with OUD and the resulting nonlinearities in naloxone costs and effectiveness.

Opioid-related overdose killed more nearly 48,000 Americans in 2017 alone (Scholl et al., 2018). Increasing naloxone access saves lives, reduces morbidity due to severe hypoxia, and costs little. Yet naloxone access remains insufficient. my findings support increased naloxone distribution to laypeople likely to experience or witness overdose, police and fire, and EMS. Increased distribution to and use by EMS could be achieved by, for example, authorizing naloxone administration by basic life support personnel in states that currently prohibit it. When resource

constraints limit a community's ability to increase distribution to all three groups, distribution to laypeople and EMS should be prioritized.

Figure 4-1. Possible health states and transitions
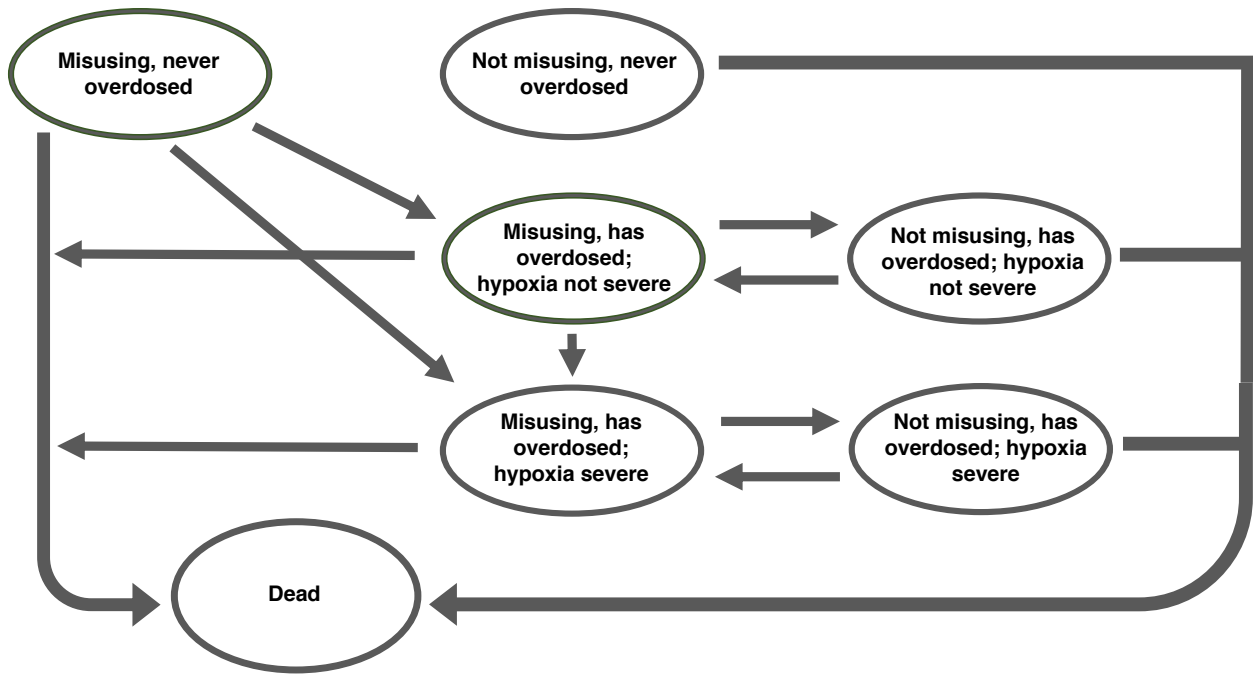
Figure 4-2. Tree of potential annual transitions for individuals in a "misusing" health state
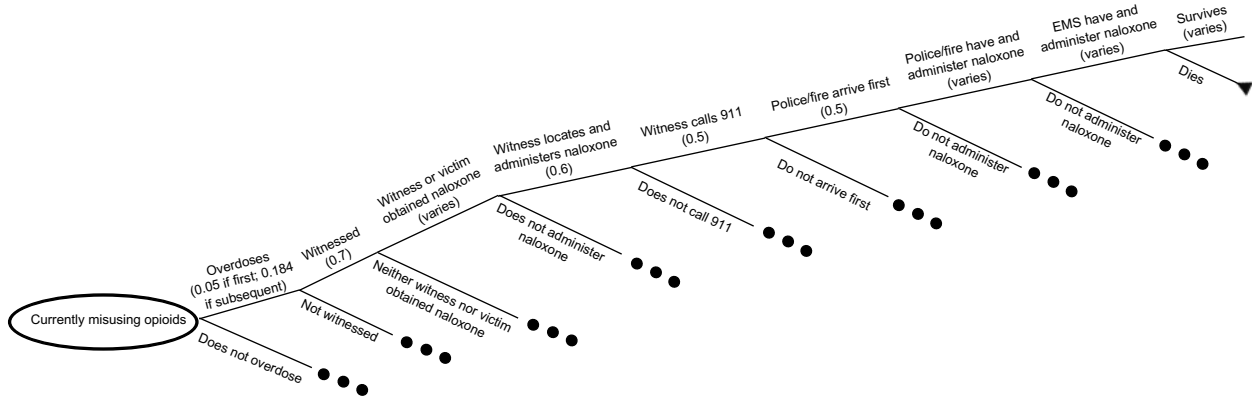
Table 4-1. Intervention levels in base case analysis

	Low (%)	High (%)
Lay distribution*	0	75
Police and fire distribution	0	100
EMS distribution	50	100

Note: All eight combinations of these levels ("strategies") are examined in the analysis. Sensitivity analyses are conducted on each of these levels to examine the effects of defining them differently.
* Lay distribution level refers to the percentage of overdoses at which at least one of the victim or witnesses has obtained naloxone. In such cases, a separate probability determines whether the naloxone is available and administered. The "high" value is less than 100% to reflect the challenge of disseminating naloxone to all individuals likely to experience or witness overdose.

Table 4-2. Results of societal and health sector analyses

A.

	Rank[a]	Overdose deaths	Deaths averted, compared to minimum (%)	Cost[b]	Effectiveness[c]	Status[d]
High LP, High PF, High EMS	1	107	21	(179.2)	5,230	_____
High LP, Low PF, High EMS	2	111	18	(178.9)	5,200	Dominated
High LP, High PF, Low EMS	3	112	18	(178.5)	5,180	Dominated
High LP, Low PF, Low EMS	4	117	14	(178.0)	5,140	Dominated
Low LP, High PF, High EMS	5	125	8	(177.0)	5,080	Dominated
Low LP, Low PF, High EMS	6	129	5	(176.5)	5,040	Dominated
Low LP, High PF, Low EMS	7	131	4	(176.1)	5,020	Dominated
Low LP, Low PF, Low EMS	8	136	_____	(175.4)	4,960	Dominated

B.

	Rank[a]	Overdose deaths	Deaths averted, compared to minimum (%)	Cost[b]	Effectiveness[c]	ICER[e]
High LP, High PF, High EMS	1	107	21	61,544	5,230	15,950
High LP, Low PF, High EMS	2	111	18	61,054	5,200	12,880
High LP, High PF, Low EMS	3	112	18	61,982	5,180	Dominated (extended)
High LP, Low PF, Low EMS	4	117	14	60,348	5,140	Dominated (extended)
Low LP, High PF, High EMS	5	125	8	59,537	5,080	Dominated (extended)
Low LP, Low PF, High EMS	6	129	5	58,956	5,040	12,000
Low LP, High PF, Low EMS	7	131	4	58,838	5,020	Dominated (extended)
Low LP, Low PF, Low EMS	8	136	_____	58,083	4,960	_____

[a] Ranked by net monetary benefit

[b] In millions of dollars

d Because all strategies but one are dominated, incremental cost-effectiveness ratio is not reported

e Incremental cost-effectiveness ratio. Compared to next-best alternative, where next-best alternative is the undominated strategy with the next highest net monetary benefit; in dollars per QALY

Note: Panel A: societal analysis; Panel B: health sector analysis. LP = layperson; PF = police and fire; EMS = emergency medical services. Cost and effectiveness values correspond to a hypothetical community with a population of 50,000, over a lifetime time horizon.

Table 4-3. Disaggregated costs of top three strategies at five years and lifetime (societal perspective)

	Rank	Training & kits	Productivity (excluding consumption)	Health, - overdose	Health, - other	Criminal justice system	Total
Five years							
High LP, high PF, high EMS	1	102,000	(94,009,000)	1,629,000	17,299,000	6,879,000	(157,388,000)
High LP, low PF, high EMS	2	63,000	(93,913,000)	1,626,000	17,282,000	6,873,000	(157,266,000)
High LP, high PF, low EMS	3	97,000	(93,866,000)	1,625,000	17,274,000	6,869,000	(157,156,000)
Low LP, low PF, low EMS	8	5,000	(93,122,000)	1,604,000	17,140,000	6,817,000	(156,007,000)
Lifetime							
High LP, high PF, high EMS	1	281,000	(259,098,000)	5,075,000	56,150,000	18,366,000	(564,054,000)
High LP, low PF, high EMS	2	160,000	(258,187,000)	5,032,000	55,825,000	18,262,000	(561,398,000)
High LP, high PF, low EMS	3	263,000	(257,752,000)	5,012,000	55,671,000	18,213,000	(559,976,000)
Low LP, low PF, low EMS	8	15,000	(250,962,000)	4,707,000	53,333,000	17,467,000	(539,955,000)

Note: All values in dollars. Negative values (savings) in parentheses. A lower value of costs (or larger absolute value of savings) is preferred. Top three strategies are included, as well as the minimum strategy for comparison.

Figure 4-3. Cost-effectiveness planes, societal perspective (A) and health care sector (B)

A.
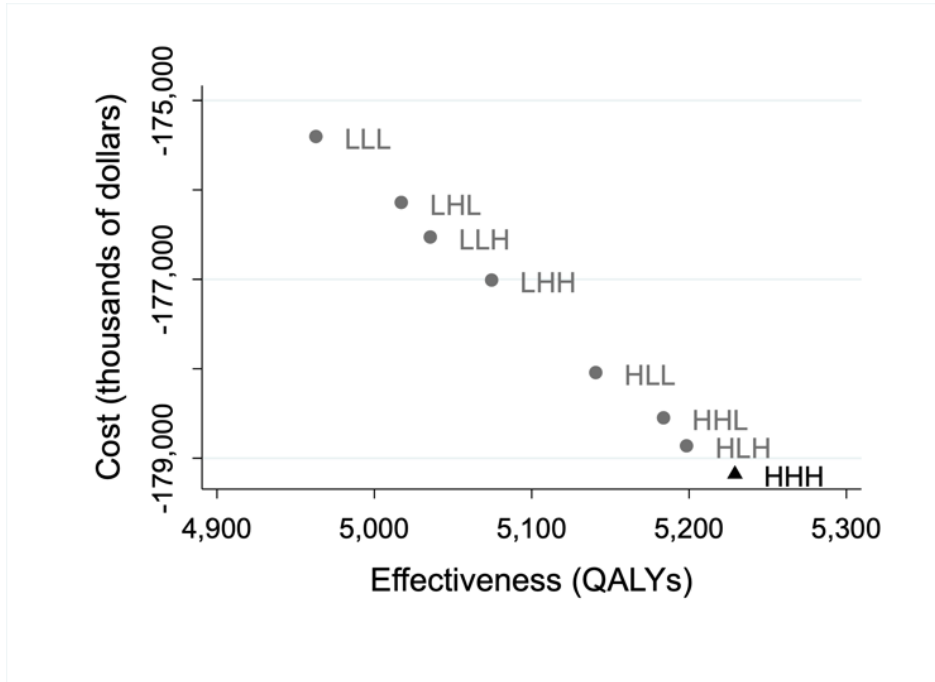
B.
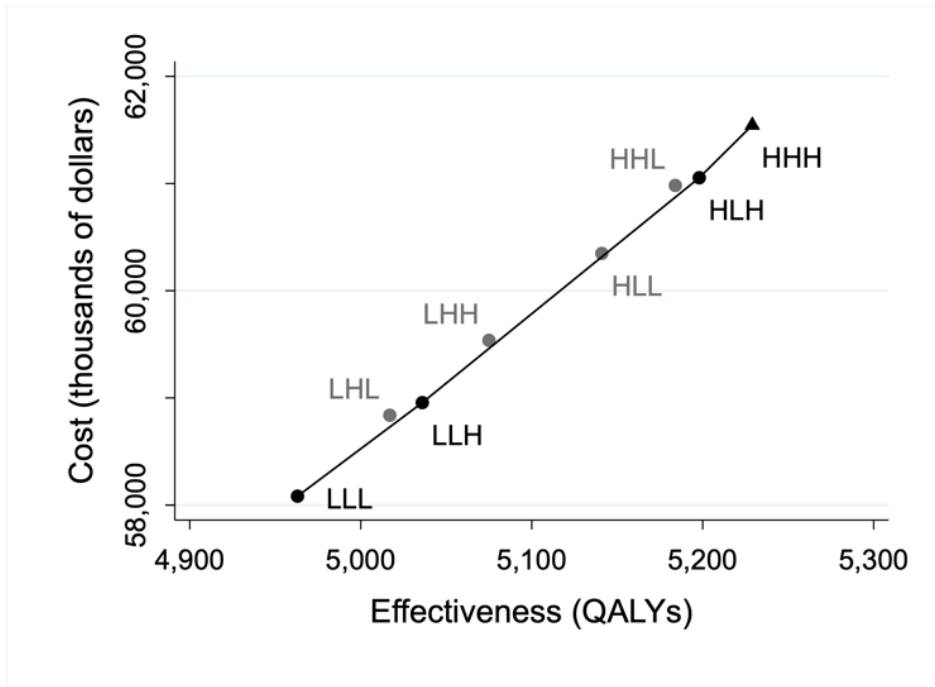
Note: Strategy labels are ordered as: layperson (high or low), police and fire (high or low), and EMS (high or low). Markers in gray indicate dominated strategies; markers in black and (in panel B) connected by the line indicate strategies that are not dominated. The triangle marker indicates the strategy that maximizes net monetary benefit.

Figure 4-4. Cost-effectiveness acceptability curves
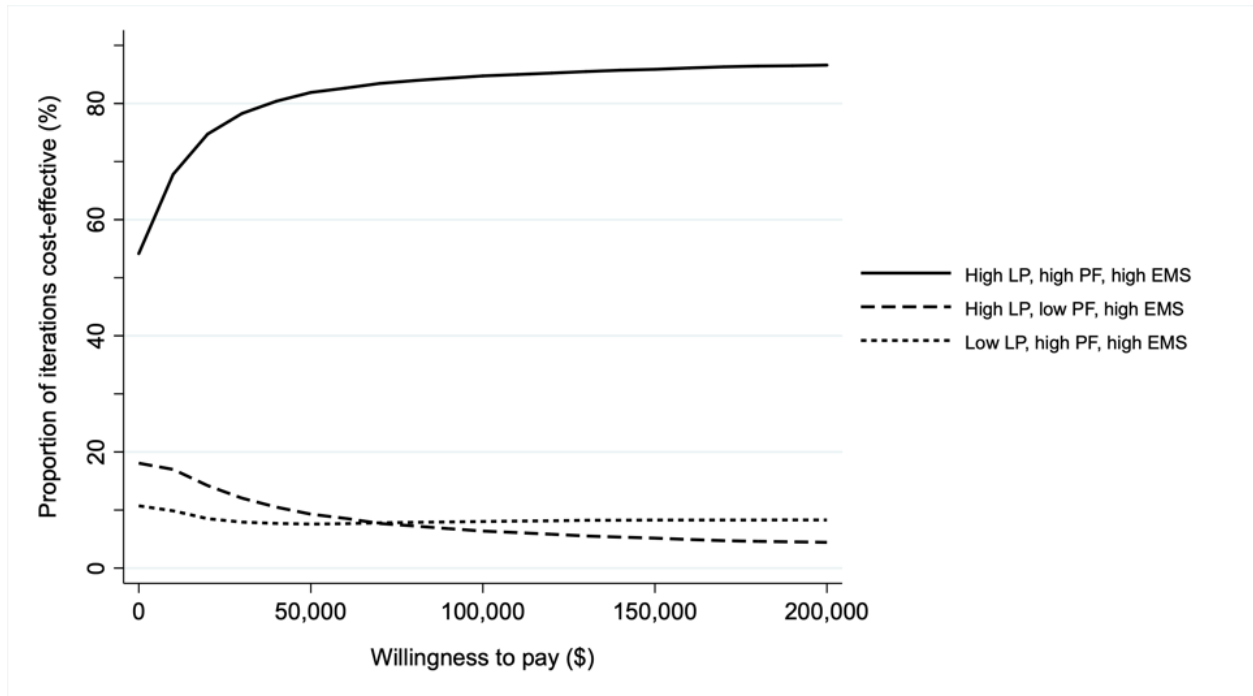
Chapter 5 – Conclusion

INTRODUCTION

This dissertation addressed two contemporary challenges in population health: (1) stagnation of

the downward trends in disability prevalence, combined with growing disparities in disability;

and (2) the opioid overdose crisis, which led to the deaths of 48,000 people in 2017 and

contributed to a 0.28 year decline in life expectancy between 2000 and 2015 (Dowell et al.,

2017; Scholl et al., 2018). In Paper 1, I used data from the nationally representative Panel Study

of Income Dynamics to better characterize the mechanisms underlying educational disparities in

difficulty with everyday life activities. Papers 2 and 3 centered on two elements of the 21st

century opioid crisis: racial disparities in opioid prescribing amid efforts to reduce unsafe

prescribing (Paper 2) and the allocation of scarce resources to equip laypeople and first

responders with naloxone, in order to ensure the greatest benefits to population health (Paper 3).

PAPER 1 - EDUCATIONAL DISPARITIES IN DISABILITY

This study estimated the population-level contributions of three key mediators of educational

disparities in incident difficulty with ADLs and IADLs among both younger and older women

and men. I took advantage of seven waves of nationally representative, longitudinal data on ADL

and IADLs, combined with information on life course factors including childhood

socioeconomic circumstances, earlier-life BMI, and occupational history. Educational disparities

in incidence of ADL/IADL difficulty were evident among both younger and older adults (under

65, 65 and over) and larger in women. Together, excess BMI, smoking history, and manual labor involvement appeared to account for roughly 60-70% of disparities in disability incidence between the most and least educated under age 65. Among women aged 65 and over, these factors tended to account for nearly 40% of that disparity. Estimates in older men were more variable, but the models indicated an explanatory power of 20-60%.

In younger women, smoking and excess BMI appeared to be the main contributors to disparities, while in younger men smoking and manual labor appeared most important. In older women, excess BMI appeared to be the main contributor to disparities. Estimates for older men were noisy, but smoking appeared to be the main contributor to disparities; higher BMI appeared to suppress educational disparities, reflecting lower average BMI among the least compared to more educated older men.

What accounts for the disparities left unexplained in this study? The role of imperfectly measured and missed mediators

Body mass index (BMI)

By taking advantage of both earlier-life and lagged contemporaneous measures of excess BMI, I was able to improve on studies that use one-time BMI to examine relationships between excess BMI and health outcomes. For example, in studies on the association between one-time BMI and mortality or morbidity, reverse causation—in which underlying illness contributes to weight loss—may downwardly bias the estimated risk of excess BMI (Abdullah et al., 2011; Mehta, 2015).

Due to data limitations, however, my estimates of excess BMI's contribution to disparities in ADL/IADL incidence may still be downwardly biased, particularly for older adults. First, in men ages 60 and over, weight loss may begin to accelerate an average of nine years before death (with variation by ultimate cause of death) (Alley et al., 2010)—much longer than my one-wave lag of excess BMI is able to account for. To the extent that ADL/IADL difficulty is on the causal pathway between excess BMI and death—which I would expect for conditions like cardiovascular disease and diabetes—this could result in underestimation of excess BMI's contribution to ADL/IADL disparities.

In addition, while the 1986 BMI measure provides valuable earlier-in-life information, it occurs relatively late in life for some in my older age group, who ranged from age 65 to 93 years in 2003. Evidence suggests that accounting for BMI during midlife improves estimates of BMI's association with mortality in older adults (Adams & Mouw, 2006); in my data, however, 22% of older respondents were 60 years or older in 1986, while 8% were 65 or older. The 1986 indicator may thus be less informative for these respondents, who may be experiencing weight loss due to age or chronic disease, resulting in potential underestimates of excess BMI's contribution to disparities. Unfortunately, data limitations precluded use of an earlier-life BMI indicator that referred to the same age for all individuals.

Finally, a growing body of work suggests that BMI trajectories predict health risks over and above static BMI (Zheng et al., 2013), but I lacked sufficient observations to characterize trajectories for my sample. In an analysis of data from the Health and Retirement Study, Zheng

et al. (2013) showed that individuals with normal but either increasing or decreasing weight were at greater risk of mortality than individuals who were overweight at baseline and whose BMI remained stable (Zheng et al., 2013). If I were able to look specifically at the effect of rising BMI—but not that of being overweight but stable—I might attribute a greater proportion of ADL/IADL disparities to BMI.

Together, these limitations suggest that my estimates of excess (or rising) BMI's contribution to disparities may be conservative. As more waves of PSID and the corresponding BMI data become available, research using earlier-in-life BMI and/or trajectories will become more feasible.

Smoking

The time-varying, categorical measure of current and former smoking allows an estimate of the average effect of smoking versus not on ADL/IADL difficulty. However, limitations in this measure could lead to some bias in those estimates. By not accounting for intensity of smoking or years since the respondent last smoked, I may obtain less accurate estimates of smoking's contribution to the incidence of ADL/IADL difficulty than if I were to model number of cigarettes smoked and years since last smoked. Moreover, an analysis accounting for these factors would enable more nuanced comparisons of smoking's role in ADL/IADL difficulty by age-gender group, further elucidating the reasons for variation in smoking's role across groups. Future research could use existing PSID measures to address these questions.

Manual labor and occupation more broadly

Despite similarly sized educational disparities in both men and women at younger ages, manual labor only appeared to explain disparities in ADL/IADL difficulty in younger men. This may suggest that women and men coded as "laborers" or "operatives" conduct substantively distinct types of work, with differential consequences for disability. Alternatively, this difference could be a product of varying lengths of time conducting manual labor by gender, which for methodological reasons I was unable to account for. More research on the contribution of manual labor to disability by gender and throughout the life course is warranted.

A broader approach to the role of work in difficulty with everyday activities may also be merited. Involvement in manual labor, defined here as reporting one's main occupation as "laborer" or "operative", likely influences ADL and IADL difficulty via effects on occupational hazards, job control, earnings, and prestige (Caston, 1989; Hayward et al., 1989; Leigh & Fries, 1992). However, other types of occupation, such as clerical and service work, may also confer disadvantages due to one or more of these dimensions (Gallo et al., 2004; Marmot et al., 1997). As a result, a more comprehensive, more sociological assessment of occupation would likely reveal that work plays a larger role in educational disparities in ADL/IADL difficulty than manual labor appears to account for in this study. This would likely be especially true for women, who disproportionately perform low-status and low-paying work not captured by my measure of manual labor. Future research could better elucidate these pathways and their relative contributions to incident difficulty with ADLs and IADLs.

Management of frailty

Excess BMI, smoking, and manual labor involvement appeared to explain less of the ADL/IADL disparities in the older group than in the younger group. Biological frailty may help explain this gap. Increased frailty is a natural consequence of age; increased ADL/IADL difficulty is thus a part of the normal aging process. However, older Americans with more education and the resources it confers may be better able to manage this frailty, making its consequences less severe. For example, frailty increases the risk of falls, which can translate into more severe, persistent, and disruptive ADL/IADL difficulty; individuals with more financial and social resources may be better able to, e.g., modify their environment to reduce the risk of falling, and/or to obtain tools such as medical alert necklaces to reduce a fall's consequences. For future research to account for ability to manage frailty as a mediator of the education-disability relationship, data on older individuals' access to and use of various management strategies would be needed. I am not aware of nationally representative studies that collect such data in detail, but smaller datasets may exist and be appropriate.

Pathways between educational attainment and the mediators

Educational attainment shapes excess BMI, smoking, and manual labor via myriad pathways, including adult income, neighborhood and social network contexts, marital selection, access to preventive services, and numerous others. The regression models in this study did not include variables on the causal pathway between education and the mediators, since our objective was to estimate the "total effect"—rather than the "controlled direct effect"—of the mediators on disability incidence. If controlled for, variables underlying the education-mediator relationship would "absorb" some of the total effect of the mediators. For example, health literacy is one plausible pathway through which educational attainment relates to smoking behavior. If I

included health literacy in the regression models, the estimated association between smoking

incident ADL/IADL difficulty would reflect only that portion of the education-smoking

relationship that is not influenced by health literacy. The goal here is not to delineate the

pathways linking education to the mediators—or, for similar reasons, the pathways linking the

mediators to disability—but rather to capture smoking's total effect on the education-disability

relationship.

Interactions between educational attainment and the mediators

The regression models assumed independence between education and the mediators, but

interactions could exist, such that the association between each mediator and incident

ADL/IADL difficulty varies by educational attainment. For example, excess BMI may be more

likely to contribute to ADL/IADL difficulty among people with less education, e.g., due to

higher risk of developing and fewer resources for managing health conditions such as diabetes,

cardiovascular disease, and arthritis. Alternatively, intensity of current and former smoking may

vary by educational status, such that these indicators are more strongly associated with incident

ADL/IADL difficulty in less educated groups.

I tested the assumption of independence by assessing whether additive interactions between

educational attainment and each mediator existed in each regression model. In a logistic

regression, additive interactions are more straightforward to calculate than multiplicative

interactions because the coefficient on the interaction term is not equal to the actual

multiplicative interaction effect (Ai & Norton, 2003; Norton et al., 2004). In addition, and unlike

multiplicative interactions, additive interactions are useful in that they provide direct insight into the proportion of people who could benefit from an intervention in one group versus another.

In the present analysis, I found no evidence of varying effects of excess BMI or manual labor on incidence across educational groups. However, the association between smoking and incident ADL/IADL difficulty appeared to be larger in people with less than a high school degree compared to those with a college degree. These results suggest that, in women, interventions that reduce smoking could reduce the risk of ADL/IADL difficulty in a larger proportion of people if they targeted those with less education. Future research could help to explain these results. Women with less education may smoke more cigarettes per day, may have less access to cessation resources and thus smoke for a greater duration, and/or may have less access to resources for mitigating the effects of smoking on their health. There was also an apparent interaction between education and smoking in older men, in which current smoking was more strongly associated with incidence in those with a high school degree compared to those without one. However, the estimated interaction effect was imprecise, and additional research would be needed to confirm this finding.

Because the main regression models do not include an interaction between educational attainment and smoking history, the estimated proportions of educational disparities attributable to smoking may be biased. Given that, in women, smoking appeared more associated with ADL/IADL difficulty in the least compared to the most educated group, the true contribution of being a current or former smoker in disparities is likely larger than estimated. In older men, the

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reverse could be true. However, imprecise estimates of both the interaction and disparities make conclusions more difficult to draw for this group.

Population-level research on conditions linking the mediators and incident disability is needed, but the requisite longitudinal, nationally representative data are lacking

Despite robust evidence that excess BMI, smoking, and manual labor involvement contribute to disability via conditions such as diabetes, osteoarthritis, cardiovascular disease, respiratory diseases, and musculoskeletal injury (Altarac, 2000; Leigh & Fries, 1992; Murray & Lopez, 1997; Samper-Ternent & Al Snih, 2012), it is unclear what proportion of those relationships can be attributed to each of these conditions at the population level. Elucidation of their relative contributions to disability and to disparities in disability would aid the targeting of downstream efforts to alleviate disability in the U.S. population. While upstream work—improving access to quality education; blocking the pathways from education to excess BMI, smoking, and manual labor; and targeting those mediators of the education-disability relationship when they do occur—is crucial, an understanding of the most prominent disease pathways between these mediators and disability would also allow for valuable interventions to prevent the incidence of disability.

PSID would be better able to support this research if additional information about the cause of ADL and IADL difficulty were collected. For example, the National Health Interview Survey (NHIS), a repeated cross-sectional survey that is also nationally representative, asks which health conditions have caused any ADL or IADL difficulty that a respondent has reported. PSID does ask, "Have you ever been told by a doctor that you have—" regarding an array of conditions, but

these measures have important limitations for the present purposes: (1) the potential for temporal mismatch with the ADL/IADL difficulty of interest (e.g., the respondent had a given condition but no longer does, and the condition did not contribute to the present difficulty), and (2) the possibility, likely unequally distributed across education groups, that the respondent would be able to report a reason for their difficulty if asked (e.g., a back or neck problem, arthritis, or a breathing problem) but has not received a formal diagnosis. Indeed, when I used these PSID indicators to conduct a preliminary mediation analysis of the relationships between (a) excess BMI, smoking, and manual labor and (b) ADL/IADL difficulty, the results were quite noisy and thus challenging to interpret.

Policy and program implications will depend on whether the ADL/IADL difficulty reflects a met or an unmet need

Researchers often use difficulty with ADLs and IADLs as a measure of disability in a population (Iezzoni et al., 2014; LaPlante, 2010; Martin & Schoeni, 2014; Palmer & Harley, 2012; Samper-Ternent & Al Snih, 2012). In PSID, respondents are asked about any difficulty conducting a given activity on one's own and without special equipment. However, the consequences of such a difficulty—and in turn the policy and program implications—are a product not only of a person's physical status, but also of the physical and social environments in which they are embedded (Clarke & Nieuwenhuijsen, 2009; Reindal, 2008). In some circumstances, the activity of interest may be conducted by another person, or special equipment may be available, thereby rendering the ADL/IADL difficulty less disruptive. Because PSID does not evaluate whether these needs are met, the extent to which my findings reflect disparities in *disability*—rather than disparities in physical status—is unknown.

However, the frequency with which ADL/IADL needs are met is likely patterned by educational attainment: I would expect education to select into a range of resources that influence once's access to adaptive technologies, social capital, and professional aid—in turn determining the disruptiveness of their ADL/IADL difficulty. If ADL/IADL difficulty more frequently translates into unmet needs among less educated individuals than among their more educated counterparts, then the consequences of disparities in ADL/IADL difficulty would actually be understated by my study's conclusions. Future research should both test this hypothesis and evaluate the everyday life needs that are most frequently unmet in less-educated groups. Policies and programs to address these gaps, with emphasis on the most socially disadvantaged, are needed.

Policy and program implications will depend on the extent to which the proximal causes identified are replaced by alternatives

This study serves an important descriptive function, helping to elucidate the pathways by which educational disparities in ADL/IADL difficulty manifest, as well as how these vary in influence by age-gender group. It also offers some prescriptive conclusions, suggesting that resources aiming to reduce educational disparities in ADL/IADL difficulty may be best targeted towards disparities in: excess BMI and (less so) smoking in younger women; manual labor and smoking in younger men; and excess BMI in older women. While estimates in older men were more variable, smoking seemed to be the main contributor to disparities; because former but not current smoking was associated with ADL/IADL difficulty in this group, interventions would likely be needed earlier in life. Although society is often wont to view health problems through a biomedical lens, efforts to reduce disparities in these groups should not be limited to the health

care system. Upstream interventions, such as evidence-based programs to improve nutrition and exercise, workplace smoking policies, and efforts to alleviate occupational hazards are needed.

However, the potential for such interventions to meaningfully and lastingly reduce disparities in ADL/IADL difficulty would depend on the extent to which the persistent educational gradient in American society—which would not be affected by interventions on the above mediators— would spawn new pathways to disability-related outcomes as the broader context of risk factors, treatment availability, and disease patterning evolve (Link & Phelan, 1995). That is, targeting more proximal causes of disparities will not eliminate those disparities if education's consequences for health are transportable to new circumstances and thus manifest via alternative pathways. As a result, broad-based efforts to alleviate the educational gradient in American society are key to addressing population-level health disparities.

PAPER 2 - DISPARITIES IN OPIOID PRESCRIBING

This study was the first, to my knowledge, to examine the association of release of the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain with subsequent overall and high-risk opioid prescribing in the population it targeted: people with chronic, non-cancer pain. In addition, it is the first to assess whether these associations varied by patient race/ethnicity, and if so whether this contributed to a widening or narrowing of racial/ethnic disparities in opioid prescribing for chronic pain. I found evidence that, in osteoarthritis and fibromyalgia patients, the guideline was associated with a gradual decline in the percentage of patients receiving opioids each month and, among those who received opioids, with a decline in average daily dose and the percentage of patients receiving a high dose (more than 90 morphine milligram

equivalents, or MME). These findings, particularly the decline in average daily dose among those prescribed opioids, suggest that clinical guidelines in which compliance is entirely voluntary may result in clinically significant shifts in prescribing behavior. At the same time, the relatively small decrease in percent receiving at least one opioid fill per month may help to allay concerns that the guideline led to widespread inappropriate discontinuation of pain management among chronic pain patients in need (Rothstein, 2017).

In both osteoarthritis and fibromyalgia, associations with the guideline were consistently detectable in white patients at an alpha of 0.05, while associations were less consistent in black and Hispanic patients. However, lack of statistical significance corresponding to other outcomes may have primarily been due to insufficient power: point estimates suggested that black and Hispanic patients were generally estimated to experience the same or larger declines as white patients. And while these differences were never statistically significant either, point estimates of racial/ethnic disparities with and absent the guideline suggest it may have contributed to a widening of black/white and Hispanic/white disparities in prescribing. There was little evidence to suggest a narrowing of disparities due to the guideline, potentially suggesting that, despite providing clinicians a framework for deciding when to prescribe opioids and in what dose, the CDC guideline did not diminish racial/ethnic disparities in prescribing. That is, my findings do not appear to support the hypothesis that the guideline reduced clinical uncertainty and, in turn, the tendency to use racial/ethnic stereotypes or bias to inform prescribing decisions. Instead, the guideline may have affected white, black, and Hispanic pain patients similarly; or it may have disproportionately affected patients of color, and particularly Hispanic patients. The latter scenario could result from an increase in clinical uncertainty due to the guideline, in which the

recommendations' encouragement that providers use personal judgment to determine each patient's prescribing needs led to increased reliance on stereotypes and bias.

Limitations of Optum's race/ethnicity measure

Optum data offer many strengths for the analysis of opioid prescribing for chronic pain, including diagnosis, prescription fill, and sociodemographic data for a large swath of Americans in all 50 states. For comparison, another leading provider of commercial claims data, Truven Health Analytics, does not provide information on patient race/ethnicity or socioeconomic status. However, a key disadvantage of Optum data is the high and unexplained rate of missingness on the race/ethnicity variable, which is central to the present analysis. In the osteoarthritis and fibromyalgia cohorts studied, race/ethnicity data were missing for 22% and 26% of observations, respectively, resulting in their exclusion from the analytic sample. Optum reports that their sociodemographic data are obtained via a combination of strategies, including reporting by the patient at the point of care, imputation using the Census, and internal imputation based on other information such as name and geographic data. However, the respective proportions of race/ethnicity obtained via each of these methods are not available.

In the present study, race/ethnicity missingness poses several challenges: it reduces the size of the analytic sample, contributing to statistical power constraints, and, by limiting the population analyzed, it may result in biased estimates. As Table 5-12 shows, individuals with incomplete race/ethnicity data were more likely to have received a mental health diagnosis and tended to have more comorbidities and pain-related visits; they also tended to experience higher rates of overall and high-risk opioid prescribing. The consequences of this missingness for the study

results are difficult to predict. If, for example, race/ethnicity missingness were more common in black compared to white patients, then my estimates could overestimate black/white disparities in prescribing. But if the differences in opioid prescribing between individuals with and without missing data were fully explained by differences in the other covariates—e.g., rates of mental health diagnosis, numbers of comorbidities, and frequency of visits—then my estimates may be correct even if the "missing" individuals were disproportionately black. Improvements in data completeness and transparency in the mechanisms for obtaining these data would enable more robust future research.

Future directions for understanding racial/ethnic disparities in management of chronic pain

Collapsing cohorts to improve clarity of trends in disparities

The present study offered useful preliminary insight into potential consequences of the 2016 guideline for racial/ethnic disparities in opioid prescribing. Next, prior to submission for publication, I will take additional steps to increase statistical power and, in turn, to provide more precise estimates of disparities in the "guideline" and "no guideline" scenarios. I will collapse osteoarthritis and fibromyalgia patients into a single cohort and will add two additional pain-related conditions: back and neck pain and chronic headache. Mirroring osteoarthritis and fibromyalgia, respectively, prescription opioids have been considered indicated for back and neck pain under some circumstances, whereas they are categorically not recommended for management of chronic headaches (Eccleston et al., 2017). Therefore, in addition to pooled analysis of the four conditions, I will also disaggregate analysis into (1) osteoarthritis and back and neck pain, and (2) fibromyalgia and chronic headache—allowing clearer investigation of the

hypothesis that the guideline would more strongly influence opioid prescribing for the latter group of conditions.

Are the observed racial/ethnic disparities in opioid prescribing offset or amplified by disparate rates of non-opioid pain management?

In this study, I was unable to examine whether chronic pain patients not receiving opioids received alternative forms of pain management—for example, lower-risk analgesics such as acetaminophen, physical therapy, or cognitive behavioral therapy. However, a meta-analysis found that black pain patients were less likely than white patients to receive *any* analgesic, while no difference between Hispanic and white patients was detected (Meghani et al., 2012). That is, black/white disparities in opioid prescribing likely reflect disparities in medication-based pain management overall. In addition, given limited access to mental health services in black and Hispanic populations, disparities in non-medication based therapies that may aid in pain management likely exacerbate rather than offset disparities in opioid prescribing (Eccleston et al., 2017; Ojeda & McGuire, 2006). Research quantifying access to a more comprehensive range of pain management techniques by race/ethnicity, as well as trends in the use of non-opioid management following growing concern about the risks of opioid prescribing, would paint a more complete picture of racial/ethnic disparities in pain management and their evolution amid the opioid crisis.

Policies to reduce unsafe opioid prescribing and discontinuation of opioid therapy

There is concern that, in the wake of efforts to address unsafe opioid prescribing—such as implementation of prescription drug management programs and release of the 2016 CDC

guideline—pain patients may have increasingly experienced abrupt discontinuation of opioid

therapy, which may in turn increase non-medical opioid use, overdose rates, and suicidal ideation

(Dowell et al., 2019; Kroenke et al., 2019; Rothstein, 2017). In an extension to the present work,

I plan to assess trends in opioid discontinuation among chronic pain patients, overall and by

race/ethnicity, before and after release of the CDC guideline—and, if discontinuation increased

following the guideline, to examine associations with rates of overdose and suicide.

A better understanding of changing trajectories of OUD and mortality by race/ethnicity is needed

The narrative surrounding the 21st century opioid crisis has tended to emphasize opioid-related

morbidity and mortality in white, and particularly rural and/or less educated white, Americans.

For example, Case and Deaton reported that, between 1999 and 2013, all-cause mortality increased

for the first time in a subset of the US population, less educated white Americans ages 45-54 years

(Case & Deaton, 2015), which the authors attribute in part to increases in drug and alcohol poisoning.

Indeed, opioid-related mortality rates have been persistently lower in black and Hispanic compared

to white Americans in recent decades (Alexander et al., 2018; Kaiser Family Foundation, 2019).

However, opioid-related mortality began to increase more sharply among non-Hispanic black and

Hispanic patients around 2013—coinciding with the sharp increase of illicitly manufactured fentanyl

in the opioid supply (Alexander et al., 2018; Kaiser Family Foundation, 2019). Moreover, while

opioid-related mortality among whites decreased between 2017 and 2018, it continued to increase in

Hispanic and non-Hispanic black Americans (Wilson et al., 2020). These differences appear to have

been driven by a decrease in prescription opioid and heroin-related overdose in white but not black

and Hispanic individuals, while increases in deaths from synthetic opioids such as fentanyl continued to increase in all three groups.

Relatively little work has aimed to explain these shifting trends by race/ethnicity, or to anticipate how race/ethnicity-specific morbidity and mortality related to opioids and other substances may evolve in coming years. One important step is to continue disaggregating policy and program effects by race/ethnicity. For example, while Good Samaritan Laws have shown promise in reducing opioid-related mortality (Rees et al., 2017), it is not clear whether their effects are consistent across racial/ethnic groups. Black and Hispanic populations may benefit less from such policies, for instance, if they are more reticent than their white counterparts to call 911 and if, when they do, law enforcement officers are less likely to adhere to the laws' requirements. A key goal of my future work will be to help alleviate these gaps in the literature.

How prevalent is opioid prescribing for cancer pain, and has this changed amid rising concern about the risks of opioid prescribing?

People living with cancer experience high rates of chronic pain, even in early and intermediate stages and following completion of active treatment (Glare et al., 2014; C. R. Green et al., 2011; van den Beuken-van Everdingen et al., 2016). Opioids have historically been used to treat many forms of cancer-related pain, and national guidelines on opioid prescribing often exclude cancer patients from their recommendations (Brown & Farquhar-Smith, 2017). Still, adverse consequences such as side effects and risk of dependency remain sources of concern in opioid prescribing for cancer-related pain (Brown & Farquhar-Smith, 2017), and the quality of evidence on opioids' effectiveness for reducing pain and improving function in these patients remains low (Wiffen et al., 2017). Little research has examined the prevalence of opioid prescribing in cancer

patients. In subsequent research, I plan to use Optum data to obtain national estimates of opioid prescribing rates overall and by cancer stage (proxied, e.g., by proximity to death) and type. More in-depth analyses I would like to conduct in this national sample of cancer patients include: trends in prescribing over time and whether these mirrored national trends for non-cancer patients, whether the 2016 CDC guideline appears to have influenced prescribing in cancer patients despite excluding this population from its recommendations, associations of opioid prescribing with incidence of diagnosed opioid use disorder and overdose, and disparities in prescribing by race/ethnicity and socioeconomic status.

PAPER 3 - NALOXONE DISTRIBUTION

Chapter 3, a cost-effectiveness analysis comparing naloxone distribution to three target groups—laypeople likely to witness or experience overdose, police and fire, and emergency medical services (EMS)—found that increasing access to naloxone access reduces morbidity due to insufficient brain oxygenation and costs society little. Yet naloxone access remains insufficient. My findings support increased naloxone distribution to laypeople likely to experience or witness overdose, police and fire, and EMS. Increased distribution to and use by EMS could be achieved by, for example, authorizing naloxone administration by basic life support personnel in states that currently prohibit it. When resource constraints limit a community's ability to increase distribution to all three groups, distribution to laypeople and EMS should be prioritized.

How do we achieve the level of naloxone access this study suggests is needed?

While evidence shows that naloxone reduces mortality at a low or even negative cost to society, and while observational studies have demonstrated the potential for community-based programs

and naloxone access laws to achieve these benefits through provision of naloxone kits and training to people who use opioids (Bird et al., 2016; Coffin & Sullivan, 2013a; McClellan et al., 2018; Alexander Y Walley et al., 2013), a more comprehensive understanding of the effectiveness of and barriers surrounding efforts to improve naloxone access is needed.

Numerous policy options for increasing naloxone availability and use exist, and they vary in strength and scope. For example, most states have enacted standing orders that allow pharmacists to dispense naloxone to individuals without a prescription, and most states allow for third-party prescribing—i.e., prescribing of naloxone to someone close to the person at risk of overdose (C. Davis & Carr, 2017). At least forty states have enacted "Good Samaritan laws" that provide legal immunity to individuals who seek medical attention at an overdose event (National Conference of State Legislatures, 2017). Several states have passed mandates that opioid prescribers co-prescribe naloxone to patients deemed at risk of overdose (Sohn et al., 2019), and many states authorize law enforcement officers to administer naloxone and to distribute additional kits following overdose (C. S. Davis et al., 2015; C. S. Davis, Ruiz, et al., 2014). There is some evidence that such policies do improve naloxone access. For example, a recent study found a nearly eight-fold increase in the rate of naloxone prescribing per 100,000 population following the passage of co-prescribing mandates in West Virginia and Vermont (Sohn et al., 2019). And Rees, Sabia, Argys, et al. (2017) found that laws authorizing laypeople and first responders to carry and administer naloxone result in a 9-11% reduction in opioid-related mortality, with no evidence of concomitant moral hazard (Rees et al., 2017).

However, each of these policies may entail a distinct set of barriers to widespread and effective implementation, including problems of awareness, funding, personal beliefs, and others. For example, despite naloxone access laws, pharmacies often fail to stock naloxone, and pharmacists may refuse to dispense it due to lack of awareness of third-party prescribing policies or beliefs about inducing moral hazard (Meyerson et al., 2018; Puzantian & Gasper, 2018). In addition, some research has found a large proportion of law enforcement personnel to be unfamiliar with naloxone access laws in their state and at risk of confiscating the life-saving medication (Banta-Green et al., 2013). Relatedly, a 2017 survey of prescribers in regional health care systems in North Dakota, Minnesota, and Wisconsin found that the majority had never prescribed naloxone for overdose prevention, and reported evidence that this was in part due to lack of awareness of the relevant state policies (Okoro et al., 2018). And years after West Virginia passed a law authorizing law enforcement to carry naloxone, a 2018 study found that less than 2% of police departments actually do so (Lurigio et al., 2018).

In order to ensure that naloxone's potential to reduce mortality and extend opportunity for recovery is realized, a more thorough mapping of these policies and programs to their consequences is needed. However, rigorous evaluations can be difficult to conduct amid a preponderance of observational data.

Naloxone access must be combined with evidence-based treatment for opioid use disorder
By reversing opioid-related overdose, naloxone provides people who use opioids additional opportunity to receive treatment for opioid use disorder, with potential to substantially extend life and improve quality of life. For this potential to be realized, however, access to evidence-

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based treatment for opioid use disorder is crucial. Evidence is clear that, compared to inpatient detoxification or residential services, intensive and non-intensive behavioral health, and treatment with the opioid antagonist naltrexone, methadone and buprenorphine treatment effectively reduce opioid-related overdose and serious acute care use (Wakeman et al., 2020).

Yet access to medication for opioid use disorder remains low. In 2016, only 36% of all substance use treatment facilities offered at least one of buprenorphine, methadone, or naltrexone (naltrexone requires opioid detoxification before treatment can be initiated, rendering it less effective than its opioid agonist counterparts) (Mojtabai et al., 2019). Access is particularly limited in rural communities, which have been hit particularly hard by opioid addiction and overdose. For example, 30% of rural Americans live in a county without a licensed buprenorphine provider, compared to just 2% of urban Americans (Andrilla et al., 2019). Numerous barriers also limit access to methadone: required daily clinic visits, inadequate insurance coverage, and clinics that are limited in geographic distribution—and which, where they do exist, may be at or near capacity (Jones et al., 2015).

Urgent action is required to improve access to evidence-based treatment for people with opioid use disorder, including those for whom naloxone reversed an otherwise fatal overdose. A recent report by the National Academies of Sciences, Engineering, and Medicine recommended an array of policies in this vein, including amending the Controlled Substances Act to allow methadone prescribing in primary care settings and to eliminate the excessive provider training requirements and patient caps that constrain buprenorphine prescribing (National Academies of Sciences, Engineering, and Medicine, 2020). Other recommendations included broadening

access to telemedicine for treatment of opioid use disorder, particularly in rural areas, and making federal funding available to address upstream housing and transportation needs among individuals with co-occurring opioid use disorder and infectious disease—factors that, among other things, may improve access and adherence to treatment (National Academies of Sciences, Engineering, and Medicine, 2020).

Naloxone access and moral hazard: A review of the evidence

Some worry that lay naloxone distribution provides an overdose safety net, leading individuals to use opioids more intensively and overdose more frequently (T. C. Green et al., 2013; Seelye, 2017). The present cost-effectiveness analysis found that, if this "moral hazard" effect were to occur, it would have to cause the overdose rate to increase by at least 20% in order for high levels of lay distribution to no longer be a component of the preferred strategy—that is, the strategy that allocates scarce resources for maximum health benefit.

Moreover, the bulk of the relevant literature is unable to detect a moral hazard effect at the population level. While rigorous large-scale evaluations of naloxone access laws and naloxone provision more broadly are rare and needed, a systematic review of 22 observational studies found no evidence that take-home (i.e., layperson) naloxone programs increased heroin use (McDonald & Strang, 2016). Two more recent studies have supported this conclusion. Using data from the National Vital Statistics System and the National Survey on Drug Use and Health, McClellan et al. (2018) employed a staggered difference-in-differences design with state random effects to examine associations between naloxone access laws and (a) opioid-related overdose deaths and (b) nonmedical opioid use (McClellan et al., 2018). The authors report a 14%

decrease in opioid-related mortality but no evidence of an effect on nonmedical opioid use. Rees and colleagues (2017) took a similar approach using the same data and found a 9-11% decrease in opioid-related mortality following the passage of a naloxone access law but, again, no evidence of change in nonmedical use. Some research suggests a decline in opioid use following naloxone training, perhaps due to increased motivation to or awareness of how to seek treatment (McDonald & Strang, 2016; Seal et al., 2005).

One study, which has received considerable media attention, reported conflicting findings. A 2018 working paper reported that naloxone access laws resulted in increased opioid-related emergency department visits and crime while failing to reduce mortality (Doleac & Mukherjee, 2018). The authors' methods have been critiqued by others in the field (Frank et al., 2018). The study is at risk of confounding, for instance, by sharp, concurrent increases in fentanyl-related mortality in states that expanded naloxone access laws. In addition, and in contrast with Rees et al. (2017), the authors used a single treatment variable to examine the association between any of several naloxone access laws and Good Samaritan laws (GSLs) and their main outcome variables (opioid-related emergency visits, opioid-related mortality, and opioid-related theft). Doleac and Mukherjee were thus unable to disentangle the effects of each policy, which may vary in strength. Indeed, Rees et al. (2017) found variation in the magnitude and precision of effect estimates across types of policy (Rees et al., 2017). Naloxone ends a high and induces sudden withdrawal symptoms, outcomes that people who use opioids generally want to avoid. There may be individuals who increase opioid use given access to naloxone, but the preponderance of evidence suggests that, at the population level, such effects on either use or mortality are not detectable.

Appendices

Appendix A. Supplementary Material for Chapter 2 (Educational Disparities)

Appendix A-1. Panel Study of Income Dynamics

The Panel Study of Income Dynamics (PSID) is the world's longest-running household panel survey and collects data on myriad social, behavioral, and health indicators. It was initiated in 1968 with a nationally representative sample of over 18,000 individuals (5,000 households) and an oversample of low-income families. PSID followed core sample members and their decedents annually until 1997 and then biennially thereafter. Response rates in PSID have equaled or exceeded response rates in other panel studies globally (McGonagle et al., 2012). More details are provided in the PSID User Manual (Institute for Social Research, 2019).

Appendix A-2. Defining disability incidence

An individual was defined as experiencing incident disability in wave t if they reported disability in that wave and had been at risk for disability in the prior wave ("t-1"). Individuals were considered at risk if they reported no difficulty on any ADL/IADL in wave t-1; were in the panel during waves t-1 and t; and had no missing ADL/IADL data in either wave. When an individual indicated that they "did not do" a given ADL or IADL, they were considered to have no difficulty rather than be missing on this indicator.

I assumed that an individual reporting an ADL/IADL disability in two consecutive waves experienced that disability throughout the two-year period. I also assumed a uniform distribution

of changes in disability status and treated any switch as occurring at the midpoint of the adjacent waves.

The modelling strategy accounted for the possibility that an individual experience more than one incident disability event. I used this approach for two reasons. First, given fluctuation in disability status throughout the life course, I wanted to capture both new and subsequent disability events. Second, since PSID began asking about ADLs and IADLs in 2003, I could not observe difficulty with ADLs/IADLs before 2003. This left truncation precluded assumptions that any observed incidence represented "first incidence".

Appendix A-3. BMI measures

Contemporaneous and 1986 BMI were left-truncated at 25, such that only excess BMI contributed to the models (Mehta et al., 2014; Preston et al., 2013). This decision was based on the finding that, when running the main model with BMI splines, BMI values of 25-30 and 30+ contributed to disability risk.

Appendix A-4. Construction of manual labor variable

This variable was fixed rather than time-varying to minimize the risk of confounding by a common cause like illness. The measure was based on PSID's "main occupation" variable, which was categorized using three-digit occupation codes from the 1970 Census of Population. From this taxonomy, I considered the following three groups manual laborers: "operatives, except transport"; "laborers, except farm"; and "farm laborers and farm foremen" (Cutler & Lleras-Muney, 2010; Leigh & Fries, 1992).

Occupation information was available for all PSID household heads and spouses between 1982 and 2001. In addition, roughly 65% of the PSID sample provided retrospective occupation information for 1968-1980. To enable use of occupation data for 1968-1980 without excluding those who had not reported retrospectively, I coded participants as "1" if they had ever participated in manual labor, and "0" if they had never reported participating in manual labor— even if occupation information was missing in some years. Excluding those who were ever missing occupation data resulted in too small a sample for analysis.

The health consequences of agricultural and non-agricultural labor may vary. In this dataset, 76% percent of manual labor observations corresponded to "operatives" (N=4,377); 4% corresponded to "farm laborers and farm foremen" (N=252), and 20% to "laborers" (N=1,135). To preliminarily assess differences in the implications of each type of manual labor for disability incidence in young men—the group in which I observed the clearest association between manual labor and disability—I constructed indicators of ever having participated in each type and included them in the regression model instead of the grouped indicator of manual labor participation. While all estimated odds ratios were greater than one, estimates on "ever laborer" and "ever farmer" were noisy, likely due to limited power (ever operative: OR=1.434, 95% CI: 1.017-2.021; ever laborer: OR=1.035, 95% CI: 0.702-1.526; ever farmer: OR=1.807, 95% CI: 0.873-3.739). Although the estimated odds ratio for ever laborer appears potentially smaller than that for the other types of manual labor, an adjusted Wald test of equality unable to reject the null hypothesis of equality among the three coefficients (p=0.329).

Appendix A-5. Additional detail on model covariates and missingness

In the main analysis, respondents with some college, technical training, and associate's degrees were grouped with those who obtained only a high school degree. However, there is evidence that these individuals experience a distinct set of health outcomes from high school graduates (Rogers et al., 2010; Zajacova et al., 2012; Zajacova & Lawrence, 2018). To examine whether they differ in risk of disability incidence, I conducted a regression in which these groups were separated (high school degree only; some college, technical training, or associate's degree) and conducted a Wald test of a difference between the corresponding coefficients. In each of the younger groups and in older men, I was unable to reject the null hypothesis that they were equivalent (younger women: F=0.43, p=0.514; younger men: F=0.35, p=0.554; older men: F=0.02, p=0.896). In older women, however, there was a potential difference in (a) the association between obtaining a high school degree and disability (OR=0.823, 95% CI=0.493-1.375, compared to no high school degree) and (b) the association between completing additional education, but not college, and disability (OR=0.577, 95% CI=0.324-1.027, compared to no high school degree) (F=3.18, p=0.075). Despite this potential difference in one of the age-gender groups, I maintained the three-category variable for several key reasons: (1) concerns about insufficient power, particularly in the older age group; (2) additional complexity of calculating disparities among all combinations of four rather than three educational groups; and (3) preliminary evidence that the differences in health outcomes by group do not operate through obesity or smoking (to my knowledge, manual labor has not been examined; Zajacova et al. 2012).

Age was calculated using birthdate and date of interview. I combined Hispanic and non-Hispanic black participants into one category due to evidence that health tends to be poorer among Hispanic black individuals compared to Hispanic non-black individuals (Chinn & Hummer, 2016; Elo et al., 2011).

Conservative imputation was conducted to reduce missingness. Missing values of model predictors were imputed if sandwiched between two waves of identical values. In addition, I used PSID's continuous "years of education" variable to reduce missingness in the education variable (0.5% of analytic sample observations; n=60). Fewer than 12 years of education was coded as "less than high school", 12-14 years as "high school degree", and 16 or more years as "college degree". A report of 15 years of education was not used for imputation, since it could result from not completing college or from completing college in three years. Finally, remaining missingness on covariates that were unlikely to change values between waves—childhood SES, race/ethnicity, and educational attainment—was imputed using available data from previous (and then subsequent) waves if available. There was no missingness on age, gender, or year.

Appendix A-6. Regression model

Equation 1 details the regression model, which was conducted separately for each age group; **X** is a vector of covariates (age, gender, childhood socioeconomic circumstances, race/ethnicity, and year).

$$\log\left(\frac{p_{it}}{1-p_{it}}\right) = \beta_0 + \beta_1 Age_{it-1} + \beta_3 Female + \beta_4 1986BMI_i + \beta_5 BMI_{it-1} + \beta_6 Current_{it-1}$$

$$+ \beta_7 Former_{it-1} + \beta_8 EverManual_i + \sum_{j=1}^{2} \beta_{9j} Education_{ij} + \sum_{k=1}^{3} \beta_{10k} Race/Ethn_{ik}$$

$$+ \sum_{m=1}^{2} \beta_{11k} ChildSES_{im} + \sum_{t=2}^{7} \beta_{12} Year_{it-1}$$

where it denotes individual i at t years since 2003, and p_{it} is the individual-level annual

probability of experiencing a disability incidence. Age is age in single years. $1986BMI_i$ is BMI

in 1986 and BMI_{it} is time-varying BMI (contemporaneous BMI). $Current_{it}$ and $Former_{it}$ are

time-varying current and former smoking status. $EverManual_{it}$ denotes ever having

participated in manual labor. $Education_{ij}$ are the indicators for educational attainment,

$Race/Ethn_{ik}$ for race/ethnicity, and $ChildSES_{im}$ for childhood socioeconomic circumstances.

$Year_{it}$ is calendar year between 2003 and 2015.

Longitudinal population weights provided by PSID were adjusted to address selective attrition.

Attrition was defined as leaving the panel after 2003 and not returning. For each year between

2003 and 2015, a logistic regression was run to predict non-attrition in the subsequent year, using

the previous wave's covariates and disability incidence measure as predictors. From this

regression, a predicted probability of non-attrition was generated for each observation and each

year. The inverse of this probability was then multiplied by the PSID-provided weight to

generate the attrition-adjusted weights applied in all models.

Regressions also took into account sample stratification, repeat observations, and (using Taylor

Series linearization) heteroskedasticity (Heeringa et al., 2011). Lack of convergence precluded

correction for family-level clustering.

Appendix A-7. Interactions between education and the mediators

The regression models assume independence between education and the mediators, but interactions could exist such that the association between each mediator and incident ADL/IADL difficulty varies by educational attainment. For example, excess BMI may be more likely to contribute to ADL/IADL difficulty among people with less education, e.g., due to higher risk of developing and fewer resources for managing health conditions such as diabetes, cardiovascular disease, and arthritis. Alternatively, intensity of current and former smoking may vary by educational status, such that these indicators are more strongly associated with incident ADL/IADL difficulty in less educated groups.

I tested the assumption of independence by assessing whether additive interactions between educational attainment and each mediator existed in each regression model. In order to compare the expected difference in incidence between two educational groups given a one-unit change in the mediator in each, I calculated the double derivative with respect to the two predictors and then conducted a Wald test of the null hypothesis that the double derivative was equal to zero. This approach was required because, in logit models, the coefficient on an interaction term is not equivalent to the interaction effect (Ai & Norton, 2003; Norton et al., 2004). It corresponded to 40 tests (five mediator indicators, including both measures of excess BMI and two comparison levels of smoking; two comparison levels of educational attainment; and four age-gender groups).

Table 5-7 shows the estimated interaction effects—i.e., the estimated difference between the marginal effect of the mediator in the educational group of interest and that in the reference group, those without a high school degree—as well as the p-value from the corresponding Wald tests. Of the 40 tests and given a conservative alpha of 0.10, four interactions were detected: in younger women, evidence that both current and former smoking are less associated with incident ADL/IADL difficulty in the most compared to the least educated group; in older women, evidence that former smoking is less associated with incidence in the most compared to the least educated group; and in older men, evidence that current smoking is more associated with incidence in the middle compared to the least educated group. No interactions were identified between education and either excess BMI or manual labor.

In women ages 33-64, being a current or former smoker appeared less associated with incidence among those with a college degree than among those with less than a high school degree. The marginal effect of former smoking (compared to never smoking) was estimated to be -0.017 (95% CI: 0. -0.055, 0.021) in those with a college degree and 0.075 (95% CI: -0.005, 0.155) in those with less than a high school degree (interaction effect: -0.092, p=0.041). The marginal effect of current smoking (compared to never smoking) was estimated to be -0.021 (95% CI: 0. -0.085, 0.0429) in those with a college degree and 0.172 (95% CI: 0.066, 0.278) in those with less than a high school degree (interaction effect: -0.193, p=0.002).

In older women, being a former smoker appeared less associated with incidence among those with a college degree compared to those with less than a high school degree. The marginal effect of former smoking (compared to never smoking) was estimated to be -0.042 (95% CI: -0.143,

0.060) in those with a college degree and 0.221 (95% CI: 0.075, 0.367) in those with less than a high school degree (interaction effect: -0.262, p=0.004).

In older men, being a current smoker may have been more associated with incidence among those with a high school degree compared to those with less than a high school degree. The marginal effect of current smoking (compared to never smoking) was estimated to be 0.150 (95% CI: 0.010, 0.290) in those with a high school degree and -0.017 (95% CI: -0.157, 0.122) in those with less than a high school degree (interaction effect: 0.168, p=0.090).

Appendix A-8. Supplementary analyses

In the analysis including sedentariness in the regressions, I used sedentariness in year of study entry to alleviate potential reverse causation. Time-varying alcohol consumption (0, 1-2, more than 2 drinks per day) was also examined but did not significantly predict incidence and was excluded from analyses.

The analysis examining incidence of persistent ADL/IADL difficulty was limited to ADL/IADL difficulty lasting two or more waves. In younger women, 54.5% of those who (a) experienced ADL/IADL difficulty incidence in a given wave, and (b) met inclusion criteria in the subsequent wave, reported no ADL/IADL difficulty in the subsequent wave. This percentage was 54.5% in younger men, 42.9% in older women, and 33.2% in older men. Across groups, 18-24% reported ADL/IADL difficulty in the subsequent wave only (i.e., a total of two consecutive waves); and 27-44% reported ADL/IADL difficulty in three or more consecutive waves. Disability was most likely to be persistent in older men.

A.

Figure 5-1. Prevalence of each ADL and IADL by age and gender

ADL prevalence by gender

B.

IADL prevalence by gender
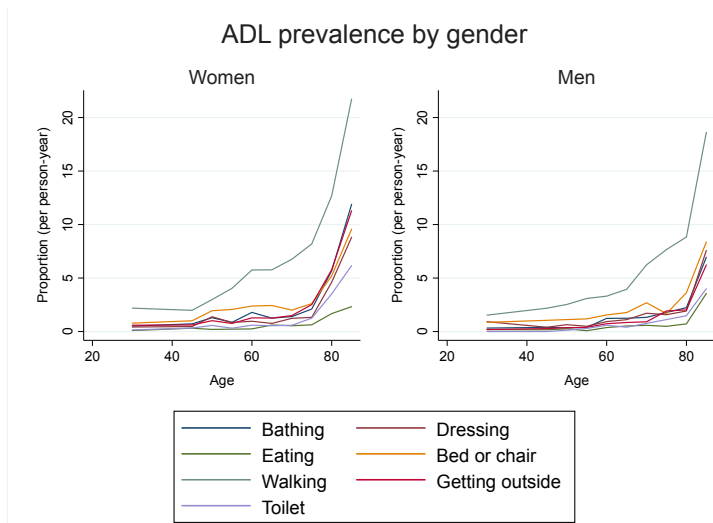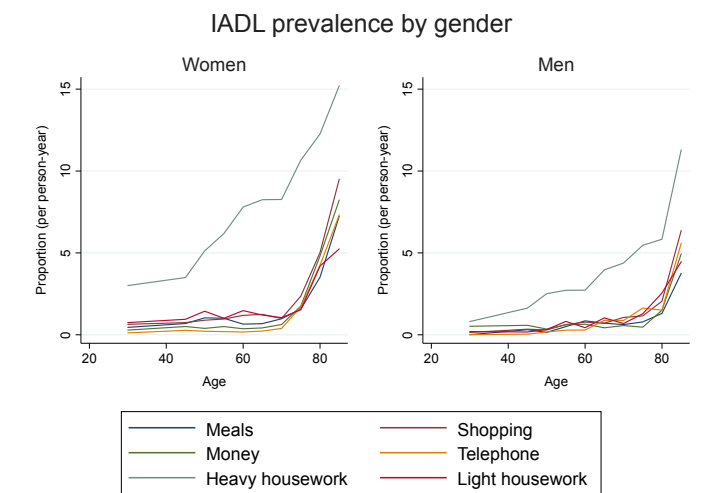
Note: Estimates are weighted.

Table 5-1. Bivariate relationships between education and mediators of interest

| | | Under 65 | | 65 and over | |
		Women	Men	Women	Men
Mediator	*Education*				
Ever smoked	Less than HS	*Ref.*	*Ref.*	*Ref.*	*Ref.*
	HS degree	-0.157*	-0.175**	0.092	-0.035
	College degree	-0.253***	-0.386***	0.109	-0.232**
Excess BMI	Less than HS	*Ref.*	*Ref.*	*Ref.*	*Ref.*
	HS degree	-1.456*	0.467	-0.838	1.604***
	College degree	-2.481***	-0.210	-1.547**	1.192***
Ever manual	Less than HS	*Ref.*	*Ref.*	*Ref.*	*Ref.*
	HS degree	-0.252***	-0.223***	-0.290***	-0.282***
	College degree	-0.518***	-0.604***	-0.452***	-0.531***

Note: * p<0.05, ** *p*<0.01, *** *p*<0.001. Estimates are unadjusted linear regression coefficients and are weighted.

Figure 5-2. Mediators by educational attainment

A.

B.

C.

Notes: Estimates weighted
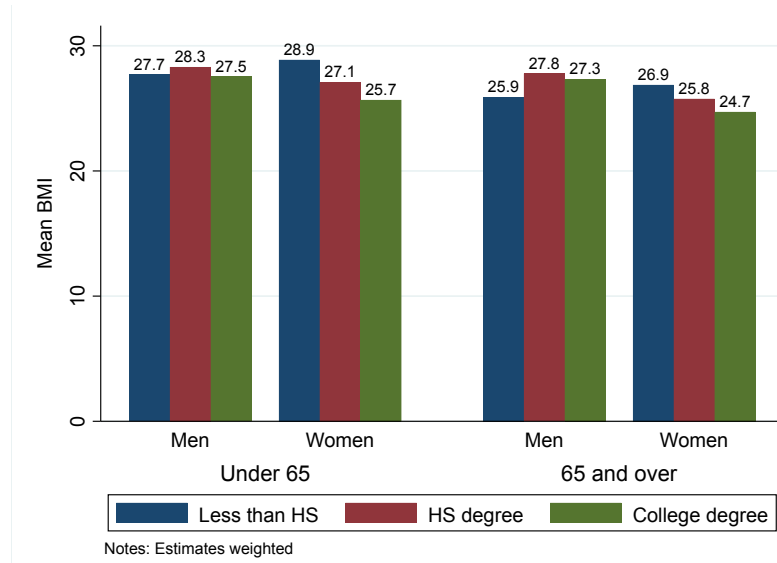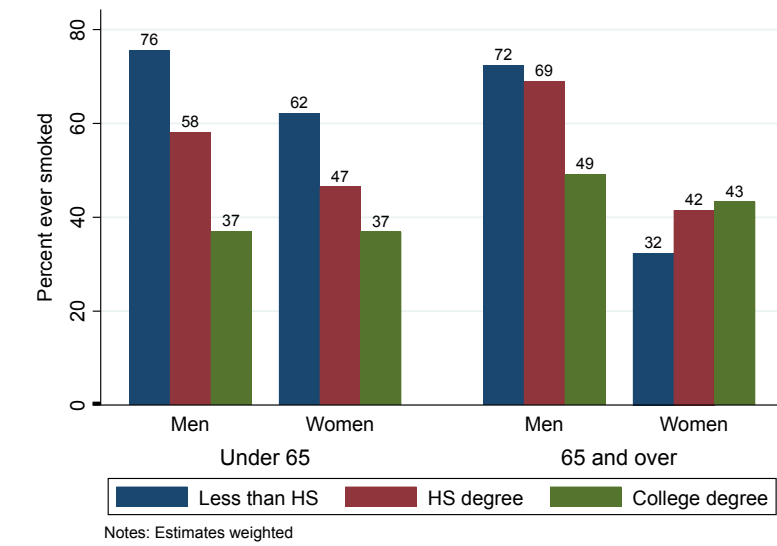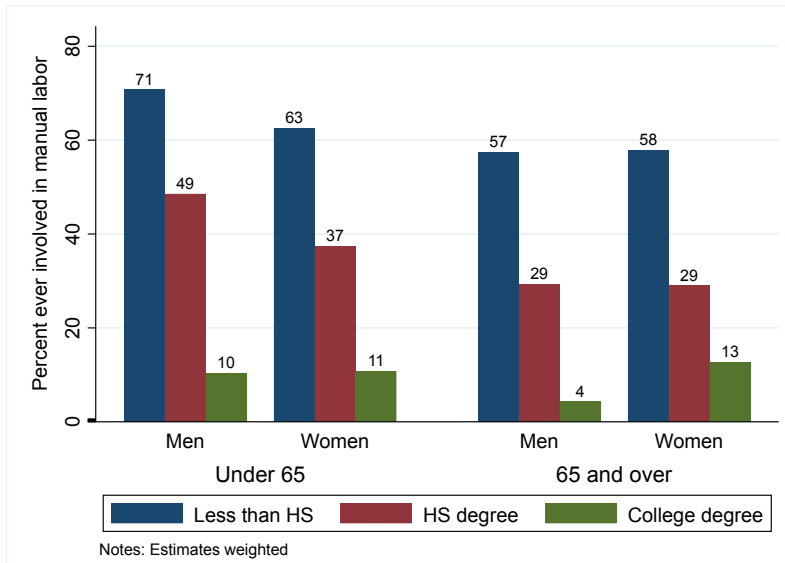
Note: Panel A: Education and contemporaneous BMI; Panel B: Education and percent ever smoked; Panel C: Education and percent ever conducted manual labor.

Table 5-2. Inclusion of sedentariness as a mediator: Observed disparities and estimates of percent explained

Under 65	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	4.6	3.2	1.5	2.9	1.7	1.3
Percent explained						
Smoking	21.7	20.1	25.3	27.4	31.2	22.4
Excess BMI	34.4	34.8	33.6	14.6	5.4	26.7
Manual	5.8	5.7	6.2	32.7	30.3	35.7
All	**56.2**	**55.6**	**57.5**	**61.4**	**55.0**	**69.8**
Sedentariness	12.6	10.3	17.8	9.3	17.4	11.0
All + sedentariness	**64.1**	**62.6**	**67.5**	**68.7**	**64.3**	**74.5**

65 and over	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	6.0	3.6	2.4	1.2	2.0	-0.8
Percent explained						
Smoking	0.0	-2.8	4.3	70.8	22.5	N/A
Excess BMI	27.7	26.4	29.8	-16.7	-10.0	N/A
Manual	8.4	9.7	6.4	25.0	10.0	N/A
All	**33.6**	**33.3**	**34.0**	**62.5**	**17.8**	N/A
Sedentariness	14.3	13.9	14.9	20.8	15.0	N/A
All + sedentariness	**46.2**	**45.8**	**46.8**	**75.0**	**29.3**	N/A

Note: PY = person-years. "Least" education = less than high school degree; "middle" = at least a high school degree; "most" = at least a college degree. N/A indicates excluded value due to a negative disparity. "Percent explained" refers to estimated percentage of educational disparities explained by the mediator of interest or the relevant combination of them.

Including sedentariness in the models appeared to reduce the total percentage explained by the three mediators of interest, reflecting their correlation. However, the proportion of disparities explained by each of the main mediators fell only slightly. Being sedentary in the year of study entry explained an estimated 9-21% of disparities.

Table 5-3. Difficulty with walking and heavy housework: Observed disparities and estimates of percent explained

Under 65	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	5.1	4.0	1.1	1.9	0.5	1.4
Percent explained						
Smoking	23.4	20.9	32.4	35.0	67.9	22.0
Excess BMI	39.6	38.6	43.2	17.9	-10.1	28.9
Manual	2.8	2.5	3.6	23.6	33.0	19.9
All	**59.0**	**56.2**	**69.4**	**61.9**	**67.9**	**59.6**

65 and over	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	5.6	2.8	2.9	0.3	0.7	-0.4
Percent explained						
Smoking	1.8	-1.8	5.3	222.9	32.9	N/A
Excess BMI	35.7	41.8	29.8	-85.7	-64.3	N/A
Manual	3.6	5.5	1.8	28.6	7.1	N/A
All	**40.0**	**41.8**	**38.2**	**150.0**	**-4.3**	**N/A**

Note: PY = person-years. "Least" education = less than high school degree; "middle" = at least a high school degree; "most" = at least a college degree. N/A indicates excluded value due to a negative disparity. "Percent explained" refers to estimated percentage of educational disparities explained by the mediator of interest or the relevant combination of them.

In the supplementary analysis of difficulty with walking and heavy housework—i.e., defining disability incidence as new difficulty with one or both of these, patterns were similar to those in the main analysis. The estimated proportion of disparities explained by manual labor tended to fall.

Table 5-4. Persistent disability: Observed disparities and estimates of percent explained

Under 65	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	2.3	1.8	0.5	2.2	1.1	1.1
Percent explained						
Smoking	23.0	17.8	42.4	36.1	44.2	27.6
Excess BMI	38.9	35.0	53.5	9.6	7.1	12.3
Manual	25.2	21.9	37.4	31.2	35.0	27.3
All	**70.5**	**61.2**	**105.1**	**61.9**	**68.1**	**55.5**

65 and over	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	4.4	3.7	0.7	1.1	0.7	0.4
Percent explained						
Smoking	0.0	0.0	0.0	35.5	20.8	57.5
Excess BMI	44.1	39.6	66.9	-3.7	-31.5	37.9
Manual	-1.0	-1.4	0.7	44.2	42.3	47.1
All	**44.5**	**40.0**	**66.9**	**58.1**	**26.2**	**105.7**

Note: PY = person-years. "Least" education = less than high school degree; "middle" = at least a high school degree; "most" = at least a college degree. "Percent explained" refers to estimated percentage of educational disparities explained by the mediator of interest or the relevant combination of them. Persistent disability is defined as reporting of disability for at least two consecutive waves.

In the supplementary analysis of persistent disability (i.e., disability lasting at least two consecutive waves), the mediators tended to explain a greater proportion of disparities in women. In younger women, this was largely due to an increase in the percent explained by manual labor. In older women, it was due to an increase in the contribution of excess weight.

Table 5-5. Separate prediction of ADL and IADL difficulty: Observed disparities and estimates of percent explained

A. ADLs

Under 65	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	4.0	3.2	0.8	2.3	1.2	1.1
Percent explained						
Smoking	23.3	21.6	30.1	38.0	46.7	28.2
Excess BMI	41.5	41.0	43.4	21.8	11.2	33.8
Manual	16.1	15.4	18.7	29.7	29.3	30.1
All	**66.8**	**64.8**	**74.1**	**69.2**	**66.1**	**72.7**

65 and over	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	5.7	2.9	2.8	0.5	1.0	-0.5
Percent explained						
Smoking	1.7	0.0	3.4	119.0	30.0	N/A
Excess BMI	22.4	24.1	20.5	-61.0	-30.5	N/A
Manual	3.9	5.2	2.7	100.0	28.0	N/A
All	**27.4**	**28.1**	**26.6**	**132.0**	**30.5**	**N/A**

B. IADLs

Under 65	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	3.4	2.5	0.9	2.1	1.3	0.8
Percent explained						
Smoking	26.8	23.7	36.0	31.7	35.1	26.2
Excess BMI	39.7	39.8	39.4	9.9	5.3	17.1
Manual	11.9	11.0	14.3	37.6	34.4	42.7
All	**66.6**	**63.5**	**75.4**	**64.8**	**60.7**	**71.3**

65 and over	Women			Men		
	Most vs. least	Middle vs. least	Most vs. middle	Most vs. least	Middle vs. least	Most vs. middle
Observed disparity (per 100 PY)	4.9	3.1	1.8	1.2	1.8	-0.6
Percent explained						
Smoking	1.7	-1.6	7.7	38.8	17.4	N/A
Excess BMI	24.9	25.8	23.3	-0.4	-0.3	N/A
Manual	23.9	25.8	20.5	-19.2	-8.8	N/A
All	**46.3**	**47.6**	**44.0**	**20.8**	**9.4**	**N/A**

Note: PY = person-years. "Least" education = less than high school degree; "middle" = at least a high school degree; "most" = at least a college degree. N/A indicates excluded value due to a

negative disparity. "Percent explained" refers to estimated percentage of educational disparities explained by the mediator of interest or the relevant combination of them.

Patterns in the percent of disparities explained were generally similar to those from the main analysis on ADLs and IADLs jointly. Disparities in ADLs and IADLs individually tended to be smaller compared to those in the joint analysis, and the estimated overall percent explained tended to be larger.

Table 5-6. Analysis of excess BMI and smoking as mediators of the manual labor-disability relationship in men ages 33-64

	Estimate	Standard error	Confounding percent
Association, manual labor and incident disability (OR)			
Reduced model	1.653	0.260	
Full model	1.481	0.231	
Difference	1.116	0.403	
Mediator coefficients (β)			
1986 BMI	0.022	0.018	3.08
Concurrent BMI	0.015	0.012	4.41
Former smoker	0.002	0.004	0.34
Current smoker	0.071	0.027	14.06
All	--	--	21.89

Note: Estimates were produced using Stata's -khb- command, which implements Karlson, Holm, and Breen's method for comparing coefficients among same-sample nested logit and probit models (Karlson et al., 2012). Errors are clustered at the individual level; estimates are unweighted. The confounding percent estimates the percentage of the association between manual labor and incidence that is explained by excess BMI and smoking.

Excess BMI and smoking were estimated to explain 22% of the association among younger men between manual labor and disability incidence in the reduced model (p=0.002). Being a current smoker appeared to be the largest mediator, explaining an estimated 14% of the association. Contrary to my hypothesis, manual labor was estimated to be positively associated with excess BMI, such that the latter appeared to be a mediator rather than a suppressor of the manual labor-disability relationship.

Table 5-7. Estimated additive interaction effects between education and the mediators of interest

	Women 33-64 years		Men 33-64 years		Women 65-94 years		Men 65-94 years	
	Est.	*p*	Est.	*p*	Est.	*p*	Est.	*p*
Contemporaneous BMI								
Less than high school	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High school degree	0.000	0.933	-0.008	0.188	0.000	0.975	-0.002	0.869
College degree	0.006	0.239	-0.006	0.321	0.001	0.931	-0.015	0.319
1986 BMI								
Less than high school	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High school degree	0.003	0.594	0.001	0.931	0.030	0.133	0.011	0.388
College degree	-0.007	0.413	0.000	0.952	0.026	0.284	0.013	0.365
Former smoker								
Less than high school	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High school degree	-0.039	0.370	-0.088	0.113	-0.174	0.031	-0.023	0.721
College degree	**-0.092**	**0.041**	-0.064	0.250	**-0.262**	**0.004**	-0.082	0.282
Current smoker								
Less than high school	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High school degree	-0.118	0.038	-0.022	0.678	-0.228	0.140	**0.168**	**0.090**
College degree	**-0.193**	**0.002**	-0.014	0.803	-0.245	0.234	0.022	0.911
Manual labor								
Less than high school	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
High school degree	-0.044	0.261	0.020	0.683	0.088	0.273	0.029	0.608
College degree	-0.025	0.620	-0.029	0.562	0.178	0.107	0.210	0.114

Note. Estimated interaction effects are the difference between (a) the marginal effect of the mediator at the educational group of interest; and (b) the marginal effect of the mediator in the reference group, those without a high school degree. A negative estimate therefore indicates a larger association in those without a high school degree. [1]P-values refer to Wald tests of the null hypothesis that the interaction effect equals zero. Bold indicates a p-value less than 0.10.

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[1] Dear reader: if you have made it to and are actually reading this page, I am impressed, grateful, and rather surprised! In return, I owe you a gift of your choice: champagne, succulent, or methods textbook.

Appendix B. Supplementary Material for Chapter 3 (Opioid Prescribing)

Table 5-8. International Classification of Disease codes used to identify certain mental health and substance use disorders

Diagnosis Category	ICD-9 Diagnostic Codes	ICD-10 Diagnostic Codes
Psychotic and bipolar disorders	295, 296.0, 296.1, 296.4-296.7, 297-298	F29, F28, F24, F23, F22, F333, F323, F319, F315, F314, F312, F304, F303, F302, F259, F209, F205, F202, F201, F200, F310, F309, F258, F251, F250, F203, F4489, F3178, F3177, F3176, F3175, F3174, F3173, F3164, F3163, F3162, F3161, F3160, F3132, F3131, F3130, F3113, F3112, F3111, F3110, F3013, F3012, F3011, F3010, F2089, F2081, F3189, F3172, F3171, F3170
Major depression	296.2, 296.3	F339, F333, F332, F331, F330, F329, F325, F324, F323, F322, F321, F320, F3342, F3341, F3340
Anxiety disorders (includes PTSD)	300.0, 300.2, 300.3, 309.81	F419, F418, F411, F410, F409, F408, F413, F4312, F4310, F4010, F4002, F4001, F4311, F4011, F4000, F40241, F40240, F40218, F40298, F40291, F40290, F40248, F40243, F40242, F40233, F40232, F40231, F40230, F40228, F40220, F40210

| Substance use disorders | 2911, 2912, 2913, 2914, 2915, 2919, 2922, 2929, 3039, 3041, 3042, 3043, 3044, 3045, 3046, 3047, 3048, 3049, 3051, 3052, 3053, 3054, 3055, 3056, 3057, 3058, 3059, 29181, 29182, 29189, 29211, 29212, 29281, 29282, 29283, 29284, 29285, 29289, 30301, 30302, 30303, 30391, 30392, 30393, 30401, 30402, 30403, 30411, 30412, 30413, 30421, 30422, 30423, 30431, 30432, 30433, 30441, 30442, 30443, 30451, 30452, 30453, 30461, 30462, 30463, 30471, 30472, 30473, 30481, 30482, 30483, 30491, 30492, 30493, 30501, 30502, 30503, 30521, 30522, 30523, 30531, 30532, 30533, 30541, 30542, 30543, 30551, 30552, 30553, 30561, 30562, 30563, 30571, 30572, 30573, 30581, 30582, 30583, 30591, 30592, 30593 | F1026, F1096, F1097, F1027, F1014, F1024, F1019, F1029, F1094, F1099, F1123, F1193, F1423, F1523, F1593, F10121, F10221, F10231, F10921, F10151, F10251, F10951, F10920, F10929, F10150, F10250, F10950, F10230, F10232, F10239, F10182, F10282, F10982, F10159, F10180, F10181, F10188, F10259, F10280, F10281, F10288, F10959, F10980, F10981, F10988, F13230, F13231, F13232, F13239, F13930, F13931, F13932, F13939, F19230, F19231, F19232, F19239, F19930, F19931, F19932, F19939, F11150, F11250, F11950, F12150, F12250, F12950, F13150, F13250, F13950, F14150, F14250, F14950, F15150, F15250, F15950, F16150, F16250, F16950, F18150, F18250, F18950, F19150, F19250, F19950, F11151, F11251, F11951, F12151, F12251, F12951, F13151, F13251, F13951, F14151, F14251, F14951, F15151, F15251, F15951, F16151, F16251, F16951, F18151, F18251, F18951 |

Table 5-9. Quasi-likelihood index criterion (QIC) values corresponding to each model selection step (osteoarthritis)

Osteoarthritis	Any fill	Average MME	MME > 90	Overlap	Fills	Days supplied	Days overlapped
Link function	Identity	Identity	Identity	Identity	Negative binomial	Negative binomial	Negative binomial
Distributional family	Gaussian	Gaussian	Gaussian	Gaussian	Negative binomial	Negative binomial	Negative binomial
Correlation structure							
Unstructured	**229,628**	N.C.	N.C.	N.C.	887,678	N.C.	N.C.
Exchangeable	229,784	**1,841,992,405**	**316,004**	**307,849.57**	**887,530**	**2,519,465**	**680,418**

Fibromyalgia	Any fill	Average MME	MME > 90	Overlap	Fills	Days supplied	Days overlapped
Link function	Identity	Identity	Identity	Log	Negative binomial	Negative binomial	Negative binomial
Distributional family	Gaussian	Gaussian	Gaussian	Binomial	Negative binomial	Negative binomial	Negative binomial
Correlation structure							
Unstructured	**1,090,400**	N.C.	N.C.	**246,880**	660,410	N.C.	N.C.
Exchangeable	1,093,155	**1,488,311,429**	**245,346**	248,758	**660,290**	**1,901,575**	**609,991**

Note: MME = morphine milligram equivalents. N.C. = No convergence. Bold indicates minimum QIC value and therefore the selected specification.

Table 5-10. Sociodemographic and clinical measures by race/ethnicity in osteoarthritis patients

	White		Black		Hispanic		Asian	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Observations	1,001,737		147,540		114,146		21,045	
Individuals	68,579		9,663		8,032		1,708	
Age (mean)	53.8	(53.78 to 53.89)	53.6	(53.46 to 53.74)	53.1	(52.93 to 53.25)	52.9	(52.53 to 53.29)
Female (%)	57.5	(57.15 to 57.89)	65.4	(64.46 to 66.35)	58.7	(57.61 to 59.77)	61.7	(59.34 to 63.96)
Education (%)								
High school degree or less	26.7	(26.34 to 27.00)	49.6	(48.64 to 50.63)	45.3	(44.23 to 46.41)	18.3	(16.49 to 20.16)
Less than college	55.5	(55.14 to 55.88)	45.9	(44.88 to 46.87)	46.3	(45.21 to 47.39)	49.2	(46.81 to 51.55)
College degree	17.8	(17.53 to 18.11)	4.5	(4.08 to 4.90)	8.4	(7.77 to 8.99)	32.5	(30.27 to 34.72)
Income (%)								
<$40K	16.9	(16.63 to 17.19)	44.8	(43.81 to 45.79)	28.6	(27.65 to 29.62)	10.9	(9.47 to 12.43)
$40K-$59K	10.8	(10.59 to 11.06)	17.9	(17.15 to 18.68)	18.0	(17.17 to 18.86)	8.3	(6.95 to 9.56)
$60K-$74K	9.3	(9.08 to 9.52)	10.2	(9.55 to 10.75)	11.9	(11.16 to 12.57)	10.3	(8.86 to 11.75)
$75K-$99K	18.4	(18.11 to 18.69)	11.9	(11.25 to 12.54)	16.6	(15.79 to 17.42)	18.2	(16.38 to 20.04)
$100K+	44.6	(44.19 to 44.94)	15.2	(14.53 to 15.96)	24.9	(23.93 to 25.82)	52.3	(49.91 to 54.65)
Any mental health diagnosis	6.3	(6.15 to 6.52)	5.4	(4.95 to 5.85)	5.5	(5.03 to 6.03)	3.7	(2.85 to 4.65)
SUD diagnosis	2.9	(2.75 to 3.00)	3.6	(3.19 to 3.93)	2.2	(1.89 to 2.54)	1.4	(0.85 to 1.96)
Other pain-related diagnosis	42.5	(42.17 to 42.91)	40.1	(39.11 to 41.07)	41.0	(39.95 to 42.10)	39.8	(37.49 to 42.14)
Elixhauser score (max per month. mean)	0.9	(0.85 to 0.87)	1.2	(1.21 to 1.27)	1.1	(1.04 to 1.09)	0.8	(0.77 to 0.87)
Days since last pain visit	42.9	(42.46 to 43.30)	44.4	(43.19 to 45.53)	42.9	(41.67 to 44.16)	45.2	(42.22 to 48.19)
Pain visits per month	2.9	(2.85 to 2.89)	2.8	(2.77 to 2.88)	2.8	(2.78 to 2.89)	2.8	(2.71 to 2.94)
Months between first and last pain diagnosis	32.9	(32.78 to 32.95)	33.4	(33.19 to 33.65)	32.5	(32.25 to 32.77)	31.4	(30.82 to 32.01)

Note: Estimates include individuals for whom data is not missing on any model predictor

Table 5-11. Sociodemographic and clinical measures by race/ethnicity in fibromyalgia patients

	White		Black		Hispanic		Asian	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Observations	685,748		75,673		77,205		16,745	
Individuals	44,761		4,724		5,380		1,429	
Age (mean)	48.1	(47.96 to 48.16)	48.8	(48.54 to 49.12)	47.4	(47.1 to 47.64)	44.7	(44.2 to 45.28)
Female (%)	71.7	(71.30 to 72.13)	77.1	(75.90 to 78.29)	71.5	(70.3 to 72.69)	64.9	(62.4 to 67.35)
Education (%)								
High school degree or less	22.5	(22.11 to 22.89)	44.0	(42.55 to 45.38)	36.8	(35.6 to 38.14)	11.1	(9.4 to 12.68)
Less than college	56.6	(56.11 to 57.03)	50.0	(48.59 to 51.45)	52.1	(50.8 to 53.46)	45.7	(43.1 to 48.28)
College degree	20.9	(20.55 to 21.31)	6.0	(5.33 to 6.69)	11.0	(10.2 to 11.86)	43.2	(40.7 to 45.82)
Income (%)								
<$40K	15.6	(15.29 to 15.96)	41.3	(39.90 to 42.70)	25.8	(24.6 to 26.93)	9.3	(7.8 to 10.82)
$40K-$59K	10.3	(10.06 to 10.63)	16.9	(15.84 to 17.98)	16.9	(15.9 to 17.95)	7.7	(6.3 to 9.08)
$60K-$74K	9.0	(8.70 to 9.23)	10.5	(9.65 to 11.40)	10.6	(9.8 to 11.40)	7.1	(5.7 to 8.40)
$75K-$99K	16.9	(16.58 to 17.28)	13.3	(12.37 to 14.31)	16.9	(15.9 to 17.95)	15.2	(13.3 to 17.05)
$100K+	48.1	(47.67 to 48.60)	17.9	(16.84 to 19.02)	29.8	(28.5 to 30.98)	60.7	(58.2 to 63.28)
Any mental health diagnosis	9.0	(8.72 to 9.25)	7.7	(6.96 to 8.49)	8.3	(7.6 to 9.07)	7.1	(5.8 to 8.47)
SUD diagnosis	3.0	(2.82 to 3.14)	4.1	(3.50 to 4.63)	2.7	(2.2 to 3.08)	1.7	(1.0 to 2.35)
Other pain-related diagnosis	36.6	(36.13 to 37.03)	37.3	(35.88 to 38.64)	36.5	(35.2 to 37.82)	36.9	(34.4 to 39.38)
Elixhauser score (max per month. mean)	0.7	(0.69 to 0.71)	1.0	(1.00 to 1.08)	0.8	(0.8 to 0.88)	0.6	(0.5 to 0.62)
Days since last pain visit	38.0	(37.48 to 38.45)	40.0	(38.51 to 41.57)	39.5	(38.1 to 40.96)	39.7	(36.4 to 42.99)
Pain visits per month	2.9	(2.91 to 2.95)	2.9	(2.83 to 2.98)	2.9	(2.9 to 3.00)	3.3	(3.1 to 3.39)
Months between first and last pain diagnosis	33.1	(32.94 to 33.17)	33.4	(33.1 to 33.77)	32.3	32.0 to 32.624	30.0	29.3 to 30.73)

Table 5-12. Comparison of individuals with missing versus complete race/ethnicity data

	Osteoarthritis			Fibromyalgia		
	Missing	Complete	p	Missing	Complete	p
Distinct individuals	27,449	98,043		22,331	63,580	
Total monthly observations	511,828	1,804,480		414,272	1,201,438	
Months with pain visits	18.6	18.4	0.002	18.6	18.9	<0.001
Age (%)						
18-25	0.7	0.6	0.069	4.4	4.0	0.007
25-34	3.5	1.9	<0.001	14.9	9.2	<0.001
35-44	13.4	8.8	<0.001	25.4	20.3	<0.001
45-54	35.5	34.2	<0.001	31.1	34.4	<0.001
55-64	46.9	54.6	<0.001	24.2	32.1	<0.001
Female (%)	59.0	58.6	0.183	72.5	72.1	0.228
Education (%)						
High school degree or less	27.3	31.4	<0.001	22.0	26.0	<0.001
Less than college	51.1	53.0	<0.001	52.9	54.8	<0.001
College degree	16.0	15.4	0.016	20.5	19.0	<0.001
Missing	5.5	0.2	<0.001	4.6	0.2	<0.001
Income (%)						
<$40K	15.7	19.1	<0.001	13.2	16.7	<0.001
$40K-$59K	9.4	11.1	<0.001	9.8	10.3	0.025
$60K-$74K	6.4	8.8	<0.001	6.6	8.3	<0.001
$75K-$99K	7.9	15.9	<0.001	8.0	14.9	<0.001
$100K+	14.9	36.1	<0.001	16.3	39.6	<0.001
Missing	45.8	9.0	<0.001	46.0	10.3	<0.001
Mental health diagnosis						
Anxiety	6.2	5.3	<0.001	8.6	7.6	<0.001
Depression	5.5	4.8	<0.001	6.9	6.4	<0.001
Psychosis/PTSD	2.4	1.8	<0.001	2.5	2.1	<0.001
SUD diagnosis	2.3	1.9	<0.001	2.4	2.2	<0.001
Elixhauser score	1.3	1.2	<0.001	1.0	1.0	<0.001
Days since last pain visit	23.6	24.6	<0.001	22.7	23.1	<0.001

Pain visits per month	3.4	3.3	<0.001	3.3	3.2	<0.001
Months between first and last pain diagnosis	32.5	32.8	0.001	32.4	32.8	<0.001
Any opioid fill in month (%)	16.9	15.5	<0.001	17.2	16.7	<0.001
Fills per month, if any	1.27	1.26	0.004	1.27	1.26	<0.001
Days supplied per month, if any	28.5	28.1	<0.001	30.4	30.6	0.120
Morphine milligram equivalents (MME), if any						
Average per day	77.8	74.4	<0.001	80.4	78.4	<0.001
Receiving > 100 MME (%)	25.0	22.9	<0.001	25.6	24.4	<0.001
Concurrent opioid/benzodiazepine prescription, if any opioid						
Any (%)	28.6	27.0	<0.001	33.6	32.4	<0.001
Number of overlapping days	8.1	7.8	<0.001	28.6	29.0	0.001

Note: SUD = substance use disorder

Table 5-13. Marginal effects of main predictors from Stage I model, osteoarthritis

	Any fill (%)	Average dose (MME)	High dose (%)	Concurrent (%)	Fills	Days supplied	Days with concurrent prescriptions
Secular trend							
Time	0.0313***	0.0469	-8.75E-03	-0.170***	-0.00034	0.00706	-0.00353
	(0.0181, 0.0445)	(-0.0441, 0.138)	(-0.0572, 0.0397)	(-0.212, -0.127)	(-0.00101, 0.000333)	(-0.0137, 0.0279)	(-0.0363, 0.0293)
Race/ethnicity							
White	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*
Black	-1.263***	-9.922***	-4.315***	-4.711***	-0.0385***	-1.110***	-1.331***
	(-1.705, -0.821)	(-11.48, -8.361)	(-5.184, -3.446)	(-5.687, -3.735)	(-0.0492, -0.0279)	(-1.517, -0.704)	(-2.067, -0.594)
Hispanic	-2.028***	-10.41***	-4.268***	-2.920***	-0.0383***	0.094	-0.662
	(-2.480, -1.576)	(-12.20, -8.621)	(-5.257, -3.279)	(-4.017, -1.823)	(-0.0504, -0.0261)	(-0.438, 0.626)	(-1.572, 0.248)
Asian	-3.820***	-5.217*	-2.333	-6.875***	-0.0267	-2.009**	0.98
	(-4.568, -3.073)	(-10.03, -0.402)	(-4.989, 0.324)	(-9.110, -4.641)	(-0.0576, 0.00419)	(-3.330, -0.689)	(-2.394, 4.355)
Level change	-0.214	0.905	0.625	0.733	0.014	0.238	0.0627
	(-0.541, 0.113)	(-0.922, 2.731)	(-0.437, 1.686)	(-0.273, 1.738)	(-0.00235, 0.0303)	(-0.211, 0.688)	(-0.734, 0.859)
Trend change	-0.0308*	-0.563***	-0.229***	-0.0578	-0.00133*	-0.0381*	-0.0435
	(-0.0557, -0.00587)	(-0.716, -0.411)	(-0.317, -0.140)	(-0.136, 0.0207)	(-0.00259, -7.65e-05)	(-0.0740, -0.00214)	(-0.104, 0.0168)
Observations	1,284,468	191,970	191,970	194,045	194,045	194,045	51,143

Note: *** p<0.001, ** p<0.01, * p<0.05. Estimates are marginal effects from model in which the exposure variables were not interacted with race/ethnicity. 95% confidence intervals are in parentheses.

Table 5-14. Marginal effects of main predictors from Stage I model, fibromyalgia

	Any fill (%)	Average dose (MME)	High dose (%)	Concurrent prescriptions (%)	Fills	Days supplied	Days with concurrent prescriptions
Secular trend							
Time	0.035***	-0.084	-0.031	-0.209***	-0.001	-0.030*	0.016
	(0.018, 0.051)	(-0.193, 0.024)	(-0.087, 0.025)	(-0.261, -0.156)	(-0.001, 0.000)	(-0.054, -0.005)	(-0.018, 0.051)
Race/ethnicity							
White	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Black	-1.069**	-9.243***	-2.323**	-4.786***	-0.038***	-1.528***	-1.160**
						(-2.133, -0.923)	
	(-1.732, -0.407)	(-11.466, -7.020)	(-3.823, -0.823)	(-6.287, -3.285)	(-0.052, -0.025)		(-2.039, -0.281)
Hispanic	-1.774***	-7.344***	-3.522***	-3.484***	-0.020**	0.068	-0.579
	(-2.364, -1.185)	(-9.879, -4.808)	(-5.087, -1.957)	(-4.984, -1.985)	(-0.035, -0.005)	(-0.642, 0.777)	(-1.593, 0.435)
Asian	-3.830***	-3.118	-1.602	-7.818***	-0.029	-1.435	-1.365
	(-4.689, -2.971)	(-10.244, 4.007)	(-5.450, 2.247)	(-11.208, -4.427)	(-0.065, 0.007)	(-3.472, 0.603)	(-4.173, 1.442)
Level change	0.149	1.946	0.925	-0.307	0.019*	0.319	-0.397
	(-0.259, 0.558)	(-0.226, 4.118)	(-0.356, 2.206)	(-1.530, 0.915)	(0.000, 0.039)	(-0.213, 0.850)	(-1.197, 0.404)
Trend change	-0.059***	-0.569***	-0.237***	-0.077	-0.001	-0.013	-0.03
	(-0.090, -0.028)	(-0.751, -0.387)	(-0.350, -0.124)	(-0.172, 0.018)	(-0.003, 0.000)	(-0.055, 0.029)	(-0.091, 0.031)
Observations	855,371	137,984	137,984	139,484	139,484	139,484	44,939

Note: *** $p<0.001$, ** $p<0.01$, * $p<0.05$. Estimates are marginal effects from model in which the exposure variables were not interacted with race/ethnicity. 95% confidence intervals are in parentheses.

Table 5-15. Marginal effects from Stage II (interacted) model, osteoarthritis

	Any fill (probability)	Average dosage (MMEs)	High dosage (probability)	Concurrent prescriptions (probability)	Prescription fills	Days supplied	Days of concurrent prescriptions
Secular trend	0.000313*** (0.000181 - 0.000445)	0.0465 (-0.0445 - 0.138)	-5.12E-05 (-0.000541 - 0.000438)	-0.00170*** (-0.00212, -0.00127)	-0.00034 (-0.00101 - 0.000333)	0.00709 (-0.0137 - 0.0279)	-0.00318 (-0.0360 - 0.0296)
Level change	0.207* (0.0376 - 0.376)	380.4*** (277.4 - 483.4)	1.297*** (0.691 - 1.902)	0.398 (-0.134 - 0.930)	1.017 (-3.088 - 5.123)	-772.7 (-7.507e+09 - 7.507e+09)	16.85 (-109.5 - 143.2)
By race/ethnicity							
White	0.238* (0.0524 - 0.425)	386.6*** (273.1 - 500.2)	1.366*** (0.699 - 2.033)	0.416 (-0.174 - 1.007)	1.592 (-2.859 - 6.044)	-979.1 (-9.508e+09 - 9.508e+09)	24.94 (-130.6 - 180.5)
Black	0.156 (-0.283 - 0.594)	265.8* (53.95 - 477.6)	1.159 (-0.106 - 2.425)	-0.0733 (-1.254 - 1.107)	0.884 (-3.174 - 4.942)	-2.35 (-53.26 - 48.56)	-15.01*** (-23.31, -6.700)
Hispanic	0.0281 (-0.434 - 0.490)	502.3*** (231.2 - 773.5)	0.852 (-0.803 - 2.507)	0.815 (-0.631 - 2.261)	-4.337 (-24.27 - 15.59)	-16.99* (-32.83, -1.154)	-20.15 (-52.92 - 12.62)
Asian	0.0262 (-0.782 - 0.835)	310.8 (-535.7 - 1,157)	1.059 (-4.138 - 6.256)	1.358 (-3.281 - 5.998)	0.444 (-1.687 - 2.575)	0.321 (-13.00 - 13.64)	-27.52 (-181.5 - 126.4)
Trend change	-0.000310* (-0.000559, -6.05e-05)	-0.563*** (-0.715, -0.411)	-0.00192*** (-0.00281, -0.00102)	-0.00058 (-0.00137 - 0.000206)	-0.00133* (-0.00259, -8.02e-05)	-0.0381* (-0.0741, -0.00224)	-0.0437 (-0.104 - 0.0166)
By race/ethnicity							
White	-0.000356* (-0.000630, -8.22e-05)	-0.572*** (-0.740, -0.404)	-0.00202*** (-0.00300, -0.00104)	-0.000606 (-0.00148 - 0.000264)	-0.0013 (-0.00269 - 8.43e-05)	-0.0407* (-0.0798, -0.00167)	-0.0217 (-0.0850 - 0.0416)
Black	-0.000234 (-0.000875 - 0.000408)	-0.393* (-0.704, -0.0824)	-0.00171 (-0.00357 - 0.000142)	0.000109 (-0.00162 - 0.00184)	-0.000931 (-0.00371 - 0.00185)	0.00324 (-0.0731 - 0.0795)	-0.161 (-0.332 - 0.00924)
Hispanic	-5.41E-05 (-0.000729 - 0.000621)	-0.746*** (-1.144, -0.349)	-0.00126 (-0.00369 - 0.00116)	-0.00119 (-0.00331 - 0.000921)	-0.00303 (-0.00629 - 0.000228)	-0.0931 (-0.197 - 0.0104)	-0.108 (-0.329 - 0.112)
Asian	-3.76E-05 (-0.00122 - 0.00114)	-0.452 (-1.693 - 0.790)	-0.00152 (-0.00914 - 0.00609)	-0.00196 (-0.00876 - 0.00484)	0.00507 (-0.00505 - 0.0152)	0.103 (-0.143 - 0.349)	-0.0789 (-0.426 - 0.268)

Race							
White	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Black	-0.0126*** (-0.0170, -0.00815)	-9.848*** (-11.40, -8.295)	-0.0417*** (-0.0503, -0.0332)	-0.0471*** (-0.0568, -0.0373)	-0.0383*** (-0.0490, -0.0277)	-1.101*** (-1.507, -0.695)	-1.338*** (-2.075, -0.601)
Hispanic	-0.0206*** (-0.0252, -0.0161)	-10.63*** (-12.40, -8.861)	-0.0413*** (-0.0511, -0.0316)	-0.0294*** (-0.0404, -0.0184)	-0.0387*** (-0.0508, -0.0265)	0.104 (-0.430 - 0.637)	-0.676 (-1.592 - 0.239)
Asian	-0.0378*** (-0.0453, -0.0303)	-4.849 (-9.718 - 0.0200)	-0.0208 (-0.0472 - 0.00551)	-0.0680*** (-0.0907, -0.0453)	-0.0234 (-0.0551 - 0.00827)	-1.907** (-3.255, -0.558)	1.045 (-2.311 - 4.402)
Age	-0.000851*** (-0.00104, -0.000665)	-0.0411 (-0.159 - 0.0774)	-0.00022 (-0.000630 - 0.000189)	0.000189 (-0.000241 - 0.000619)	-0.00107*** (-0.00157, -0.000565)	0.0996*** (0.0773 - 0.122)	0.0500** (0.0158 - 0.0843)
Female	-0.0104*** (-0.0131, -0.00765)	-8.382*** (-9.556, -7.209)	-0.0370*** (-0.0433, -0.0307)	0.0393*** (0.0329 - 0.0457)	-0.0226*** (-0.0303, -0.0148)	0.0518 (-0.264 - 0.367)	-0.131 (-0.645 - 0.382)
Education							
High school degree or less	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Some college	-0.00104 (-0.00438 - 0.00231)	5.079*** (3.847 - 6.311)	0.0208*** (0.0140 - 0.0275)	0.000465 (-0.00697 - 0.00790)	0.0219*** (0.0136 - 0.0302)	-0.589*** (-0.922, -0.256)	-0.851** (-1.387, -0.315)
College degree	-0.0193*** (-0.0238, -0.0149)	5.966*** (4.033 - 7.899)	0.0288*** (0.0178 - 0.0398)	-0.0104 (-0.0216 - 0.000770)	0.0317*** (0.0176 - 0.0457)	-2.924*** (-3.498, -2.350)	-2.347*** (-3.385, -1.308)
Income							
<$40K	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
$40K-$59K	-0.0182*** (-0.0233, -0.0131)	-1.327 (-3.141 - 0.487)	-0.00087 (-0.0106 - 0.00887)	-0.0185*** (-0.0295, -0.00751)	0.0113 (-0.000565 - 0.0232)	-1.346*** (-1.817, -0.874)	-0.241 (-0.970 - 0.488)
$60K-$74K	-0.0198*** (-0.0254, -0.0143)	-1.627 (-3.675 - 0.422)	0.000973 (-0.00997 - 0.0119)	-0.0284*** (-0.0404, -0.0164)	0.0228** (0.00854 - 0.0370)	-1.599*** (-2.149, -1.049)	-0.134 (-0.973 - 0.704)
$75K-$99K	-0.0292*** (-0.0339, -0.0245)	-2.191* (-4.013, -0.368)	0.00167 (-0.00792 - 0.0113)	-0.0313*** (-0.0419, -0.0208)	0.0133* (0.00181 - 0.0248)	-2.497*** (-2.975, -2.020)	-0.870* (-1.604, -0.135)

$100K+	-0.0433*** (-0.0477, -0.0389)	-4.191*** (-5.974, -2.408)	-0.00318 (-0.0123 - 0.00594)	-0.0518*** (-0.0615, -0.0421)	0.0113* (0.000228 - 0.0223)	-4.250*** (-4.687, -3.813)	-1.767*** (-2.519, -1.014)
Mental health diagnosis							
Anxiety, PTSD	0.00894*** (0.00561 - 0.0123)	-2.921* (-5.149, -0.694)	-0.00257 (-0.0135 - 0.00835)	0.0215*** (0.0118 - 0.0312)	-1.54E-05 (-0.0116 - 0.0115)	0.229 (-0.177 - 0.636)	0.772** (0.301 - 1.243)
Depression	0.0121*** (0.00928 - 0.0149)	-0.0327 (-2.237 - 2.171)	0.00488 (-0.00469 - 0.0145)	0.117*** (0.108 - 0.126)	0.00767 (-0.00209 - 0.0174)	0.743*** (0.343 - 1.142)	1.078*** (0.530 - 1.627)
Psychosis, schizophrenia, or bipolar disorder	0.00202 (-0.00431 - 0.00835)	-2.509 (-6.774 - 1.756)	-0.0113 (-0.0292 - 0.00665)	0.0446*** (0.0255 - 0.0636)	-0.0094 (-0.0280 - 0.00915)	-0.0769 (-0.739 - 0.586)	-0.0267 (-0.655 - 0.602)
Substance use disorder diagnosis	0.0526*** (0.0488 - 0.0563)	0.6 (-2.355 - 3.555)	0.0331*** (0.0227 - 0.0435)	0.0489*** (0.0400 - 0.0577)	0.0441*** (0.0347 - 0.0536)	2.044*** (1.598 - 2.489)	1.357*** (0.863 - 1.852)
Elixhauser comorbidity score	0.00893*** (0.00837 - 0.00949)	1.561*** (1.297 - 1.824)	0.00643*** (0.00497 - 0.00789)	0.00741*** (0.00608 - 0.00874)	0.0119*** (0.00979 - 0.0141)	0.0707* (0.0131 - 0.128)	0.0577 (-0.0518 - 0.167)
Other pain-related diagnosis	0.0389*** (0.0377 - 0.0402)	4.914*** (4.330 - 5.498)	0.0232*** (0.0198 - 0.0266)	0.0199*** (0.0165 - 0.0232)	0.0868*** (0.0815 - 0.0922)	0.729*** (0.582 - 0.875)	0.834*** (0.545 - 1.123)
Days since last visit	-0.000211*** (-0.000226, -0.000196)	-0.0519*** (-0.0645, -0.0394)	-0.000288*** (-0.000356, -0.000220)	-0.000914*** (-0.000998, -0.000831)	-0.00113*** (-0.00124, -0.00101)	-0.00614*** (-0.00968, -0.00260)	-0.0264*** (-0.0380, -0.0149)
Number of visits	0.0125*** (0.0122 - 0.0129)	1.830*** (1.673 - 1.987)	0.00858*** (0.00774 - 0.00941)	0.00362*** (0.00296 - 0.00428)	0.0196*** (0.0185 - 0.0207)	0.0808*** (0.0516 - 0.110)	0.0226 (-0.0310 - 0.0762)
Observations	1,284,468	191,970	194,045	194,045	194,045	194,045	51,143

*** $p<0.001$, ** $p<0.01$, * $p<0.05$

Note: Estimates are marginal effects. 95% confidence intervals are in parentheses.

Table 5-16. Marginal effects from Stage II (interacted) model, fibromyalgia

	Any fill (probability)	Average dosage (MMEs)	High dosage (probability)	Concurrent prescriptions (probability)	Fills	Days supplied	Days of concurrent prescriptions
Secular trend	0.000346*** (0.000181 - 0.000512)	-0.084 (-0.193 - 0.0244)	-0.000161 (-0.000730 - 0.000407)	-0.00202*** (-0.00253, -0.00151)	-0.000528 (-0.00134 - 0.000285)	-0.0296* (-0.0542, -0.00494)	0.0161 (-0.0187 - 0.0508)
By race/ethnicity							
White	-0.000676*** (-0.00101, -0.000337)	-0.594*** (-0.792, -0.395)	-0.00236*** (-0.00358, -0.00114)	-0.000727 (-0.00181 - 0.000359)	-0.00117 (-0.00286 - 0.000524)	-0.0104 (-0.0556 - 0.0349)	-0.0053 (-0.0702 - 0.0596)
Black	0.000745 (-0.000213 - 0.00170)	-0.395 (-0.809 - 0.0193)	-0.00149 (-0.00440 - 0.00142)	-0.00091 (-0.00346 - 0.00164)	-7.48E-05 (-0.00346 - 0.00331)	0.0111 (-0.0898 - 0.112)	-0.0684 (-0.227 - 0.0898)
Hispanic	-0.00117** (-0.00198, -0.000364)	-0.580* (-1.067, -0.0925)	-0.00218 (-0.00550 - 0.00114)	-0.00143 (-0.00431 - 0.00144)	-0.00106 (-0.00501 - 0.00290)	-0.0547 (-0.177 - 0.0676)	-0.253* (-0.464, -0.0429)
Asian	-0.000571 (-0.00213 - 0.000989)	-0.43 (-1.572 - 0.711)	-0.000105 (-0.00995 - 0.00974)	0.00314 (-0.00248 - 0.00876)	-0.00704 (-0.0178 - 0.00368)	-0.105 (-0.370 - 0.160)	0.0887 (-0.330 - 0.508)
Level change	0.401*** (0.190 - 0.613)	386.9*** (263.7 - 510.1)	3,654 (-22,712 - 30,021)	-110 (-2,529 - 2,309)	1.114 (-1.838 - 4.066)	1.722 (-184.3 - 187.8)	-1.575 (-44.94 - 41.79)
By race/ethnicity							
White	0.459*** (0.229 - 0.688)	402.5*** (268.1 - 536.9)	3,055 (-13,204 - 19,314)	0.959 (-1.914 - 3.832)	1.275 (-2.161 - 4.712)	8.657 (-38.09 - 55.40)	3.103 (-45.68 - 51.89)
Black	-0.516 (-1.171 - 0.139)	266.8 (-15.67 - 549.3)	140.7 (-1,929 - 2,210)	1.855 (-12.07 - 15.78)	0.0556 (-2.312 - 2.424)	-7.535 (-87.95 - 72.88)	-34.59 (-172.6 - 103.5)
Hispanic	0.792** (0.238 - 1.345)	391.7* (59.65 - 723.8)	13,966 (-242,748 - 270,680)	7.559 (-51.98 - 67.10)	1.122 (-6.000 - 8.245)	-51.5 (-2,145 - 2,042)	-13.93*** (-17.91, -9.952)
Asian	0.388 (-0.679 - 1.455)	289.6 (-489.9 - 1,069)	0.049 (-8.107 - 8.205)	-10,156 (-230,394 - 210,082)	-1.288* (-2.373, -0.203)	-15.03 (-42.63 - 12.58)	1.063 (-58.71 - 60.84)
Trend change	-0.000593*** (-0.000905, -0.000281)	-0.571*** (-0.753, -0.389)	-0.00223*** (-0.00336, -0.00111)	-0.000762 (-0.00175 - 0.000228)	-0.00112 (-0.00266 - 0.000427)	-0.013 (-0.0551 - 0.0290)	-0.0296 (-0.0905 - 0.0312)
Race							
White	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*	*Ref.*

Black	-0.0114***	-9.234***	-0.0269***	-0.0470***	-0.0383***	-1.529***	-1.154*
	(-0.0180, -0.00480)	(-11.46, -7.012)	(-0.0399, -0.0138)	(-0.0633, -0.0308)	(-0.0518, -0.0248)	(-2.135, -0.922)	(-2.034, -0.273)
Hispanic	-0.0183***	-7.415***	-0.0339***	-0.0257**	-0.0189*	0.0626	-0.606
	(-0.0242, -0.0124)	(-9.914, -4.916)	(-0.0474, -0.0203)	(-0.0423, -0.00906)	(-0.0338, -0.00405)	(-0.647 - 0.772)	(-1.621 - 0.409)
Asian	-0.0382***	-3.169	-0.0244	-0.0906***	-0.0289	-1.411	-1.44
	(-0.0469, -0.0296)	(-10.33 - 3.995)	(-0.0578 - 0.00893)	(-0.136, -0.0452)	(-0.0655 - 0.00763)	(-3.452 - 0.630)	(-4.227 - 1.347)
Age	0.00110***	0.299***	0.00143***	0.00187***	-0.000909***	0.254***	0.158***
	(0.000945 - 0.00125)	(0.224 - 0.374)	(0.000957 - 0.00190)	(0.00134 - 0.00240)	(-0.00139, -0.000433)	(0.229 - 0.279)	(0.125 - 0.190)
Female	0.003	-8.787***	-0.0385***	0.0481***	-0.0321***	0.179	0.339
	(-0.000916 - 0.00692)	(-10.65, -6.923)	(-0.0487, -0.0283)	(0.0350 - 0.0613)	(-0.0436, -0.0206)	(-0.309 - 0.668)	(-0.320 - 0.999)
Education							
High school degree or less	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Some college	-0.00582*	3.350***	0.00785	0.00158	0.0170***	-0.490*	-0.184
	(-0.0106, -0.00109)	(1.616 - 5.084)	(-0.00258 - 0.0183)	(-0.0102 - 0.0133)	(0.00692 - 0.0271)	(-0.951, -0.0287)	(-0.775 - 0.407)
College degree	-0.0290***	1.889	-0.00291	0.00416	0.0158	-3.064***	-1.345*
	(-0.0348, -0.0232)	(-0.741 - 4.520)	(-0.0189 - 0.0131)	(-0.0144 - 0.0227)	(-0.00136 - 0.0330)	(-3.824, -2.303)	(-2.388, -0.303)
Income							
<$40K	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
$40K-$59K	-0.0157***	-2.299	-0.0158*	-0.00452	0.00224	-0.3	-0.00295
	(-0.0229, -0.00850)	(-4.866 - 0.267)	(-0.0312 - -0.000449)	(-0.0213 - 0.0123)	(-0.0128 - 0.0173)	(-0.932 - 0.333)	(-0.809 - 0.803)
$60K-$74K	-0.0273***	-7.268***	-0.0251**	-0.0253**	0.00574	-0.999**	-0.445
	(-0.0351, -0.0196)	(-9.979, -4.556)	(-0.0419, -0.00829)	(-0.0437, -0.00685)	(-0.0116 - 0.0231)	(-1.700, -0.297)	(-1.402 - 0.511)
$75K-$99K	-0.0372***	-7.031***	-0.0226**	-0.0166*	-0.00333	-0.818*	-1.003*
	(-0.0436, -0.0308)	(-9.511, -4.550)	(-0.0372, -0.00804)	(-0.0328, -0.000300)	(-0.0174 - 0.0108)	(-1.471, -0.165)	(-1.798, -0.208)
$100K+	-0.0534***	-9.274***	-0.0249***	-0.0300***	-0.0037	-2.383***	-0.821*
	(-0.0592, -0.0475)	(-11.63, -6.921)	(-0.0383, -0.0114)	(-0.0447, -0.0153)	(-0.0169 - 0.00951)	(-2.973, -1.792)	(-1.594, -0.0471)
Mental health diagnosis							
Anxiety, PTSD	0.00262	-0.563	0.00631	0.0231***	0.0128	0.283	0.314
	(-0.00129 - 0.00653)	(-2.986 - 1.859)	(-0.00621 - 0.0188)	(0.0133 - 0.0329)	(-0.00173 - 0.0273)	(-0.181 - 0.746)	(-0.209 - 0.838)
Depression	0.0106***	-0.264	-0.000726	0.128***	-0.00252	0.332	0.258
	(0.00731 - 0.0139)	(-2.680 - 2.152)	(-0.0123 - 0.0108)	(0.116 - 0.139)	(-0.0140 - 0.00899)	(-0.106 - 0.769)	(-0.320 - 0.835)

Psychosis, schizophrenia, or bipolar disorder	-0.00297	-2.244	-0.0132	0.0389***	-0.0116	-0.453	-0.293
	(-0.0102 - 0.00425)	(-7.025 - 2.537)	(-0.0336 - 0.00718)	(0.0245 - 0.0534)	(-0.0324 - 0.00916)	(-1.185 - 0.280)	(-0.918 - 0.333)
Substance use disorder diagnosis	0.0619***	2.657	0.0238***	0.0336***	0.0604***	2.605***	1.409***
	(0.0570 - 0.0668)	(-0.629 - 5.944)	(0.0106 - 0.0371)	(0.0231 - 0.0441)	(0.0475 - 0.0732)	(2.115 - 3.094)	(0.894 - 1.924)
Elixhauser comorbidity score	0.00908***	1.024***	0.00262**	0.00636***	0.00905***	0.0532	0.126*
	(0.00832 - 0.00984)	(0.692 - 1.356)	(0.000998 - 0.00425)	(0.00492 - 0.00780)	(0.00639 - 0.0117)	(-0.0212 - 0.127)	(0.00704 - 0.245)
Other pain-related diagnosis	0.0345***	3.574***	0.0140***	0.0252***	0.0765***	1.166***	0.983***
	(0.0330 - 0.0361)	(2.890 - 4.257)	(0.00993 - 0.0180)	(0.0212 - 0.0292)	(0.0700 - 0.0829)	(0.986 - 1.345)	(0.668 - 1.298)
Days since last visit	-0.000201*** (-0.000222, -0.000180)	-0.0341***	-0.000295***	-0.00246***	-0.00103***	-0.0129***	-0.0225***
		(-0.0495, -0.0187)	(-0.000416, -0.000174)	(-0.00271, -0.00220)	(-0.00117, -0.000899)	(-0.0180, -0.00789)	(-0.0344, -0.0107)
Number of visits	0.0105***	1.609***	0.00421***	0.00192***	0.0193***	0.112***	0.0655*
	(0.0101 - 0.0109)	(1.403 - 1.815)	(0.00340 - 0.00503)	(0.00110 - 0.00275)	(0.0178 - 0.0208)	(0.0734 - 0.151)	(0.00477 - 0.126)
Observations	855,371	137,984	137,984	139,484	139,484	139,484	44,939

*** $p<0.001$, ** $p<0.01$, * $p<0.05$

Note: Estimates are marginal effects. 95% confidence intervals are in parentheses.

Table 5-17. Predicted means from Stage I models: Sensitivity analysis with narrowed implementation period

	Any fill (%)	Average dose (MME)	High dose (%)	Concurrent prescriptions (%)
Osteoarthritis				
Observed	**14.03**	**48.26**	**12.35**	18.99
	13.76, 14.30	**46.66, 49.85**	**11.45, 13.25**	18.15, 19.82
Counterfactual	**15.04**	**58.94**	**15.76**	19.20
	14.52, 15.57	**55.62, 62.25**	**13.94, 17.59**	17.60, 20.81
Fibromyalgia				
Observed	**14.67**	**47.85**	**11.30**	23.45
	14.32, 15.01	**45.94, 49.76**	**10.22, 12.39**	22.48, 24.41
Counterfactual	**15.87**	**56.32**	**15.83**	24.52
	15.21, 16.53	**52.44, 60.20**	**13.64, 18.02**	22.66, 26.38

Note: MME = morphine milligram equivalents. 95% confidence intervals below estimates. Estimates refer to predicted means for December 2017. Bold indicates observed and counterfactual estimates with non-overlapping confidence intervals. The counterfactual scenario is that in which the guidelines were not released but all other predictors were as observed.

Table 5-18. Predicted means from Stage I models: Sensitivity analysis excluding observations after September 2017 (following the President's declaration of a public health emergency)

	Any fill (%)	Average dose (MME)	High dose (%)	Concurrent prescriptions (%)
Osteoarthritis				
Observed	13.73	**49.39**	**13.01**	19.93
	13.47, 14.00	**47.82, 50.95**	**12.12, 13.90**	19.12, 20.75
Counterfactual	14.15	**56.60**	**15.78**	19.99
	13.77, 14.54	**54.22, 58.99**	**14.47, 17.10**	18.83, 21.15
Fibromyalgia				
Observed	**14.43**	49.66	12.25	23.92
	14.09, 14.77	47.83, 51.49	11.19, 13.31	22.96, 24.88
Counterfactual	**15.38**	56.51	15.21	24.91
	14.89, 15.87	53.68, 59.35	13.62, 16.79	23.61, 26.22

Note: MME = morphine milligram equivalents. 95% confidence intervals below estimates. Estimates refer to predicted means for September 2017. Bold indicates observed and counterfactual estimates with non-overlapping confidence intervals. The counterfactual scenario is that in which the guidelines were not released but all other predictors were as observed.

Table 5-19. Three-month predicted means from Stage I models (October-December 2017)

	Any fill (%)	Average dose (MME)	High dose (%)	Concurrent prescriptions (%)
Osteoarthritis				
Observed	**13.99**	**48.89**	**12.25**	19.22
	13.73, 14.25	**47.34, 50.44**	**11.38, 13.12**	18.41, 20.03
Counterfactual	**14.82**	**59.23**	**16.19**	19.64
	14.34, 15.30	**56.19, 62.27**	**14.52, 17.86**	18.17, 21.12
Fibromyalgia				
Observed	**14.67**	48.44	**11.19**	23.86
	14.34, 15.01	46.57, 50.30	**10.15, 12.24**	22.91, 24.82
Counterfactual	**15.7**	57.85	**15.6**	25.5
	15.09, 16.30	54.27, 61.44	**13.60, 17.60**	23.75, 27.25

Note: MME = morphine milligram equivalents. 95% confidence intervals below estimates. Estimates refer to predicted means for October through December 2017. Bold indicates observed and counterfactual estimates with non-overlapping confidence intervals. The counterfactual scenario is that in which the guidelines were not released but all other predictors were as observed.

Appendix C: Supplementary Material for Chapter 4 (Naloxone Distribution)

Table 5-20. Impact inventory: Impacts considered in analyses of health sector perspective and societal perspective

Sector	Type of impact	Included in this reference case from…perspective?	
		Healthcare sector	*Societal*
Formal health care sector			
Health	*Health outcomes (effects)*		
	Longevity effects	X	X
	Health-related quality-of-life effects	X	X
	Other health effects (e.g., adverse events and secondary transmissions of infections)		
	Medical costs		
	Paid for by third-party-payers	X	X
	Paid for by patients out-of-pocket	X	X
	Future related medical costs (payers and patients)	X	X
	Future unrelated medical costs (payers and patients)	X	X
Informal healthcare sector			
Health	Patient time costs		X
	Unpaid caregiver time costs		Only for caretaking of minors
	Transportation costs		
Non-healthcare sectors (with examples of possible items)			
Productivity			
	Labor market earnings		X
	Cost of unpaid lost productivity due to illness		X
	Cost of uncompensated household production		X
	Criminal justice		X
	Other consumption		X
	Other social services		

Decision-analytic model and parameter estimates

Table 5-21 shows the base case estimates and ranges corresponding to each model parameter. The annual probability of overdose depended on whether the individual had overdosed

previously. However, it did not vary with time; that is, an individual with opioid use disorder (OUD) for ten years without a prior overdose is, in my model, as likely to overdose the following year as an individual in their first year of misuse.

The extent to which a dose of naloxone reduces mortality likely depends on whether it is the first or a subsequent dose the victim has received. However, prior research has not examined the exact nature of this relationship. In the base case analysis, I treat all doses equally. In a threshold analysis, I vary the effectiveness of subsequent EMS and police and fire doses from high (as effective as if it were the first dose) to low (no further reduction in mortality). I conduct two-way sensitivity analysis to identify any joint thresholds of effectiveness at which the model conclusions change.

In the base case, laypeople and first responders were assumed to obtain a new kit after every use and every two years, to reflect naloxone expiration. However, sensitivity analyses considering wide variation in the probability that a layperson has obtained naloxone account for the possibility that laypeople do not immediately obtain a new kit when needed.

Table 5-21. Base case parameter point estimates and ranges

Probabilities and Relative Risks

Parameter	Point Estimate	Range	Rationale	References
Per capita number of police and firefighters in the US	0.003	(0.001-0.005)	The Bureau of Labor Statistics reported 657,690 police and sheriff's patrol officers and 315,910 firefighters nationwide in 2016, corresponding to a per capita estimate of 0.003. In my hypothetical community of 50,000, this corresponds to 150 police and firefighters.	Occupational Outlook Handbook. US Bureau of Labor Statistics; 2018. Available from: https://www.bls.gov/ooh.
Per capita number of EMTs and paramedics in the US	0.0008	(0.0002-0.032)	The Bureau of Labor Statistics reported 244,960 EMTs and paramedics nationwide in 2016, corresponding to a per capita estimate of 0.0008. In my hypothetical community of 50,000, this corresponds to 40 EMTs.	Occupational Outlook Handbook. US Bureau of Labor Statistics; 2018. Available from: https://www.bls.gov/ooh.
Prevalence of opioid use disorder in the US	0.008	(0.004-0.012)	The 2016 National Survey on Drug Use and Health (NSDUH) estimated that 2.1 million people aged 12 and older had an opioid use disorder in 2016. This includes pain reliever use disorder and heroin use disorder, and corresponds to approximately 0.8% of the US population. In my hypothetical community of 50,000, this corresponds to 400 people with OUD.	Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52) [Internet]. Vol. 7. Rockville, MD; 2017. Available from: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf%0Ahttps://store.samhsa.gov/shin/content//SMA17-5044/SMA17-5044.pdf
Proportion of people with OUD who have previously overdosed at initialization of model	0.4	N/A	The model begins with a population of opioid users who have been misusing for ten years. Starting with an annual probability of overdose of 0.05 (see justification below), in ten years roughly 40% of this population will have experienced at least one prior overdose and 60% of the population will never have overdosed.	Darke S, Williamson A, Ross J, Mills KL, Havard A, Teesson M. Patterns of nonfatal heroin overdose over a 3-year period: findings from the Australian treatment outcome study. J Urban Health. United States; 2007 Mar;84(2):283–91.
Annual probability of initial overdose[+]	0.07	(0.0125-0.125)	This is the annual probability that a person with OUD will overdose, given that they have never overdosed. Probability of overdose in scientific studies is often reported over the lifetime of the user, and little longitudinal data on overdose probability exists. However, a 2007 longitudinal cohort study following users over a three-year period found an annual overdose rate of approximately 5% among study participants who had not overdosed in the past year (Darke, Williamson, Ross, Mills, Havard, & Teesson,	Darke S, Williamson A, Ross J, Mills KL, Havard A, Teesson M. Patterns of nonfatal heroin overdose over a 3-year period: findings from the Australian treatment outcome study. J Urban Health. United States; 2007 Mar;84(2):283–91.

			2007). In the past decade, overdose rates have increased sharply. During calibration, this estimate was increased to 0.07 so that, in line with the literature, 50-60% of people with OUD will have overdosed at least once by 15-20 years after initiation.	
Annual probability of subsequent overdose[+]	0.30	(0.15-0.45)	This is the annual probability that a person with OUD will overdose, given that they have overdosed previously. Prior overdose is a risk factor for future overdose. The aforementioned longitudinal cohort study found that the odds of overdosing over the three-year follow-up were 3.5 times as high for participants with a history of overdose. During calibration, this estimate was increased to 0.30, which reflects the sharply increased rates of overdose over the past decade.	Darke S, Williamson A, Ross J, Mills KL, Havard A, Teesson M. Patterns of nonfatal heroin overdose over a 3-year period: findings from the Australian treatment outcome study. J Urban Health. United States; 2007 Mar;84(2):283–91.
Probability overdose is witnessed[+]	0.79	(0.55-0.9)	Most estimates place the proportion of overdoses witnessed at 0.8. However, these estimates tend to be collected via self-report. Such data select for nonfatal overdoses; the true proportion of overdoses witnessed is thus likely to be lower. Zador, Sunjic, & Darke (1996) examined coronial files of all cases of heroin-related deaths, and found that 58% of heroin overdose deaths occurred in the presence of others. That study selected for fatal overdoses, likely underestimating the true value. After weighting by the probability that an overdose is/is not fatal (which takes into account the probability that it is a first-time vs. subsequent overdose, and the fatality rates of each), I estimate a probability of 0.79 that an overdose is witnessed.	Zador D, Sunjic S, Darke S. Heroin-related deaths in New South Wales, 1992: Toxicological findings and circumstances. Med J Aust. 1996 Feb 19;164(4):204-6. Darke S, Ross J, Hall W. Overdose among heroin users in Sydney, Australia: I. Prevalence and correlates of non-fatal overdose. Addiction. England; 1996 Mar;91(3):405–11. Lagu T, Anderson BJ, Stein M. Overdoses among friends: drug users are willing to administer naloxone to others. J Subst Abuse Treat. United States; 2006 Mar;30(2):129–33. Powis B, Strang J, Griffiths P, Taylor C, Williamson S, Fountain J, et al. Self-reported overdose among injecting drug users in London: extent and nature of the problem. Addiction. 1999;94(0965–2140 (Print)):471–8. Sergeev B, Karpets A, Sarang A, Tikhonov M. Prevalence and Circumstances of Opiate Overdose among Injection Drug Users in the Russian Federation. J Urban Heal. 2003;80(2):212–9. Sherman SG, Cheng Y, Kral AH. Prevalence and correlates of opiate overdose among young injection drug users in a large U.S. city. Drug Alcohol Depend. 2007;88:182–7. Strang J, Powis B, Best D, Vingoe L, Griffiths P, Taylor C, et al. Preventing opiate overdose fatalities with take-home

naloxone: pre-launch study of possible im pact and acceptability. Addiction. 1999;94(2):199–204.

				Galea S, Worthington N, Piper TM, Nandi V V, Curtis M, Rosenthal DM. Provision of naloxone to injection drug users as an overdose prevention strategy: early evidence from a pilot study in New York City. Addict Behav. England; 2006 May;31(5):907–12.
Probability that witness administers naloxone[+]	0.7	(0.4-0.9)	When asked, 75-90% of laypeople with a history of opioid misuse express capability and willingness to administer naloxone in cases of overdose (Strang, Powis, Best, Vingoe et al., 1999; Galea, Worthington, et al; Lagu, Anderson, & Stein, 2006). However, individuals may not have their naloxone at all times (Galea, Worthington, et al., 2006), reducing the probability that a witness with naloxone administers. Empirical studies suggest that laypeople equipped with and trained to use naloxone will administer it in 44%-80% of overdose events (Seal, Thawley, Gee, Bamberger, Kral, et al., 2005; Sherman, Gann, Scott, Carlberg, Bigg, & Heimer, 2008; Tobin, Sherman, Beilenson, et al., 2009). Because, in reality, the possibility that a given witness will not have their naloxone available at an overdose may be in part counterbalanced by the possibility that another witness has obtained naloxone, I estimate this parameter as 0.7.	Seal KH, Thawley R, Gee L, Bamberger J, Kral AH, Ciccarone D, et al. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: A pilot intervention study. J Urban Heal. 2005;82(2):303–11. Sherman SG, Gann DS, Scott G, Carlberg S, Bigg D, Heimer R. A qualitative study of overdose responses among Chicago IDUs. Harm Reduct J. England; 2008 Jan;5:2. Strang J, Powis B, Best D, Vingoe L, Griffiths P, Taylor C, et al. Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability. Addiction. 1999;94(2):199–204. Tobin KE, Sherman SG, Beilenson P, Welsh C, Latkin CA. Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives. Int J Drug Policy. Netherlands; 2009 Mar;20(2):131–6. Wagner KD, Valente TW, Casanova M, Partovi SM, Mendenhall BM, Hundley JH, et al. Evaluation of an Overdose Prevention and Response Training Programme for Injection Drug Users in the Skid Row Area of Los Angeles, California. Int J Drug Policy. 2010;21(3):581–6.
Probability that witness calls 911 given that lay naloxone was not administered[+]	0.5	(0.3-0.85)	Many of the studies estimating the proportion of overdose witnesses who call 911 do not differentiate by whether naloxone was administered. Those that do tend to be smaller studies or retrospective. For example, of 43 participants in the Staying Alive program in Baltimore, MD, 65% reported calling 911 when they witnessed an overdose and did not	Banta-Green C, Kuszler P, Coffin P, Schoeppe J. Washington's 911 Good Samaritan Drug Overdose Law: Initial Evaluation Results [Internet]. 2011. Available from: http://adai.uw.edu/pubs/infobriefs/ADAI-IB-2011-05.pdf%0AFind Galea S, Worthington N, Piper TM, Nandi V V, Curtis M, Rosenthal DM. Provision of naloxone to injection drug users as

administer naloxone (Tobin, Sherman, Beilenson, Welsh, & Latkin, 2009). In a similar study, Bennett, Bell, et al., 2011 found that, prior to participating in an overdose prevention program, participants reported calling 911 in 34% of overdose events. Other estimates range from 46% to 58% (Galea, Worthington, et al., 2006; Seal, Downing, et al., 2003; Sherman, Gann, et al., 2008). Some evidence suggests that Good Samaritan Laws may increase the probability of calling 911 (Banta-Green, Kuszler, Coffin, & Schoeppe, 2011; McClellan, Lambdin, Ali, et al., 2018), although barriers to these policies' effectiveness remain (Koester, Mueller, Raville, et al., 2017; Zadoretzky et al., 2017).

an overdose prevention strategy: early evidence from a pilot study in New York City. Addict Behav. England; 2006 May;31(5):907–12.

Koester S, Mueller SR, Raville L, Langegger S, Binswanger IA. Why are some people who have received overdose education and naloxone reticent to call Emergency Medical Services in the event of overdose? Int J Drug Policy [Internet]. Elsevier B.V.; 2017;48:115–24. Available from: http://dx.doi.org/10.1016/j.drugpo.2017.06.008

Lankenau SE, Wagner KD, Silva K, Kecojevic A, Iverson E, McNeely M, et al. Injection drug users trained by overdose prevention programs: responses to witnessed overdoses. J Community Health. Netherlands; 2013 Feb;38(1):133–41.

Mcclellan C, Lambdin BH, Ali MM, Mutter R, Davis C, Wheeler E, et al. Opioid-overdose laws association with opioid use and overdose mortality. Addict Behav [Internet]. 2018;(December 2017)

Seal KH, Downing M, Kral AH, Singleton-Banks S, Hammond J-P, Lorvick J, et al. Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area. J Urban Health. United States; 2003 Jun;80(2):291–301.

Sherman SG, Gann DS, Scott G, Carlberg S, Bigg D, Heimer R. A qualitative study of overdose responses among Chicago IDUs. Harm Reduct J. England; 2008 Jan;5:2.

Tobin KE, Sherman SG, Beilenson P, Welsh C, Latkin CA. Evaluation of the Staying Alive programme: training injection drug users to properly administer naloxone and save lives. Int J Drug Policy. Netherlands; 2009 Mar;20(2):131–6.

Tracy M, Piper TM, Ompad D, Bucciarelli A, Coffin PO, Vlahov D, et al. Circumstances of witnessed drug overdose in New York City: implications for intervention. Drug Alcohol Depend. Ireland; 2005 Aug;79(2):181–90.

Zadoretzky C, McKnight C, Bramson H, Des Jarlais D, Phillips M, Hammer M, et al. The New York 911 Good Samaritan Law and Opioid Overdose Prevention Among People Who Inject Drugs. World Med Heal Policy [Internet]. 2017;9(3):318–40. Available from: http://doi.wiley.com/10.1002/wmh3.234

Probability that witness calls 911 given lay naloxone administered[+]	0.5	(0.1-0.85)	Several studies suggest that overdose witnesses are less likely to call 911 if they have administered naloxone. For example, Doe-Simkins, Quinn, Xuan, et al. (2014) found in a retrospective cohort study that in about 25% of overdose events in which participants administered naloxone, 911 was called or emergency medical services were present. Walley, Xuan, et al. (2013) found that 911 was called or emergency medical services were present in 32.5% of events in which naloxone was administered by participants in San Francisco's DOPE project. Other studies have reported similar results, with estimates ranging from 10% to 29% (Koester et al., 2017; Lankenau et al., 2013; Sherman et al., 2008; Seal et al., 2005; Enteen et al., 2010; Bennett et al., 2011). However, many of these studies only capture individuals who return to community-based programs to report their experience administering naloxone, a non-representative group. Selection bias may thus threaten the validity of these estimates. Given a lack of high-quality data and conflicting experiences among experts on the ground, I estimate that the probability of calling 911 does not depend on naloxone administration, but conduct sensitivity analyses to investigate the possibility that it does.	Bennett AS, Bell A, Tomedi L, Hulsey EG, Kral AH. Characteristics of an overdose prevention, response, and naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania. J Urban Health. United States; 2011 Dec;88(6):1020–30. Doe-Simkins M, Quinn E, Xuan Z, Sorensen-Alawad A, Hackman H, Ozonoff A, et al. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. BMC Public Health. England; 2014 Apr;14:297. Enteen L, Bauer J, McLean R, Wheeler E, Huriaux E, Kral AH, et al. Overdose prevention and naloxone prescription for opioid users in San Francisco. J Urban Health. United States; 2010 Dec;87(6):931–41. Koester S, Mueller SR, Raville L, Langegger S, Binswanger IA. Why are some people who have received overdose education and naloxone reticent to call Emergency Medical Services in the event of overdose? Int J Drug Policy [Internet]. Elsevier B.V.; 2017;48:115–24. Available from: http://dx.doi.org/10.1016/j.drugpo.2017.06.008 Lankenau SE, Wagner KD, Silva K, Kecojevic A, Iverson E, McNeely M, et al. Injection drug users trained by overdose prevention programs: responses to witnessed overdoses. J Community Health. Netherlands; 2013 Feb;38(1):133–41. Seal KH, Thawley R, Gee L, Bamberger J, Kral AH, Ciccarone D, et al. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: A pilot intervention study. J Urban Heal. 2005;82(2):303–11.

Sherman SG, Gann DS, Scott G, Carlberg S, Bigg D, Heimer R. A qualitative study of overdose responses among Chicago IDUs. Harm Reduct J. England; 2008 Jan;5:2.

Walley, A. Y., Xuan, Z., Hackman, H. H., Quinn, E., Doe-simkins, M., Sorensen-alawad, A., … Ozonoff, A. (2013). Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts : interrupted time series analysis, 174(January), 1–13. https://doi.org/10.1136/bmj.f174

Zadoretzky C, McKnight C, Bramson H, Des Jarlais D, Phillips M, Hammer M, et al. The New York 911 Good Samaritan Law and Opioid Overdose Prevention Among People Who Inject Drugs. World Med Heal Policy [Internet]. 2017;9(3):318–40. Available from: http://doi.wiley.com/10.1002/wmh3.234

Probability that police and fire arrive before EMS, if 911 is called[+]	0.5	(0-1)	The probability that police and fire arrive first to the scene of an overdose will vary widely depending on the community, and there is a dearth of research estimating the distribution of this parameter. Therefore, I arbitrarily set the base case estimate at 0.5, and, in sensitivity analyses, examine the full range of zero to one.	
Probability that first responders (EMS/police and fire) administer naloxone if available	0.89	(0.8-1)	First responders may not always recognize an overdose as such or may fail to administer naloxone for other reasons. Sumner, Mercado-Crespo, Spelke, et al. (2016) find that Sumner et al. find that, out of 124 fatal overdose cases in which EMS attempted resuscitation, they administered naloxone 66% of the time. Women, older individuals, and those without clear evidence of illicit drug use were less likely to receive naloxone. Since Sumner et al. (2016) only looked at fatal cases, I adjust my estimate to account for the estimated 6% of overdoses that are fatal, assuming that first responders administer naloxone 90% of the time in ultimately nonfatal cases. Police and fire may differ from EMS on this parameter, but due to a lack of available dataIassume that it is the same for all first responders.	Sumner, S. A., Mercado-Crespo, M. C., Spelke, M. B., Paulozzi, L., Sugerman, D. E., Hillis, S. D., & Stanley, C. (2016). Use of Naloxone by Emergency Medical Services during Opioid Drug Overdose Resuscitation Efforts. *Prehospital Emergency Care: Official Journal of the National Association of EMS Physicians and the National Association of State EMS Directors*, 20(2), 220–225. https://doi.org/10.3109/10903127.2015.1076096

Probability of mortality due to overdose, given initial overdose and that (a) the victim is alone or (b) the witness does not administer naloxone or call emergency services	0.054	(0.0125-0.12)	Although the overall increase in mortality due to overdose for opioid users over a lifetime is significant, the probability of an individual overdose being fatal is low. In a large cohort study of Australian heroin users, the probability of mortality given first overdose was 0.03. This is a conservative estimate of mortality given no medical intervention, because unwitnessed mortalities or deaths outside of hospitals cannot be ascertained from emergency room records or surveys of living users of opioids, and are therefore highly dependent on death records. During calibration, I thus adjusted this value upward to 0.054, in order to approximate the 47,600 opioid overdose deaths in 2017. The upper bound is high to account for the uncertainty in this parameter, as well as rising fatalities and fentanyl prevalence in recent years.	Darke S, Mills KL, Ross J, Teesson M. Rates and correlates of mortality amongst heroin users: findings from the Australian Treatment Outcome Study (ATOS), 2001-2009. Drug Alcohol Depend. Ireland; 2011 Jun;115(3):190–5. Darke S, Ross J, Hall W. Overdose among heroin users in Sydney, Australia: I. Prevalence and correlates of non-fatal overdose. Addiction. England; 1996 Mar;91(3):405–11. Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. 2013;346(7894).
Probability of mortality due to overdose, given it is a subsequent overdose and that (a) the victim is alone or (b) the witness does not administer naloxone or call emergency services	0.164	(0.06-0.38)	In a large cohort study of Australian heroin users, the adjusted hazard ratio for mortality compared to first overdose was 3.03 (1.22-7.52). Using the estimate of probability of mortality given first overdose (0.03), the probability of overdose from subsequent overdose was calculated using this relative risk, and adjusted upward to 0.164 during calibration. The upper bound is high to account for the considerable uncertainty in this parameter, as well as rising fatalities and fentanyl prevalence in recent years.	Darke S, Mills KL, Ross J, Teesson M. Rates and correlates of mortality amongst heroin users: findings from the Australian Treatment Outcome Study (ATOS), 2001-2009. Drug Alcohol Depend. Ireland; 2011 Jun;115(3):190–5. Galea S, Worthington N, Piper TM, Nandi V V, Curtis M, Rosenthal DM. Provision of naloxone to injection drug users as an overdose prevention strategy: early evidence from a pilot study in New York City. Addict Behav. England; 2006 May;31(5):907–12. Strang J, Powis B, Best D, Vingoe L, Griffiths P, Taylor C, et al. Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible im pact and acceptability. Addiction. 1999;94(2):199–204.
Relative risk of mortality due to overdose, given that one of the three parties (layperson, police and fire, or EMS) administers naloxone.[+]	0.48	(.3-.7)	Studies of lay naloxone distribution programs have found between 89% and 100% overdose survival following naloxone administration (Bennett, Bell, Tomedi, et al., 2011; Enteen, Bauer, McLean, et al., 2010; Strang, Manning, Mayet, et al., 2008). A meta-analysis of lay naloxone programs found the odds of overdose reversal to be 8.58 times higher when lay naloxone was administered, compared to no administration (Giglio, Li, & DiMaggio, 2015).	Belz, D. et al., 2006. Naloxone use in a tiered-response emergency medical services system. *Prehospital Emergency Care*, 10(4), pp.468–471. Bennett AS, Bell A, Tomedi L, Hulsey EG, Kral AH. Characteristics of an overdose prevention, response, and naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania. J Urban Health. United States; 2011 Dec;88(6):1020–30.

Research on naloxone administration by EMS (both basic and advanced life support personnel) has found overdose survival rates of between 45 and 80% following administration (Belz, Lieb, Rea, et al., 2006; Gulec, Lahey, Suozzi, et al., 2018).

Because some of these cases may not have been fatal without naloxone, the relative risk of mortality following administration is estimated to be 0.6 in the base case analysis. However, because of the potential importance of this estimate to the model results, I vary it from zero (no mortality when naloxone is administered) to one (no *reduction* in mortality when naloxone is administered) in sensitivity analysis.

There are actually three separate relative risk parameters in the model, each describing mortality reduction due to administration by a different group (laypeople, police and fire, and EMS).

Lay naloxone administration occurs before first responder administration, saving time and reducing mortality. However, this advantage may be offset by the medical care that first responders can provide; moreover, first responders may be more likely to possess multiple doses of naloxone than laypeople (i.e., a full kit), improving their ability to reduce mortality since multiple doses are often required for successful reversal (Belz et al., 2006; Gulec et al., 2018).

Given the dearth of data examining the net effect of these competing factors, I assume in the base case that the mortality benefit is equal across the three groups. However, this may not be accurate, and in particular may underestimate the effectiveness of lay distribution. One-way sensitivity analysis on the effectiveness of naloxone distribution by laypeople allows evaluation of this possibility. Moreover, in the probabilistic sensitivity analysis, I allow each parameter to independently vary at the same time, in

Enteen L, Bauer J, McLean R, Wheeler E, Huriaux E, Kral AH, et al. Overdose prevention and naloxone prescription for opioid users in San Francisco. J Urban Health. United States; 2010 Dec;87(6):931–41.

Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a meta-analysis. Inj Epidemiol [Internet]. Cham: Springer International Publishing; 2015 Dec 22;2(1):10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5005759/

Gulec, N. et al., 2018. Basic and Advanced EMS Providers Are Equally Effective in Naloxone Administration for Opioid Overdose in Northern New England. *Prehospital Emergency Care*, 22(2), pp.163–169. Available at: https://doi.org/10.1080/10903127.2017.1371262.

Strang J, Manning V, Mayet S, Best D, Titherington E, Santana L, et al. Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses. Addiction. England; 2008 Oct;103(10):1648–57.

Walley, A. Y., Xuan, Z., Hackman, H. H., Quinn, E., Doe-simkins, M., Sorensen-alawad, A., … Ozonoff, A. (2013). Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts : interrupted time series analysis, *174*(January), 1–13. https://doi.org/10.1136/bmj.f174

order to examine a wider range of possible circumstances.

There is no combination of interventions in which the base case probability of mortality is zero; this accounts for cases in which the victim is not reached in time or the overdose cannot be reversed by naloxone (e.g., some cases of polydrug toxicity).

These mortality parameters are also applied to the probability of developing hypoxia if an overdose is survived.

As described below, regardless of whether EMS have naloxone available, they reduce mortality by an estimated 20% by managing cardiac and breathing conditions. Thus, the 52% reduction due to administration of naloxone by EMS is on top of this existing 20% reduction, and is thus applied to the smaller remaining risk of mortality. The situation is analogous for naloxone administered by police and fire.

			EMS who arrive at the scene of an overdose without naloxone can other provide medical assistance before the victim receives naloxone at the emergency department. I assume that, compared to receiving no naloxone or other medical assistance, this reduces mortality by 20%.	
Relative risk of mortality, given that EMS arrive but do not have naloxone.[+]	0.8	(.65-.95)	Yokell, Delgado, Zaller, et al. (2014) report that 0.2% of emergency room visits for overdose that resulted in death. This would correspond to a relative risk of 0.067 if these were first overdoses. However, this is an underestimate of mortality given EMS assistance without naloxone, because it does not account for victims who died before reaching the hospital, and because some of these victims will have received naloxone. I increase the relative risk accordingly.	Yokell M, Delgado M, Zaller N, Wang N, McGowan S, Green T. Presentation of prescription and nonprescription opioid overdoses to us emergency departments. JAMA Intern Med [Internet]. 2014 Dec 1;174(12):2034–7. Available from: http://dx.doi.org/10.1001/jamainternmed.2014.5413

Relative risk of mortality, given that police and fire arrive first but do not have naloxone.[+]	.95	(.8-1)	If police and fire arrive to the scene before EMS but are not equipped with naloxone, they may still reduce average mortality via rescue breathing or ventilation by bag-valve. I assume that, compared to receiving no naloxone or other medical assistance, this reduces mortality by 5%.	Belz, D., Lieb, J., Rea, T., & Eisenberg, M. S. (2006). Naloxone use in a tiered-response emergency medical services system. *Prehospital Emergency Care*, *10*(4), 468–471. https://doi.org/10.1080/10903120600885134
Probability of cessation given no recent overdose	0.15	(0.05-0.3)	In a prospective study of injection drug users in San Francisco (Evans, Hahn, Lum, et al., 2009), 28.8% ceased injecting for three months or more during follow-up; median time to cessation from initial interview was 331 days. In a similar study in Canada, Bruneau, Brogly, Tyndall, et al. (2004) found that 18.5% ceased injection for seven months or more. In both studies, however, heroin users were less likely to quit. Huo, Bailey, and Ouellet (2006) found that 16% of their sample ceased injection for a median of 16 months. I estimate that 15% of individuals in my cohort who have not recently overdosed cease use for at least 12 months.	Bruneau J, Brogly SB, Tyndall MW, Lamothe F, Franco EL. Intensity of drug injection as a determinant of sustained injection cessation among chronic drug users: the interface with social factors and service utilization. Addiction. 2004 Jun;99(6):727–37. Evans JL, Hahn JA, Lum PJ, Stein ES, Page K. Predictors of injection drug use cessation and relapse in a prospective cohort of young injection drug users in San Francisco, CA (UFO Study). Drug Alcohol Depend. 2009;101(3):152-157. doi:10.1016/j.drugalcdep.2008.12.007. Huo D, Bailey SL, Ouellet LJ. Cessation of injection drug use and change in injection frequency: the Chicago Needle Exchange Evaluation Study. Addiction. 2006;101(11):1606-1613. doi:10.1111/j.1360-0443.2006.01577.x.
Probability of cessation, given recent overdose	0.15	(0.025-0.3)	Evans et al. (2009) found that the individuals who had recently overdosed were 76% less likely to cease injection than those who had not recently overdosed. However, Huo et al. (2006) found that overdose was not a significant predictor of cessation. A study by Shah, Galai, Celentano, et al. (2006) of the ALIVE cohort found that median time to cessation was longer for individuals who had experienced overdose in the prior 6 months (time ratio = 1.48, 95% CI: 1.12-1.96). However, given the limited available data and the contrasting experiences of experts on the ground,	Evans JL, Hahn JA, Lum PJ, Stein ES, Page K. Predictors of injection drug use cessation and relapse in a prospective cohort of young injection drug users in San Francisco, CA (UFO Study). Drug Alcohol Depend. 2009;101(3):152-157. doi:10.1016/j.drugalcdep.2008.12.007. Huo D, Bailey SL, Ouellet LJ. Cessation of injection drug use and change in injection frequency: the Chicago Needle Exchange Evaluation Study. Addiction. 2006;101(11):1606-1613. doi:10.1111/j.1360-0443.2006.01577.x.

			estimate the post-overdose cessation rate as equal to the rate not following overdose. I reduce the lower bound on this parameter in order to examine the possibility that cessation rates are lower among those who recently overdosed.	Pollini RA, McCall L, Mehta SH, Celentano DD, Vlahov D, Strathdee SA. Response to overdose among injection drug users. Am J Prev Med.; 2006 Sep;31(3):261–4. Shah, N. G., Galai, N., Celentano, D. D., Vlahov, D., & Strathdee, S. A. (2006). Longitudinal predictors of injection cessation and subsequent relapse among a cohort of injection drug users in Baltimore , MD , 1988 – 2000, *83*, 147–156. https://doi.org/10.1016/j.drugalcdep.2005.11.007
Relative risk of cessation, given Emergency Department visit	1	(1-1.2)	Individuals who receive treatment for overdose in the Emergency Department (ED) may receive Screening, Brief Intervention, and Referral to Treatment (SBIRT) to address opioid misuse and use disorder; in addition, they may receive ED-initiated buprenorphine/naloxone (Suboxone) to begin treating OUD. However, evidence suggests that SBIRT interventions do not improve substance use outcomes. Moreover, D'Onofrio, O'Connor, Pantalon, et al. (2017) find that ED-initiated buprenorphine/naloxone entails no difference in outcomes at six or twelve months follow-up. However, ED-initiated therapy may improve and become more widespread in the future; to account for this possibility, I set the upper bound of this parameter to 1.2 (20% higher "risk" of cessation given ED visit).	Bogenschutz, M. P., Donovan, D. M., Mandler, R. N., Perl, H. I., Forcehimes, A. A., Crandall, C., … Douaihy, A. (2014). Brief intervention for patients with problematic drug use presenting in emergency departments: A randomized clinical trial. *JAMA Internal Medicine*, *174*(11), 1736–1745. https://doi.org/10.1001/jamainternmed.2014.4052 D'Onofrio, G., O'Connor, P. G., Pantalon, M. V., Chawarski, M. C., Busch, S. H., Owens, P. H., … Fiellin, D. A. (2015). Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: A randomized clinical trial. *JAMA, -Journal of the American Medical Association*, *313*(16), 1636–1644. https://doi.org/10.1001/jama.2015.3474 Roy-Byrne, P., Bumgardner, K., Krupski, A., Dunn, C., Ries, R., Donovan, D., … Zarkin, G. A. (2014). Brief intervention for problem drug use in safety-net primary care settings: A randomized clinical trial. *JAMA, -Journal of the American Medical Association*, *312*(5), 492–501. https://doi.org/10.1001/jama.2014.7860 Saitz, R., Palfai, T. P. A., Cheng, D. M., Alford, D. P., Bernstein, J. A., Lloyd-Travaglini, C. A., … Samet, J. H. (2014). Screening and brief intervention for drug use in primary care: The ASPIRE randomized clinical trial. *JAMA, -Journal of the American Medical Association*, *312*(5), 502–513. https://doi.org/10.1001/jama.2014.7862
Annual probability of relapse given cessation	0.15	(0.13-0.18)	Using an 8-year observational study of heroin users in Chicago, I calculated an approximate probability of relapse for a former user in recovery. The probability of relapse falls dramatically with increased time in recovery; following Coffin & Sullivan (2013), I assumed that the probability of relapse falls by half after 10 years in recovery, and again after 15 years. I	Dennis ML, Foss MA, Scott CK. An eight-year perspective on the relationship between the duration of abstinence and other aspects of recovery. Eval Rev. 2007;31(6):585-612. doi:10.1177/0193841X07307771. Giglio RE, Li G, DiMaggio CJ. Effectiveness of bystander naloxone administration and overdose education programs: a

accounted for this by back-calculating a single annual probability that results in the correct proportion of the population remaining in recovery after 20 years.

meta-analysis. Inj Epidemiol. 2015;2(1):10. doi:10.1186/s40621-015-0041-8.

Gossop M, Marsden J, Stewart D. Dual dependence: assessment of dependence upon alcohol and illicit drugs, and the relationship of alcohol dependence among drug misusers to patterns of drinking, illicit drug use and health problems. Addiction. 2002;97(2):169-178.

Parmar MKB, Strang J, Choo L, Meade AM, Bird SM. Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths. Addiction. 2017;112(3):502-515. doi:10.1111/add.13668.

Seal KH, Downing M, Kral AH, et al. Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area. J Urban Health. 2003;80(2):291-301. doi:10.1093/jurban/jtg032.

Relative risk of overdose given that person has received naloxone (hypothetical moral hazard)[+]	1	(0.8-1.2)	While some people with substance abuse disorder report that they might use more intensively if naloxone were available (e.g., Kirane, Ketteringham, Bereket, et al., 2016), a review of lay naloxone distribution programs, finds no empirical evidence of this hypothesis. In fact, several studies show a reduction in opioid use following naloxone training. I thus use a base-case relative risk at 1 and vary the parameter in both a promotional and restrictive direction. In threshold analyses, I vary this parameter even more widely.	Kirane H, Ketteringham M, Bereket S, et al. Awareness and attitudes toward intranasal naloxone rescue for opioid overdose prevention. J Subst Abuse Treat. 2016;69:44-49. doi:10.1016/j.jsat.2016.07.005. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction. 2016;111(7):1177-1187. doi:10.1111/add.13326.

Costs and cost inputs

Parameter	Value	Range		References
Hourly wage of health professional trainer ($)	58.00	(48-70)	$29.42 is the Medicare reimbursement for 15 to 30 minutes of alcohol and/or substance abuse structured screening and brief intervention services (G0396).	Reimbursement for SBIRT. Substance Abuse and Mental Health Services Organization. Available from: https://www. Integration.samhsa.gov/sbirt/Reimbursement_for_SBIRT.pdf

				Inocencio TJ, Carroll N V, Read EJ, Holdford DA. The economic burden of opioid-related poisoning in the United States. Pain Med. 2013;14(10):1534-1547. doi:10.1111/pme.12183.
Hourly wage of person with OUD ($)	18.11	(14.50-27.70)	Calculated by reducing the average hourly wage for Americans in 2017 by 17.5%, in order to account for low labor participation by people using illicit substances.	U.S. Department of Justice National Drug Intelligence Center. (2011). *The Economic Impact of Illicit Drug Use on American Society*. Washington, D.C. Available from: https://www.justice.gov/archive/ndic/pubs44/44731/44731p.pdf
				Employment, hours, and earnings from the current employment statistics survey (National). US Bureau of Labor Statistics; 2018. Available from: https://data.bls.gov/pdq/SurveyOutputServlet?request_action=wh&graph_name=CE_cesbref3.
Hourly wage of police and fire ($)	27.30	(13.70-41)	Weighted average of median hourly income for firefighters and patrol officers in 2016, inflated to 2017.	Occupational Outlook Handbook. US Bureau of Labor Statistics; 2018. Available from: https://www.bls.gov/ooh.
Hourly wage of EMS personnel ($)	16.05	(8-24)	The median pay for EMTs & paramedics was $15.71 in 2016, whichIinflate to July 2017 dollars.	Occupational Outlook Handbook. US Bureau of Labor Statistics; 2018. Available from: https://www.bls.gov/ooh.
Number of trainees per trainer (first responder trainings)	20	(5-100)	This parameter scales the cost of trainer wages to account for the fact that multiple first responders (police and fire/EMS) will typically be trained simultaneously.	
Number of trainers per training (layperson trainings)	5	(1-20)	This parameter scales the cost of trainer wages to account for the fact that multiple laypeople will sometimes be trained simultaneously—e.g., by community-based programs. Other times, laypeople will receive one-on-one training, for instance when obtaining naloxone at a pharmacy. This parameter takes both types of circumstance into account.	

Duration of layperson trainings (minutes)	15	(5-60)	Training length varies. Some community-based programs may last thirty minutes or an hour and involve broader training (e.g., in CPR administration), while naloxone obtained from a pharmacist via standing order may involve less training.	Guide to developing and managing overdose prevention and take-home naloxone projects [Internet]. Harm Reduction Coalition; 2012 [cited 2018 May 8]. Available from: http://www.overdosepreventionstrategies.org/wp-content/uploads/2015/03/od-manual-final-links.pdf. Personal communication with Lemont Gore (Michigan Unified), Leo Beletsky (Northeastern University), and Dominick Zurlo (New Mexico Department of Health).
Duration of trainings for police and fire (minutes)	60	(15-90)	Training length varies. In the DOPE project, provider trainings typically lasted 90 minutes, while others last about an hour. Overall, training in naloxone administration may be growing shorter as easier-to-use naloxone becomes available, and as police and fire become increasingly familiar with signs and management of overdose.	Guide to developing and managing overdose prevention and take-home naloxone projects [Internet]. Harm Reduction Coalition; 2012 [cited 2018 May 8]. Available from: http://www.overdosepreventionstrategies.org/wp-content/uploads/2015/03/od-manual-final-links.pdf. Personal communication with Gina Dahlem (University of Michigan).
Duration of trainings for EMS (minutes)	30	(7.5-45)	Training EMS personnel in naloxone administration is assumed to take roughly half as long as training for fire and law enforcement, because it is subsumed in their broader medical training.	
Cost of naloxone kit (two doses)	61.50	(6-300)	Gupta et al. report that the average price of injectable naloxone from the four dominant manufacturers was $24 per dose in 2016, while the cost of nasal spray (Narcan®) was $150. However, ADAPT Pharma offers a public interest price of $37.50 per intranasal dose. In the base case analysis, I assume that 50% of naloxone is injectable and that 50% is nasal spray (at $37.50 per dose), corresponding to a weighted average price of $30.75 per dose, or $61.50 per kit. Some community-based programs report lower prices per kit; for instance, Yokell, Green, Bowman, et al., (2011) report a cost of approximately $3 per dose. I adjust the range of possible costs accordingly. A wide range accounts for a large variety of possible circumstances. The lower bound reflects a situation in which all naloxone is injectable or the public interest price of Narcan® falls. The upper bound reflects a situation in which all naloxone is Narcan® and there is no public interest pricing.	ADAPT Pharma® Expands Program Offering Free NARCAN® (naloxone HCl) Nasal Spray to Eligible Schools and Universities. Adapt Pharma; 2018. Available from: http://adaptpharma.com/adapt_press_release/march-19-2018-adapt-pharma-expands-program-offering-free-narcan/. Gupta R, Shah N, Ross JS. The Rising Price of Naloxone — Risks to Efforts to Stem Overdose Deaths. N Engl J Med. 2016;373(25):1-3. doi:10.1056/NEJMp1002530.

			While the average price of a naloxone kit is assumed to be equal regardless of the distribution target, laypeople may be more likely to receive injectable naloxone from community-based programs because of its affordability, while police and fire and basic life support personnel may be more likely to receive intranasal naloxone because of its ease of administration. As a result, naloxone kit prices for each group are allowed to vary independently in sensitivity analyses. Note that a threshold analysis is also conducted to examine the effect of further price increases in naloxone.	
Cost of ambulance transport ($)	500	(470-530)	National median Medicare payment per transport with add-on payments.	Ambulance providers: costs and Medicare margins varied widely; transports of beneficiaries have increased; 2012. United States Government Accountability Office. Available from: https://www.gao.gov/assets/650/649018.pdf.
Cost of Emergency Department visit ($)	16,760	(13,410-20,110)	Yokell, Delgado, Zaller, et al. (2014) tabulate charges associated with Emergency Department visits due to prescription and non-prescription opioid overdose, as well as subsequent inpatient stays. my estimate is a weighted average of expenditures for patients who are versus are not subsequently hospitalized ($29,807 and $3,397, respectively; proportion hospitalized is 0.506).	Yokell, M., Delgado, M., Zaller, N., Wang, N., McGowan, S., & Green, T. (2014). Presentation of prescription and nonprescription opioid overdoses to us emergency departments. *JAMA Internal Medicine*, *174*(12), 2034–2037. Retrieved from http://dx.doi.org/10.1001/jamainternmed.2014.5413
Productivity cost per overdose ($)	610	(550-670)	Market and household productivity costs due to overdose. This does not include the productivity cost of mortality due to overdose, which is reflected in the model when an individual dies.	Inocencio TJ, Carroll N V, Read EJ, Holdford DA. The economic burden of opioid-related poisoning in the United States. Pain Med. 2013;14(10):1534-1547. doi:10.1111/pme.12183.
Average annual market and non-market productivity of the general population	25-34: 64,686 35-34: 87,023 45-54: 83,354 55-64: 67,990 65-74: 38,504		Grosse, Krueger, and Pike (2018) estimated age-specific annual market and non-market productivity for Americans in 2016. I inflated these to 2017 dollars and, in sensitivity analysis, varied them by up to 20% in each direction.	Grosse, S. D., Krueger, K. V, & Pike, J. (2018). Estimated annual and lifetime labor productivity in the United States , 2016 : implications for economic evaluations. *Journal of Medical Economics*, *0*(0), 1–8. https://doi.org/10.1080/13696998.2018.1542520

	75+: 16,017			
Average per person annual consumption for the general population	25-34: 24,665 35-34: 25,524 45-54: 35,790 55-64: 38,653 65-74: 30,547 75+: 19,230		The 2017 Bureau of Labor Statistics' Consumer Expenditure Survey estimates average consumption per consumer unit. This includes average health care consumption. I use this to calculate per-person consumption and, in sensitivity analyses, varied them by up to 20% in each direction.	Consumer Expenditure Survey. U.S. Bureau of Labor Statistics. Available from: https://www.bls.gov/cex/2017/combined/age.pdf
Productivity cost due to OUD for individual not in treatment	12,100	(9,680-14,520)	On average, individuals with OUD have lower societal productivity due to factors such as greater unemployment, lower earnings, and absenteeism due to incarceration. This estimate was obtained by averaging the 2017-inflated results of three costing papers.	Birnbaum, H. G., White, A. G., Schiller, M., Waldman, T., Cleveland, J. M., & Roland, C. L. (2011). Societal Costs of Opioid Abuse, Dependence and Misuse in The United States. *Pain Medicine*, *12*, 657–667. https://doi.org/10.1016/S1098-3015(10)72532-8 Florence, C., Luo, F., Xu, L., & Zhou, C. (2016). The Economic Burden of Prescription Opioid Overdose, Abuse and Dependence in the United States, 2013 Curtis. *Medical Care*, *54*(10), 901–906. https://doi.org/10.1097/MLR.0000000000000625. Mark, T. L., Woody, G. E., Juday, T., & Kleber, H. D. (2001). The economic costs of heroin addiction in the United States. *Drug and Alcohol Dependence*, *61*, 195–206.
Criminal justice system costs	5,000	(4,000-6,000)	This estimate captures the policing, legal, and incarceration costs associated with opioid misuse, as well as costs to victims of crimes committed by individuals (e.g., due to lost property). Incarceration costs exclude those associated with absenteeism, which are captured in productivity costs. The estimate reflects an average of the 2017-inflated results of three costing papers.	Birnbaum, H. G., White, A. G., Schiller, M., Waldman, T., Cleveland, J. M., & Roland, C. L. (2011). Societal Costs of Opioid Abuse, Dependence and Misuse in The United States. *Pain Medicine*, *12*, 657–667. https://doi.org/10.1016/S1098-3015(10)72532-8 Florence, C., Luo, F., Xu, L., & Zhou, C. (2016). The Economic Burden of Prescription Opioid Overdose, Abuse and Dependence in the United States, 2013 Curtis. *Medical Care*, *54*(10), 901–906. https://doi.org/10.1097/MLR.0000000000000625. Mark, T. L., Woody, G. E., Juday, T., & Kleber, H. D. (2001). The economic costs of heroin addiction in the United States. *Drug and Alcohol Dependence*, *61*, 195–206.
Excess health care costs for individual with	11,000	(8,800-13,200)	Excess medical costs beyond those of a typical American are generated by people with OUD who are not in treatment, including costs due to septicemia,	Birnbaum, H. G., White, A. G., Schiller, M., Waldman, T., Cleveland, J. M., & Roland, C. L. (2011). Societal Costs of Opioid Abuse, Dependence and Misuse in The United States.

Parameter	Value	Range		References
OUD, not in treatment			HIV and Hepatitis C, and others. Direct health care expenditures due to overdose are not included here, as these are parameterized elsewhere in the model. This estimate was obtained by averaging the 2017-inflated results of two costing papers, excluding the direct medical costs of overdose used elsewhere in this model. In the model, individuals who are currently misusing accrue these costs.	*Pain Medicine*, *12*, 657–667. https://doi.org/10.1016/S1098-3015(10)72532-8 Mark, T. L., Woody, G. E., Juday, T., & Kleber, H. D. (2001). The economic costs of heroin addiction in the United States. *Drug and Alcohol Dependence*, *61*, 195–206.
Excess health care costs for individual with OUD, in treatment	5,800	(4,640-6,960)	Individuals receiving treatment for OUD may generate fewer medical costs on average; in addition to treatment costs, however, costs due to chronic complications such as HIV and Hepatitis C persist. This estimate was obtained by averaging the 2017-inflated results of three costing papers, as well as a U.S. Department of Defense estimate of annual methadone treatment cost. In the model, individuals who are not currently misusing accrue these costs.	Birnbaum, H. G., White, A. G., Schiller, M., Waldman, T., Cleveland, J. M., & Roland, C. L. (2011). Societal Costs of Opioid Abuse, Dependence and Misuse in The United States. *Pain Medicine*, *12*, 657–667. https://doi.org/10.1016/S1098-3015(10)72532-8 Florence, C., Luo, F., Xu, L., & Zhou, C. (2016). The Economic Burden of Prescription Opioid Overdose, Abuse and Dependence in the United States, 2013 Curtis. *Medical Care*, *54*(10), 901–906. https://doi.org/10.1097/MLR.0000000000000625. Mark, T. L., Woody, G. E., Juday, T., & Kleber, H. D. (2001). The economic costs of heroin addiction in the United States. *Drug and Alcohol Dependence*, *61*, 195–206. U.S. Department of Defense Office of the Secretary. (2016). *TRICARE; Mental Health and Substance Use Disorder Treatment* (Vol. 81). Washington, D.C. Retrieved from https://www.govinfo.gov/content/pkg/FR-2016-09-02/pdf/2016-21125.pdf

Utilities

Parameter	Value	Range		References
Currently misusing opioids	0.8	(0.73-0.9)	Individuals misusing opioids experience lower health-related quality of life on average, due to a variety of complications of substance use.	Nosyk B, Sun H, Guh DP, et al. The quality of eight health status measures were compared for chronic opioid dependence. J Clin Epidemiol. 2010;63(10):1132-1144. doi:http://dx.doi.org/10.1016/j.jclinepi.2009.12.003. Pyne JM, Tripathi S, French M, McCollister K, Rapp RC, Booth BM. Longitudinal association of preference-weighted health-related quality of life measures and substance use disorder

Parameter				References
				outcomes. Addiction. 2011;106(3):507-515. doi:10.1111/j.1360-0443.2010.03299.x.
				Zaric GS, Barnett PG, Brandeau ML. HIV transmission and the cost-effectiveness of methadone maintenance. Am J Public Health. 2000;90(7):1100-1111. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1446290/.
Relative increase for recovery health state utility	1.07	(1-1.123)	On average, health-related quality of life increases upon cessation from opioid misuse, but—due to chronic conditions related to opioid misuse—does not recover entirely.	Nosyk B, Sun H, Guh DP, et al. The quality of eight health status measures were compared for chronic opioid dependence. J Clin Epidemiol. 2010;63(10):1132-1144. doi:http://dx.doi.org/10.1016/j.jclinepi.2009.12.003. Pyne JM, Tripathi S, French M, McCollister K, Rapp RC, Booth BM. Longitudinal association of preference-weighted health-related quality of life measures and substance use disorder outcomes. Addiction. 2011;106(3):507-515. doi:10.1111/j.1360-0443.2010.03299.x. Vanagas G, Padaiga Z, Bagdonas E. Cost-utility analysis of methadone maintenance treatment in Lithuania. Medicina (Kaunas). 2010;46(4):286-292. Zaric GS, Barnett PG, Brandeau ML. HIV transmission and the cost-effectiveness of methadone maintenance. Am J Public Health. 2000;90(7):1100-1111. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1446290/.
Absolute reduction in utility due to long-term effects of severe hypoxia	0.119	(0-0.2)	The effects of hypoxia exist on a continuum. I estimate that, on average, individuals with severe hypoxia will experience a decline in utility equivalent to moving from a modified Rankin scale score of 0 (no symptoms) to a score of 1 (no significant disability, but some symptoms).	Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Making. 2010;30(3):341-354. doi:10.1177/0272989X09349961.

Other

Parameter				References
Start age of cohort	35	(25-45)	Using data from the 2016 National Survey on Drug Use and Health, Lipari, Ahrnsbrak, Pemberton, and Porter (2017) found that the average age of initiating heroin use was 25.5, and that the average aeg of initiating prescription pain reliever misuse was 24.4. I thus estimate the average age of nonmedical opioid use overall to be 25. Best, Ghufran, Day, et al. (2008) found the average	Best, D. W., Ghufran, S., Day, E. D., Ray, R., & Loaring, J. (2008). Breaking the habit: a retrospective analysis of desistance factors among formerly problematic heroin users. *Drug and Alcohol Review*, (July 2007), 619–624. https://doi.org/10.1080/09595230802392808

		length of heroin use to be roughly ten years. To approximate a cross-sectional population of individuals with opioid use disorder, I thus model a cohort of individuals starting at age 35. I use the annual probability of first overdose to adjust the proportion who, at ten years, will have previously overdosed.	Lipari, R. N., Ahrnsbrak, R. D., Pemberton, M. R., & Porter, J. D. (2017). Risk and Protective Factors and Estimates of Substance Use Initiation: Results from the 2016 National Survey on Drug Use and Health. *NSDUH Data Review*, (September). Retrieved from https://www.samhsa.gov/data/sites/default/files/NSDUH-DR-FFR3-2016/NSDUH-DR-FFR3-2016.pdf
Mortality rate of long-term opioid user, excluding mortality due to overdose (per person-year)	Mean age less than 35 and out of treatment: 0.0187 Mean age less than 35 and in treatment: 0.0073 Mean age 35 or over and out of treatment: 0.0298 Mean age 35 or over and in treatment: 0.0113	A systematic review and meta-analysis by Sordo, Barrio, Bravo, et al. (2017) estimates crude mortality rates (CMRs) for individuals with opioid dependence who are in vs. out of medication-assisted treatment. Because mortality due to overdose is accounted for elsewhere in the model, the CMRs included reflect rates of mortality due to all other causes of death. Sordo et al. break down the reviewed studies by whether the average age of the population studied was less than 35 years or 35+. I apply their estimates accordingly; however, given the sharp rise in all-cause mortality at older ages, I also incorporate age-specific mortality rates for the general population: when the relevant estimate from Sordo et al. is smaller than the age-specific mortality rates, I apply the latter. In sensitivity analyses, I vary these rates from 20% below to 20% above the base case estimates.	Murphy, S. L., Xu, J., Kochanek, K. D., & Arias, E. (2018). *Mortality in the United States, 2017*. Hyattsville, MD. Retrieved from https://www.cdc.gov/nchs/data/databriefs/db328-h.pdf Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., … Pastor-barriuso, R. (n.d.). Mortality risk during and after opioid substitution treatment : systematic review and meta-analysis of cohort studies. https://doi.org/10.1136/bmj.j1550

Note: + indicates that, in addition to the main sensitivity analyses, a threshold analysis was conducted for that parameter given its uncertainty and/or potential to influence the results; that is, the parameter was varied from zero to one to identify any thresholds at which the preferred strategy changed.

Table 5-22. Distribution assumptions and distribution parameters used in probabilistic sensitivity analysis

Description of Variable	Base case estimate	Low	High	Distribution	Mean	Standard Deviation
Starting age of cohort	35	25	45	Normal	35	5
Probability of overdose given no prior overdose	0.07	0.0125	0.125	Beta	0.07	0.028
Probability of overdose given prior overdose	0.3	0.15	0.45	Beta	0.3	0.075
Probability that overdose is witnessed	0.79	0.55	0.9	Beta	0.79	0.1
Probability that layperson witness would administer naloxone, if available	0.7	0.4	0.9	Beta	0.7	0.15
Probability that witness will call FRs	0.5	0.3	0.85	Beta	0.5	0.17
Probability that witness will call FRs if administered naloxone	0.5	0.1	0.85	Beta	0.5	0.175
Probability that police and fire arrive first	0.5	0	1	Beta	0.5	0.25
Probability that first responders administer naloxone given it is available	0.89	0.8	1	Beta	0.89	0.05
Mortality due to first overdose (given no naloxone, no first responders)	0.054	0.013	0.12	Beta	0.054	0.03
Mortality due to subsequent overdose (given no naloxone, no first responders)	0.164	0.06	0.38	Beta	0.108	0.108
Relative risk of mortality given administration of layperson naloxone (compared to no naloxone, no FRs)	0.48	0.3	0.7	Beta	0.48	0.2

Parameter	Value	Low	High	Distribution	Mean	SE
Relative risk of mortality if police and fire come but do not administer naloxone (compared to no naloxone, no FRs)	0.95	0	1	Beta	0.95	0.2
Relative risk of mortality if police and fire come and do administer naloxone (compared to no naloxone, no FRs)	0.48	0.3	0.7	Beta	0.48	0.2
Relative risk of mortality if EMS come but do not administer naloxone (compared to no naloxone, no FRs)	0.8	0	1	Beta	0.8	0.2
Relative risk of mortality if EMS come and do administer naloxone (compared to no naloxone, no FRs)	0.48	0.3	0.7	Beta	0.48	0.2
Probability of experiencing hypoxia due to overdose	0.05	0	0.3	Beta	0.05	0.125
Reduction in utility due to experience of hypoxia	0.119	0	0.2	Beta	0.119	0.041
Probability of cessation following overdose	0.15	0.025	0.3	Beta	0.15	0.063
Probability of cessation if no overdose	0.15	0.05	0.3	Beta	0.15	0.05
Probability of relapse if in recovery/treatment	0.15	0.13	0.18	Beta	0.15	0.015
Relative risk of cessation if the individual interacts with FRs	1	0.8	1.2	Normal	1	0.1
Utility if not in treatment	0.8	0.73	0.9	Beta	0.8	0.05
Relative increase in utility for individual in treatment/recovery	1.07	1	1.123	Normal	1.07	0.005

Hourly wage of EMS receiving naloxone training	16.05	8	24	Gamma	16.05	3.995
Hourly wage of layperson receiving naloxone training	18.11	24.5	27.7	Gamma	18.11	4.811
Hourly wage of police and fire receiving naloxone training	27.3	13.65	40.95	Gamma	27.3	6.825
Hourly wage of individual conducting naloxone training	58	48	70	Gamma	58	6
Length of naloxone training for laypersons (hours)	0.25	0.083	1	Gamma	0.25	0.375
Length of naloxone training for police and fire (hours); length of training for EMS is estimated to be half of this value	1	0.25	1.5	Gamma	1	0.25
Ratio of trainer to laypeople (inverse of number of trainees per trainer)	0.2	0.1	1	Beta	0.2	0.05
Ratio of trainer to EMS	0.05	0.01	0.2	Beta	0.05	0.02
Ratio of trainer to police and fire	0.05	0.01	0.2	Beta	0.05	0.02
Cost of naloxone kit (laypeople)	61.5	6	300	Gamma	61.5	27.75
Cost of naloxone kit (police and fire)	61.5	6	300	Gamma	61.5	6.7
Cost of naloxone kit (EMS)	61.5	6	300	Gamma	61.5	6.7
Criminal justice costs	5000	4000	6000	Gamma	5000	500
Excess health care costs, not in treatment	11000	8800	13200	Gamma	11000	1100
Excess health care costs, in treatment	5800	4640	6960	Gamma	5800	580
Excess productivity costs, not in treatment	12100	9680	14520	Gamma	12100	1210

Multiplier, consumption	1	.8	1.2	Normal	1	.1
Multiplier, productivity	1	.8	1.2	Normal	1	.1

Cost calculations

Costs are inflated to 2017 dollars using a CPI-based calculator.

Health care costs

Both the societal and the health sector perspective took into account the annual health care costs accrued by individuals in the model. Health costs reflect direct health care costs, including expenditures related to treatment, emergency transport, health insurance administration, and research and prevention efforts to address opioid use disorder (time costs of lay naloxone training were considered productivity costs). Health costs were calculated as the sum of (a) age-specific consumer expenditures on health care for the general population, and (b) estimated excess health care costs for individuals with opioid use disorder who are in or out of treatment (where treatment refers to any specialty treatment for opioid addiction). Individuals not currently misusing accrue costs associated with treatment, while those misusing accrue costs associated with not being in treatment. Tabale 5-21 details these parameters.

Productivity and criminal justice system costs

In the societal perspective, market and non-market productivity costs due to absenteeism (such as that caused by incarceration or overdose), greater unemployment, and lower earnings were taken into account. Following the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine, productivity costs were calculated as productivity costs due to OUD *minus* average, annual, age-specific productivity for the general population *plus* consumption (note that health care consumption was not double-counted).

Criminal just system costs due to policing, legal adjudication, incarceration, and victimization were also included in the societal perspective.

Naloxone training and distribution costs

The cost of training one first responder (police and fire or EMS) in naloxone use was calculated as the sum of first responder wages and trainer wages, multiplied by the length of training (taking into account that multiple first responders may be trained simultaneously). The initial cost of first responder distribution was equal to the total cost of a single first responder training and naloxone kit, multiplied by the number of first responders receiving naloxone nationwide. This parameter varied depending on the proportion of first responders equipped with naloxone (i.e., depending on which strategy was under consideration). Further costs accrued in subsequent years, as first responders received new naloxone kits and training refreshers.

The cost of training one layperson in naloxone use was calculated as the sum of layperson and trainer wages, multiplied by the length of training (taking into account that multiple laypeople may be trained simultaneously). The initial cost of lay distribution was equal to the total cost of a single layperson training and naloxone kit, multiplied by the number of laypeople receiving naloxone in the entire population—which depended on the strategy under consideration. In high layperson strategies in the base case analysis, this number was estimated as .75 times the number of people with OUD. However, because of positive spillover in which naloxone distributed to one person may be administered to someone else, this may be an overestimate of reality: ensuring that, at 75% of overdose scenes, the victim or at least one witness has at some time obtained naloxone can likely be achieved by distributing naloxone to fewer than 75% of people using (or their loved ones). This slightly disadvantages the high lay distribution strategies; however, sensitivity analyses on the cost parameters suggest that this error in distribution costs does not importantly influence the results. Further costs accrued in subsequent years, as laypeople received new naloxone kits and training refreshers.

Model calibration and validation

In step one of calibration, I adjusted the annual probability of overdose (given no prior overdoses) such that 50-60% of those surviving at 10-20 years after initiation would have a lifetime history of overdose (Darke et al., 1996, 2011; Sherman et al., 2007; Alexander Y Walley et al., 2013). I did so by modelling a cohort of novice individuals misusing opioids (age 25; holding all else in the model equal) and calculating the proportion of those surviving at years 10, 15, and 20 who had previously overdosed (Table 5-23). Since none of the strategies truly represents the status quo, I calibrated across strategies. By adjusting the probability of overdose (given no prior overdoses) from a starting value of 0.04 to 0.07, I found that, depending on the strategy, 36-38% of surviving model participants have overdosed at 10 years, 48-50% at 15 years, and 58-64% at 20 years.

In step two of calibration, I adjusted several parameters—the probability of subsequent overdose, the mortality rates associated with first and subsequent overdoses (absent intervention), and the relative risk of mortality due to naloxone administration—in order to approximate the estimated 47,600 opioid overdose deaths nationwide in 2017. WhileIreport my main results in terms of a hypothetical community, for this step of calibration, I scale the model up to the national population level. Since none of the strategies truly represents the status quo, I sought parameter estimates such that the number of deaths would be too high in the low LP/low PF/low EMS condition and too low in the other strategies. Table 5-23 details the changes made during each step.

Table 5-23. Model calibration

Step 1: Calibrate probability of first overdose to get percent of those still alive at 10-20 years who have ever overdosed close to 50-60%.

Parameter	Starting Value	Adjustment factor	New Value
Probability of overdose given no prior overdose	0.04	1.75	0.07

Step 2: Calibrate to number of 2017 opioid overdose deaths (47,600 in 2017)

Parameter	Starting Value	Adjustment factor	New Value
Probability of overdose given prior overdose	0.175	1.7	0.30
Probability of mortality due to overdose absent intervention, given no prior overdose	0.03	1.8	0.054
Probability of mortality due to overdose absent intervention, given prior overdose	0.0909	1.8	0.164
Relative risk of mortality due to naloxone administration	0.6	0.8	0.48

To validate the model, I first checked that the lifetime percentage of overdose deaths averted in the high LP/low EMS/low PF strategy was similar to that in two modelling studies of lay naloxone distribution (Coffin & Sullivan, 2013b; Uyei et al., 2017a) and one empirical study of the effect of naloxone access laws on mortality (Rees et al., 2017). To compare with Coffin and Sullivan (2013), I set the proportion of laypersons who have obtained naloxone in the "high LP" strategy to 0.2; in this case, 5.1% of fatal overdoses were averted over five years and 3.6% over the lifetime, compared to that study's 10.6% and 6.5%, respectively. To compare with Uyei, Fiellin, Buchelli, et al. (2017), I set the proportion of laypersons who have obtained naloxone in the "high LP" strategy to 0.3; then, 6.7% of fatal overdoses were averted over 20 years,

compared to that study's 6.3%. I hypothesize that Coffin and Sullivan's estimate was higher than ours because they made higher estimates on two parameters: (a) the probability that a witness is overdosed and (b) the probability that, given that the witness had obtained naloxone, they would have it available and administer it. Based on my assessment of the literature, I believe that 70% and 79%, respectively, are appropriate estimates.

Rees, Sabias, Argys, et al. (2017) find that Naloxone Access Laws correspond to a 21% reduction in opioid deaths after two years. When I set the proportion of laypersons who have obtained naloxone to 0.75 (as in the base case analysis), 20% of fatal overdoses were averted after two years.

Second, I compared the percentage of lay naloxone kits used with that in three empirical studies (Doe-Simkins et al., 2014; Enteen et al., 2010; Alexander Y Walley et al., 2013). At two years after distribution, Walley et al. (2013) found that approximately 11% of kits of lay kits had been used, while in my model 6.2% had. At roughly five years after distribution, Enteen et al. (2010) and Doe-Simkins et al. (2014) found that 18.5% and 5.9%, respectively, of lay kits had been used, compared to 7.0% in my model. I suspect that my model is underestimating the share of kits that will be used because I assumed that a lay kit will be replaced every two years or as soon as it is used, which is optimistic. Because this underestimation would cause my main results to be somewhat conservative but would not be expected to change the ranking of strategies, I did not change the model further.

Results

Results of varying the proportion of each group receiving naloxone in "high" strategies

In sensitivity analyses, I examined the level of distribution to each target group as a continuous variable (between 0% and 100% coverage). The net monetary benefit associated with each strategy increased monotonically with the percentage of each target group receiving naloxone (Figure 5-3). That is, there was no point at which the health gains due to increased distribution to any group are outweighed by increased costs. However, the validity of this analysis may be limited by the fact that I model costs as linearly increasing with greater levels of distribution, which does not capture the effects of non-random distribution in the target population and increasing costs as target individuals become harder to reach.

Figure 5-3. Net monetary benefit as a function of proportion in each target group receiving naloxone, given high distribution to the other groups
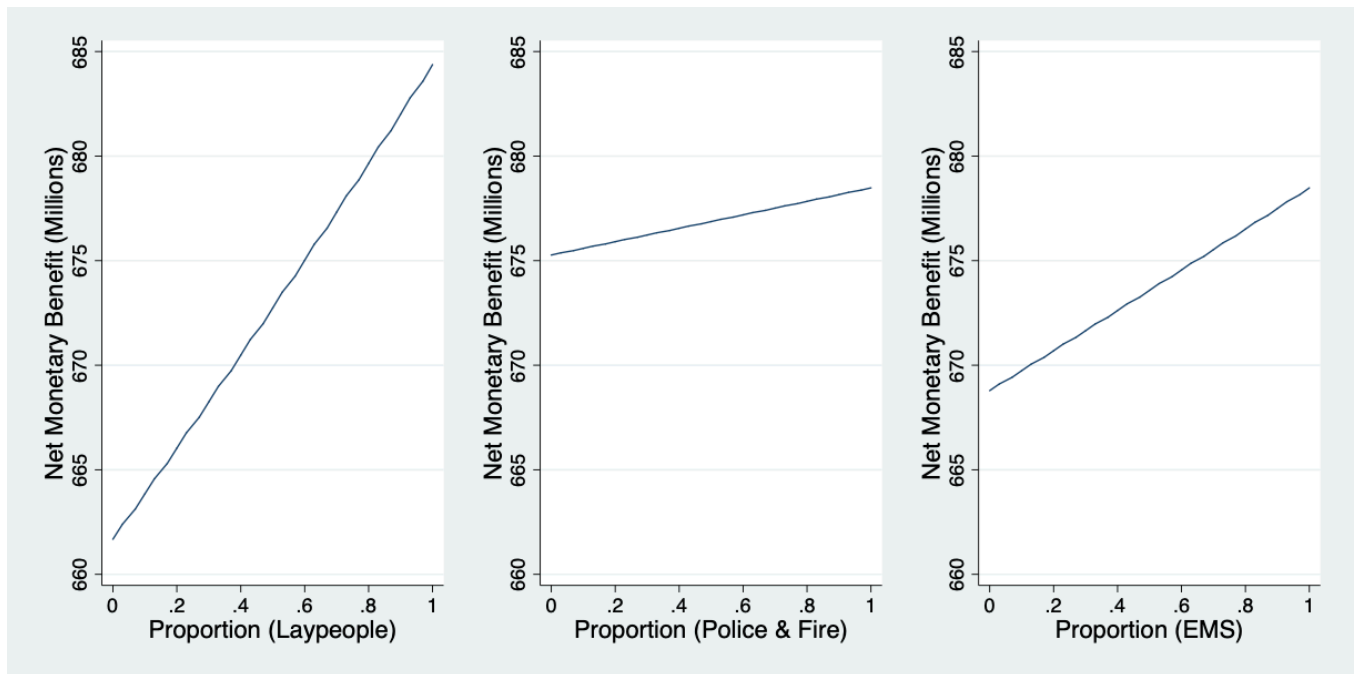
Note: In this model, net monetary benefit increases monotonically with the percentage of each target group receiving naloxone. That is, there is no point at which the health gains of increased distribution are outweighed by increased costs.

Threshold analyses (societal perspective)

Table 5-24 details the results of varying some parameters from zero to one, to identify thresholds
at which the preferred strategy changes, and to account for the possibility that the true parameter
value could be outside of my estimated range. Threshold analyses identified thresholds in nine
parameters that influenced the preferred strategy: the probability an overdose is witnessed,
naloxone kit costs, the reduction in mortality associated with each possible intervention, and
(hypothetical) moral hazard (Table 5-24). Each of these thresholds occurred at an extreme or
unlikely value.

Table 5-24. Results of threshold analyses

Parameter	Threshold Value	Preferred Strategy Below	Preferred Strategy Above
Probability of overdose given no prior overdoses	None	N/A	N/A
Probability of overdose given prior overdoses	None	N/A	N/A
Probability that the overdose is witnessed	0.049	High LP, low PF, high EMS	Maximum
Probability witness administers naloxone, if available	0.008	Low LP, high PF, high EMS	Maximum
Probability that witness will call 911	None	N/A	N/A
Probability that EMS have naloxone in "low EMS" strategies	None	N/A	N/A
Probability that police and fire arrive before EMS	0.030	High LP, low PF, high EMS	Maximum
Probability that PF have naloxone in "low PF" strategies	None	N/A	N/A

Relative risk of mortality: lay naloxone	0.986	Maximum	Low LP, high PF, high EMS
Relative risk of mortality: PF, without naloxone	0.092	High LP, low PF, high EMS	Maximum
Relative risk of mortality: PF naloxone	0.954	Maximum	High LP, low PF, high EMS
Relative risk of mortality: EMS, without naloxone	0.020	High LP, low PF, low EMS	Maximum
Relative risk of mortality: EMS naloxone	0.994	Maximum	High LP, high PF, low EMS
Cost of naloxone kit distributed to all parties ($)	1,432	Maximum	High LP, low PF, high EMS
Cost of lay naloxone kit ($)[a]	5,264	Maximum	High LP, low PF, high EMS
Relative risk of overdose given availability of lay naloxone (hypothetical moral hazard)	1.23	Maximum	Low LP, high PF, high EMS

Note: A strategy is preferred if it maximizes net monetary benefit compared to the other strategies. WTP set at $50,000. Some thresholds that do not affect the preferred strategy are excluded. Two thresholds on the probability that an overdose is witnessed are excluded because they occur at probabilities less than 0.005.
[a] This threshold analysis can also be used to evaluate greater costs of naloxone distribution more broadly—due, e.g., to difficulty reaching target laypeople.

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