PRESCRIPTION OPIOIDS, OPIOID USE DISORDERS, AND OPIOID DEATHS ACROSS 21 OECD NATIONS

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ABSTRACT

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AND OPIOID DEATHS ACROSS 21 OECD NATIONS

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Since the 1990s, the United States has seen increased prescription opioid consumption (POC) and an increase in the prevalence of opioid use disorders (OUD) and the opioid disorder death (ODD) rate. This paper examines three factors that may have fueled the opioid crisis: increased supply of prescription opioids, increased demand for opioids because of pain and economic related despair. A regression analysis of twenty-one OECD nations was used to examine the determinants of and the relationships between POC, OUDs, and ODDs. Over 1991-2019, consumption did not have a significant effect on OUDs or ODDs, but over 2003-2019 it had a positive significant effect on both. These results held if the US was removed from the sample, supporting some supply side effect across the panels after 2003. Furthermore, OUDs have a large, positive and significant effect on ODDs, indicating two possible pathways direct (straight from consumption) and indirect (through an effect on opioid use disorders) that POC relates to increased ODDs. One model estimates that 39% of the increase in US opioid fatalities is attributable to increased POC between 2003-2010.

Dedicated to:
My mother, Shireen Brohi (Ammi)
My father, Mian Mohsin Kalim Siddiqui (Abu)
My sister, Sidra Jabeen (Chotu)

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KEY TO ABBRERVIATIONS

POC	Prescription Opioid Consumption
PO(s)	Prescription Opioid(s)
OUD(s)	Opioid Use Disorder(s)
ODD(s)	Opioid Disorder Death(s)
IHME	Institute for Health Metrics and Evaluation
WB	World Bank
ILO	International Labor Organization
OECD	Organization of Economic Co-operation and Development
FRED	Federal Reserve Bank of St. Louis
FDA	US Food and Drug Administration
GDPH	GDP per Head (Base Yr 2015, Constant Prices, PPP)
Age(d)_65+	Percent of the Population Aged 65 and Above
HCE-PH	Healthcare Expenditure per Head
CNCP	Chronic Non-Cancer Pain
MAT	Medication Assisted Treatment
NMAT	Non-Medication Assisted Treatments
ER	Extended Release
DDP	Depressive Disorders Prevalence (Rate)
MSD	Musculoskeletal Disorders
LFPR	Labor Force Participation Rate
US	United States

CHAPTER 1: INTRODUCTION

The US opioid epidemic is a crisis, with opioid deaths estimated at over 47,300 in 2019, surpassing the deaths from road accidents and firearms at 44,200 and 37,000 fatalities, respectively (Global Burden of Disease Collaborative Network 2020b). Since the 1990s, when prescription opioid (PO) began to be used to treat chronic non-cancer pain (CNCP), prescription opioid consumption (POC) expanded greatly, as has opioid use disorders (OUDs) and opioid disorder deaths (ODDs) (Kenan, Mack, and Paulozzi 2012).

There are multiple factors at play in the opioid epidemic, as well as debate regarding the importance of each. In this thesis I consider three factors:

- Is the crisis the result of increased opioid demand? Has the incidence of pain increased?
- Is the crisis driven by increased supply, driven by the increased legal availability of opioids through prescriptions?
- Are systemic societal issues driving "deaths of despair" in the crisis? And is the US experience unique?

The idea of 'deaths of despair' came from Case and Deaton (2017) who identified increased death rates among middle-aged white non-Hispanic Americans without a four-year degree (Case and Deaton 2020). Case and Deaton identified three main causes of deaths of despair: drug overdoses (largely from opioids), alcohol liver diseases, and suicides (Case and Deaton 2020). They hypothesize that the decline in real wages and detachment from the labor force affected more than just living standards, but also the social, physical, and mental health of the population (Case and Deaton 2015). In addition, in the last decade the opioid epidemic began

spreading into new demographics including young adults and communities of color (Case and Deaton 2020).

The large spike in opioid disorder deaths (ODDs) in the United States (US) is not evident in other wealthy developed nations. While most countries have seen an increase in POCs, and some increase in ODDs, the levels are far lower than in the US. In 2019, Germany's POC was about 23.5% less than the US, but their ODDs were 90% lower (Global Burden of Disease Collaborative Network 2020a). Using the variation across countries in experiences with pain, prescription opioid supply, and despair, a panel of twenty-one high income 1990 members of the OECD are analyzed to identify the relative importance of these factors using data from 1991 to 2019.

CHAPTER 2: LITERATURE REVIEW

Opioids are an important medical drug but also a dangerous substance, as they bind to the opioid receptors of the brain resulting in psychological and physiological effects (Inturrisi 2002). Opioids can activate "reward processes in the absence of significant pain" and feelings of pleasure, which can motivate repeated use (Kosten and George 2002). The repeated use can result in dependence where the drug is required for normal functioning and "dose reduction or cessation will result in withdrawal symptoms" (Juurlink and Dhalla 2012; Kosten and George 2002). Opioid withdrawal is an unpleasant experience with symptoms that can include abdominal pain, nausea, and diarrhea (Juurlink and Dhalla 2012). Thus, continued opioid use not only provides pleasure, but also helps avoid withdrawal symptoms, making it difficult to stop using and further reinforcing dependence (Juurlink and Dhalla 2012). Chronic opioid use also creates tolerance, whereby the same dose of an opioid over time will have a declining effect on pain relief, pleasure creation and withdrawal avoidance. As a result of tolerance the user will require ever higher doses to attain the same effect (Juurlink and Dhalla 2012).

On the physiological side, opioids also depress the respiratory system. When the respiratory depression is so great, that the user experiences hypoxia (lack of oxygen) there is an overdose that can result in death (White and Irvine 1999). The dosage at which a user will overdose and/or die varies with individual, genetic, and environmental factors; it is difficult to know when a specific user may experience hypoxia (White and Irvine 1999). As the addictive, dependence, and tolerance characteristics of opioids positively reinforce use, there is an ever increasing probability of overdose with continued use (White and Irvine 1999). Given the unknowns, some users unintentionally overdose.

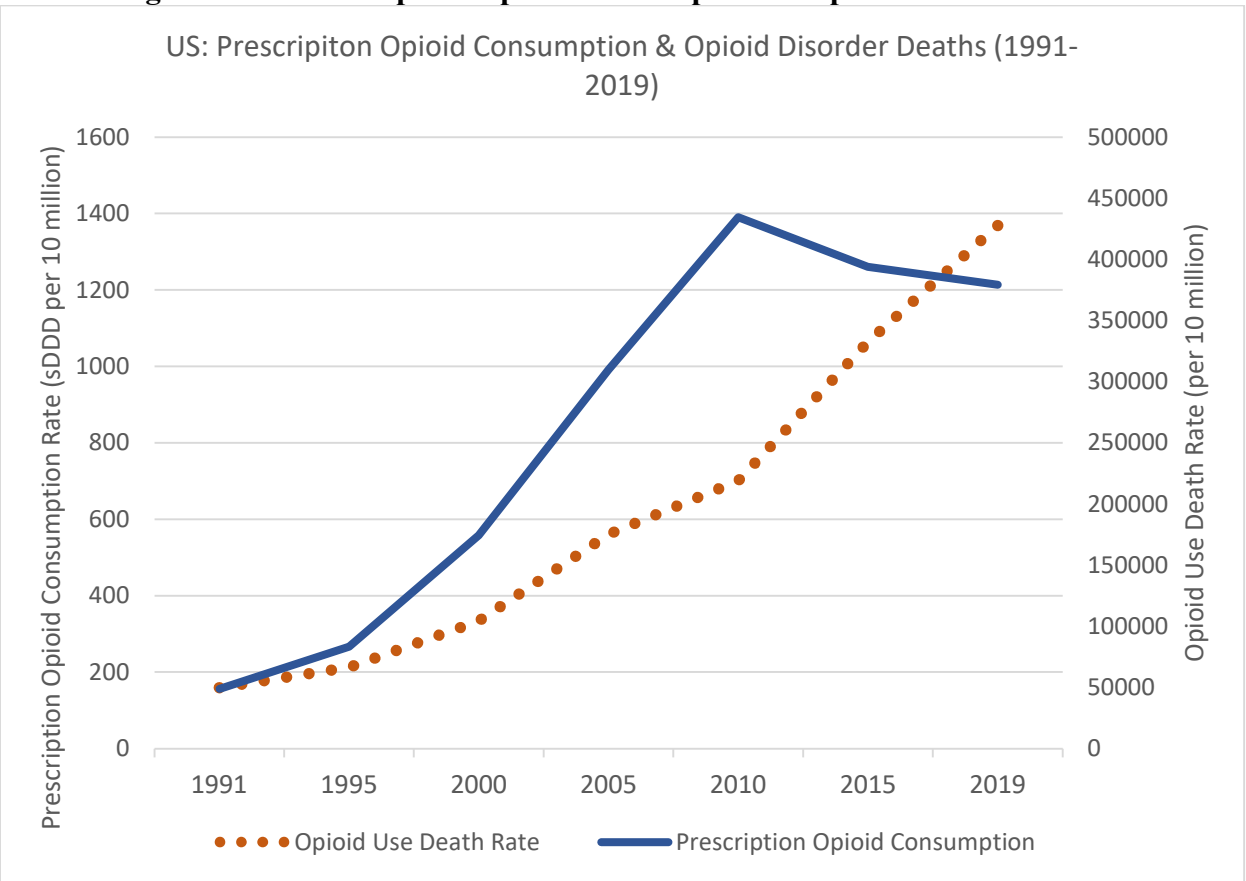
Historically as opioids became more widely available in the 19th century their use was expanded to treat all types of pain, from joint pain to wounds on the battlefield, as well as for ailments as common as the cough and baby colic (Macy 2019). Such widespread use brought to light opioids' many negative properties as users developed opioid use disorders (OUD). Many countries subsequently limited legal use to medical purposes with a physician's prescription (Juurlink and Dhalla 2012). At the same time, physicians were cautioned on the risks of opioid use and thus prescribed them sparingly.

Until the 1990s, prescription opioids (POs) continued to be used in specific circumstances such as anesthesia during operations or for a brief time after an injury or an operation. However POs were rarely used to treat chronic pain, (i.e. pain lasting over three months and/or after tissue has healed) "due to concerns of addiction and poor outcomes" (Tompkins, Hobelmann and Compton 2017). Chronic pain ideally was treated using a multidisciplinary pain treatment program that tackled the physical, mental, and medical aspects of pain in order to improve patient functioning (Tompkins et al. 2017). Analysis of clinical outcomes showed that these programs could be effective in helping patients return to employment as well as reduce medical expenditures (Tompkins et al. 2017). Under these practices, POC rates were low and OUD and ODDs generally rare in developed nations.

Unfortunately, in the last few decades the US has seen a decline in the use of multidisciplinary pain management (Kosten and George 2002). One factor was reduced reimbursement from health insurance for these programs, as there was a shift that "emphasized [a] fee-for-service model of health care delivery" (Tompkins et al. 2017). Without the availability of multidisciplinary pain management, chronic pain treatment was often left to primary care providers who were not well trained for this specialized health concern. Yet as

physicians continued to be hesitant to prescribe long-term opioids, the supply and demand of prescription opioids stayed low and generally steady, with the consumption in the US remaining under 70 mg of morphine equivalence (MME) per capita until 1990 (Walther Center n.d.). Then in the mid-1990s, US prescription opioid consumption began to increase before spiking to hit a peak of almost 750 MME/person in 2011 (Walther Center n.d.). These changes can be seen in Figure 1.

Figure 1: US Prescription Opioid Consumption & Opioid Disorder Deaths



Source: Institute for Health Metrics and Evaluation (IHME)

In the US, increased prescription opioid consumption (POC) was bolstered by two developments. First, a movement to medically treat pain for end-of-life care and chronic cancer gained traction. In 1986, the World Health Organization developed cancer pain treatment guidelines that included opioids (Tompkins et al. 2017). This movement also bled into general

medical standards of care with all types of pain requiring assessment and treatment (Tompkins et al. 2017). At the same time, pharmaceutical companies aggressively campaigned doctors, organizations advocating for pain relief, and government agencies such as the US Food and Drug Administration (FDA) to lower the hesitancy for using prescription opioids for a wider set of conditions, including chronic pain. They argued that providing pain relief was important for patients to function and the risk of side effects (such as substance abuse) was low. They successfully convinced medical boards to change guidelines and the Drug Enforcement Agency to loosen their scrutiny of high rates of opioid prescription (Tompkins et al. 2017). Together these two movements changed the way pain was treated.

One reason pharmaceutical companies encouraged prescription opioids at this time was because they had new patent-protected extended release (ER) versions of opioids, which garnered higher prices and larger profits than selling generic opioids. Physicians were told of the advantages of ER opioids in providing steady hours long pain relief in a pill form. The first to patent an ER pill was Purdue Pharma with MS-Contin, the brand name for ER morphine. Purdue purposefully downplayed the known risk of substance use disorders, so physicians came to be more comfortable prescribing opioids for chronic use (Macy 2019). A key to gaining the trust of physicians was the use of a few selected small studies that were repeatedly misinterpreted to support the claim that chronic prescription opioid use rarely led to substance use disorders (Tompkins et al. 2017). These claims percolated into the peer-reviewed medical literature and training materials of healthcare professionals without support in clinical research (Tompkins et al. 2017).

Under this backdrop, in 1996 Purdue Pharma released Oxycontin, an extended release (ER) version of oxycodone, marketing it as safe for long term use. Oxycodone is an opioid that is

1.5 times as potent as morphine (per milligram) (Von Korff et al. 2008). Its FDA-approved literature stated that "addiction was very rare" and "delayed absorption of Oxycontin was believed to reduce the abuse liability" (Mallatt 2020; Tompkins et al. 2017). Unfortunately, as opioid consumption increased so did the incidence of opioid use disorders (OUDs) and opioid deaths (ODDs).

In the 2000s, the FDA became alarmed by the increase in opioid use disorders (OUDs) and warned physicians of the risks, urging them to reduce the prescription of opioids. Additionally they were concerned prescribed ER-PO's were being resold illegally to those with OUDs who could crush the pills thereby releasing the entirety of the ER dose immediately (Maclean et al. 2020). In Virginia federal court, Purdue Pharma has "admitted that it marketed and sold its dangerous opioid products to healthcare providers, even though it had reason to believe those providers were diverting them to abusers" (Department of Justice 2020). Thus in 2010, the FDA pressured Purdue Pharma to reformulate Oxycontin to be "crush-resistant and therefore harder to snort or inject," hoping that it would reduce interest in diverting them (Maclean et al. 2020; Alpert, Powell and Pacula 2018). As was the goal, these two policies created a supply squeeze, showing up in a decline of prescription opioid sales after its peak in 2011 (Walther Center n.d.). The resulting difficulty in accessing legal prescription opioids pushed patients with OUDs, who had been getting prescriptions, into the black market (Mallatt 2020). Additionally, the decline in opioid prescriptions, reduced the availability of POs being resold on the black market, leading many to switch to heroin. Heroin use is more dangerous than the use of POs as there are no production standards or quality controls, and thus a user cannot know what substance(s) they are consuming or its dose. For example, heroin is often laced with fentanyl, a synthetically lab produced opioid, is a 100 times as potent as morphine per milligram

(CDC 2021). Fentanyl increases the high for a consumer while also increasing respiratory depression (Von Korff et al. 2008). The increased uncertainty that comes with using illegal opioids, results in a higher risk of overdose, often unintentional, for the user (Ruhm 2018). In the US and Canada, overdoses due to heroin laced with fentanyl have been key to rising opioid disorder deaths since 2010 (Ruhm 2018).

Substance abuse treatment that can help manage abuse disorders and reduce overdose risk, have two main types, medication assisted treatment (MAT) and non-medication assisted treatments (NMAT). Research shows that MAT is superior in reducing overdose and relapse because it uses medications (mixed opioid agonist-antagonists such as Buprenorphine) to prevent opioid withdrawal symptoms and reduce cravings, similar to how nicotine gum is used to counter the withdrawal effects of stopping tobacco use (Michels, Stöver, and Gerlach 2007). One study looked at 30 European nations from 1995 to 2013 found the "implementation of opioid substitution treatment programs" reduced drug related death rates" (Marotta and McCullagh 2018).

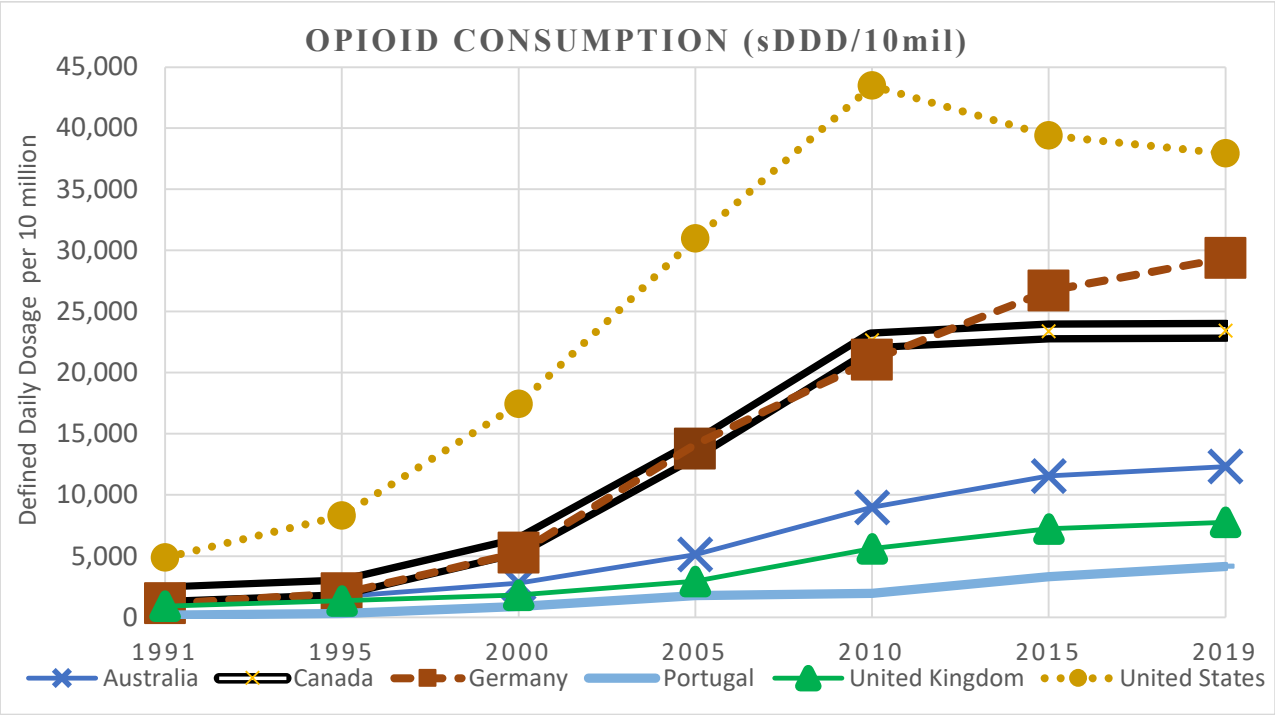
Unfortunately, in the U.S, there is a historical preference towards abstinence based NMAT based on 12-step types of programs and a shortage of MATs. Furthermore, as MAT requires a specially licensed physician, it comes with increased costs, further reducing access. Also, before the Affordable Care Act came into effect in 2014, most health insurance did not cover any substance abuse treatment. Since then, treatment has been covered for those who have health insurance, though deductibles and copays are often substantial. In comparison, in most wealthy OECD countries universal coverage and access for mental health care, including MAT, is more accessible. The United States' lack of affordable, accessible, and effective treatment options may contribute to its higher opioid disorder deathrate.

As shown in Figure 2, the US was far from the only country experiencing an increase prescription opioid consumption, yet it has many unique aspects. For one, across 1991- 2019, the US has always had the highest rate of POC among wealthy 1990 OECD members. The higher absolute starting point is important to note, because though the US's POC rate increased by 6.77 times between 1991-2019, that was the fourth lowest rate of growth among the panel of 21 OECD nations, only surpassing Sweden, Denmark, and New Zealand. The average 1990 OECD member has POC increase by 18.76 times between 1991 and 2019 or over 2.75 times as fast as the US's POC growth. At the same time, the US saw a greater proportion of its POC use to be in the form of oxycodone, which is a more potent and addictive version of opioid than other opioids like morphine or hydrocodone. In contrast, in Norway the number of oxycodone prescriptions written increased by a multiple of six between 2006 and 2017, yet the mean dose prescribed remained low (Muller, 2019). Furthermore, increased consumption in other developed countries seems to have started a bit later than the US, by when the US experience increased awareness of the abuse potential from increased prescription opioid consumption. Furthermore, as nations saw an increase in POC, most seem to have controlled the consumption more quickly than the US, which may relate to the lower subsequent OUD and ODDs. However, a few other nations have also experienced significant increases in not only POC but also OUDs and ODDs: the UK, Australia, and Canada, though not near the levels seen in the US. In Canada, the POC began rising in the late 1990s until being stabilized in 2010. Yet Canada's OUDs and ODDs continued to rise after 2010, likely because similar to the US the patients had switched to buying heroin and risked it being laced with a lethal dose of fentanyl (Ruhm 2018).

One interesting case is Germany, where a sharp increase in the use of strong opioids has not resulted in an opioid crisis. Germany's opioid use disorder (OUD) rate has increased but

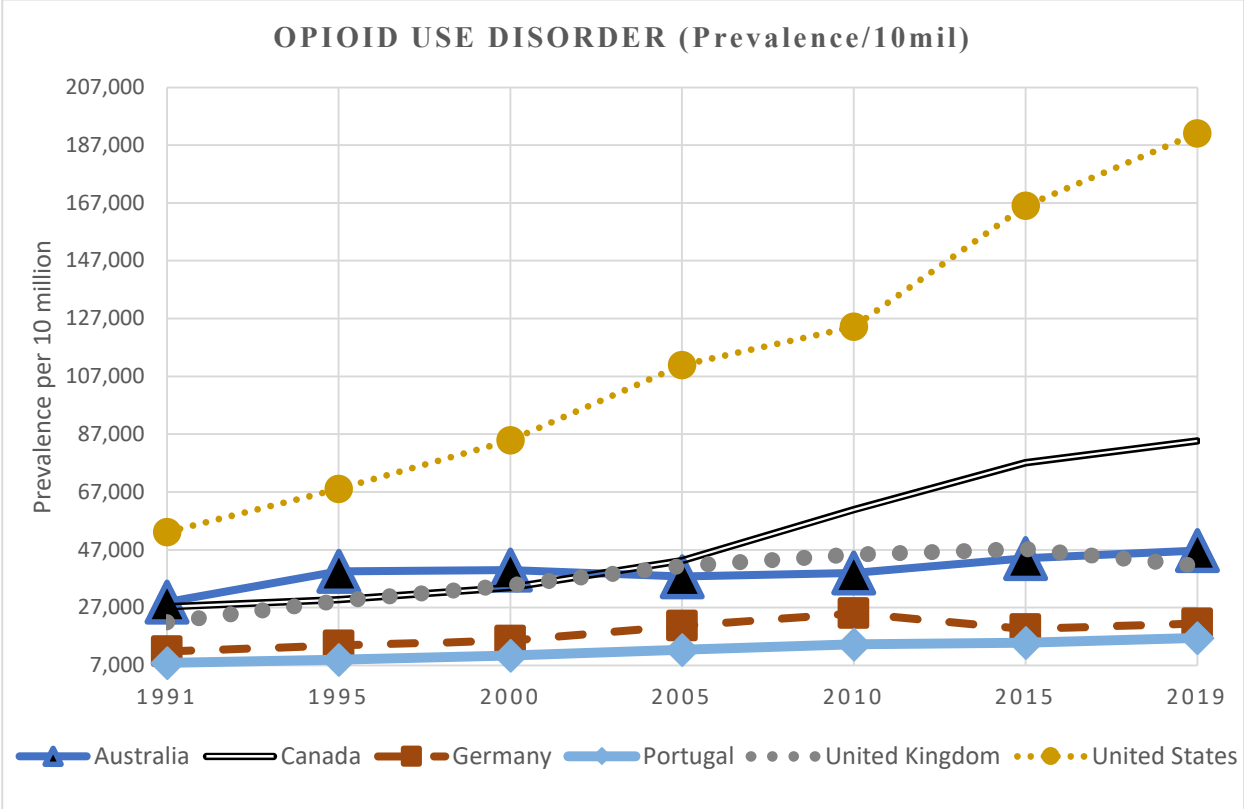
remains low among the OECD nations and its ODD rate has barely changed since 1991 (IMHE). From, 1991 and 2019, Germany's POC rate multiplied by 24.9 to become the second highest rate among OECD nations (IMHE). In comparison to the US, in 1991 Germany's POC rate was 77% lower, but by 2019 that gap had reduced significantly with Germany's POC rate only 23% lower (IMHE). In the early 1990s, cancer patients made up over 70% of POC in Germany, but by the early 2000s non-cancer patients were now consuming over 70% of POs, most often for back pain and osteoarthritis (Rosner et al 2019). This switch in PO usage is like that seen in the US, though it seems to have occurred a few years later in Germany. Thus, the German increase in POC rate was driven by more prescriptions for CNCP, at higher doses of more potent opioids. In 2011, among patients with "statutory health insurance," oxycodone had 26.8% market share of POs and fentanyl 32.3%. (Rosner et al 2019). This usage was despite the 2008 German national guidelines for long-term use of PO for CNCP does not recommend opioids (especially strong opioids) as first line treatment (Rosner et al, 2019). Uniquely even from the US, Germany's most commonly used prescription opioid is fentanyl, which is even more potent than oxycodone. Yet while Germany's POC rate increased by 2490% over 1991-2019, the opioid use disorder (OUD) rate had a more moderate increase at 82% and the ODD rate barely increased by 6% (IHME). The lack of an opioid epidemic in Germany despite high POC usage, indicates that factors other than increased supply may affect conversion into an opioid epidemic. A comparison of six OECD nations' POC, OUD, and ODDs is shown in Figures 2, 3, and 4.

Figure 2: Opioid Consumption in 6 OECD Nations



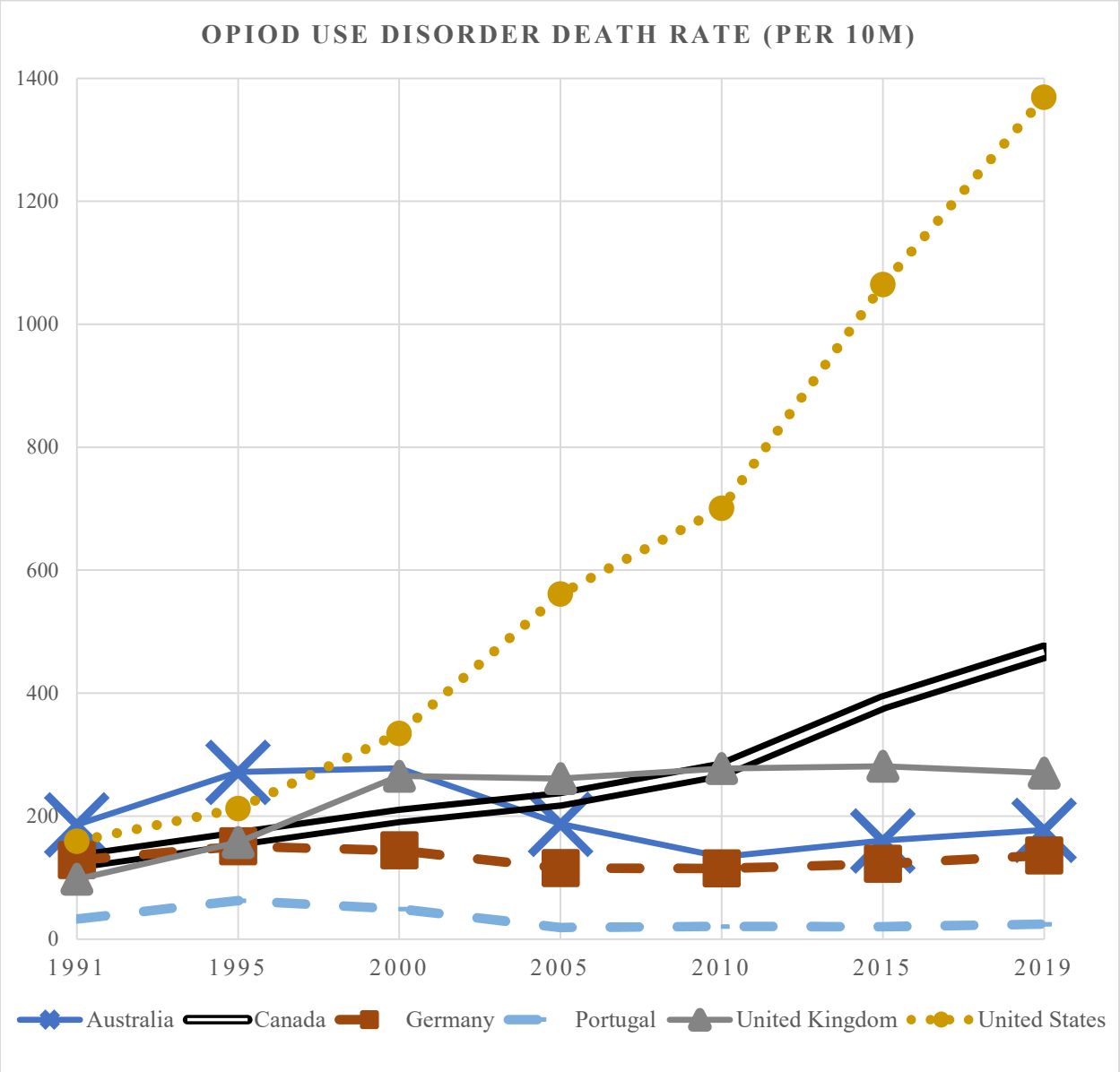
Source: Institute for Health Metrics and Evaluation (IHME)

Figure 3: Opioid Use Disorder Prevalence in 6 OECD Nations



Source: Institute for Health Metrics and Evaluation (IHME)

Figure 4: Opioid Disorder Deaths in 6 OECD Nations (1991-2019)



Source: Institute for Health Metrics and Evaluation (IHME)

In addition to the US, the increased use of prescription opioids (POs) for chronic non cancer pain relief is also occurred in several OECD nations. Thus, a possible factor driving the increased use of POs may be that the population is experiencing increased pain leading to increased demand for pain relief being fulfilled by prescription opioids (POs). For one, all OECD nations have an increasingly elderly population, with Japan having the oldest in the world. Not

only do the elderly have a greater chance of pain through ailment or injury, but studies indicate that they also have "decreased tolerance of (severe) pain and a slower resolution" (Gibson and Farrell 2004). This means that the elderly experience severe pain more often, for longer periods of time, and "received pain treatment more often" (Rustøen et al., 2005). Thus, a more elderly population correlates to increased prescription opioid consumption, which could be a pathway to greater OUDs and ODDs. In order to consider possible 'demand' factors, I will examine the disorders most frequently treated with chronic prescription opioids in OECD nations: neoplasms/cancers, injuries, and musculoskeletal disorders (back pain, osteoarthritis, etc) (Rosner et al 2019). Clinical studies have shown connections between the occurrence of these physiological disorders with POC, OUD and ODD. Looking at a panel of injured patients in Sweden, von Oelreich et al (2019) found an association with chronic opioid use and increased the risk of death. Dong et al (2020) showed that among construction workers with musculoskeletal disorders PO use tripled. Lee et al (2017), found that 6-8% of patients who had a "cancer curative intent surgery" and prescribed opioids during recovery developed persistent opioid use. Slosberg et al (2004) found that comparing treatment of pain for musculoskeletal disorders (MSD) in US clinical offices in 1980 and 2000 showed that for chronic pain, not only had opioid prescriptions doubled but "more potent opioids (hydrocodone, oxycodone, morphine)" were being prescribed.

The third factor considered is 'despair' caused by economic changes, represented by as changes in labor force participation rate (LFPR), employment in agriculture, construction or manufacturing. Economic factors are explored because in the US, communities hit by economic hardship are often where the opioid epidemic hit the earliest and hardest. Case and Deaton documented rising death rates from opioid use as well as suicide and alcohol use as 'deaths of

despair' (Case and Deaton 2020). Their research indicated that these increased deaths disproportionately affected American middle-aged white non-Hispanic workers without a four-year degree (Case and Deaton 2020). Other research has provided more evidence of an economic connection with opioid disorder deaths, including Venkataramani et al (2019), which looked at a set of 112 US counties that in 1999 had an automotive assembly plant within commuting distance. They performed a difference-in-difference analysis of opioid overdose mortality for counties affected by a plant closure against comparable county without a closure in 1999-2016. The study found that opioid mortality significantly increased with plant closures, and within five years of a closure the opioid overdose mortality rate had risen by 85% more relative to comparable counties with no closures (Venkataramani et al 2019). Another study has found a relationship between male labor force participation and US county level opioid overdoses (Denk 2019). Several studies have also shown a connection between depressive disorders with PO use, OUD and ODDs. Using a longitudinal analysis Sullivan et al (2006) found that those with depressive disorders (such as anxiety and depression) were 4.43 times more likely to report chronic opioid use than those without disorders. Other studies have calculated odds ratios that indicate depressive disorders are a risk factor for POC, OUD and ODD (Edlund et al. 2010a). Braden et al (2009) uses claims data from health plans from 1997-2005 to look for long-term (>90 days) opioid use among those with against those without a depression diagnosis the prior two years. They found that "persons with a history of depression are more likely to receive long-term opioid therapy for non-cancer pain" at higher doses, with lengthier supplies and more potent opioids then those without a history of depression (Braden et al 2009).

CHAPTER 3: DATA & METHODS

3.1 Data

In this thesis I use a quantitative comparison of macro-variables across a panel of countries to tease out the factors that contribute to prescription opioid consumption (POC), opioid use disorders (OUDs) and opioid disorder deaths (ODDs). A panel analysis assumes that the countries are expected to have similar responses to similar changes and is best done on a complete (or close to complete) dataset over a period (Babones 2014). The lack of a complete data set is a limiting factor for identifying the cohort of countries and the variables considered. This paper will evaluate a comparable group of countries defined as high-income by the World Bank in 1990 with populations of over half a million and to ensure a complete dataset as possible, the countries were limited to 1990 OECD members. The twenty-one countries that fit these criteria were Austria, Australia, Belgium, Netherlands, France, United Kingdom, United States, Canada, New Zealand, Germany, Italy, Greece, Ireland, Japan, Spain, Portugal, Denmark, Finland, Norway, Sweden, and Switzerland.

Data were gathered from four sources: (1) Organization for Economic Co-operation and Development (OECD n.d.), (2) Global Burden of Disease (GBD) Project at University of Washington's Institute for Health Metrics and Evaluation (IHME), (3) World Bank (WB), (4) International Labor Organization (ILO) and (5) Federal Reserve Bank of St. Louis (FRED). These organizations provide information on their original data sources (often government agencies) and transparency of their processing (including code) that generates their estimates. The possibility of errors in data collection and estimation, such as measurement errors, still exist but the work of these organizations to standardize, verify, and weight data to be comparable

across countries provides a reasonably good data set for analysis. Figure A1 shows the IHME's process for calculating the prevalence of OUDs.

The outcome data examined includes prescription opioid consumption (POC), the prevalence of opioid use disorders (OUD), and opioid disorder deathrate (ODD), in relation to factors within three categories: (1) prescription drug supply (2) factors that drive demand for pain management and (3) variables of despair. Data sources are provided in Table 1, and summary statistics for all variables used in the analysis are found in Table 2.

For opioid supply, prescription opioid consumption (POC) is indicated by prescription opioids sales in units of standardized defined daily dose (sDDD) of opioids as the rate per million population per day from the IHME website that was originally sourced from the International Narcotics Control Board (INCB) (Global Burden of Disease Collaborative Network 2020a). POC per capita provides quantifiable comparable measure of the country-level supply of POs, which will reflect the result of country level policies. The IMHE also provides estimated opioid disorder deaths (ODDs) rate and the prevalence of OUD. Prevalence is defined as the rate "of current cases (new and existing)" among the population within a period (CDC 2020).

Next to investigate the degree demand for POs is a factor, as the need for pain relief may have increased, the variables for prevalence of injuries, musculoskeletal disorders (MSD), and cancers are included. These three physiological disorders were included because across the literature they encompass what research indicate are the most frequent ailments contributing to increased POC. (Caudill-Slosberg, Schwartz and Woloshin 2004; Solomon et al. 2006; Azevedo São Leão Ferreira, Kimura and Jacobsen Teixeira 2006; Edlund et al. 2010b; Carmona-Bayonas et al. 2017; Lee et al. 2017; Musich et al. 2019; Rosner et al. 2019; von Oelreich et al. 2020). While these three sets of disorders do not encompass every diagnosis that leads to POC, the hope

is to provide coverage of the majority. A study by Vitzthum et al (2020b), showed that there was different rates of "persistent posttreatment opioid use, diagnoses of opioid abuse or dependence, and admissions for opioid toxicity" among the most common types of cancer. The data showed that survivors of liver, pancreas, and head and neck cancers have the highest rates of opioid abuse and rates for admission for opioid toxicity. (Vitzthum et al. 2020a). Thus, four categories of cancers were included in the analysis: liver, pancreas, head and neck cancers, and all other.

Table 1: Data Collected + Sources

Variables		*Includes:*	*Sources*
D_{it}	$Despair_{it}$	Employment in Construction (%) Employment in Manufacturing (%) Employment in Agriculture (%) Labor Force Participation Rate (LFPR) (%) Depressive Disorders Rate	WB/ILO FRED IHME
P_{it}	$Pain_{it}$	Prevalence of Injuries Rate Musculoskeletal Disorders Rate Cancer Rate (head and neck, liver, pancreatic, and other)	IMHE
C_{it}	$Control_{it}$	Healthcare Expenditure per Head (HCE-PH) Population Aged 65+ (Age_65+) (%) GDP per Head (real, constant prices, PPP)	IMHE OECD
POC_{it}	$Prescription\ Opoid\ Consumption_{it}$	Opioid Consumption Rate (standardized defined daily dose (sDDD))	IMHE
OUD_{it}	$Opioid\ Use\ Disorder_{it}$	Prevalence Rate of Opioid Use Disorders	IMHE
ODD_{it}	$Opoid\ Use\ Death\ Rate_{it}$	Opioid Use Death Rate	IMHE
i	$Countries$	In 1990: Member of OECD Population > 500,000 Defined as High Income by World Bank	IMHE OECD WB ILO
t	*Years*	1991-2019	

Sources: FRED, IMHE, OECD, WB, ILO

Variables used to examine the role of "despair" were chosen by seeing what past research explored, thus I include the labor force participation rate, prevalence of depressive disorders, and

employment in construction, manufacturing, and agriculture. Several studies indicate a connection between LFPR and employment in construction, manufacturing, and agriculture with increased POC, OUD, and ODD. Prevalence of depressive disorders (DDP), which includes anxiety and depression, is included in an attempt to measure psychological despair. DDP are included because clinical studies have showed increased odds ratios for POC, OUD and ODD among those with DDP then those without (Sullivan et al. 2006; Braden et al. 2009; Edlund et al. 2010b). Three variables are included as controls: healthcare expenditure per head (HCE-PH), GDP per head, and percent of the population aged sixty-five and above, with HCE-PH will be used as an indicator for medical treatment access in each country.

Looking at the US, the prescription opioid consumption rate increased by 677% between 1991 and 2019 and the (estimated) opioid death rate increased by 706%. However, an increased POC use is not unique, as the opioid consumption rates have increased substantially in every one of the twenty-one countries of the panel. The lowest POC increase for 1991-2019 was 99% in Sweden. Yet, Australia POC increased by 896% during this period. At the same time, the 2019 absolute POC level in the U.S. was much higher than all the other countries studied, with a POC ranging from between 1.29 times that of Germany to 27.5 times that of Japan.

Table 2: Descriptive Statistics

Variable	N	Mean	Std. Dev.
Prescription Opioid Consumption (sDDD/10M)	609	7,016	7,917
Opioid Use Disorders (prevalence rate, per 10M, age std)	609	29,237	24,183
Opioid Use Disorders Deaths (prevalence rate, per 10M, age std)	609	1.90	1.65
GDP per Head (real, USD)	609	41,535	9,781
Labor Force Participation Rate (%, ages 15-64)	609	73.39	5.61
Employed in Construction (%)	599	7.23	1.64
Employed in Manufacturing (%)	599	15.54	4.34
Employed in Agriculture (%)	609	4.85	3.60
Injuries (prevalence rate, per 100K, age std)	609	30,457	8,768
Musculoskeletal Disorders (prevalence rate, per 100K, age std)	609	21,366	2,213
Head and Neck Cancers (prevalence rate, per 100K, age std)	609	58.80	19.45
Liver Cancers (prevalence rate, per 100K, age std)	609	7.45	5.90
Pancreatic Cancers (prevalence rate, per 100K, age std)	609	8.37	1.74
All Other Cancers (prevalence rate, per 100K, age std)	609	8,801	3,642
Depressive Disorders (prevalence rate, per 100K, age std)	609	387,435	70,578
Healthcare Expenditure per Head (USD)	609	3,433	1,283

Sources: FRED, IMHE, OECD, WB, ILO

3.2 Methods

When using a country-level panel dataset, there are many factors that vary across countries as well as over time and thus much concern of biased estimates. Ordinary least squares

(OLS) regression would be inappropriate within a panel data context because potential omitted variables bias as well as heteroskedasticity can result in inefficient estimation (Kollmeyer 2021). The analysis in this thesis uses a set of regressions and tests, relying on panel data methods to control for time-invariant omitted variable bias (Bollen and Brand 2008). A Breusch Pagan Lagrange Multiplier Test (LM Test) is used to test for unobserved heterogeneity (Petersen 2004). A Hausmann test is used to test the null hypothesis that the "effect is not correlated with other regressors" (Park n.d.). If the Hausman's null is rejected, it indicates the time invariant variables are not random and the random effects model would provide biased and inconsistent estimators. In that case, fixed effects estimation is more appropriate (Petersen 2004). A set of time indicator variables are included in the estimation to control for any unmeasured effects across time that affect all countries (Allison 2009).

Given the panel nature of the data where units (such as countries) are quite different, A modified Wald test is used to test for group heteroskedasticity (i.e., the variance is different for different countries) (Wooldridge 2010). Also in panel data, especially where the number of occasions (T) is greater than the number of units (N), there can be both cross-sectional correlation (across units) and longitudinal correlation (over time) (Rabe-Hesketh and Skrondal 2012; Wursten 2018). Cross-sectional correlation is tested using a CD-test from Pesaran (2004) and Pesaran (2015), which tests for mean correlation between panel units (Wursten 2017). Longitudinal correlation (over time) are tested using two bias-corrected statistics introduced by (Born and Breitung 2016) of LM(k) and Q(p), which tests autocorrelation of order k and up to order p, respectively (Wursten 2017).

If both cross-sectional and longitudinal correlations exist, process proposed by Beck and Katz (1995) will be implemented. This process is implemented in Stata using the *xtpcse*

command; it assumes that the errors are heteroskedastic and contemporaneously correlated across panels (Statacorp 2017; Bailey and Katz 2011). The command also uses a Prais-Winstein transformation to estimate the parameters by making the observations uncorrelated across time. In addition an AR(1) structure is included, where a common autocorrelation parameter across the panels (rho ρ) is used to "accommodate longitudinal dependence" (Rabe-Hesketh and Skrondal 2012). The resulting panel-corrected standard errors are robust to cross-sectional correlation misspecification (Rabe-Hesketh and Skrondal 2012). Lastly, structural breaks in the panel data are considered using Stata package xtbreak, to conduct a sequential test for multiple breaks at unknown breakpoints which estimates the number and location of breaks using an algorithm from Bai and Perron (2003). The algorithm calculates the sum of squared residuals (SSR) for different number of breaks and different location and choose the one with the smallest SSR (Bai and Perron 2003).

Figure 5: Relationships between Opioid Disorder Deaths, Opioid Use Disorders and Prescription Opioid Consumption

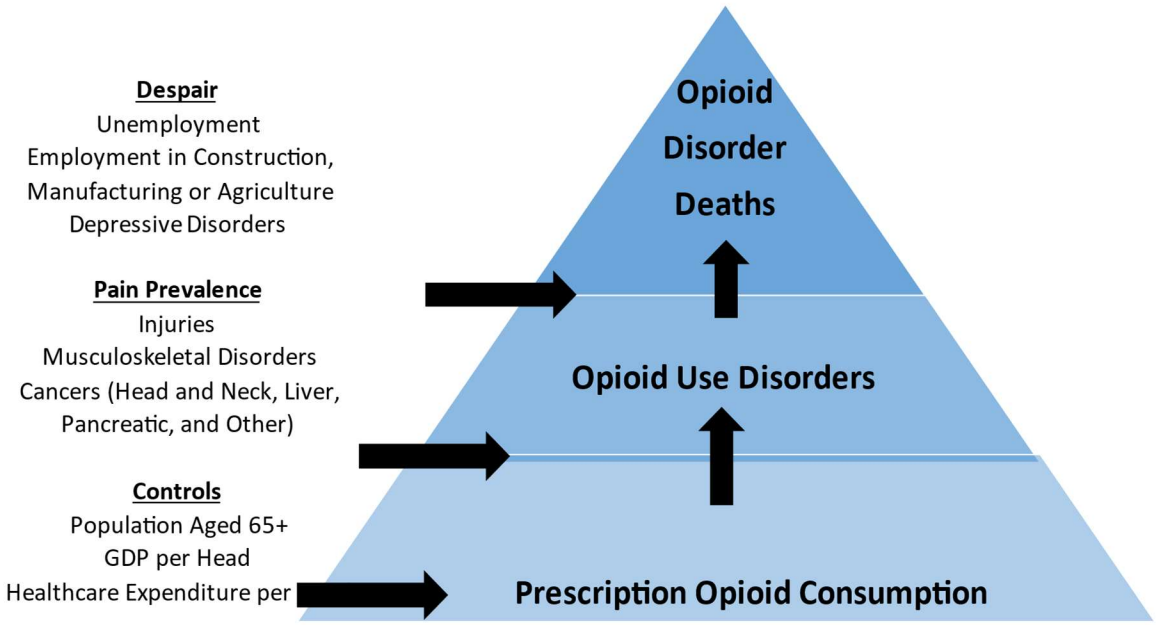


Figure 5 illustrates possible relationships, represented by a series of regression models laid out in Table 3. $\boldsymbol{POC_{it}}$ is prescription opioid consumption measured in standard defined daily does per million per day for country $\boldsymbol{i}$ in year t. The despair variables ($\boldsymbol{D_{it}}$) used are labor force participation rate of the population ages 15-64, employment in sectors (construction agriculture or manufacturing), and the prevalence of depressive disorders. The pain variables ($\boldsymbol{P_{it}}$) are comprised of the prevalence of injuries, musculoskeletal disorders, and neoplasms (head and neck, liver, pancreatic, and other0. The controls ($\boldsymbol{C_{it}}$) included are GDPH, HCE-PH, and population aged sixty-five and above. $\boldsymbol{t_t}$ represents a set of dummy variables for each year, $\boldsymbol{\alpha_i}$ a country fixed effects and $\boldsymbol{\varepsilon_{it}}$ the error term.

The analysis will consider lags of a year of the independent variables for all the models. I will also consider longer lags for POC because it is unclear the time between initial use and OUD develops. A study by Maxwell (2011) looks at the Treatment Episode Data Set for 1992-2008, which is a survey of US patients admitted to substance abuse treatment. The survey includes the variables of the patient's original substance abused and how many years before admission they first started using it. This was used to determine the lag between first use and treatment for those who were admitted for opioid abuse. It found that "the length of time between first regular use of other opioids or illicit methadone and entrance to treatment ('lag') decreased from 9-10 years in 1992 to 6-7 years in 2008." (Maxwell 2011) Thus, I will consider longer lags for some models with lags of 2 to 10 years for POC on OUD/ODD for 1991-2011 as well as the periods before and after the structural break: 1991-2002 and 2003-2019.

Table 3: Regression Models

$\boldsymbol{Prescription\ Opioid\ Consumption}_{it} = \boldsymbol{\beta_1}(\boldsymbol{P_{it}}) + \boldsymbol{\beta_1}(\boldsymbol{D_{it}}) + \boldsymbol{\beta_3}(\boldsymbol{C_{it}}) + \boldsymbol{t_t} + \boldsymbol{\alpha_i} + \boldsymbol{\varepsilon_{it}}$
$\boldsymbol{Opioid\ Use\ Disorder}_{it} = \boldsymbol{\beta_1}(\boldsymbol{POC_{it}}) + \boldsymbol{\beta_2}(\boldsymbol{P_{it}}) + \boldsymbol{\beta_3}(\boldsymbol{D_{it}}) + \boldsymbol{\beta_4}(\boldsymbol{C_{it}}) + \boldsymbol{t_t} + \boldsymbol{\alpha_i} + \boldsymbol{\varepsilon_{it}}$
$\boldsymbol{Opioid\ Deaths}_{it} = \boldsymbol{\beta_1}(\boldsymbol{OUD_{it}}) + \boldsymbol{\beta_2}(\boldsymbol{POC_{it}}) + \boldsymbol{\beta_3}(\boldsymbol{D_{it}}) + \boldsymbol{\beta_4}(\boldsymbol{C_{it}}) + \boldsymbol{t_t} + \boldsymbol{\alpha_i} + \boldsymbol{\varepsilon_{it}}$

Variables		*Includes:*
$\boldsymbol{D_{it}}$	$\boldsymbol{Despair}_{it}$	Labor Force Participation Rate (%) Employment in Construction (%) Employment in Manufacturing (%) Employment in Agriculture (%) Depressive Disorders Prevalence
$\boldsymbol{P_{it}}$	$\boldsymbol{Pain}_{it}$	Injuries Prevalence Rate Musculoskeletal Disorders Neoplasms (head and neck, liver, pancreatic, other)
$\boldsymbol{C_{it}}$	$\boldsymbol{Control}_{it}$	Population Aged 65+ (%) GDP per Head (Constant Prices, PPP) Healthcare Expenditure per Head (Constant Prices, PPP)
$\boldsymbol{POC_{it}}$	$\boldsymbol{Prescription\ Opoid\ Consumption}_{it}$	Opioid Consumption (sDDD per day per capita)
$\boldsymbol{OUD_{it}}$	$\boldsymbol{Opioid\ Use\ Disorder}_{it}$	Opioid Use Disorders (Prevalence Rate)
$\boldsymbol{ODD_{it}}$	$\boldsymbol{Opoid\ Disorder\ Death\ Rate}_{it}$	Opioid Disorder Death Rate
$\boldsymbol{i}$	$\boldsymbol{Countries}$	Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, Luxembourg, Netherlands, New Zealand, Norway, Portugal, Spain, Switzerland, United Kingdom, United States
$\boldsymbol{t}$	*Years*	1991-2019

CHAPTER 4: RESULTS & ANALYSIS

Following the procedure laid out in the methods section, the series of tests are conducted: the Hausman tests for random effects, the Pearson (2004) CD tests for cross sectional independence, the Wooldridge (2002) test for serial correlation and the Wald test statistic for groupwise heteroskedasticity. The Hausman test's null hypothesis is rejected, supporting the use of a fixed effects estimation. The data exhibit serial correlation, groupwise heteroskedasticity, longitudinal correlation, cross-sectional correlation and AR1 serial correlation, Thus, the Beck and Katz (1995) process is applied, where a Prais-Winstein transformation addresses the longitudinal correlation and the panel-corrected standard errors to address cross-sectional correlation (Rabe-Hesketh and Skrondal 2012). The structural break tests reveal a break in data in 2003, thus a separate regression will be run for the period 2003-2019. Results for the models for PO_{it}, OUD_{it}, and ODD_{it} are provided in Tables 4, 5, 6, A1 and A2 Throughout the analysis and estimation, variables used are expressed in either natural logarithms or in percentage terms.

In Table 4, model (4-1) shows the results of the regression for prevalence rates of injuries, musculoskeletal disorders (MSD), prevalence of cancers (head & neck, pancreatic, liver, and other), prevalence of depressive disorders, labor force participation rate (LFPR), employment in 3 sectors (construction, manufacturing, agriculture), healthcare expenditure per head (HCE-PH), GDP per head (GDPH), and population aged 65 and over (Age_65+) on the prescription opioid consumption (POC) rate.

The prevalence of injuries, lagged as well as in the present, does not show a significant effect on POC across the panels. Next, musculoskeletal disorders (MSD) have a significant positive coefficient with a present 10% increase estimated to increase POC by 6.77%. The large

effect of musculoskeletal disorders could be explained by their increased treatment with POs in many OECD nations (Rosner et al. 2019; Caudill-Slosberg et al. 2004). These chronic disorders include back pain and osteoarthritis, which often require chronic pain treatment.

Table 4: Results for Prescription Opioid Consumption

Prescription Opioid Consumption (Ln) (1991-2019)			
	(4-1)		**(4-2)**
Injuries (Ln)	-0.020	**Lagged Injuries (Ln)**	-0.017
Musculoskeletal Disorders (Ln)	0.677*	**Lagged Musculoskeletal Disorders (Ln)**	0.574
Head & Neck Cancers (Ln)	-0.147	**Lagged Head & Neck Cancers (Ln)**	-0.113
Pancreatic Cancers (Ln)	0.549***	**Lagged Pancreatic Cancers (Ln)**	0.538***
Liver Cancer (Ln)	-0.425***	**Lagged Liver Cancer (Ln)**	-0.405***
Other Cancers (Ln)	-0.607***	**Lagged Other Cancers (Ln)**	-0.677***
Depressive Disorders (Ln)	0.120	**Lagged Depressive Disorders (Ln)**	-0.035
LFPR (%)	0.017***	**Lagged LFPR (%)**	0.017***
Employment in Construction (%)	-0.030***	**Lagged Employment in Construction (%)**	-0.033***
Employment in Manufacturing (%)	-0.007	**Lagged Employment in Manufacturing (%)**	-0.010
Employment in Agriculture (%)	-0.057***	**Lagged Employment in Agriculture (%)**	-0.055***
Healthcare Expenditure per Head (Ln)	0.562***	**Lagged Healthcare Expenditure per Head (Ln)**	0.594***
GDP per Head (Ln)	-0.009	**Lagged GDP per Head (Ln)**	-0.015
Age 65+ (%)	0.017	**Lagged Age 65+ (%)**	0.026
Rho (ρ)	0.947	**Rho (ρ)**	0.945
R^2	0.970***	**R^2**	0.971***
# of Countries	21	**# of Countries**	21
# of Time Periods	29	**# of Time Periods**	28
N	599	**N**	579

*: p<0.05 **: p<0.01 ***: p<0.001

As opioids were first championed to help those with chronic cancer pain, the increase in prescription for cancers may have contributed to increased PO use. Thus, four groups of cancers were included in the regression: head and neck, liver and pancreatic, and the rest are grouped into the other cancer category. The results show that the prevalence of head & neck cancers in the present and lagged were not significant to POC. The prevalence of pancreatic cancers had a significant positive effect on POC in the present of 0.549 and lagged of 0.538. Yet, liver cancers have a significant negative effect on POCs in the present and past with coefficients of -0.425 and -0.405 respectively. For every 10% increase in the prevalence of liver cancer rate there is a decline in POC by about 4.25%. All other cancers have a significant negative effect on POC with a coefficient of -0.607 in model (4-1).

Next, I consider despair caused by economic changes in the job market and the effects seen in the prevalence of depressive disorders (anxiety and depressions) in the population. Depressive disorders have no significant relationship to POC. For every 1% increase in LFPR there is small but significant increase in POC estimated 0.017%. Employment in construction and agriculture both have a significant effect on POC with coefficients of (-0.030) and (-0.057). These are small protective effects, but highly significant. While employment in manufacturing has no significant effect.

Among the controls: GDPH and Age_65+ do not have a significant effect on POC. Healthcare expenditure per head (HCE-PH) has a significant positive coefficient of 0.562. Model (4-2) provides estimates using lagged variables, which are shown to investigate concerns about endogeneity. In model (4-2) with lagged coefficients show the same sign and similar magnitudes as in (4-1).

Table 5: Results for Opioid Use Disorders

Opioid Use Disorder (Ln)		
	(5-1) **1991-2019**	**(5-2)** **2003-2019**
Prescription Opioid Consumption (Ln)	0.014	0.190***
Injuries (Ln)	0.246***	0.120
Musculoskeletal Disorders (Ln)	1.696***	1.948***
Head & Neck Cancers (Ln)	0.377***	0.116
Pancreatic Cancers (Ln)	-0.281*	0.023
Liver Cancer (Ln)	-0.061	-0.002
Other Cancers (Ln)	-0.179	-0.084
Depressive Disorders (Ln)	-0.162	0.278
LFPR (%)	-0.005	-0.024***
Employment in Construction (%)	0.008	0.031
Employment in Manufacturing (%)	-0.008*	-0.033***
Employment in Agriculture (%)	0.004	-0.010
Healthcare Expenditure per Head (Ln)	0.139	0.156
GDP per Head (Ln)	0.355**	0.170
Age 65+ (%)	-0.025*	-0.043**
AR1 Coefficient (ρ)	0.972	0.917
R^2	0.981***	0.993***
# of Countries	21	21
# Time Periods	29	17
N	599	356

*: p<0.05 **: p<0.01 ***: p<0.001

Next, in Table 5, are regressions on the dependent variable of prevalence of opioid use disorders (OUD), with the independent variables of POC, injuries, musculoskeletal disorders, cancers (head and neck, pancreatic, liver, the rest), depressive disorders, LFPR, employment in

construction, employment in manufacturing, employment in agriculture, healthcare expenditure per head (HCE-PH), GDPH, and population aged 65+. Model (5-1) looks at data for the years 1991-2019, while due to structural breaks found in 2002, the regressions for the period of 2003-2019 are examined in (5-2). Table A1 in the Appendix has the same setup as Table 5 except the independent variables are lagged by 1 year in the specifications.

The results show there is a strong significant effect of prescription opioid consumption (POC) on opioid use disorders for time period 2003-2019. An increase of 10% in POC would correspond to 1.9% increase in opioid use disorders (OUD) These results support clinical studies that shows the initiation and use of POC increase the risk for opioid use disorders (Musich et al. 2019). However, across 1991-2019, POC does not show an effect on OUD.

There also are significant effects of some of the pain variables on OUDs. For 1991-2019, a 10% increase in musculoskeletal disorders increases OUDs by 16.96%, a significant positive effect. This large positive coefficient on musculoskeletal disorders, where pain is chronic and where prescription opioids may be given continuously may support that an increased use of POCs for chronic non-cancer pain influences OUDs. There are some differences for the coefficients of the 2003-2019 regressions, most conspicuously the coefficient for musculoskeletal disorders is about 15% larger at 1.948 than across 1991-2019. Injuries and head and neck cancers also have significant positive effects on OUDs with coefficients of 0.264 and 0.377 respectively for 1991-2019 though not significant when restricting regression to 2003-2019. At the same time, pancreatic cancers have a significant negative relationship with OUDs, which is hard to explain given the clinical research. Liver, other cancers and depressive disorders are not significant to OUDs in all specifications in Table 5 and A1. In Table A1, lagged injuries

in models (A1-1) and (A1-2) show a significant effect on OUDs of (0.325) and (0.229) respectively.

Regarding the employment despair variables of labor force participation rate (LFPR) and employment (agriculture construction, manufacturing, agriculture). Present LFPR has no significant effect in the 1991-2019 model of (5-1) but has a significant effect in models (5-2) for 2003-2019, at (-0.024). In table A1, lagged LFPR has a small significant negative effect on OUD prevalence in the specifications, with coefficients of (-0.01) and (-0.026) for (A1-1) and (A1-2) respectively. The negative relationship of LFPR with OUD is consistent with the deaths of despair hypothesis, as LFPR decreases OUD increases, though the effect seen is small. Employment in agriculture or construction (present or lagged), shows no significance for OUDs in these models. Employment in manufacturing both in the present and lagged have small significant negative effects. Using specification (5-1), a 10% decline in manufacturing employment would correspond to a decline in (-0.08%) of OUDs for 1991-2019 and (-0.33%) for 2003-2019.

In all of Table 5 and A1's models, the control variables healthcare expenditure per head (HCE-PH), GDPH and percent of population aged 65 and above are included. In the period 1991-2019, present and lagged GDPH had no significant effect on OUD. However, for 2003-2019, GDPH is not significant to OUD. Healthcare expenditure per head is insignificant to OUDs in any specification. Across Table 5 and A1, the percentage of the population 65 and above (65+) effect on OUD is significant in (5-1) of (-0.025), in (5-2) of (-0.043), and in (A1-2) of (-0.037).

Table 6: Results for Opioid Use Disorder Deaths

Opioid Use Disorder Deaths (Ln)				
	1991-2019		2003-2019	
	(6-1)	(6-2)	(6-3)	(6-4)
Opioid Use Disorders (Ln)	0.473***	0.469***	0.656***	0.697***
Opioid Consumption (Ln)	0.008		0.145***	
Injuries (Ln)	0.207	0.211	0.135	0.178
Musculoskeletal Disorders (Ln)	0.058	0.063	-0.306	-0.251
Head & Neck Cancers (Ln)	-0.086	-0.080	-0.275**	-0.188*
Pancreatic Cancers (Ln)	0.484***	0.474***	0.967***	1.086***
Liver Cancer (Ln)	-0.086	-0.081	-0.176**	-0.285***
Other Cancers (Ln)	-0.080	-0.078	0.129	0.147
Depressive Disorders (Ln)	1.186***	1.177***	1.339***	1.343***
LFPR (%)	-0.000	-0.000	-0.007	-0.006
Employment in Construction (%)	-0.017*	-0.017*	-0.022**	-0.027***
Employment in Manufacturing (%)	-0.012*	-0.012*	-0.040***	-0.037***
Employment in Agriculture (%)	-0.012	-0.011	-0.006	-0.014
Healthcare per Head (Ln)	0.384***	0.380**	0.239	0.333
GDP per Head (Ln)	0.538***	0.535***	0.593**	0.540**
Age 65+ (%)	-0.013	-0.014	0.018	0.014
AR1 Coefficient (ρ)	0.961	0.962	0.928	0.925
R^2	0.911***	0.911***	0.970***	0.969***
# of Countries	21	21	21	21
# of Time Periods	29	29	18	18
N	599	599	377	377

*: p<0.05 **: p<0.01 ***: p<0.001

Table 6 presents results for models where the dependent variable is the natural log of the rate of opioid use disorder deaths (ODD) and the independent variables are a combination of: OUD, POC, with injuries, musculoskeletal disorders, cancers (head and neck, pancreatic, liver, other), depressive disorders, LFPR, employment in 3 sectors (construction manufacturing, agriculture), healthcare expenditure per head (HCE-PH), GDPH and population aged 65+. Tables A2 provides the results of the same specifications as Table 6, with all the independent variables set as a one-year lag. Given results of structural breaks testing, (6-1), (6-2), (A2-1) and (A2-2) are for the years 1991-2019, while (6-3), (6-4), (A2-3) and (A2-4) are for the years 2003-2019.

The effect of OUDs is a highly significant determinant of opioid deaths, in every specification of Tables 6 and A2. In 1991-2019, for every 10% increase in opioid use disorder prevalence the opioid death rate is estimated to increase by of 4.73% in (6-1), 4.69% in (6-2), 5.43% in (A2-1) and 5.3% in (A2-2). For the period of 2003 to 2019, the coefficients are larger at (0.656) for (6-3) and (0.697) for (6-4), (0.742) for (A2-3) and (0.816) for (A2-4). The large magnitudes of these coefficients indicate a strong relationship between opioid use disorders and opioid disorder deaths.

Prescription opioid consumption (POC) is not significant to opioid disorder deaths (ODDs) across 1991-2019. Over 2003-2019, a 10% increase of POC relates to 1.45% increase in (6-3) and lagged 10% increase of POC to a 1.76% increase in ODDs.

The despair employment variables of present values of LFPR, employment in 3 sectors (construction, manufacturing, agriculture) are included in Table 6 while the lagged values are included in Tables A2. LFPR and employment in agriculture is not significant to ODDs in any specification in present or lagged form. The percentage of employment in construction and

manufacturing in the present show a significant negative effect across all specifications. A 1% increase in construction employment during 1991-2019, model (6-1) indicates a decline in -0.017% and over 2003-2019, model (6-3) a decline of -0.022%. The 1% increase in manufacturing employment indicates a significant decline of -0.012% for 1991-2019 and -0.04% for 2003-2019. These indicate a negative relationship, as employment in construction or manufacturing decreases, the ODD increases.

The prevalence of pain variables (injuries, cancers, musculoskeletal disorders, and depressive disorders) are included in the models of tables 6 and A2. Present and lagged injuries, musculoskeletal disorders, and other cancers have no significant effect on ODD across all the specifications. Present liver cancers have a significant negative effect on ODD for 2003 to 2019, while lagged liver cancers has a significant negative effect across 1991-2019 and 2003-2019. The present and lagged prevalence of head and neck cancers also shows a negative significant effect across 2003-2019 but no significant effect for 1991-2019. Pancreatic cancers, present and lagged, have a large significant effect on ODDs of 0.484 in (6-1) and 0.967 in (6-3). The prevalence of depressive disorders (DDP) both in the present (Table 6) and lagged (Table A2) show large positive and significant coefficients for ODDs in all specifications, providing some support for the connection to despair. The coefficients are larger for 2003-2019 at 1.186 in model (6-1) and 1.177 in model (6-2), than 1991-2019 at 1.339 in model (6-3) and 1.343 in model (6-4). Present and lagged HCE-PH shows a significant positive effect for ODDs across 1991-2019 but not for 2003-2019. The coefficient for present and lagged GDPH show a positive significant effect on ODD. Across the models the coefficient for population 65+ does not show significance in any specification of present or lagged variables. The high AR1 coefficients indicates control of time trends, while inclusion of fixed effects control for country-specific effects.

The unique experience of the US with the opioid epidemic can be seen in Figures 2, 3, and 4. These figures trace the course of prescription opioid consumption rate, prevalence of opioid use disorder, and opioid death rate in the US and five other countries over 1991-2019. The US prescription opioid consumption is the highest in the group at 38,000 sDDD per million in 2019. At the same time, the growth in US POC use between 1991-2019 is 19th was 677%. The US is one of the wealthiest countries with the 5th highest real GDP per capita in 2019 at $60,651 and it's GDPH grew 57% between 1991-2019 the 6th highest rate of increase. Also, while all the OECD countries have aging population, the US is 18th in the percentage of the population aged 65 and over at 16.2% in 2019, increasing 28% between 1991-2019. The US's labor force has seen declining in construction, manufacturing and agriculture. Employment in agriculture sector, went from 1.93% to 1.36%, decreasing 29.5%. The LFPR (shown in figure A3) has gone through a few cycles between 1991 and 2019. Excluding the endpoints, the US has experienced three local maxima of LFPR in 1992, 2003 and 2010. The US LFPR started in 1991 at 6.8%, the absolute maximum occurred in 2010 at 9.63%; by 2019 LFPR had dropped to its lowest level at 3.67%. The US LFPR is 5th lowest in 2019, and it is one of only two of twenty-one countries whose LFPR declined between 1991-2019, the other was Denmark but in 2019 Denmark's LFPR was still higher at 79% then the USs' LFPR at 73%. The LFPR and issues with healthcare access illustrate some of the other unique issues the US is facing.

The regressions from Table 4, 5, and 6 were also run excluding the United States to check robustness of the results. Without the US, all of the relationships between POC, OUD, and ODDs matched significance and sign of the corresponding regression with the US. Without the US, there were a few differences in the results. One difference without the US was that the prevalence of musculoskeletal disorder (present or lagged) did not show a significant effect on

prescription opioid consumption, while with the US there are significant positive coefficients. For example, in model (4-1) a 10% increase in musculoskeletal disorders relates to a 11.19% increase in opioid use disorders. This difference could be due to the higher rates of opioid prescriptions for musculoskeletal disorder in the US.

I also ran model (5-1) and (6-2) with longer lags (2 to 10 years) for POC on OUD and ODD respectively. For 1991-2011, POC starts showing significance when lagged by 5+ years on OUD and lagged by 7+ years on ODD. For 1991-2002, POC starts showing significance lagged by 7+ years on OUD and when lagged by 10 years on ODD. Lastly for 2003-2019, POC starts showing significance on both OUD and ODD contemporaneously. This indicates some evidence across the panel that the time lag between initial POC and OUD as well as POC and ODD seems to be falling over the last 3 decades. (Maxwell 2011)

CHAPTER 5: CONCLUSIONS

The opioid epidemic is a complex phenomenon and there are many factors playing a role in the crisis. The results of this thesis' analysis support the idea that there are multiple pathways that affect the three outcomes of the epidemic: prescription opioid consumption (POC), opioid use disorders (OUD), and opioid disorder deaths (ODDs). Over 1991-2019, the US saw sharp increases, with POC increasing by 677%, OUD by 259% and ODD by 759%. The goal of this thesis was to consider how these outcomes were affected by the factors of: (1) increased demand for pain relief (2) increased supply (availability) of prescription opioids (3) despair (depressive disorders, LFPR, employment in construction, manufacturing and agriculture). Model (4-1) indicates POC is affected significantly by some cancers (pancreatic, liver, other), musculoskeletal disorders (MSD), labor force participation rate (LFPR), employment in sectors of agriculture and construction, and healthcare expenditure per head (HCE-PH). Model (5-2) indicates that OUD is significantly affected by POC, MSD, LFPR, employment in manufacturing and population aged 65+. Model (6-3)'s results indicate that ODD is significantly affected by OUD, POC, neoplasms (head and neck, pancreatic, other), depressive disorders, employment in industry & construction, and GDPH.

For ODDs (using estimates from model (6-3), I calculated the effects of POC. Over 2003-2019: a 70.9% change in US' POC corresponds to a 18.7% increase in ODD (39% of the increase in ODD during that period). The estimations indicate the largest factors for ODDs is OUDs and POCs.

For ODDs (using estimates from model 6-3), I calculated the effects of four significant variables (POC, OUD, and GDPH). Over 2003-2019: a 70.9% change in POC corresponds to a

18.7% increase in ODD; a 22.6% increase in OUDs to a 14.8% increase in ODDs; and a 21% increase in GDPH to a 13% increase in ODDs. These four variables explain about 96% of the total US ODD increase experienced for 2003-2019. For 1996-2010, approximately 39%, and 31% of the ODD increase can be explained by OUD and POC, respectively (using model 6-3).

It's clear the US's POC rate is at an extreme among the cohort of twenty-one nations, but it's not the only one. Between 1991-2019, the US had the 2nd highest increase in DDP at 12%, while at the same time the average change in the non-US countries was a *drop* of 4%. This 12% increase in DDP would indicate a 4.7% increase in ODDs between 1991-2019 (using model 6-1). These results point to how increased psychological pain significantly influences the opioid epidemic.

Other variables play more minor roles or indirect roles in the ODD rate: For example, employment in manufacturing and construction also has a significant relationship to ODDs across 1991-2019. Using model (6-1), the US' 29% decline in manufacturing employment, corresponds to a 0.35% increase in ODD and the 12.7% increase in construction employment corresponds to a 0.22% decline in ODD. These are not substantial changes. Musculoskeletal disorders (MSD) don't affect ODDs directly but has an effect on POC and OUDs both of which can affect ODDs. Both POC and OUDs are significantly positively affected by MSDs. Between 1991-2019, the US saw an increase of 8.1% in MSD, the highest among the cohort, while on average the other twenty countries saw an increase of only 1.2%. The US's 8.1% increase in MSD corresponds to an 5.5% increase in POC using model (4-1) and 13.7% increase in OUDs using model (5-1).

Also, the regressions indicate the relationship between POC, OUD, and ODD hold across a panel of 20 wealthy OECD nations that excludes the US. Lastly, the literature and

results indicate support that there is a lag between initiation of prescription opioid consumption and the development of opioid use disorders and opioid related deaths. This lag may help explain why opioid deaths have continued to go up even as POC's peaked in the US in 2001.

There is much that remains unclear and requires further study. Future research could examine other factors that affect the opioid epidemic. For example, illegal drug markets have an influence on the prevalence of opioid use disorders and opioid deaths. In the US, as regulators tightened opioid prescriptions around 2010, many with OUD began buying opioids illegally. Thus, while POC dropped, ODDs continued to rise. Many of these deaths have been attributed to the increased fentanyl being sold with heroin in the illegal markets but may also be affected by the lag between start of use of prescription opioids and opioid use disorders and related deaths. Alternate models and techniques could be applied such as partial least squares structural equation modelling or case studies of a few countries. A larger sample of countries could be used to ground the results presented in this paper, though it is a challenge to find complete data for some countries over this longer time of period.

APPENDIX

Table A1: Additional Results for Opioid Use Disorders

Opioid Use Disorder (Ln)		
	(A1-1) **1991-2019**	**(A1-2)** **2003-2019**
Lagged Prescription Opioid Consumption (Ln)	0.015	0.172***
Lagged Injuries (Ln)	0.325***	0.229*
Lagged Musculoskeletal Disorders (Ln)	1.886***	2.008***
Lagged Head & Neck Cancers (Ln)	0.343***	0.150
Lagged Pancreatic Cancers (Ln)	-0.200	0.079
Lagged Liver Cancer (Ln)	-0.077	-0.043
Lagged Other Cancers (Ln)	-0.292	-0.134
Lagged Depressive Disorders (Ln)	-0.123	0.236
Lagged LFPR (%)	-0.010*	-0.026***
Lagged Employment in Construction (%)	0.003	0.019
Lagged Employment in Manufacturing (%)	-0.010*	-0.033***
Lagged Employment in Agriculture (%)	0.009	0.000
Lagged Healthcare Expenditure per Head (Ln)	0.187	0.243
Lagged GDP per Head (Ln)	0.385**	0.189
Lagged Age 65+ (%)	-0.021	-0.037*
AR1 Coefficient (ρ)	0.972	0.917
R^2	0.982***	0.993***
# of Countries	21	21
# Time Periods	28	17
N	579	357

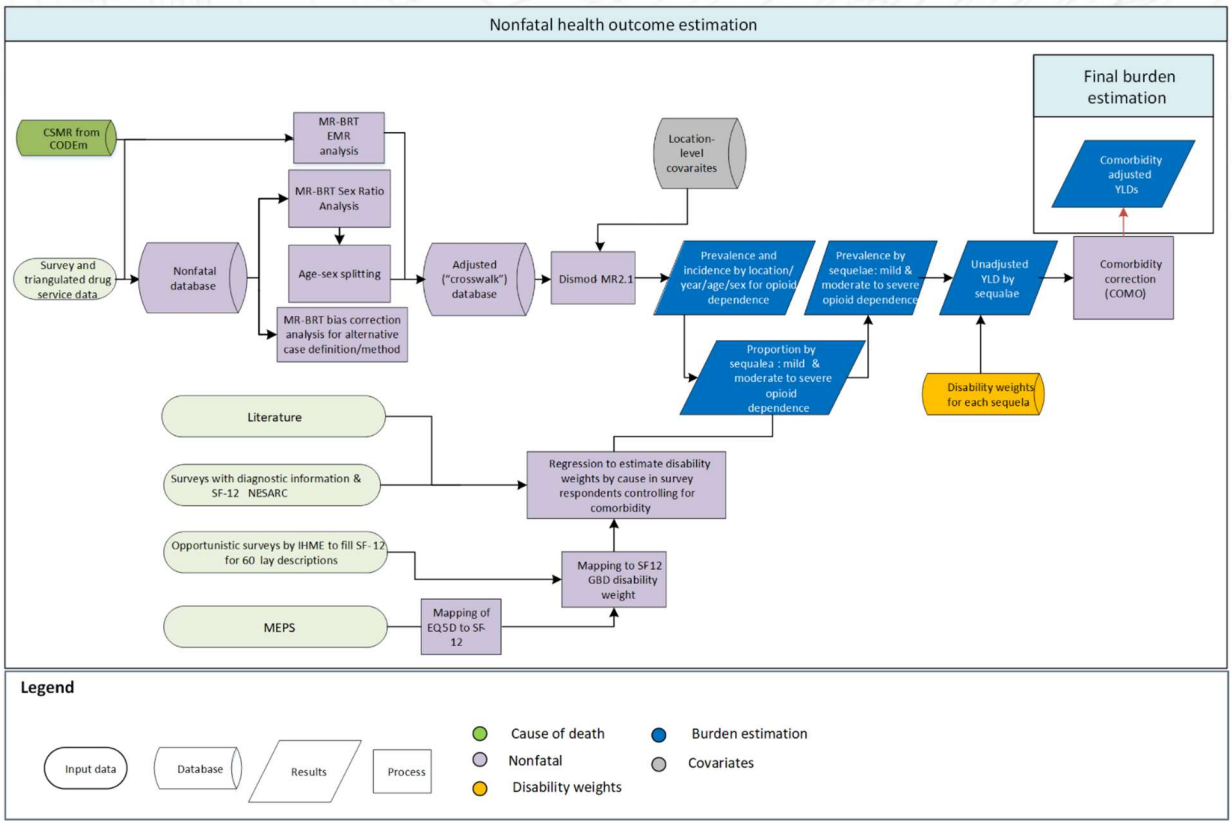
*: p<0.05 **: p<0.01 ***: p<0.001

Table A2: Additional Results for Opioid Use Disorder Deaths

Opioid Use Disorder Deaths (Ln)				
	1991-2019		2003-2019	
	(A2-1)	(A2-2)	(A2-3)	(A2-4)
Lagged Opioid Use Disorders (Ln)	0.543***	0.530***	0.742***	0.816***
Lagged Opioid Consumption (Ln)	0.004		0.176***	
Lagged Injuries (Ln)	0.134	0.145	0.058	0.124
Lagged Musculoskeletal Disorders (Ln)	0.066	0.108	-0.490	-0.401
Lagged Head & Neck Cancers (Ln)	-0.174	-0.167	-0.371***	-0.231*
Lagged Pancreatic Cancers (Ln)	0.341**	0.324**	0.820***	1.013***
Lagged Liver Cancer (Ln)	-0.127*	-0.123*	-0.140*	-0.287***
Lagged Other Cancers (Ln)	0.038	0.025	0.195	0.286
Lagged Depressive Disorders (Ln)	1.196***	1.169***	1.437***	1.533***
Lagged LFPR (%)	-0.001	-0.001	-0.006	-0.003
Lagged Employment in Construction (%)	-0.017*	-0.017*	-0.022**	-0.030***
Lagged Employment in Manufacturing (%)	-0.014**	-0.014**	-0.039***	-0.038***
Lagged Employment in Agriculture (%)	-0.014	-0.014	-0.010	-0.023
Lagged Healthcare Expenditure per Head (Ln)	0.261*	0.262*	0.079	0.165
Lagged GDP per Head (Ln)	0.523***	0.516***	0.689***	0.611**
Lagged Age 65+ (%)	-0.019	-0.021	0.022	0.020
AR1 Coefficient (ρ)	0.962	0.965	0.914	0.898
R^2	0.920***	0.917***	0.970***	0.970***
# of Countries	21	21	21	21
# of Time Periods	28	28	17	17
N	579	579	357	357

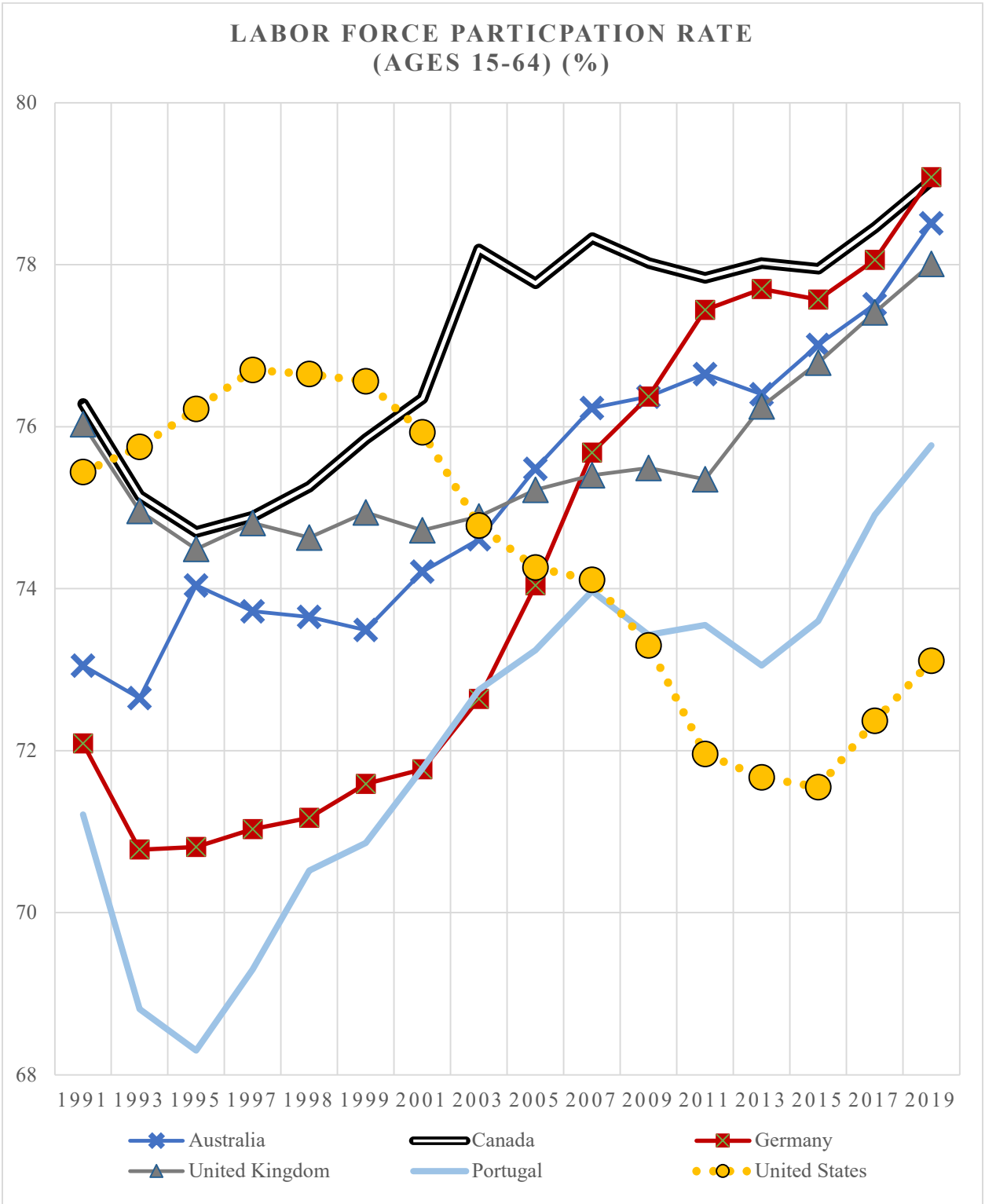
*: p<0.05 **: p<0.01 ***: p<0.001

Figure A1: Opioid Use Disorders Estimation



Source: http://ghdx.healthdata.org/gbd-2019/code/nonfatal-10

Figure A2: LFPR in 6 OECD Nations



Source: Organization for Economic Co-operation and Development (OECD)

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