PATTERNS OF PRESCRIPTION OPIOID USE IN U.S. HOUSEHOLDS

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ABSTRACT

Marissa Joanna Seamans: Patterns of Prescription Opioid Use in U.S. Households
(Under the direction of M. Alan Brookhart)

Opioid prescriptions in the United States have increased 300% over the past two decades, totaling 238 million dispensed in 2011. Increased prescribing has been attributed to multiple factors including changes in pain treatment guidelines and pharmaceutical marketing, but given high rates of prescription drug sharing between family members, the household context of opioid use may also be a contributing factor.

Using large healthcare claims databases from 2000-2014, we compared individual- and household-level characteristics of 27 million new users of prescription painkillers who shared their health plan with one or more household members. Furthermore, we estimated 1-year risks of opioid use for 18 million household members of new prescription opioid versus non-opioid users using weighted Kaplan-Meier estimators. Finally, we used a novel instrumental variable approach comparing household members of ankle fracture versus sprain patients to isolate potential person-to-person influence of opioid use from social and behavioral commonalities of household members.

New users of prescription opioids were more likely to have a household member with a history of prescription opioid use than new users of non-opioids. The 1-year risk of opioid initiation for household members of opioid users was 11.83% (95% CI, 11.81, 11.85) compared to 11.11% (95% CI, 11.09, 11.14) for household members of non-opioid users. Compared to non-opioids, opioids prescribed to one household member was associated with 0.71% (95% CI: 0.68, 0.74) higher 1-year risk of prescription opioid use in another household member. Fracture patients were more likely to receive opioids than sprain patients (30-day risk difference: 23%).

The 1-year risk of opioid initiation for household members of ankle fracture patients was 11.5% compared to 11.8% for household members of ankle sprain patients. Household members of fracture patients were less likely to initiate opioids than household members of sprain patients (1-year risk difference: -0.26%; 95% CI: -0.30, -0.22). The 1-year instrumental variable risk difference was -1.13% (95% CI: -1.29, -0.97).

Prevalent and incident use of prescription opioids appeared to cluster within households, which may be due to person-to-person influence or other commonalities within households. Understanding potential mechanisms underlying these household patterns may inform policies for drug prescribing and control measures.

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LIST OF ABBREVIATIONS

ASIPP	American Society of Interventional Pain Physicians
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
DAG	Directed Acyclic Graph
DEA	Drug Enforcement Agency
FDA	Food and Drug Administration
GI	Gastrointestinal
HCPCS	Health Care Procedure Classification Codes
HIV	Human Immunodeficiency Virus
ICD-9	International Classification of Disease
IQR	Interquartile range
IV	Instrumental Variable
JCAHO	Joint Commission on the Accreditation of Health Care Organizations
K-M	Kaplan-Meier
MME	Morphine Milligram Equivalents
NDC	National drug codes
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds ratio
PDMP	Prescription Drug Monitoring Program
PS	Propensity score
RD	Risk difference
RR	Risk ratio
US	United States

CHAPTER 1
STATEMENT OF SPECIFIC AIMS

Opioid prescribing in the United States increased 300% from 1999-2011, with 238 million prescriptions dispensed in 2011.[1-3] Over the same period, emergency room encounters involving opioids nearly quadrupled to over 480,000 visits,[4] and in 2011, fatalities from opioids were higher than deaths from motor vehicle crashes, heroin, and cocaine.[1] Although opioids are indicated for acute, post-surgical pain and palliative care, increasingly they are prescribed for minor surgeries and chronic non-cancer pain despite limited evidence of long-term effectiveness.[5,6] Increases in opioid use have raised concerns about opioid abuse and overdose, yet a growing concern is the diversion of opioids from patients to other individuals—often family members—for nonmedical use. Given the high rates of prescription drug sharing within households,[7,8] social networks such as families likely play an important role in shaping norms and attitudes surrounding opioid use. However, no large epidemiological study has investigated characteristics of families that use prescription opioids and their patterns of use, including potential mechanisms such as person-to-person influence. Given the high morbidity and societal cost associated with prescription opioids—estimated to exceed $70 billion annually and tantamount to the economic burden of asthma and HIV[9]—taking into account the risks within families could be a critical step in designing policies to address the opioid overuse epidemic.

This study takes advantage of information on households within large healthcare data to investigate the social context of prescription opioid use in the United States and assess the potential role of person-to-person influence in increasing opioid use. As part of this research, we

evaluate the utility of assessing household covariates to potentially improve validity of traditional pharmacoepidemiology studies using large databases. We apply an innovative study design that accounts for prior household opioid exposure with the goal of estimating the family risk of opioid use attributable to the introduction of opioids into a household. We then explore the potential use of injury type as a novel instrumental variable to disentangle person-to-person influence of opioid use (i.e., peer effects) from other commonalities within households, such as the tendency for similar individuals to associate (i.e., homophily) and environmental confounding. These methods improve understanding of the household context as a potential source of information and as a target for public health intervention. Moreover, this study urges a new perspective within pharmacoepidemiology to consider the social context of drug use in the assessment of drug safety and quality improvement.

The specific aims and hypotheses of this study are:

Aim 1. Describe individual-level, household-level, and ecologic characteristics of commercial insurance beneficiaries who initiate use of prescription opioids as compared to non-opioid analgesics, specifically prescription non-steroidal anti-inflammatory drugs (NSAIDs).

Hypothesis (1): Prescription opioid initiators will be more likely to have household members with a history of controlled prescription medication use, prevalent psychiatric comorbidities, and greater healthcare utilization than prescription NSAID initiators.

Aim 2. Determine the 1-year risk of prescription opioid initiation among household members of patients initiating prescription opioid versus non-opioid therapy.

Hypothesis (2): Based on the documented transmission of behaviors such as alcohol use and smoking within households,[10] we hypothesize that, compared to use of non-opioid analgesics, prescription opioid use by a patient will be associated with higher risk of opioid initiation among household members.

Subaims (2):

2a. Estimate 1-year risk differences (RD) and 95% confidence intervals (CI) for opioid initiation among household members overall and within subgroups.

2b. Assess the degree to which associations could be explained by unmeasured confounding using bias analyses.

Aim 3. Assess the potential use of injury type as an instrumental variable for opioid receipt to estimate peer effects of prescription opioid use within households.

Hypothesis (3): Injury type will be associated with the introduction of opioids into a household and allow identification of peer effects in the presence of unmeasured confounding and homophily bias.

Subaims (3):

3a. Propose a binary instrument for opioid treatment based on injury type.

3b. Determine the strength of the instrument and assess instrumental conditions.

3c. Estimate 1-year risk differences for opioid initiation by injury type.

CHAPTER 2
BACKGROUND AND REVIEW OF THE LITERATURE

A. BACKGROUND

Opioid prescribing in the United States

Prescription opioid analgesics such as hydrocodone and oxycodone products are commonly prescribed to adults in the United States, and their use has increased substantially over the past two decades. From 1999 to 2011, the number of prescription opioids dispensed annually from retail pharmacies grew from less than 50 million to over 230 million.[11] Approximately 4.3 million US adults age 18 years and older are estimated to be taking opioids regularly in any given week,[12] and 1 in 25 adults are prescribed opioids for chronic use. [2,13,14] In 2009 alone, enough opioids were sold to medicate every US adult with a typical 5mg dose of hydrocodone every 4 hours for 1 month.[15] In addition to increasing use, the average dose of an opioid prescription (in milligrams of morphine equivalents) in a given year also increased 600% between 1997-2007.[16] Globally, the US continues to be the top consumer of the strongest opioids, consuming 99%, 81%, and 65% of the world's supply of hydrocodone, oxycodone, and hydromorphone, respectively.[6] Since 2006, hydrocodone with acetaminophen (e.g., Vicodin) has been *the* leading prescription medication dispensed in the United States with over 130 million dispensed per year.[11] Increases in opioid prescribing have also been documented in U.S. emergency departments between 2001 and 2010, although non-opioid analgesic prescribing remained unchanged.[17]

Factors contributing to opioid overuse

Increases in prescription opioid use in the US have been attributed to several factors. First, changes in clinical guidelines for the treatment of chronic non-cancer pain such as back and neck pain have been suggested to have spurred widespread prescribing of opioids.[18-20] Prior to the 1980s, opioids were indicated for short-term use to treat pain related to surgery, trauma, or extensive burns. This limited indication was based on evidence that long-term exposure to opioids could lead to analgesic tolerance, and physical and psychological dependence. Beginning in the late 1980s, pain specialists and advocacy groups averred the under-treatment of chronic non-cancer pain and argued that long-term opioid therapy is safe and effective; however, this position was based on results from short-term clinical trials among cancer patients.[21-23] As campaigns for the awareness of pain as the "fifth vital sign" and the fundamental right to pain relief[24] using opioids as a "more humane alternative to the options of surgery or no treatment"[23] garnered support from physicians and patients, state medical boards in the 1990s began to liberalize laws governing the prescribing of opioids by primary care physicians.[25] Subsequently, in 2000, the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) endorsed the therapeutic use of opioids for chronic non-cancer pain.[26]

During this time, pharmaceutical companies aggressively (and ultimately illegally[27-29]) promoted particular opioid products to physicians. For example, Purdue Pharma funded over 20,000 pain-related educational programs during the 2000s, including partnerships with JCAHO's pain management programs,[30] and spent over $200 million in 2001 to market and promote OxyContin, a sustained release oxycodone hydrochloride product. Marketing tactics included targeting the highest prescribers of opioids in the US, many of whom lacked appropriate training in pain medicine,[27] and OxyContin-branded promotional materials, which was unprecedented in the history of schedule II opioids.[27] Within 5 years of OxyContin's FDA approval in 1995, sales of the drug rose from $50 million to over $1 billion,[27] constituting 80 to 90% of Purdue Pharma's revenues. In less than a decade after its FDA approval, OxyContin

became the most abused analgesic product in the US.[31] More recently, in August 2015, the FDA approved OxyContin for use in children ages 11-16 years.

Consequences of opioid overuse

Mortality

In 2011, prescription opioids were involved in over 16,000 deaths, and since 2005, opioid-related deaths have exceeded fatalities from firearms and motor vehicle accidents for persons aged 35-54 years.[32] Between 1999 and 2009, the prescription opioid related overdose death rate in the US increased from 1.54 to 6.05 deaths per 100,000 person-years,[16] whereas deaths involving heroin and cocaine increased 12% and 23%, respectively. Ecologic analyses suggest that increases in overdose deaths parallel increases in sales of prescription opioids, overall and for specific opioids.[33] Many unintentional overdose deaths from prescription opioids involve non-prescribed use. For example, a 2006 vital records review in West Virginia revealed that opioid analgesics were involved in 275 (93%) unintentional overdose deaths, and over half involved non-prescribed use of opioids.[30] In addition, benzodiazepine use concurrent with opioids carries increased risk of overdose: in 2010, the overdose mortality rate among North Carolina patients co-prescribed opioids and benzodiazepines was 7 deaths per 10,000 person-years (95% CI: 6.3, 7.8), compared with 0.7 deaths per 10,000 person years (95% CI: 0.6, 0.9) for patients receiving only opioids.[34]

Emergency room visits

In 2011, prescription opioids were involved in over 480,000 emergency room (ER) visits, representing a 300% increase since 1993.[35] Largest increases in ER visits have been observed for opioids that are frequently prescribed: 642% for fentanyl, 347% for oxycodone, and 342% for hydromorphone.[18] Moreover, opioid types that are stronger vs. weaker than morphine (e.g., buprenorphine, methadone, hydromorphone, fentanyl, oxycodone, and hydrocodone vs.

codeine, pentazocine, and tramadol) were associated with unintentional drug overdose in a matched case-control study using New Mexico Prescription Monitoring Program (PDMP).[36] In addition, formulations that are extended- vs. immediate-release are associated with higher risk of adverse events.[31,37-39]

Drug sharing

Another consequence of overprescribing is that opioids are diverted from patients to other persons for nonmedical and medical purposes. Many of the prescription opioids that are used non-medically and involved in fatal and non-fatal overdose cases are obtained from patients with legitimate prescriptions, rather than from illegal channels or from doctor shopping.[40] Drug sharing (also called drug diversion) is often a consequence of drugs retained after dental or medical procedures[41] because of overprescribing or nonadherence.[41] Reasons for opioid nonadherence include lack of analgesic efficacy, therapeutic alternatives, or concerns about adverse side effects and potential addiction.[42,43] Despite these concerns, patients rarely dispose of unused medications, which create opportunities for non-prescribed use.[44] Drug diversion has been documented among veterans and their families: 65% of veterans held onto leftover opioids after the illness or injury, and over a third described sharing opioids with a friend or family member.[45] In the 2012 National Survey on Drug Use and Health, 70% of respondents aged 12 years and older reported non-prescribed use of pain relievers, and the majority obtained the drugs for free from friends or relatives (54%), or bought or took opioids from friends or relatives (15%).[8] In particular, 1 in 10 adolescents reported non-prescribed use of pain relievers in their lifetime; of these adolescents, 50% or more reported use of hydrocodone, propoxyphene, or codeine products, and 26% used oxycodone products.[46]

Opioid addiction and abuse

Researchers have also called to attention the risk of iatrogenic opioid addiction, defined as drug dependence when taken as prescribed.[47] Opioid analgesic use disorders have increased to nearly 2 million, a trend that has been attributed in part to prescribing practices.[48-50] Opioid abuse is defined as the intentional nonmedical use of prescription opioids to obtain a euphoric or psychotropic effect.[51] In 2009, opioid pain relievers were second to marijuana as the most commonly abused drug in the United States.[8] Potential opioid abuse has been identified in previous studies using administrative claims data of approximately 632,000 privately insured residents of Maine from 2005-2006.[52] Pharmacy dispensing patterns suggesting high-risk utilization included one or more early refills (i.e., two consecutive opioid prescriptions for which the days supplied for the first prescription was over 10% higher than the number of days between prescriptions), dose escalation (i.e., two or more consecutive 50% increases in mean milligrams of morphine per month), and number of pharmacies where opioid prescriptions were filled. These indicators were associated with having a medical claim associated with diagnosis codes related to opioid abuse: early refill aOR: 3.39 (95% CI: 2.86-4.03); dose escalation aOR: 1.88 (95% CI: 1.31-2.68); number of pharmacies where opioid prescriptions were filled aOR: 2.14 (95% CI: 1.82-2.51); and having 4 or more vs. 1-3 prescriptions aOR: 7.34 (95% CI: 6.14-8.76). Demographic characteristics such as age and sex and comorbidities, including non-opioid substance abuse, depression, posttraumatic stress disorder, hepatitis, cancer, mental, health outpatient facility visits, and hospital visits were associated with opioid abuse.

Regulatory activities to curb prescription drug abuse

Because opioids are the most commonly misused prescription drug class,[8] measures to control indiscriminate prescribing are critical. Federal regulations limit the distribution of controlled substances including prescription opioids according to their potential for abuse and dependence. The Drug Enforcement Administration (DEA) divides all substances with abuse

and dependence potential into five schedules that place limits on their distribution.[53] Schedule I covers substances with no accepted medical use, thus do not include any prescription drugs. Schedule II controlled substances have high potential for abuse which may lead to psychological and physical dependence and include most commonly prescribed opioids. Schedule III substances have a potential for abuse and include opioids such as codeine. Schedule IV substances have lower potential for abuse, and included propoxyphene until 2010, when it was withdrawn from the market for its cardiac toxicity. Schedule V substances cover limited quantities of cough preparation that contain opioids. Examples of prescription opioids, as well as other scheduled prescription drugs, are listed according to their schedules in Table 2.1.

In addition to federal regulatory activities, all states except Missouri, Washington D.C., and Guam have implemented Prescription Drug Monitoring Programs (PDMP) to help identify potential drug abuse and refer patients to counseling or substance abuse treatment. PDMPs are databases that collect patient-level information on drugs dispensed, including drug name, quantity, date, dispenser identity, and prescriber identity.[54] Although PDMP information is available to providers and pharmacists, resource utilization is low, with only 22 states requiring practitioners to consult the database before prescribing or dispensing monitored drugs (Figure 2.1).[55] While all states with PDMPs (except Nebraska) monitor Schedule II – IV substances, several states have expanded the authority of PDMPs to monitor non-scheduled substances. Other state-to-state differences in PDMPs include type of governing agency (e.g., board of pharmacy, state health department, office of public safety), and requiring a PDMP to work with an advisory committee overseeing the program's implementation, monitoring, and evaluation.[56]

Evaluation studies of the effectiveness of PDMPs to curb opioid prescribing and adverse events have been inconclusive and limited by the lack of baseline data prior to PDMP implementation.[57] In Florida, where PDMPs and state legislation addressing high-volume dispensing pain clinics (also known as "pill mills") were implemented in July -September 2011, total opioid volume in morphine milligram equivalents (MMEs) was 2.5kg/month lower after

program implementation, an amount equivalent to approximately 500,000 tablets of 5 mg hydrocodone bitartrate (Vicodin) per month.[58] However, another time-series analysis found little change in opioid prescribing attributable to regulation,[56] whereas another found heterogeneity in per-capita dispensing across states.[56] Some have posited that strategies to curb prescription opioid use may be having unintended consequences, as the prevalence of heroin abuse and heroin-related mortality have increased in recent years.[59-61] Because many interventions within states occur jointly, drawing causal conclusions about the effectiveness of specific systems-level interventions has proved challenging.

B. COMPARATIVE EFFICACY AND SAFETY OF ANALGESICS

Opioids

Drugs of the opioid class, which includes natural opiates (morphine, codeine), semi-synthetic opioids (oxycodone, hydromorphone, hydrocodone) and synthetic opioids (methadone, buprenorphine, fentanyl) act upon the central nervous system to induce analgesia through two mechanisms involving the release of endogenous opioids and the direct activation of opioid G-protein coupled receptors (mu, delta, kappa, and the nociceptin orphanin peptide receptor).[62] Although all receptors induce analgesia when activated, the mu receptor is most commonly activated by exogenous opioids. Polymorphisms in the mu opioid receptor gene partially explain the heterogeneity between individuals in analgesic response to opioids.[63]

While the agonist action of opioids on mu receptors induces analgesia, mu receptors also play an important role in the abuse potential of many opioids,[64,65] such as morphine, hydrocodone, hydromorphone, fentanyl, oxycodone, and buprenorphine,[66,67] as well as heroin, a natural opiate, by producing changes in neuronal excitability, leading to sensations of euphoria and sedation. Unlike other analgesics, opioids have no ceiling effect, such that additional analgesia can be achieved by escalating the dose while the patient has pain. However, dose escalation is associated with increased risk of increased pain sensitivity (hyperalgesia).[68] Opioid

side effects include immunosuppression, chronic constipation and bowel obstruction, dryness of mouth (resulting in tooth decay),[69] QT interval prolongation and myocardial infarction, and respiratory depression,[5,70] which can lead to opioid-related ER visits,[35,37] hospitalizations,[71] and death.[16]

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are another class of analgesics that suppress pain by acting both peripherally and centrally on pain receptors.[72] In the ascending pain pathway, NSAIDs prevent the sensitization of peripheral pain receptors by inhibiting the cyclooxygenase enzyme from producing prostaglandins, a group of lipid compounds that promote inflammation and pain. In the descending pain pathway, NSAIDs prevent pain perception by blocking prostaglandin synthesis in the spinal dorsal horn, which receives and processes sensory information.[73]

NSAIDs do not carry the risk of abuse and are considered to be generally well-tolerated and safe for treating post-operative pain except when there are strong contraindications;[72] however, NSAIDs have well-known side effects including gastrointestinal complications and cardiovascular risks such as myocardial infarction, heart failure, and hypertension.[74]

Relative efficacy

A 2014 systematic review and meta-analysis of randomized controlled trials comparing non-injectable opioids versus placebo or other analgesics examined the efficacy of opioids for treating chronic low-back pain among adults. The study found little evidence of short-term efficacy of opioids, but the trials had high drop-out, were short in duration, and had varying definitions of functional improvement.[75] The study identified one trial to date that examined the relative efficacy of opioids and NSAIDs for treating flare-ups of low-back pain and found that celecoxib, an NSAID, was more effective than tramadol, an opioid product, over a 6-week

period.[76] However, because drop-out was higher in the opioid group than in the NSAID group, there could be selection bias.

Recommendations for treating non-cancer pain

Clinical problems including adverse events and inter-individual variability of analgesic response are problems with opioid therapy. The American Society of Interventional Pain Physicians (ASIPP) recommends that long-acting opioids in high doses be prescribed to chronic non-cancer pain patients only in specific circumstances where short-acting or moderate doses of long-acting opioids are ineffective.[77] High, moderate, and low doses are defined as ≥91mg, 41-90mg, and up to 40 mg of morphine-equivalents, respectively.[77] The Washington State Agency Medical Directors' Group dosing guidelines for primary care physicians recommend that the total daily dose of opioids not exceed 120 milligram oral morphine equivalents; however, 8% of commercially insured patients who were prescribed opioids for chronic non-cancer pain had mean daily doses exceeding this upper limit.[78] Similarly, the American Academy of Neurology recommends that total daily dose not exceed 80-120mg morphine-equivalents unless pain and function do not improve, and consulting with a pain management specialist. [79] However, much uncertainty remains regarding efficacy and safety issues: a 2009 review by the American Pain Society and the American Academy of Pain Medicine based 21 of their 25 recommendations for long-term opioid therapy on "low-quality evidence." [80]

Other groups have also published guidelines,[75,79,81,82] indicating a lack of overall consensus on the use of opioids for treating pain. Given the low risk of NSAID abuse, and their ability to address both inflammation and pain in patients without serious contraindications,[72] prescription NSAIDs may be a therapeutic alternative for the majority of patients seeking pain relief and help mitigate concerns about opioid overuse, abuse, and associated costs.

C. PREDICTORS OF OPIOID USE

Individual-level predictors

The most important predictors of opioid initiation are pain severity and indication. The most common nonmalignant pain conditions for which opioids are prescribed include back and neck pain, headaches, and migraines.[83] In a national commercially insured population in 14 US states, the most common pain diagnoses among long-term opioid users were back pain (37%), neck pain (18%), arthritis/joint pain (18%), and headache (16%).[37] However, there is little evidence that long-term opioid therapy is effective for managing these conditions.

Although opioid use has increased across all age groups,[84,85] the incidence of long-term opioid use tends to be highest among older women.[86] In a commercially insured population, older age is a documented predictor of heavy opioid utilization, with the highest use among those over age 41 years.[78]

Eighty percent of opioid analgesic recipients in North Carolina in 2010 received concurrent benzodiazepine prescriptions,[34] compared with 5% of the adult US population receiving benzodiazepines.[87] An administrative claims analysis of older adults with arthritis found that, compared to NSAID initiators, opioid initiators had greater use of prescription medications (benzodiazepines, antidepressants, proton pump inhibitors, and oral corticosteroids), and were more likely to have renal impairment and have more co-morbidities and outpatient visits to physicians and inpatient admissions prior to the index analgesic prescription date.[88] However, this subpopulation with arthritis had high age-related co-morbidities and overlooks the majority of opioid users who are treated for short-term pain relief.

Despite their contraindications, prevalence of mood disorders and history of substance abuse are also associated with opioid receipt in routine care settings [89-91] and heavy utilization of opioids.[78]

Provider-level predictors

Barnett et al. investigated associations between physician characteristics and long-term opioid use by capitalizing on natural variation in emergency room encounters.[92] Long-term opioid use was higher among patients who were treated by high-intensity prescribers than among patients treated by low-intensity prescribers (adjusted OR: 1.30; 95% CI: 1.23, 1.37), where prescribing intensity was defined relative to overall prescribing rates within the same hospital.

Medical specialties may be associated with prescription opioid use. A study of IMS Health National Prescription Audit data found that primary care specialties (family practice, internal medicine, and general practice including osteopathic medicine and preventive medicine) accounted for 44% of all opioid prescriptions dispensed from US pharmacies in 2012; however, the percentage of all prescriptions that were opioid analgesics was highest in specialties typically associated with treating painful conditions, such as pain medicine, physical medicine/rehabilitation, emergency medicine, surgery, and dentistry.[93]

Ecologic predictors

Southern and western states have higher prescribing rates than other regions of the country, after accounting for differences in healthcare utilization, prescription drug monitoring, and availability of prescribers.[94] Given documented increases in annual prescribing rates of opioids among all ages,[86] calendar year is also an important ecologic predictor of opioid initiation.

D. POTENTIAL ROLE OF HOUSEHOLD CONTEXT

Increasing prescription opioid use may also be a consequence of household characteristics. A claims-based study examined individual and household characteristics of a commercially insured population of patients diagnosed with opioid abuse.[95] Among patients with

an opioid abuse or dependence diagnosis in administrative claims, 90% potentially had access to opioids through their own prescriptions (80%) or those of immediate family members on the same health insurance plan (10%).[96] Among patients without their own claim for a prescription opioid, 51% of patients diagnosed with opioid abuse had a family member with a pharmacy dispensing claim for opioids, compared with 42% of patients without an opioid abuse or dependence diagnosis (who were randomly selected based on having a medical claim that matched an abuser's index date).[96] Because these data are from administrative claims, they do not rely on self-report, which may be subject to social desirability bias for reporting potential access to opioids. However, given the low negative predictive value of drug abuse diagnoses in claims, the generalizability of the study results may be limited. Moreover, household or community risks of opioid use due to a single exposure remain unknown, likely due to methodological challenges of identifying person-to-person influence or peer effects in non-experimental studies.

E. IDENTIFYING PEER EFFECTS WITHIN SOCIAL NETWORKS

Household diffusion of prescription opioid use is likely to occur given high rates of prescription drug sharing between family members, and the documented spread of substance use behaviors from one spouse to another.[97] Peer effects (also known as social contagion) are observed when one individual's behavior or characteristic influences the behaviors or characteristics of other people in the same social network, such as friends, coworkers, or members of the same household. In non-experimental settings, identifying person-to-person influence or peer effects is challenging because other social commonalities of members of the network (i.e., homophily, the tendency for similar individuals to associate) can bias estimates of peer effects, particularly when the reasons for network membership are predictors of the behavior under study.[98] Previous studies estimating peer effects have taken the approach of regressing the outcome of individual *i* at time *t* + 1 denoted $Y_i(t+1)$ on $Y_i(t)$, the outcome of

individual *k* denoted $Y_k(t)$, $Y_k(t+1)$, and covariates for individual *i* at *t* + 1 denoted $Z_i(t+1)$, and interpreting the coefficient for $Y_k(t+1)$ as the peer effect.[10] This approach has been criticized because even in the absence of peer effects, associations between two individuals could be explained by unmeasured environmental confounding or other characteristics that influence network membership or formation of a social tie.[99] To the extent that measured covariates cannot fully control for unmeasured environmental confounding or differences in the degree of homophily between exposure groups, residual bias is likely to remain in non-experimental studies of peer effects within social networks.

Instrumental variable (IV) methods have been proposed to account for unmeasured confounding and homophily bias in studies of peer effects of health behaviors.[100] This quasi-experimental approach has been shown to be useful in comparative effectiveness research,[101,102] where unmeasured confounding by indication or frailty can threaten study inferences. This method has also been applied to examine peer effects of smoking.[103] IV methods replace the assumption of no unmeasured confounding between exposure and outcome with key assumptions about an observed exogenous variable (the proposed instrument) and its associations with the exposure and outcome.

Three instrumental conditions must be met for a proposed instrument to be valid:

1) the instrument is associated with the treatment or exposure of interest

2) the instrument affects the outcome exclusively through the treatment or exposure

3) the instrument and the outcome do not share common causes

These conditions allow identification of bounds of the average causal effect of the treatment of interest in the total study population. In addition, the assumptions of homogeneity or monotonicity ("no defiers" of the treatment assigned by the instrument) must hold to identify a point estimate; with monotonicity, the proposed instrument identifies the local average treatment effect in a subpopulation of "compliers" – that is, those who would follow the treatment assigned

by the instrument.[104] To quantify uncertainty, upper and lower bounds for the average causal effect can be derived using the Balke and Pearl method.[105]

Assumption 1 can be assessed empirically by estimating Pr(X=1|Z), where X is dichotomous variable for exposure, and Z is a dichotomous instrumental variable. The compliance percentage, Pr(X=1|Z=1) – Pr(X=1|Z=0), measures the strength of the instrument. However, Z and X may be associated because Z has a causal effect on X, or because Z and X share an unmeasured common cause U. When the latter is true, biases that affect the IV estimate can be amplified when the compliance percentage is small.[106] Assumptions 2 and 3 are not empirically verifiable and rest on expert knowledge, although falsification tests can be conducted to rule out extreme violations of the instrumental conditions.[107]

Mendelian randomization analyses have been conducted to investigate potential peer effects of obesity in large longitudinal social networks of friends and spouses, and demonstrate the potential for IV methods to account for unmeasured confounding (with assumptions).[100,103] However, other applications of IV methods remain scarce, likely due to the challenge of finding suitable instruments that create natural variation in one person but not simultaneously in another. We explore a novel instrumental variable approach based on injury type to disentangle peer effects from homophily within households and evaluate the assumptions for inference based on this study design.

F. SUMMARY

> "*Because diversion can result in addiction or fatal overdose, decisions about prescribing need to take the risks to family and community into account in addition to the direct risks to patients.*"[69]

This research capitalizes on household information in large administrative data to examine patterns of prescription opioid use and the household context within which opioids are used. Assessing the household context of prescription drug use is a novel idea in

pharmacoepidemiology and may reveal potential effect modifiers or confounders. In addition, peer effects of prescription drug use within households has not been previously investigated, though which we propose an innovative instrument to account for unmeasured confounding and homophily. Estimating the potential public health impact of prescribing therapeutic alternatives to opioids within households may assist with the design of targeted quality improvement initiatives that can reduce the substantial harms associated with prescription opioids.

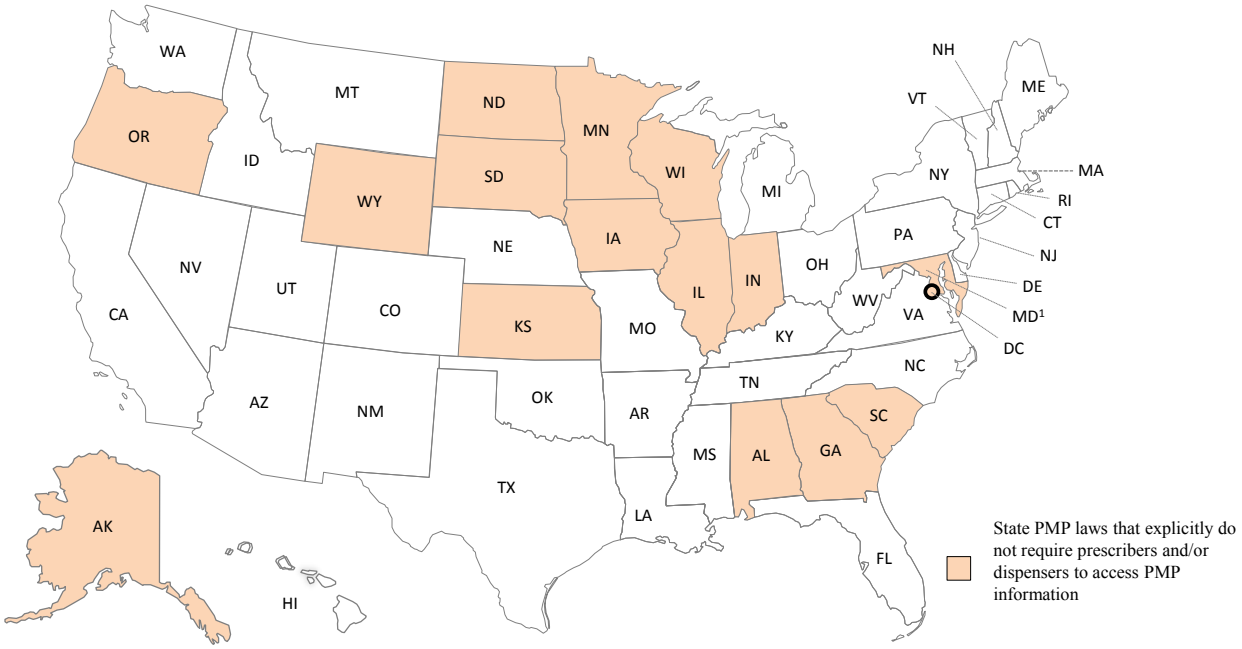
G. TABLES AND FIGURES

Table 2.1 Prescription medications according to DEA controlled substance scheduling

Schedule	Prescription Opioids	Stimulants	Anxiolytics
II	hydromorphone (Dilaudid®) methadone (Dolophine®) meperidine (Demerol®) oxycodone (OxyContin®, Percocet®) fentanyl (Sublimaze®, Duragesic®) Oxymorphone Other Schedule II narcotics: morphine, opium, codeine, and hydrocodone combination products (Vicodin®)	amphetamine (Dexedrine®, Adderall®) methamphetamine (Desoxyn®) methylphenidate (Ritalin®)	
III	Products containing not more than 90 milligrams of codeine per dosage unit (Tylenol with Codeine®) buprenorphine (Suboxone®)		
IV	Propoxyphene (Darvon) – withdrawn 11/19/2010 due to cardiac toxicity at therapeutic doses		alprazolam (Xanax®) carisoprodol (Soma®) clonazepam (Klonopin®) clorazepate (Tranxene®) diazepam (Valium®) lorazepam (Ativan®) midazolam (Versed®) temazepam (Restoril®) triazolam (Halcion®)
V	cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams (Robitussin AC®, Phenergan with Codeine®)		

Source: US Department of Justice, Drug Enforcement Administration, Office of Diversion Control. Available at: http://www.deadiversion.usdoj.gov/schedules/index.html#define Accessed August 26, 2015.

Figure 2.1 Map of states that do not require accessing PDMP data



Data current through May 2016. Missouri does not have an operational PDMP or PDMP legislation. Source: National Association of State Controlled Substances Authorities. Available at: http://www.namsdl.org/library/CAE654BF-BBEA-211E-694C755E16C2DD21/ Accessed March 11, 2017.

CHAPTER 3
METHODS

This study was conducted using the Truven Health Analytics Inc. MarketScan Commercial Claims and Encounters Database ("MarketScan", Copyright © 2014 Truven Health Analytics Inc. All Rights Reserved) covering the years 2000-2014. All aims used separate cohorts based on distinct inclusion and exclusion criteria. The Office of Human Research Ethics of the University of North Carolina at Chapel Hill deemed the study exempt from human subjects review (study number 15-2861).

A. STUDY DATA

MarketScan contain standardized, de-identified person-level information on enrollment, paid inpatient and outpatient services and procedures, outpatient pharmacy claims, and provider and health plan information of commercial insurance beneficiaries who are employees of mid- to large-sized companies, their spouses, and dependents. Beneficiaries are assigned a unique enrollment ID, which can also be used to identify individuals enrolled on the same health insurance plan based on the first 6–9 digits, with the last two digits denoting an enrollee's relationship with the primary beneficiary (e.g., 01 employee, 02 spouse, 03 dependent). Because MarketScan oversamples the South and has poor coverage of the West, our study may not directly generalize to the U.S. commercially insured population. However, MarketScan is one of the largest, fully integrated, and most complete commercial insurance claim databases available for the U.S with median follow-up of 3 years. Beneficiaries can be tracked across insurance plans, healthcare sites, provider types, and over time.[108] The size of the database

increased from 4 million to 47 million between 2000-2014. Households have been identified in previous studies examining spillover effects of children's vaccination.[109]

B. STUDY POPULATION

Aim 1

The study cohort consisted of all persons who initiated use of prescription opioids or prescription NSAIDs between January 1, 2000 and December 31, 2014 and were enrolled with at least one other person on the same health insurance plan ("households"). Initiation was defined as a prescription fill recorded in the Outpatient Pharmaceutical Claims file with no record of opioid or NSAID use in the prior 180 days. Eligible index dates were those occurring between 6/29/2000 and 12/31/2014 to ensure observation of the 180-day baseline period (Figure 3.1). Patients who filled prescriptions for opioids and NSAIDs on the same date were excluded to make comparisons rigorous. In addition, restricting to patients without a malignancy diagnosis or use of hospice care served to help identify patients with similar indications. Administrative codes used in the definitions of study inclusion and exclusion are presented in Appendix A Table 1.

Aim 2

The study cohort consisted of all household members of patients who initiated use of prescription opioids or NSAIDs between January 1, 2000 and December 31, 2014. Henceforth, we refer to the index patient as "Patient 0" in his or her household. Initiation was defined as a prescription fill for an eligible opioid or NSAID after a 365-day period of continuous enrollment without recorded opioid or NSAID use, to ensure non-overlap of household use periods. Household members entered either the opioid or NSAID cohort at the index date defined by Patient 0. Eligible index dates were those occurring between 1/1/2001 and 12/31/2014 to ensure observation of the 365-day baseline period (Figure 3.2). We applied the same exclusion

criteria to Patient 0 as Aim 1. In addition, we applied the following exclusion criteria to household members: non-continuous enrollment with prescription drug coverage, to ascertain prior exposure and covariates; and baseline use of prescription opioids or NSAIDs, in order to estimate risk of opioid initiation.

Aim 3

The study cohort consisted of all household members of patients diagnosed with an ankle sprain or ankle fracture between January 1, 2000 and December 31, 2014. Eligibility was restricted to the first ankle injury diagnosis in claims after a 365-day period without a recorded ankle injury, to identify patients without repeat injuries (Figure 3.3). Eligible index dates were those occurring between January 1, 2001 and December 31, 2014. The index date for household members was anchored to the date of an eligible ankle injury diagnosis for the index injury patient. Household members were excluded if they did not have continuous enrollment with prescription drug coverage during the 1-year baseline, or had baseline use of prescription opioids.

C. EXPOSURE, OUTCOME, AND COVARIATES

a) OPIOID EXPOSURE

Pharmacy dispensing billing claims for oral or transdermal synthetic and semisynthetic opioids were identified in the Outpatient Pharmaceutical Claims file by their generic string name. Eligible opioids included Tramadol Hydrochloride/Acetaminophen, Tramadol Hydrochloride, Hydrocodone Bitartrate/Acetaminophen, Propoxyphene/Acetaminophen, Fentanyl, Oxycodone Hydrochloride/Acetaminophen, Oxycodone Hydrochloride, Morphine Sulfate, Hydrocodone Bitartrate, Methadone Hydrochloride, Hydromorphone Hydrochloride, Hydrocodone Bitartrate/Homatropine, Acetaminophen with Codeine, Fentanyl Citrate, Codeine Phosphate. Claims for apomorphine (used primarily to treat Parkinson's disease), methadone (used

primarily to treat opioid dependence), and potassium guaiacolsulfonate/hydrocodone bitartrate (cough suppressant) were excluded.

Prescription NSAIDs included Diclofenac Potassium, Diclofenac Sodium, Diclofenac Sodium/Misoprostol, Esomeprazole Magnesium/Naproxen, Etodolac, Famotidine/Ibuprofen, Fenoprofen Calcium, Flurbiprofen, Ibuprofen, Ibuprofen Lysine, Indomethacin and Indomethacin Sodium, Ketoprofen, Ketorolac Tromethamine, Lansoprazole/Naproxen, Meclofenamate Sodium, Mefenamic Acid, Meloxicam, Nabumetone, Naproxen, Naproxen Sodium, Naproxen Sodium/Sumatriptan Succinate, Oxaprozin, Piroxicam, Sulindac, Tolmetin Sodium. Intravenous, intramuscular, rectal, and nasal preparations were excluded.

Electronic pharmacy dispensing records are considered the gold standard for capturing prescription drug exposure compared with self-reported medication use or prescribing records in outpatient medical records because reimbursement by insurance companies is based on complete and accurate claims.[110] Given that opioids are controlled substances and thus unavailable as samples or over-the-counter, we expect outpatient prescription opioid claims to be relatively sensitive and highly specific. However, prior opioid exposure from prescriptions paid in cash or received in inpatient settings cannot be identified using outpatient billing claims, which could introduce prevalent user bias. Likewise, we expect the positive predictive value of prescription NSAID exposure to be high; however, we are unable to verify over-the-counter NSAID use. Although over-the-counter NSAID use may lead to exposure misclassification, sensitivity analyses have shown that prescription claims data can provide valid estimates of drug-outcome relationships even when a large proportion of drug use is over-the-counter.[111] As such, missing over-the-counter NSAID exposure is not expected to be a source of bias in our study.

b) OUTCOME ASSESSMENT

Our primary outcome for Aims 2 and 3 was initiation of prescription opioids by household members of the index user. Initiation of opioids was assessed using the generic string name from the Outpatient Pharmaceutical claims databases as described above under a) Opioid Exposure.

Considerations for claims-based definitions of opioid initiation are similar to those described above under a) Opioid exposure. Some individuals may pay for opioids out-of-pocket or receive prescription opioids in inpatient settings, which would not produce an outpatient insurance claim. Under-ascertainment of true events will bias the risk difference even with perfect specificity and nondifferential sensitivity.[112]

c) INJURY TYPE (INSTRUMENTAL VARIABLE)

In Aim 3, the proposed instrumental variable was based on the type of index ankle injury which defined the study cohorts. Administrative codes for identifying the injuries are presented in Table 3.1. MarketScan does not have information on pain severity or functional status within levels on injury type.

d) COVARIATES

Household characteristics

Household characteristics, including size, presence of children under age 18 years, and region of residence, and household socioeconomic status were potential confounding variables identified for Aims 2 and 3 using Directed Acyclic Graphs (Figure 3.4). Household size was defined as the total number of individuals (including Patient 0 or the index injury patient) enrolled within a given household throughout the baseline period. Presence of children under age 18 years (yes/no) was defined based on whether there were children enrolled throughout the baseline period who were under age 18 years at the time of household cohort entry.

Household region of residence was defined using the REGION variable in MarketScan (Northeast, North Central, South, West, Unknown). Given important geographic variation in opioid prescribing, households of unknown region of residence were excluded from the analyses. Information on household socioeconomic status is unavailable in MarketScan. To the extent that the region variable and patient-level covariates (which are affected by socioeconomic status) cannot account for differences in socioeconomic status between treatment groups, residual confounding may bias our results.

Provider characteristics

Data to identify healthcare providers associated with a given medical encounter or prescription are incomplete in MarketScan. Members of the same household tend to have the same healthcare providers, thus clustering of prescription opioid use within households may reflect unmeasured confounding by provider preference. Methods to account for confounding by provider characteristics and other unmeasured environmental confounders are discussed in Aims 2 and 3.

Patient characteristics

Age, sex, baseline pain conditions, psychiatric comorbidities, gastrointestinal (GI) complications,[113] healthcare utilization (cancer screening, number of outpatient physician visits, emergency room visits in the prior week and month), and baseline prescription medication use were assessed as predictors of opioid initiation for all aims based on literature review. Baseline covariates were assessed in the 6 months prior to the index date for Aim 1; for Aims 2 and 3, baseline covariates were assessed during the year prior to the index date and were not updated after cohort entry. MarketScan does not have data on pain severity or the specific indication for the analgesic received by Patient 0 or the index injury patient. If distributions of household

covariates differ across unmeasured patient characteristics that may be associated with treatment type, residual confounding may be an issue.

We adjusted for baseline characteristics of household members to improve precision of our estimates. Methods for adjustment are described further in the Statistical Analysis section below. Key covariates are presented in Appendix Table A.1.

D. STATISTICAL ANALYSIS

Aim 1: Describe household characteristics of opioid initiators

We compared distributions of characteristics of households initiating prescription opioids versus prescription NSAIDs, including demographics, baseline healthcare utilization, and prevalent use of other pharmacologic agents by the index patient and household members. Proportions were calculated using the number of households that initiated prescription opioids or prescription NSAIDs. Differences in covariate distributions between treatment groups were estimated by subtracting the prevalence in the NSAID group from the prevalence in the opioid group. Mean age and mean outpatient visits for household members were calculated based on their means within a household. Because Aim 1 is purely descriptive, no formal hypothesis testing was conducted.

Aim 2: Determine the 1-year risk of opioid initiation among household members of patients initiating prescription opioid versus non-opioid therapy

We estimated the 1-year risk of opioid initiation among household members (excluding Patients 0) within each treatment group using the complement of the Kaplan-Meier estimator with time in days from the index date as the time scale. Household members were individually censored at the earliest of an event, at 1 year of follow-up, loss to follow up (defined as disenrollment), or administrative censoring on December 31, 2014.

Inverse probability weighted Kaplan-Meier survival curves were used to derive 1-year risks and risk differences (RD) for opioid initiation adjusting for baseline confounders and

predictors of informative censoring or initiation.[114] Weights were the product of stabilized inverse probability of treatment and stabilized inverse probability of censoring weights estimated using logistic regression models. Models for the denominator of weights included confounders and potential predictors described above. Age, number of outpatient visits during baseline, and household size were modeled using restricted quadratic splines[115] and calendar year as a categorical variable with each year as a separate category. Treatment weights were calculated as the complement of the propensity score (PS) for members of opioid households and (1-PS) for members of NSAID households and stabilized by the marginal probability of household exposure to opioids in the cohort. Censoring weights were calculated as the complement of the probability of dropout (PD) for those who disenrolled, and (1-PD) for those who remained under observation and stabilized by the marginal probability of disenrollment in the cohort. Estimates of precision were obtained using non-parametric bootstrap resampling with replacement.

We explored potential heterogeneity of the association between household opioid availability and opioid initiation across pre-specified subgroups: potential indication for Patients 0 (back pain [yes vs. no]; fracture [yes vs. no]; age of household member (0-5, 6-11, 12-17, 18-25, 26-35, 36-45, 46-55, ≥56 years); and region of residence. Subgroup differences were examined by stratifying the original cohort and repeating the primary analysis described above within each stratum.

We performed two sensitivity analyses. First, the primary analysis was performed after restricting to two-adult (age >18 years) households. Second, we examined the potential influence of an unmeasured confounder (e.g., socioeconomic status, healthcare provider, or environmental characteristics) by applying bias formulas under simplifying assumptions.[1] This method has been applied to previous analyses of contagion effects in social networks.[98] In the case of an unmeasured binary confounder U, the bias (B) in the contagion effect on the risk difference scale is

$B = (\pi_1 - \pi_0)\gamma$, where

$\gamma = \frac{\mathrm{P}(Y_{t+1}|U=1,Y_i(t),Y_k(t),Y_k(t+1),Z_i(t+1))}{\mathrm{P}(Y_{t+1}|U=0,Y_i(t),Y_k(t),Y_k(t+1),Z_i(t+1))}$ (i.e., effect of unmeasured confounder on household member's opioid initiation risk conditional on patient's measured risk factors)

$\pi_1 = P(U = 1|Y_k(t+1) = 1, Y_k(t), Y_i(t), Z_i(t+1))$ (i.e, prevalence of confounder among opioid households)

$\pi_0 = P(U = 1|Y_k(t+1) = 0, Y_k(t), Y_i(t), Z_i(t+1))$ (i.e., prevalence of confounder among NSAID households)

The "biased" point estimate was corrected by subtracting the bias factor *B* from the point estimate.[116] Corrected confidence limits were derived by applying the bias factor to each bootstrapped sample.[116] Assuming homogeneity of the prevalence difference of an unmeasured binary confounder between household exposure groups in all inverse probability weighted strata, and homogeneity of the difference in opioid initiation risk between levels of the unmeasured confounder within all inverse probability weighted strata, we evaluated a range of values for γ, π_1, π_0 that could potentially reduce our observed risk difference to the null. Explaining away an association by a potential unmeasured confounder is not sufficient to conclude that there is no true effect.[116] Moreover, this simple sensitivity analysis assumes that the unmeasured confounder affects outcome irrespective of exposure.[116]

Aim 3: Assess the potential use of injury type as an instrumental variable for opioid receipt to estimate potential peer effects of prescription opioid use within households

We specified injury type as a binary instrument (ankle fracture vs. ankle sprain) for opioid receipt. Assuming that injury type is random, but ankle fractures are more likely to be treated with opioids than ankle sprains (i.e., relevance), we expect the proposed instrument to improve the exchangeability of patient populations and their households, including unmeasured confounders and the degree of homophily between household members (i.e., independence). The exclusion restriction condition holds if injury type in the index patient has no direct effect on opioid initiation among household members except through introducing opioids into the

household. Although both potential therapies cannot be observed in the same patient, deterministic monotonicity assumes that there are no patients who would receive opioids after an ankle sprain, but would not receive opioids after a fracture. We relaxed this condition assuming stochastic monotonicity, which allows point identification of a local average treatment effect that is weighted more heavily on patients for whom the instrumental variable has a strong effect on opioid receipt.[117] We evaluated the plausibility of these assumptions by estimating the strength of the proposed instrument (i.e., compliance percentage, Pr(X=opioid|Z=1) – Pr(X=opioid|Z=0)), examining balance of measured covariates across the proposed instrument, and using subject-matter knowledge.

We estimated crude and inverse-probability-weighted cumulative incidence curves[114] using the Kaplan Meier estimator, reporting risk difference in opioid initiation among household members. Adjusted cumulative incidence curves were estimated by weighting events and person-time by the product of the inverse probability of injury type given baseline covariates and inverse probability of informative censoring given injury type and baseline covariates. Upper and lower bounds for the average causal effect in the entire study population were derived using the Balke and Pearl method.[105] To account for within-household clustering, estimates of precision were obtained by nonparametric grouped bootstrap sampling of households with replacement. We repeated these analyses restricting to household members 18 years or older.

All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) on the pharmacoepidemiology secure server maintained by the Cecil G. Sheps Center, University of North Carolina at Chapel Hill.

E. TABLES AND FIGURES

Figure 3.1 Study schematic for Aim 1

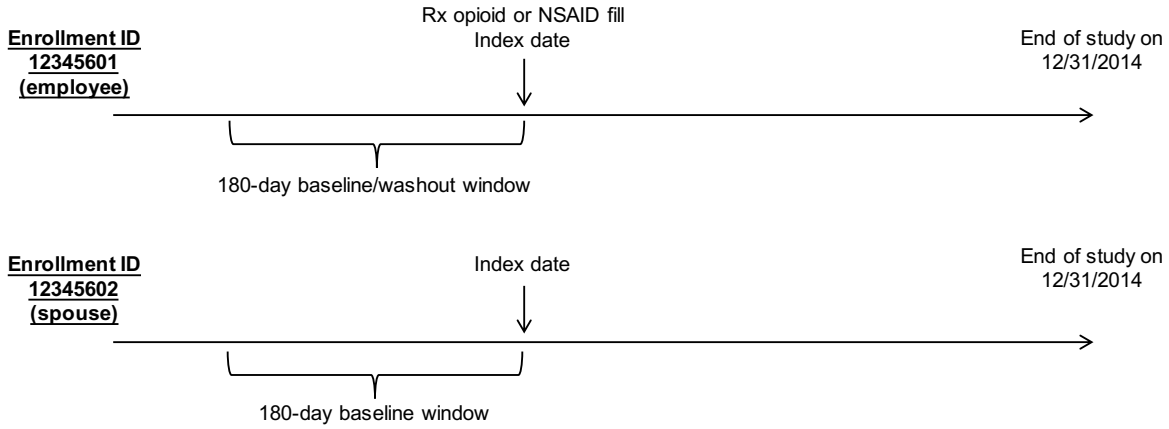


Figure 3.2 Study schematic for Aim 2

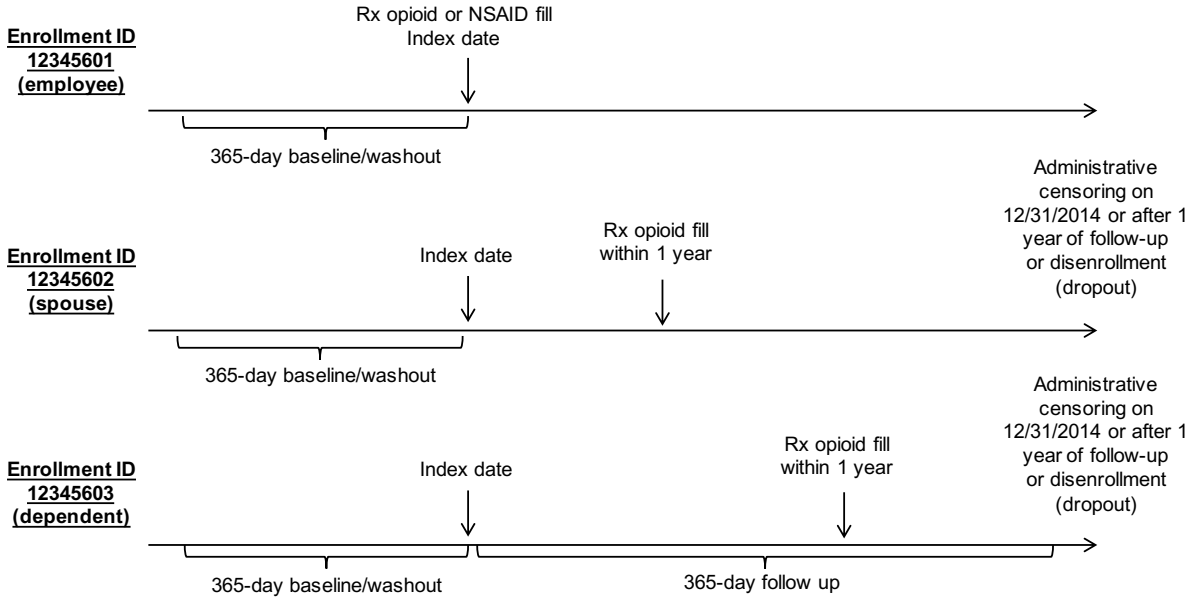


Figure 3.3 Study schematic for Aim 3

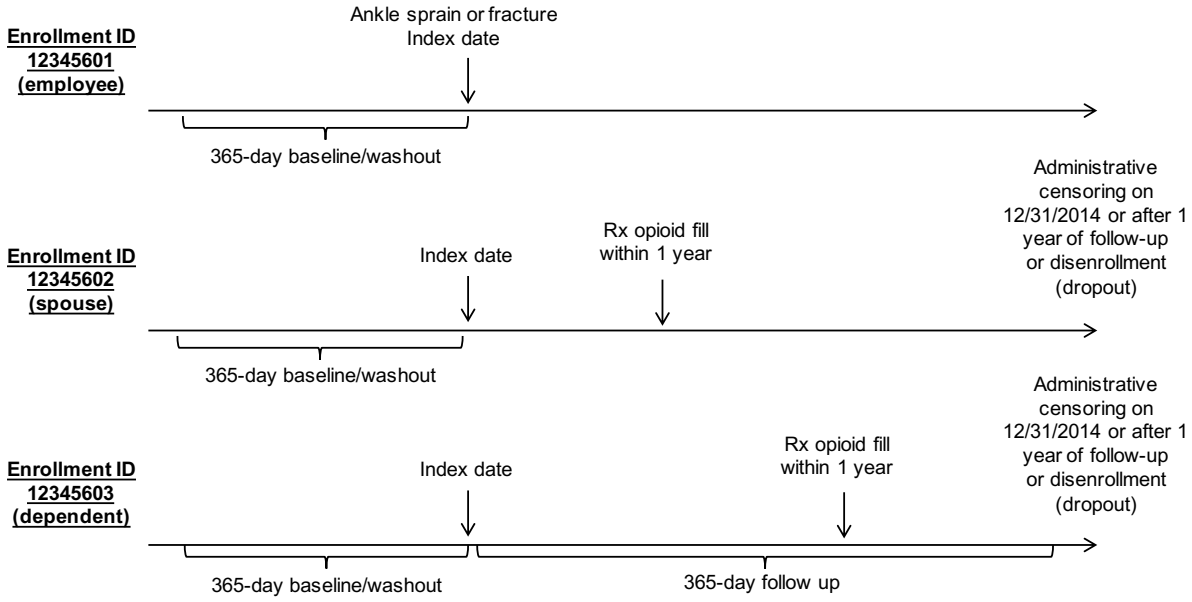
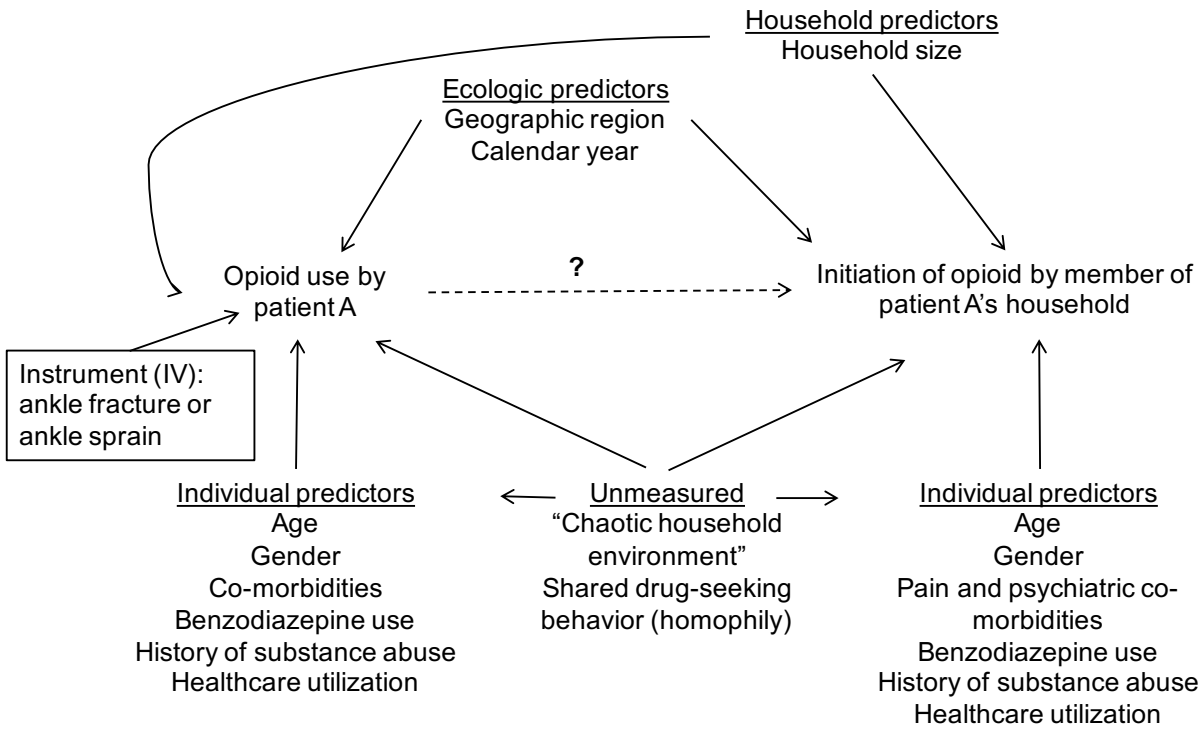


Figure 3.4 Conceptual model of ankle type as a proposed instrument to identify peer effects



CHAPTER 4
RESULTS: LOOKING AROUND VERSUS LOOKING FURTHER BACK: EXPLOITING INFORMATION ABOUT HOUSEHOLDS IN EPIDEMIOLOGIC STUDIES OF MEDICATION USE

A. INTRODUCTION

The new-user design is considered to be a reasonable default strategy for nonexperimental studies of drug treatment effects in healthcare databases because it minimizes selection bias and adjustment for post-treatment variables.[118] However, identifying "true" incident drug use and important confounders in administrative claims databases is challenging due to lack of clinical information, unrecorded use of generic and sample medications,[119,120] and insufficient time under observation to assess baseline co-morbidities.[121] Traditionally, database studies establish a fixed look-back period to assess comorbidities and absence of prior exposure. However, researchers are increasingly looking back further in patients' medical history,[122,123] attempting to exploit all available baseline information to improve the assessment of co-morbid conditions[124] and prior exposure.[125] By excluding patients with some history of medication use, longer look-back periods help to create a more specific new-user cohort,[121] but medical information remote to the start of follow-up may be poor proxies for unmeasured risk factors[124] and therefore not likely to assist with confounding control.

Interestingly, employer-based insurance in the United States is often clustered by family, allowing researchers using administrative healthcare databases to identify members of the same household. Given the similarity of health-related behaviors within households, such as diet, exercise, and medication adherence,[126] collecting information about a patient by "looking around" at the medical history of his or her family members may offer additional insights to further "looking back" in the patient's medical history. Covariates collected on other household

members could represent an alternative way to identify important proxies for unmeasured risk factors of the patient and help control confounding in non-experimental studies.

We explored the utility of collecting information on the medical history of patients' household members in the new-user design. To mimic a comparative safety study, we identified a large population of commercial insurance beneficiaries in the United States initiating use of prescription opioids or prescription non-steroidal anti-inflammatory drugs (NSAIDs) as an active comparator and examined differences in baseline patient and household covariates across treatment groups.

B. METHODS

Data Source and Study Population

Truven Health Analytics' MarketScan Commercial Claims and Encounters 2001-2014 database (MarketScan) contains de-identified, fully paid, and adjudicated individual-level claims for inpatient, outpatient, and prescription drug services of over 230 million unique commercial insurance beneficiaries followed across insurance plans, healthcare sites, provider types, and over time.[108] Beneficiaries include employees of medium to large companies and any family members such as a spouse or dependents enrolled on the same health insurance plan.[108] Because MarketScan oversamples the South and has less coverage of the West, the population is not representative of the US commercially insured population. However, MarketScan is one of the largest and most complete administrative claims databases available for the US. The Institutional Review Board of the University of North Carolina at Chapel Hill deemed the study exempt from review.

We identified a retrospective new-user active comparator cohort of patients initiating use of a prescription opioid or a prescription NSAID between January 1, 2001 and December 31, 2014 using outpatient pharmacy dispensing claims. Eligible opioids were limited to oral and

transdermal formulations and excluded cough preparations. Initiation was defined as the first prescription fill for an opioid or NSAID without evidence of prior fills of either drug class during the 180-day lookback. Patients were required to have at least 180 days of continuous insurance enrollment with prescription drug coverage prior to the index date to characterize exposure and covariates. Patients with a baseline malignancy diagnosis or use of hospice care were excluded.

Next, we identified members of the initiator's household, defined as individuals sharing the initiator's health plan throughout baseline. After excluding singly enrolled initiators, eligible households comprised the initiator and one or more household members.

Covariates

We assessed baseline covariates for initiators and household members during the 180 days preceding the new-user's initiation date. Demographics included age, sex, region of residence, household size (including the initiator), and presence of children age <18 years. Household covariates were categorized as dichotomous variables if one or more household members (excluding the initiator) had claims for concomitant use of prescription medications, psychiatric and pain comorbidities, and healthcare utilization (hospitalizations, emergency room visits, and outpatient visits). History of chronic obstructive pulmonary disease (COPD) and gastrointestinal (GI) bleeding was assessed as potential negative controls. Concomitant medications were identified using therapeutic class variables. Diagnoses and procedures were defined using the International Classification of Diseases, Ninth Revision, Clinical Modification and the Current Procedural Terminology codes, respectively.

Statistical Analyses

We calculated percentages for dichotomous covariates based on the total number of households within each treatment group. Mean age and outpatient visits for household

members was calculated based on their means within a household. All analyses were conducted in SAS version 9.4 (SAS Institute, Inc., Cary, NC).

C. RESULTS

Between January 2001 and December 2014, 24,670,728 prescription opioid and 13,288,800 prescription NSAID initiators met the study inclusion criteria. After excluding patients who were singly enrolled (27% opioid vs. 28% NSAID), the final cohort included 18,083,946 opioid households and 9,549,940 NSAID households. Household size was similar in both treatment groups (**Table 4.1**). However, opioid-using households were more likely to reside in the South and have children under age 18 years than NSAID-using households.

Opioid initiators were younger, more likely to be male and have used benzodiazepines, amphetamines, antibiotics, SSRIs, and sleeping aids, but less likely to have used muscle relaxants and statins than NSAID initiators (**Table 4.1**). Whereas NSAID initiators were more likely to have arthritis and back pain, opioid initiators were more likely to have fractures and emergency room visits. Opioid initiators were also more likely to have psychiatric and substance abuse comorbidities than NSAID initiators.

Age and sex distributions of household members of opioid and NSAID initiators were similar. However, prevalent use of prescription opioids was higher among household members of opioid initiators than household members of NSAID initiators (16.4% vs. 14.5%). In contrast, prevalent use of prescription NSAIDs was higher among household members of NSAID initiators than opioid initiators (12.3% vs. 10.4%). Prevalent use of other prescription medications except statins was modestly higher among household members of opioid initiators than among household members of NSAID initiators (**Figure 4.1**). Back and neck pain and psychiatric co-morbidities were more prevalent in household members of opioid initiators than those of NSAID initiators, however, history of COPD and GI bleeding was similar.

D. DISCUSSION

We explored the utility of assessing household-level characteristics of new users to improve confounding control in a hypothetical study of analgesic initiators. We found substantial differences in patient-level characteristics by treatment. Although modest in magnitude, we observed differences in their household characteristics, which may indicate potential confounding. Given that members of a household (or other social group) tend to be similar (i.e., homophily) or see the same healthcare provider, greater household use of preventive healthcare services or adherence to preventive medications may associate with positive health behaviors in the patient under study. Conversely, household use of controlled prescription medications may associate with other negative health behaviors and lifestyle factors, such as smoking and alcohol consumption, in the patient. Therefore, adjustment for various household characteristics could help to control confounding in comparative studies as proxies for unobserved behavioral and lifestyle variables.

Although prescription drug-sharing behaviors cannot be directly observed in administrative claims, drug-sharing is known to occur within social networks[8] including friends and family. Thus, prevalent household use of the prescription analgesics under study could indicate potential misclassification of new drug exposure among patients who appear to be initiators. Because even small departures from perfect sensitivity and specificity of exposure measurement can impact inferences from epidemiologic studies,[127] potential exposure misclassification error due to prevalent household use should be addressed using sensitivity analyses. Researchers might consider restricting to “new households” in which no household member has evidence of drug utilization during baseline. While this “new-household” design would allow for a more specific, exposure-free cohort, such a restriction will limit generalizability of study inferences, precision, and applicability for real-world pharmacotherapy decisions.

Household characteristics could also be potentially important effect modifiers. For example, household opioid and benzodiazepine use was higher among opioid initiators than

NSAID initiators, despite similar household demographics. Given that opioids and benzodiazepines combined were the most common cause of polysubstance overdose deaths in the US from 2005-2009 (1.27 deaths/100,000 person-years),[16] opioid-related overdose or hospitalization risk could be higher in households with prevalent benzodiazepine use. Assessing the household availability of medications could help target quality improvement measures.

Studies in pharmacoepidemiology increasingly attempt to exploit longer and more intensive "look-back" periods"[128] to identify co-morbidities, prior exposures, and proxies for unmeasured risk factors.[122,124,128] We considered the possibility of learning more about a patient by "looking around" to collect information on members of their household. Although our study did not reveal large difference in household characteristics between the treatment groups, prevalent household use of the treatment under study raises concerns about possible exposure misclassification of "new" users. Given the limited data available in typical healthcare databases and multiple sources of bias in comparative studies of medications,[129] we encourage researchers to consider whether household information might be useful in various types of pharmacoepidemiologic research.

E. TABLES & FIGURES

Figure 4.1 Covariate balance among initiators and their households

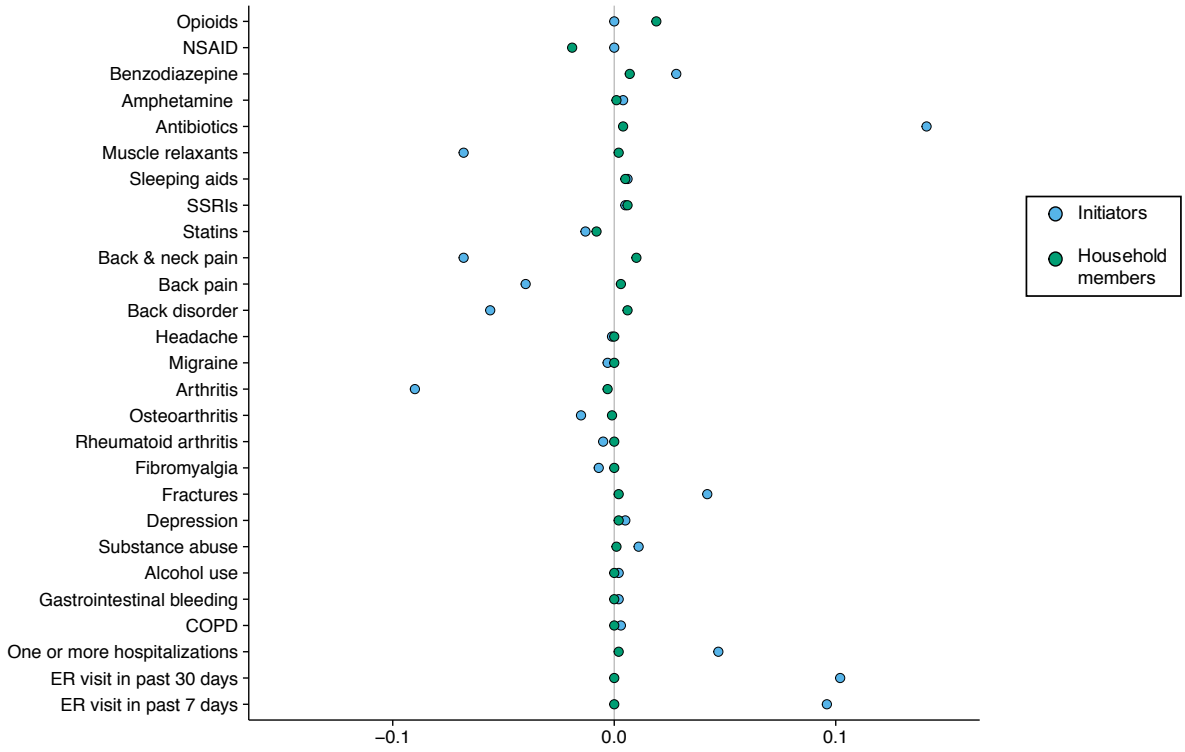


Table 4.1 Patient and household characteristics of prescription opioid and prescription NSAID initiators, MarketScan Commercial Claims and Encounters, 2001-2014

Household characteristics	Opioid households n = 18,083,946 (%)	NSAID households n = 9,549,940 (%)	PD (ppts)
Size (median, IQR)	3.4 (1.26)	3.3(1.24)	
Children age <18 years	54.1	52.8	1.3
Region of residence			
Northeast	11.0	13.5	-2.5
North central	25.1	25.5	-0.4
South	43.7	40.2	3.5
West	19.2	19.5	-0.3
Unknown	1.1	1.2	-0.1

Characteristic	New user (%)	Other members (%)	New user (%)	Other members (%)	New users PD (ppts)	Other members PD (ppts)
Age, y (mean, SE)	37.1 (16.33)	32.3 (15.5)	40.1 (14.78)	32.5 (15.69)		
Sex, male	47.1	51.0	44.8	51.2	2.3	-0.2
Prescriptions						
Opioids	-	16.4	-	14.5	-	1.9
NSAID	-	10.4	-	12.3	-	-1.9
Benzodiazepine	9.2	6.9	6.4	6.2	2.8	0.7
Amphetamine	1.6	1.0	1.2	0.9	0.4	0.1
Antibiotics	50.2	27.2	36.1	26.8	14.1	0.4
Muscle relaxants	6.6	4.6	13.4	4.4	-6.8	0.2
Sleeping aids	4.4	4.3	3.8	3.8	0.6	0.5
SSRIs	8.7	7.9	8.2	7.3	0.5	0.6
Statins	10.6	12.3	11.9	13.1	-1.3	-0.8
Chronic pain						
Back & neck pain	15.5	12.2	22.3	11.2	-6.8	1.0
Back pain	9.1	6.8	13.1	6.5	-4.0	0.3
Back disorder	13.1	10.2	18.7	9.6	-5.6	0.6
Headache	4.0	2.4	4.1	2.4	-0.1	0.0
Migraine	2.0	1.4	2.3	1.4	-0.3	0.0

Arthritis	13.7	9.2	22.7	9.5	-9.0	-0.3
Osteoarthritis	3.1	2.6	4.6	2.7	-1.5	-0.1
Rheumatoid arthritis	1.0	1.1	1.5	1.1	-0.5	0.0
Fibromyalgia	1.5	1.4	2.2	1.4	-0.7	0.0
Injuries						
Fractures	5.7	1.4	1.5	1.2	4.2	0.2
Comorbidities						
Depression	4.5	3.7	4.0	3.5	0.5	0.2
Substance abuse	2.7	1.6	1.6	1.5	1.1	0.1
Alcohol use	0.5	0.3	0.3	0.3	0.2	0.0
GI bleeding	0.7	0.5	0.5	0.5	0.2	0.0
COPD	0.8	0.7	0.5	0.7	0.3	0.0
Healthcare utilization						
One or more hospitalizations	7.9	2.9	3.2	2.7	4.7	0.2
ER visit in past 30 days	18.3	1.8	8.1	1.8	10.2	0.0
ER visit in past 7 days	16.5	0.6	6.9	0.6	9.6	0.0
Outpatient visits (mean, SD)	2.3 (2.42)	1.6 (1.88)	2.2 (2.15)	1.7 (1.91)		

Abbreviations: chronic obstructive pulmonary disease, COPD; emergency room, ER; gastrointestinal, GI; nonsteroidal anti-inflammatory drugs, NSAIDs; prevalence difference, PD; percentage points, ppts; standard deviation, SD; selective serotonin reuptake inhibitors, SSRIs.

CHAPTER 5
RESULTS: POTENTIAL ACCESS TO PRESCRIPTION OPIOIDS AND RISK OF PRESCRIPTION OPIOID INITIATION IN US HOUSEHOLDS

A. INTRODUCTION

Opioid prescribing in the US has increased 300% over the past twenty years and totaled 238 million prescriptions dispensed in 2011.[1-3] Globally, the US continues to be the largest consumer of the world's supply of hydrocodone (99%) and oxycodone (81%),[6] with hydrocodone/acetaminophen *the* leading prescription drug dispensed by US retail pharmacies.[11] This increase in opioid prescribing has been attributed to changes in prescribing guidelines,[84] attitudes towards pain relief,[24] aggressive pharmaceutical marketing,[27] and the liberalization of laws governing the ability for physicians to prescribe opioids without training in pain management.[25] Opioid side effects include QT interval prolongation and respiratory depression, which can lead to opioid-related ER visits,[35,37] hospitalizations,[71] and death.[16] In 2011, prescription opioids were involved in over 480,000 emergency room (ER) visits and 16,000 deaths, surpassing the mortality burden from firearms and motor vehicle accidents for Americans ages 35–54 years.[15] Accidental ingestion of prescription opioids also caused over 5,000 ER visits among children ages 5 and under in 2011, which underscores the harms of the broad availability of opioids in US households.[4]

Opioids are often prescribed in doses exceeding clinical guidelines for patients with non-cancer pain,[130] and in large quantities, resulting in surpluses of opioids stored in household medicine cabinets.[41] Unused medications create opportunities for non-prescribed use and drug sharing among friends and family members, who may perceive these medications to be low risk given their storage at home.[45] For example, a third of veterans on prescription opioid therapy

report sharing unused medications with family members,[45] and over 70% of nonmedical opioid users obtain the drugs from family members and friends.[7,8] Because prescription medication sharing is common,[131] families and other social networks likely shape norms and behaviors surrounding the use of prescription opioids. Given the documented spread of substance use behaviors such as heavy drinking within social networks,[97,132,133,134] it is likely that prescription opioid use can also spread within social networks, such as between members of the same household. However, previous studies have largely focused on opioid abuse,[135] thus, the extent to which potential access to opioids prescribed to one person increases the risk of prescribed opioid use in another person within the same household remains unknown.

The aim of the current study was to evaluate the association between household opioid availability and prescription opioid initiation in a large population of commercial insurance beneficiaries including employees, spouses, and dependents who gained access to prescription opioids through a household member. Specifically, we compared the 1-year risk of opioid initiation due to the introduction of prescription opioids versus a therapeutic alternative (prescription nonsteroidal anti-inflammatory drugs [NSAIDs]) in the household. We further examined associations within subgroups of age, geographic region, and potential indications and conducted bias analyses to quantify the extent to which our results could be explained by unmeasured confounding.

B. METHODS

Data Source

Data were from Truven Health Analytics' MarketScan Commercial Claims and Encounters databases 2000-2014 (MarketScan). MarketScan contains standardized, de-identified person-level information on enrollment, paid inpatient and outpatient services and procedures, outpatient pharmacy claims, and provider and health plan information of commercial insurance beneficiaries of mid- to large-employer sponsored commercial insurance,

their spouses, and dependents (collectively, households). Households are identified in the enrollment details file using the first 6-9 digits of the enrollment ID, with the last two digits denoting an enrollee's relationship with the primary beneficiary. MarketScan is one of the largest, fully integrated, and most complete commercial insurance claims databases available for the U.S, where beneficiaries can be tracked across insurance plans, healthcare sites, provider types, and over time[108] with a median follow up of 3 years. The size of the database increased from 3.7 million enrollees to 47.2 million between 2000-2014.

Study Population

This retrospective cohort study included household members of patients who initiated new use of prescription opioids or prescription NSAIDs based on outpatient pharmacy dispensing claims (henceforth, we refer to the index patient as "Patient 0"). New use was defined as the first pharmacy dispensing claim after a 365-day baseline period of continuous enrollment without evidence of prescription opioid or prescription NSAID use in claims. Household members were defined as enrollees sharing the same health insurance plan as Patient 0 based on the first 6-9 digits of the enrollment ID. We generalized the "new-user" design[136] to "new-households" by requiring all household members to have continuous prescription drug coverage with no record of prescription opioid or NSAID use during the baseline period. Household members entered either the opioid or NSAID cohort at the index date anchored to the date of initiation by Patient 0. Eligible index dates are those occurring between 1/1/2001 and 12/31/2014 to ensure observation of the 1-year baseline. To make comparisons between cohorts more rigorous and improve exchangeability of Patients 0, household members of patients who initiated both prescription opioids and NSAIDs on the same day, had a history of malignancy, or used hospice services during the baseline period were also excluded.

Opioid Medication Exposure

Pharmacy dispensing billing claims for the most commonly prescribed synthetic and semisynthetic opioids and NSAIDs were identified in the Outpatient Pharmaceutical Claims file by their generic string name. Opioids and NSAIDs were restricted to oral and transdermal formulations (**Appendix Table A.1**). We excluded claims for opioids used primarily to treat Parkinson's disease (apomorphine), opioid dependence (methadone), and cough (potassium guaiacolsulfonate/hydrocodone bitartrate) to improve identification of patients with similar indications.

Outcome Assessment

Our primary outcome was initiation of prescription opioids by members of Patient 0's household. Initiation by a household member was assessed similarly to cohort eligibility defined by Patient 0 using the dispensing date for an eligible opioid in the Outpatient Pharmaceutical claims database.

Covariates

Baseline covariates for household members were assessed during the one year prior to the household index date defined by Patient 0. Potential confounders of the association between potential access to prescription opioids and opioid initiation were identified *a priori* using directed acyclic graphs. Potential confounding variables included household size, composition (children age <18 years, yes/no), region of residence (Northeast, North Central, South, West), calendar year of cohort entry, and history of substance use diagnosis for Patient 0 (yes/no). To improve statistical efficiency, we adjusted for individual-level predictors of opioid initiation and potentially informative censoring, including age, sex, baseline pain and psychiatric co-morbidity (dichotomous variables for yes/no), healthcare utilization (number of outpatient

visit, continuous; emergency room visit in prior 7 or 30 days, yes/no), and use of scheduled prescription medications (dichotomous variables for yes/no for each drug class).

Statistical Analysis

We estimated the 1-year risk of opioid initiation among household members (excluding Patients 0) within each treatment group using the complement of the Kaplan-Meier estimator with time in days from the index date. Household members were individually censored at the earliest of an event, at 1 year of follow-up, loss to follow up (defined as disenrollment), or administrative censoring on December 31, 2014.

Inverse probability weighted Kaplan-Meier survival curves were used to derive 1-year risks and risk differences (RD) for opioid initiation adjusting for baseline confounders and informative censoring.[114] Weights were the product of stabilized inverse probability of treatment and stabilized inverse probability of censoring weights estimated using logistic regression models. Models for the denominator of weights included confounders and potential predictors described above. Age, number of outpatient visits during baseline, and household size were modeled using restricted quadratic splines[115] and calendar year as a categorical variable with each year as a separate category. Treatment weights were calculated as the complement of the propensity score (PS) for members of opioid households and (1-PS) for members of NSAID households and stabilized by the marginal probability of household exposure to opioids in the cohort. Censoring weights were calculated as the complement of the probability of dropout (PD) for those who disenrolled, and (1-PD) for those who remained under observation and stabilized by the marginal probability of disenrollment in the cohort. Estimates of precision were obtained using non-parametric bootstrap resampling with replacement.

We explored potential heterogeneity of the association between household opioid availability and opioid initiation across pre-specified subgroups: potential indication for Patients 0 (back pain [yes vs. no]; fracture [yes vs. no]; age of household member (0-5, 6-11, 12-17, 18-

25, 26-35, 36-45, 46-55, ≥56 years); and region of residence. Subgroup differences were examined by stratifying the original cohort and repeating the primary analysis described above within each stratum.

We performed two sensitivity analyses. First, the primary analysis was performed after restricting to two-adult (age >18 years) households. Second, we assessed the extent to which unmeasured confounding bias could explain our results.[98,116] All analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC).

C. RESULTS

Characteristics of the Study Sample

The study sample comprised 12,695,280 members of 5,871,003 opioid households and 6,359,639 members of 3,015,932 NSAID households, after excluding 84,810 (1%) households without information on geographic region (**Figure 5.1**). Opioid and NSAID households were of similar size (median, 3 enrollees; interquartile range [IQR], 2-4 enrollees), but opioid households were more likely to reside in the south than NSAID households (**Table 5.1**). Demographic characteristics were similar between cohorts: the median age of household members was 22 years (IQR, 11-45 years), and less than half were female. Overall, covariates were balanced between household exposure groups. However, compared to members of NSAID households, slightly greater proportions of members of opioid households had used ADHD medications, antibiotics, benzodiazepines, SSRIs, and sleep medications, but not beta-blockers, statins, or muscle relaxants during baseline. Members of opioid households were also more likely than members of NSAID households to have a history of back and neck pain, migraine, depression, fractures, substance abuse, and cancer screening, and less likely to have diabetes mellitus and arthritis. However, utilization of outpatient and inpatient services and emergency room visits were similar between household exposure groups.

Unadjusted Analysis

Members of opioid households and NSAID households were followed for a median of 1 year (IQR, 0.6-1.0). During 14,846,450 person-years of follow-up, 1,786,014 individuals initiated use of prescription opioids and 4,187,048 individuals disenrolled from their health plan (21% NSAID, 22% opioid). Overall, the 1-year risk of prescription opioid initiation was 11.32% (95% confidence interval [CI], 11.30-11.34).

Inverse Probability Weighted Analysis

All potential confounders and predictors of opioid initiation or dropout identified a priori were included in corresponding propensity score models for treatment and censoring weights. The means of the treatment and censoring weights were 1.00 (range, 0.36-6.06) and 0.98 (range, 0.36-3.59), respectively. Cumulative incidence curves for opioid initiation over 1 year of follow-up in households with opioid versus NSAID availability are presented in **Figure 5.2**. The 1-year risk of opioid initiation was 11.83% (95% CI, 11.81-11.85) had all individuals been exposed to prescription opioids in the household, compared to 11.11% (95% CI, 11.09-11.14) had they been exposed to prescription NSAIDs in the household (**Table 5.2**). The adjusted 1-year RD in opioid initiation due to potential access to household opioids was 0.71% (95% CI, 0.68-0.74).

Subgroup Analyses

The risk difference for the association between household opioid availability and opioid initiation was modified by the household member's age (**Table 5.2**). The RD was largest among enrollees age 26-35 years (RD, 1.26% [95% CI, 1.08-1.43]) and age 18-25 years (RD, 0.91% [95% CI, 0.81-1.01]) compared to all other age groups. Risk differences also differed by geographic region, with the largest risk difference observed in the West (RD, 0.95% [95% CI,

0.88-1.02]) and smallest in the North Central region (RD, 0.44% [95% CI, 0.38-0.51]). There were also subgroup differences according to potential patient indication.

Sensitivity Analyses

Within two-adult households (n = 2,706,922), opioid initiation in one adult compared to NSAID initiation was associated with increased risk of opioid initiation in the other adult (RD, 1.08% [95% CI, 0.90-1.39]). The results of the sensitivity analysis evaluating potential unmeasured confounding bias are presented in **Appendix Table B.1**. Independent of measured confounders, small imbalances in the prevalence of an unmeasured binary confounder across levels of household opioid availability (prevalence difference = 0.9%) reduced our observed estimate of the risk difference (0.71%) to 0, assuming the unmeasured confounder is weakly associated with opioid initiation within levels of household opioid availability (RD = 0.9%). Alternative scenarios that resulted in lesser reductions of our observed estimate are presented in **Appendix Table B.1**.

D. DISCUSSION

We conducted a large, retrospective, cohort study comparing the risk of opioid initiation among commercial insurance beneficiaries who were newly exposed to prescription opioids versus prescription NSAIDs through a household member's prescription. We observed a 0.71% absolute increase in risk of prescription opioid use among individuals with potential access to prescription opioids, compared to those with potential access to prescription NSAIDs, through a household member's prescription.

The association between household opioid availability and opioid initiation varied across geographic region, potential indication, and age subgroups, with the largest association among individuals age 26-35 years. Given high rates of drug overdose in this age group,[137] identifying

at-risk patients could help target quality improvement initiatives aimed to reduce the harms of the broad availability of prescription opioids.

Previous studies on prescription opioids have used MarketScan[138-141] but none examined patterns of use within families. In other administrative databases, research has focused on within-family environmental transmission of drug abuse.[134] Because prescription opioid abuse can develop from opioid therapy for legitimate pain management,[142] understanding patterns of prescription opioid use within households and other social networks may be an important step towards addressing the prescription opioid epidemic.

Assuming no unmeasured confounding, the relationship between potential access to household opioids and opioid initiation could be explained by multiple mechanisms. First, family members may serve as a source of prescription opioids to be shared with other members, which may lead to one seeking her own prescription. Second, household opioid use may shape attitudes and norms of opioid use.[135] Third, spousal correspondence of opioid use may be due to homophily, defined as the inclination of similar individuals to associate.[99] In this analysis, we did not seek to disentangle the latter two mechanisms (e.g., person-to-person influence of opioid use vs. homophily). While elucidating potential mechanisms through which opioid use propagates within households can help target interventions, understanding the potential public health impact of prescribing therapeutic alternatives to opioids such as prescription NSAIDs may be a first step towards addressing the opioid overuse epidemic.

We assessed the robustness of our estimates to the possibility of unmeasured confounding in sensitivity analyses (**Appendix Table B.1**). Our estimate for the association between household opioid availability and opioid initiation was sensitive to modest imbalances of an unmeasured covariate between treatment groups even if the covariate is weakly associated with opioid initiation. In this study, healthcare provider was unmeasured and may potentially confound the association between opioid initiation in Patient 0 and opioid initiation by other household members. A previous study estimated physician preference for prescribing the

same analgesic to unrelated patients to be over 20%,[143] thus it is plausible that our results could be explained by unmeasured provider preference if household members have the same healthcare provider. Alternatively, unmeasured environmental or system-level factors or household socioeconomic status may have given rise to confounding.[98]

We generalized the "new-user" design[136] commonly used in pharmacoepidemiology to leverage information on households in large administrative databases and restrict to enrollees who had no prior access to opioids or NSAIDs in the household. The benefit of our "new-household" approach is the exclusion of households with prevalent use of prescription opioids, which may be affected by differential attrition, adherence, physiologic adaptation, or early adverse effects.[136] We used households with prescription NSAIDs as an active comparator group to contextualize households with prescription opioids, minimize potential bias due to differential allocation of prescription opioids to certain patients, and ask a clinically important question about therapeutic alternatives to prescription opioids. However, restriction limits the generalizability of our inferences and applicability to real-world pharmacotherapy decisions.

Despite our attempt to improve the internal validity of our estimates, we could not verify co-residence of household members, identify household members on another health plan or with public insurance who may have initiated opioids, or other sources of access to opioids. Misclassification of prior exposure could introduce prevalent user bias, whereas under-ascertainment of true events will bias the risk difference even with perfect specificity and nondifferential sensitivity.[112] Other databases with residential addresses to link patients or with provider or system characteristics could help address potential exposure and outcome misclassification. Because MarketScan overs-samples the South and has poor coverage of the West, our study may not directly generalize to the U.S. commercially insured population.

The cohort and primary outcome were identified using pharmacy dispensing billing claims. Electronic pharmacy dispensing records are considered the gold standard of prescription drug exposure compared with self-reported medication use or prescribing records in

outpatient medical records because reimbursement by private insurance companies is based on complete and accurate claims.[110] Although opioids paid in cash or received in inpatient settings were not captured in our data, approximately 15% of opioid prescriptions in 2008 were paid in cash[144] and 90% of opioids are dispensed from retail pharmacies.[53] Similarly, pharmacy dispensing billing claims were used to identify an active comparator group comprised of patients initiating prescription NSAIDs. Although we expect the sensitivity of prescription NSAID exposure to be high, we lack information on over-the-counter (OTC) NSAID use. However, OTC NSAID exposure is not expected to be a substantial source of bias in our study, as sensitivity analyses have shown that prescription claims data can provide valid estimates of drug-outcome relationships even when a large proportion of drug use is OTC.[111]

To our knowledge, this is the first study to investigate the association between household availability of prescription opioids and prescription opioid initiation in a heterogeneous population of households in the United States. Understanding the context and patterns of prescription drug use within households may inform clinical decision-making and help design policies and targeted quality improvement interventions for prescribing drugs with high abuse, dependence, and diversion potential.

E. TABLES & FIGURES

Figure 5.1 Derivation of cohort in the MarketScan Commercial Claims and Encounters databases, 2000-2014

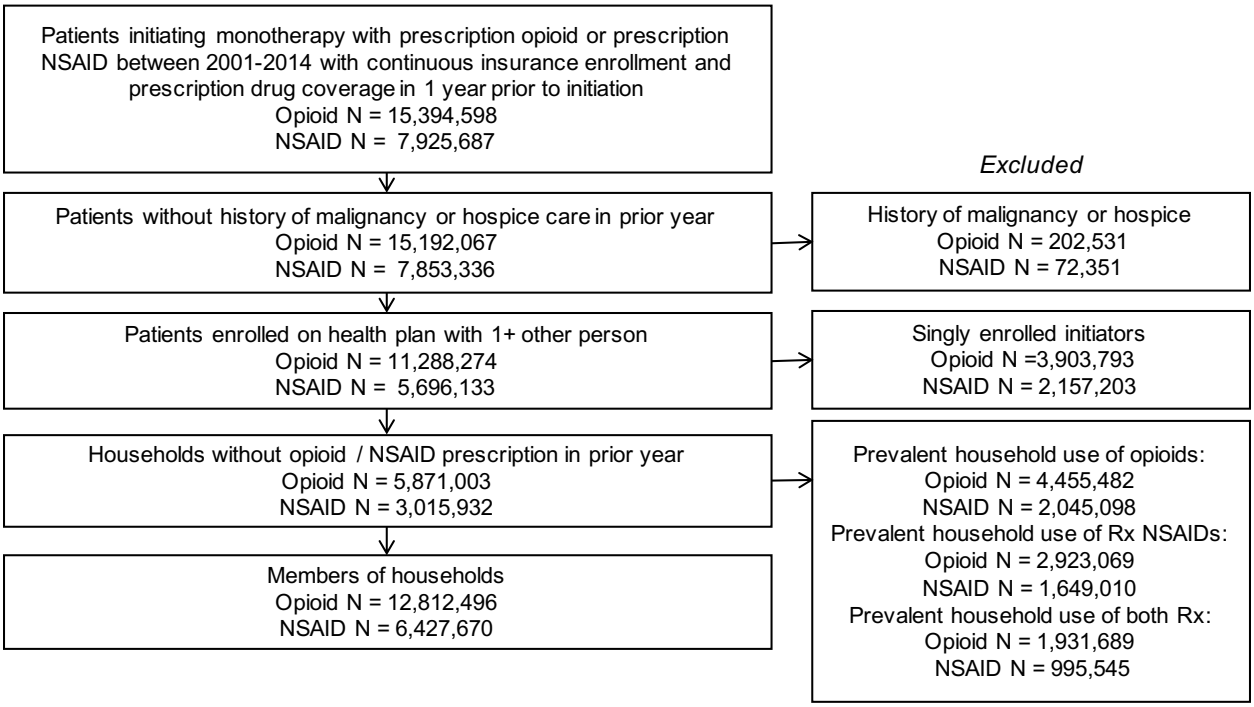


Table 5.1 Baseline characteristics of household members of prescription analgesic initiators, MarketScan Commercial Claims and Encounters 2000-2014

	(%)	
Characteristic	Opioid n = 12 695 280	NSAID n = 6 359 639
Demographics		
Sex, Female	48.5	48.1
Age, median (IQR)	22 (11-45)	21 (11-45)
Age group		
<6 y	10.8	10.4
6-11 y	15.1	15.6
12-17 y	15.7	16.5
18-25 y	11.8	13.1
26-35 y	7.4	6.3
36-45 y	14.8	13.7
46-55 y	16.2	15.8
≥56 y	8.3	8.7
Baseline mediation use		
Use of benzodiazepines	3.1	2.8
Use of ADH medications	1.5	1.4
Use of antibiotics	36.0	35.8
Use of muscle relaxants	1.0	1.0
Use of sleep medications	1.8	1.6
Use of SSRIs	4.6	4.1
Use of statins	6.0	6.2
Preexisting pain conditions		
Back and neck pain	7.6	7.0
Back pain	3.7	3.5
Back disorder	5.9	5.7
Headache	2.3	2.4
Migraine	1.0	1.0
Arthritis	6.3	6.3
Osteoarthritis	0.9	0.9
Rheumatoid arthritis	0.4	0.4
Fibromyalgia	0.9	0.8
Fractures	1.7	1.7
Preexisting comorbidities		
Depression	2.8	2.6
Substance abuse	1.0	1.0
Alcohol use	0.3	0.3
Gastrointestinal bleeding	0.5	0.5
COPD	0.4	0.4
Healthcare utilization		
ER visit in past 30 days	1.1	1.1
ER visit in past 7 days	0.4	0.3
Outpatient visits, mean (SD)	2.3 (2.95)	2.4 (3.03)
Inpatient days, mean (SD)	0.1 (1.40)	0.1 (1.42)

Abbreviations: SD, standard deviation; IQR, interquartile range; ADHD, attention deficit hyperactivity disorder; SSRIs, selective serotonin reuptake inhibitors; COPD, chronic obstructive pulmonary disease. Covariates are defined in Appendix Table A.1. Baseline characteristics were assessed in the 1 year prior to the index date.

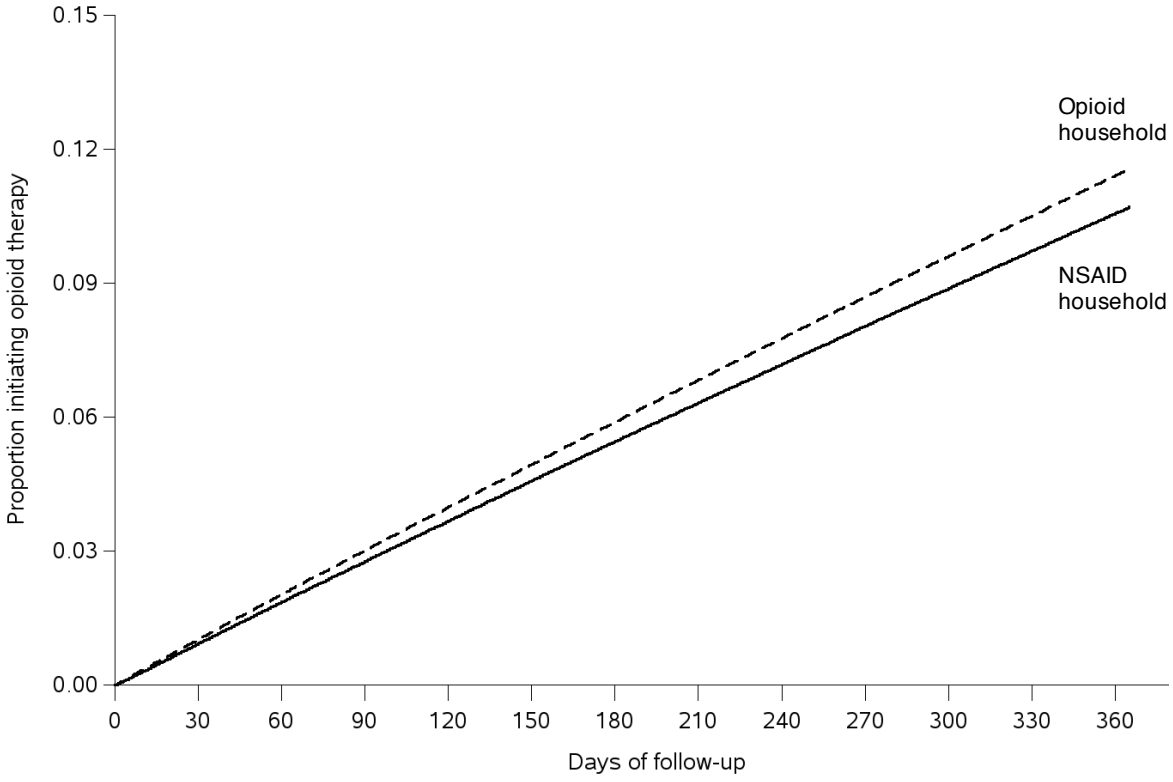
Table 5.2 Cumulative incidence of opioid initiation among household members of prescription opioid vs. prescription NSAID initiators overall and by age, region, and potential indication for opioid initiation by Patient 0, MarketScan Commercial Claims and Encounters 2000-2014

	Opioid	NSAID		
Opioid initiation	1-Year Risk, % (95% CI)[a]	1-Year Risk, % (95% CI)	Risk Difference % (95% CI)	Risk Ratio (95% CI)
Unadjusted	11.68 (11.66, 11.70)	10.60 (10.57, 10.63)	1.08 (1.05, 1.11)	1.10 (1.10, 1.11)
Inverse-probability weighted	11.83 (11.81, 11.85)	11.11 (11.09, 11.14)	0.71 (0.68, 0.74)	1.06 (1.06, 1.07)
Subgroup analyses				
Age				
0-5 years	3.6 (3.5, 3.6)	3.2 (3.1, 3.2)	0.41 (0.35, 0.48)	1.13 (1.11, 1.15)
6-11 years	3.7 (3.7, 3.8)	3.3 (3.3, 3.4)	0.41 (0.36, 0.45)	1.12 (1.11, 1.14)
12-17 years	10.2 (10.2, 10.3)	9.5 (9.4, 9.5)	0.77 (0.70, 0.86)	1.08 (1.07, 1.09)
18-25 years	13.7 (13.6, 13.7)	12.8 (12.7, 12.8)	0.91 (0.81, 1.01)	1.07 (1.06, 1.08)
26-35 years	18.8 (18.7, 18.9)	17.5 (17.4, 17.7)	1.26 (1.08, 1.43)	1.07 (1.06, 1.08)
36-45 years	16.0 (16.0, 16.1)	15.3 (15.2, 15.4)	0.72 (0.62, 0.80)	1.05 (1.04, 1.05)
46-55 years	15.7 (15.6, 15.7)	15.1 (15.0, 15.1)	0.62 (0.52, 0.71)	1.04 (1.03, 1.05)
56+ years	17.1 (17.0, 17.2)	16.3 (16.1, 16.4)	0.85 (0.73, 1.00)	1.05 (1.04, 1.06)
Region				
Northeast	9.6 (9.6, 9.7)	9.1 (9.0, 9.1)	0.57 (0.47, 0.66)	1.12 (1.11, 1.14)
North Central	11.5 (11.4, 11.5)	11.0 (11.0, 11.1)	0.44 (0.38, 0.51)	1.08 (1.07, 1.09)
South	13.2 (13.1, 13.2)	12.4 (12.3, 12.4)	0.76 (0.71, 0.81)	1.07 (1.06, 1.08)
West	11.2 (11.2, 11.3)	10.3 (10.2, 10.3)	0.95 (0.88, 1.02)	1.07 (1.06, 1.08)
Family history (Patient)				
Back/neck pain	12.1 (12.0, 12.1)	11.3 (11.3, 11.4)	0.78 (0.71, 0.85)	1.07 (1.06, 1.08)
No back/neck pain	11.8 (11.8, 11.8)	11.0 (11.0, 11.0)	0.81 (0.77, 0.84)	1.07 (1.07, 1.08)
Fracture	12.1 (12.0, 12.2)	11.7 (11.5, 11.9)	0.42 (0.21, 0.61)	1.04 (1.02, 1.05)
No fracture	11.8 (11.8, 11.9)	11.0 (11.0, 11.0)	0.82 (0.79, 0.85)	1.07 (1.07, 1.08)
Sensitivity analyses				
Two-adult households [b]	17.7 (17.6, 17.9)	16.6 (16.5, 16.8)	1.08 (0.90, 1.32)	1.06 (1.05, 1.08)

*Abbreviations: CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs.

[a] Risks and risk differences adjusted for household size, household composition, year of cohort entry, region and/or age, sex, family history of substance abuse, pain and psychiatric co-morbidities, use of scheduled and unscheduled prescription medications, and healthcare utilization.
[b] Households with two adults age >18 years.

Figure 5.2 Inverse probability weighted cumulative incidence curves for opioid initiation by household availability of prescription nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, MarketScan Commercial Claims and Encounters, 2000-2014
Estimates adjusted for household size, region, year of cohort entry, family history of substance abuse, age, sex, baseline pain and psychiatric co-morbidities, use of scheduled and unscheduled prescription medications, and healthcare utilization



CHAPTER 6
RESULTS: ESTIMATING PEER EFFECTS OF PRESCRIPTION OPIOID USE WITHIN USE HOUSEHOLDS: AN INSTRUMENTAL VARIABLE APPROACH

A. INTRODUCTION

Over the past two decades, the use of prescription opioids among US adults has increased 300%.[145] This increase has been attributed to multiple factors, including changes in opioid prescribing guidelines, shifts in attitudes towards pain relief, aggressive pharmaceutical marketing tactics, liberalization of state laws allowing physicians to prescribe opioids, and prescriber practices.[1,92] Over the same period, opioid-related overdoses and deaths became the leading cause of unintentional death for US adults, raising concerns about opioid overuse.[146] However, containing the opioid epidemic has proved challenging and likely requires a combination of patient, provider, systems-level interventions[57] to address the broad "environmental availability" of prescription opioids.[147]

Increased prescribing of opioids may also be driven by peer effects. Peer effects (also known as person-to-person influence or social contagion) are observed when one individual's behavior or characteristic influences the behaviors or characteristics of other people in the same social network, such as friends, coworkers, or members of the same household. Given high rates of prescription drug sharing between family members and documented peer effects of substance use between spouses,[97] it is likely that opioid use may also spread from one family member to another. However, household or community risks of opioid use due to a single exposure remains unknown, likely due to methodological challenges in estimating peer effects from non-experimental studies.

Unmeasured confounding is commonly acknowledged as a threat to inference from non-experimental studies of treatment effects, but homophily (i.e., the tendency for similar individuals to associate) is another source of bias when estimating peer effects of drug treatment or other health behavior. Previous studies examining correlations of health behaviors in dyads have taken the approach of regressing the outcome of one individual on the lagged outcome of another, and interpreting the parameter as a peer effect.[10] However, when the reasons that two individuals associate are also predictors of the behavior under study (for example, unrecorded prescription drug abuse), correlations in behaviors cannot be disentangled from person-to-person influence, even in the absence of a unmeasured confounding.[98,99] To the extent that measured covariates cannot fully control for unmeasured environmental confounding or differences in the degree of homophily between exposure groups, residual bias is likely to remain in estimates of potential peer effects.

Instrumental variable (IV) methods have been proposed to account for unmeasured confounding and homophily bias in studies of peer effects of health behaviors.[100] This quasi-experimental approach has been shown to be useful in comparative effectiveness research,[101,102] where unmeasured confounding by indication or frailty can threaten study inferences. IV methods replace the assumption of no unmeasured confounding between exposure and outcome, with key assumptions about the relationship of an observed exogenous variable, the exposure, and outcome. We sought to evaluate the utility of an instrumental variable approach to investigate whether peer effects potentially contribute to increases in opioid use in the United States.

The objective of this study is to evaluate an instrumental variable approach to estimate peer effects of prescription opioid use among members of the same household. Specifically, we considered injury type as a binary instrument for prescription opioid treatment among ankle injury patients to estimate and compare the risk of prescription opioid use in other household members using administrative healthcare claims data from 2000-2014. We chose this example

because ankle injuries are common, [148] and ankle fractures are more likely to be treated with opioids than ankle sprains.

B. METHODS

Data Source and Study Population

The study sample comprised a cohort of ankle injury patients and their household members in Truven Health's MarketScan Commercial Claims and Encounters Databases (MarketScan) 2000-2014.[108] MarketScan contains prospectively collected person-level data on commercial insurance beneficiaries in the US who are employees of mid- to large-size companies or spouses and dependents who can be tracked across time and health plans. Patients with an inpatient or outpatient diagnosis for ankle fracture (International Classification of Disease (ICD-9) diagnosis codes 824.0-824.9) or ankle sprain (ICD-9: 845.00, 845.01, 845.02, 845.03, 845.09) who were enrolled with 1 or more household members during baseline were included. Analyses was restricted to the patient's first ankle injury in claims, defined as no ankle injury in the prior year. Patients and household members were required to have continuous enrollment with prescription drug coverage and no record of prescription opioid use in the 1-year prior to the index injury. To keep comparisons rigorous, households of patients who had both ankle fracture and sprain diagnoses were excluded.

Instrumental Variable Approach

We explored an instrumental variable (IV) approach to address possible unmeasured confounding and latent homophily.[149] To be valid, an instrument must be an observed variable that (1) predicts treatment receipt (also known as the relevance condition); (2) has no direct effect on the outcome (the exclusion restriction condition); and (3) does not share common causes with the outcome (the independence condition). When these conditions hold, an instrument can identify bounds on the average treatment effect in the entire study population.

Assuming homogeneity of the treatment effect on the additive scale by the instrument among treated and untreated subpopulations, or no effect modification by confounders, a point estimate for the average treatment effect in the entire study population can be identified.[104] Alternatively, under the assumption of monotonicity, an instrument can identify a point estimate of the local average causal effect for a subpopulation of "compliers" whose treatment is affected by the instrument.[104]

We specified injury type as a binary instrument (ankle fracture vs. ankle sprain) for opioid treatment. Assuming that injury type is random, but ankle fractures are more likely to be treated with opioids than ankle sprains (i.e., relevance), we expect the instrument to make the patient population and their households exchangeable by balancing covariates that are predictive of the outcome and the degree of homophily between household members (i.e., independence). The exclusion restriction condition holds if injury type in the index patient has no direct effect on opioid initiation among household members except through introducing opioids into the household. Deterministic monotonicity assumes that there are no patients who would receive opioids after an ankle sprain, but would not receive opioids after a fracture. We relaxed this condition assuming stochastic monotonicity, which allows point identification of a local average treatment effect that is weighted more heavily on patients for whom the instrumental variable has a strong effect on opioid receipt.[117] We evaluated the plausibility of these assumptions by estimating the strength of the instrument (i.e., compliance percentage), examining balance of measured covariates across the instrument, and using subject-matter knowledge.

Prescription Opioid Exposure

For the index injury patients, opioid receipt was defined as an outpatient pharmacy dispensing claim for an eligible synthetic or semisynthetic opioid within 30 days after the injury diagnosis. Opioids were restricted to oral and transdermal formulations and excluded opioids

used primarily to treat Parkinson's disease (apomorphine), opioid dependence (methadone), and cough (potassium guaiacolsulfonate/hydrocodone bitartrate).

Endpoint

Our primary outcome was initiation of eligible synthetic or semisynthetic opioids by household members of injury patients. Opioid initiation was defined similarly to opioid receipt in the index injury patient using outpatient pharmacy dispensing records. Household members of ankle injury patients were followed from the index injury to opioid initiation (event), disenrollment (loss to follow-up), or administrative censoring after 1 year or on December 31, 2014.

Covariates

We assessed baseline covariates for household members during the year prior to the index injury. Covariates potentially associated with both injury type and opioid initiation among household members were identified *a priori* using directed acyclic graphs[150] and included region of residence (Northeast, North Central, South, West), household size, household composition (children age <18 years, yes/no), and calendar year of cohort entry. To improve statistical efficiency in the models for inverse probability weights described below, we included baseline covariates of household members that are potentially predictive of opioid initiation, including demographics, psychiatric and pain co-morbidities (dichotomous variables for yes/no), healthcare utilization (number of outpatient visit, continuous; emergency room visit in prior 7 or 30 days, yes/no), and use of scheduled prescription medications (dichotomous variables for yes/no for each drug class; see Appendix Table A.1 for definitions).

Analyses

We estimated crude and inverse-probability-weighted cumulative incidence curves[114] by injury type using the Kaplan Meier estimator, reporting risk difference in opioid initiation among

household members. Adjusted cumulative incidence curves were estimated by weighting events and person-time by the product of the inverse probability of injury type given baseline covariates and inverse probability of informative censoring given injury type and baseline covariates. Upper and lower bounds for the average causal effect in the entire study population were derived using the Balke and Pearl method.[105] To account for within-household clustering, estimates of precision were obtained by nonparametric grouped bootstrap sampling of households with replacement. We repeated these analyses restricting to household members 18 years or older. All analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC).

C. RESULTS

Between 2000-2014, 363,241 individuals were enrolled within 153,478 ankle fracture households and 2,459,122 individuals were enrolled within 1,012,374 ankle sprain households. Fracture patients were older and more likely to be male than sprain patients (**Appendix Table C.1)**. Among ankle injury patients, injury type was associated with opioid treatment: approximately 28% of fracture patients initiated an opioid within 30 days after the diagnosis, compared to 5% of sprain patients, yielding 23% compliance (**Figure 6.1**).

Characteristics of household members of ankle injury patients by injury type and opioid initiation by the injury patient are presented in **Table 6.1**. Measured covariates were balanced between injury type groups, lending support to the idea that the proposed instrument is independent of unmeasured confounders. Because covariates were well-balanced across levels of the proposed instrument and the proposed instrument was strong, bias components were small (**Figure 6.2**). However, within levels of injury type, covariates were less balanced between household members who were enrolled with patients who received opioids after the injury versus those who did not (**Appendix Table C.2**).

The distribution of events and person-time at risk by injury type is presented in **Table 6.2**. Overall, 270,582 persons initiated opioids, 623,254 were lost to follow-up, and 1,928,527

were administratively censored over 2,181,230 person-years follow-up. The overall 1-year risk of opioid initiation among household members of ankle injury patients was 11.7%. The 1-year risk of opioid initiation among household members of fracture patients was 11.4% versus 11.7% among household members of sprain patients.

Risk differences by model type and population are presented in **Table 6.3**. The 1-year intent-to-treat opioid initiation risk difference, comparing household members of sprain patients to household members of fracture patients, was -0.27% (95% confidence interval (CI): -0.30, -0.24). Accordingly, the 1-year instrumental variable risk difference of opioid initiation among household members of compliant injury patients was -1.15% (95% CI: -1.30, -1.04). The Balke-Pearl bounds of the 1-year risk difference were (-11.1%, 67.6%).

In sensitivity analyses, restricting to the 215,089 adults enrolled with fracture patients and 1,438,042 adults enrolled with sprain patients yielded an intent-to-treat risk difference estimate of –0.50% (95% CI: -0.54, -0.45). Compliance among injury patients within this subgroup remained at 23%. The instrumental variable analyses yielded a 1-year risk difference of -1.85% (95% CI: -2.37, -1.99) among household members of compliant injury patients.

D. DISCUSSION

Using an innovative instrumental variable based on injury type, we investigated potential peer effects of prescription opioid use due to a single household exposure using large administrative claims data. When an instrument is valid, IV methods enable identification of peer effects by accounting for unmeasured confounding and homophily bias that can threaten inference from nonexperimental studies of social networks.[100] In our simple network structure consisting of households of commercial insurance beneficiaries, we observed 0.27% higher 1-year risk of opioid initiation among individuals in households of patients with less severe injuries (sprains) than among individuals in households of patients with more severe injuries (fractures). Accordingly, our instrumental variable analyses suggest that opioid use in one person is

associated with lower 1-year risk of opioid initiation by a family member, compared to no opioid use. Because of our large sample size, estimates were precise; however, the magnitude of a potential peer effect was small and bounds were wide, ranging from a strong negative to a strong positive effect, reflecting a high degree of uncertainty about our estimate given the data and instrumental conditions.

Inference from studies applying instrumental variable methods rely heavily on unverifiable assumptions,[151] and violations of these conditions may have contributed to our seemingly counterintuitive results. Injury type was a moderately strong instrument for opioid treatment receipt in our study sample, satisfying the relevance condition. Yet, biases that affect the IV estimate can be amplified if the instrument-treatment relationship is due to confounding rather than a causal effect.[106] We assessed the potential for bias amplification by visualizing associations between the IV and measured covariates using bias component plots.[152] Because covariates were balanced and our instrument was moderately strong, bias components were small. However, these diagnostics apply to the full study population and would not be relevant to bias in the local average treatment effect estimated among the "compliers" except under strong assumptions of representativeness or homogeneity of effects.[152]

Characteristics of household members were more balanced between injury type groups than treatment groups, providing evidence to support the independence condition, assuming that bias due to potential measured confounders is similar in type to unmeasured confounding.[152] We did not have information on household socioeconomic status or other shared environmental factors. To the extent that measured covariates are poor proxies and cannot account for these sources of bias, our results may reflect residual confounding.

The exclusion restriction condition cannot be empirically validated and may not hold if injury type is associated with concomitant prescribing of other medications associated with opioid initiation among household members, such as benzodiazepines. Other mechanisms through which injury type in one person could affect opioid initiation among their household

members could be through changes in their social relationships. For instance, caregivers to ankle fracture patients likely experience additional challenges to those experienced by household members caring for ankle sprain patients, which may increase the likelihood of opioid initiation. Alternatively, compared to fractures, sprains may be associated with greater healthcare-seeking behavior by the patient after the index injury independent of opioid treatment and baseline healthcare utilization (because not all sprain necessitate medical care), and correlate with greater healthcare use among household members, resulting in downward bias of our estimate of potential peer effects.

We targeted estimation of the local average treatment effect among household members of compliant patients assuming monotonicity. However, it is possible that there are patients who would receive opioids after a sprain, but would not receive opioids after a fracture, thereby "defying" the treatment indicated by the instrument. Assuming monotonicity holds, our instrumental variable analysis results generalize to a subpopulation of household members of "compliant" ankle injury patients who would receive opioids after a fracture but would not receive opioids after a sprain. This group comprises 23% of our patient sample but is otherwise unknown.

We further assumed that any peer effects would be confined to the household, such that opioid receipt occurring in one household does not affect the potential outcomes in another household. This assumption could not be evaluated with the data, but information on physical addresses or provider identifiers could provide additional insights on peer effects in more complex social network structures. Furthermore, we could not verify co-residence of household members and do not know whether patients who filled a prescription for opioids consumed the medications. Additionally, other potential sources of opioid medication exposure or initiation, such as those occurring in inpatient settings or prescriptions paid without using pharmacy benefits, were not be captured in our data. However, less than 15% of opioid prescriptions in 2008 were paid in cash[144] and 90% are dispensed from retail pharmacies.[53]

Applications of IV methods are increasingly common,[102,153-155] but few studies have applied these methods to investigate peer effects of health behaviors.[100,103] The paucity of IV studies of peer effects is likely due to the challenge of finding a suitable instrument that can account for latent homophily (again, the tendency for similar individuals to associate). O'Malley et al. formalized IV methods to identify peer effects among friends and spouses, using genes as IVs for obesity.[100] Given that polymorphisms in genes that encode dopamine and opioid receptors and signaling are associated with developing opioid dependence,[156] a Mendelian randomization approach may be used to identify peer effects of opioid use among friends or spouses. Other sources of random variation in one individual but not in other persons of the same social network could be considered potential instruments for identifying peer effects.

To our knowledge, our study is the first to consider injury type as a novel instrument to estimate peer effects within social networks. Although limitations of instrumental variable analyses often include imprecision, this was not the case in our study using large administrative claims databases. Electronic pharmacy dispensing records are considered the gold standard of prescription drug exposure compared with self-reported medication use or prescribing records in outpatient medical records because reimbursement by private insurance companies is based on complete and accurate claims.[110] In contrast to studies using self-reported prescription drug use behaviors,[157] our study is less likely to suffer from social desirability bias. Moreover, rather than focus on opiate abuse to define a study population or as an outcome,[49,96,158-160] we considered prescribed use of opioids to reduce the potential for selection bias and outcome misclassification error in addressing the overuse epidemic.

In summary, although we found an inverse association between injury type and risk of opioid initiation among household members of injury patients, potential peer effects of opioid use remain uncertain. Results from instrumental variable analyses should be interpreted with caution given unverifiable assumptions,[161] but injury type may be a promising source of natural variation to estimate peer effects in other social contexts.

E. TABLES & FIGURES

Table 6.1 Characteristics of household members of injury patients by injury type and opioid receipt by index patient

	Injury Type (Instrument)		Opioid Treatment	
	Sprain n = 2,459,122	Fracture n = 363,241	Untreated n = 2,613,556	Treated n = 208,807
Characteristic	(%)	(%)	(%)	(%)
Household size; mean (SD)	4.4 (1.32)	4.3 (1.39)	4.4 (1.33)	4.2 (1.36)
Region				
Northeast	17.3	18.3	17.8	13.2
North Central	28.2	28.2	28.2	28.3
South	32.8	34.1	32.6	37.7
West	21.6	19.4	21.4	20.8
Age; median (IQR)	21 (12-44)	22 (12-44)	22 (12-44)	20 (12-44)
Age categories				
<6	7.7	7.3	7.6	8.5
6-11	15.8	15.7	15.8	16.1
12-17	18.0	17.8	17.9	18.9
18-25	11.9	12.0	11.8	14.0
26-35	5.3	5.9	5.4	5.0
36-45	19.7	19.4	20.0	15.1
46-55	17.3	16.1	17.3	16.2
56-65	4.2	5.8	4.3	6.2
Sex, Female	48.3	48.1	48.2	48.6
Baseline mediation use				
ADHD medications	1.7	1.7	1.7	1.9
Antibiotics	37.2	35.6	37.0	37.2
Beta-blockers	2.6	2.7	2.6	3.0
Benzodiazepines	3.1	3.0	3.1	3.2
Muscle relaxants	1.9	1.7	1.9	1.9
NSAIDs	6.5	6.1	6.5	6.6
Sleep medications	1.8	1.8	1.8	2.0
SSRIs	4.8	4.8	4.8	5.1
Statins	5.3	5.4	5.2	5.7
Pain conditions				
Back and neck pain	10.4	9.4	10.3	9.1
Back pain	5.3	4.8	5.3	4.6
Back disorder	8.2	7.5	8.2	7.1
Headache	3.1	2.8	3.1	2.9
Migraine	1.4	1.2	1.3	1.3
Arthritis	9.4	9.1	9.4	8.6
Osteoarthritis	1.3	1.3	1.3	1.2
Rheumatoid arthritis	0.6	0.6	0.6	0.6
Fractures	2.5	3.0	2.6	2.5
Fibromyalgia	1.3	1.1	1.2	1.0
Comorbidities				
COPD	0.3	0.3	0.3	0.4
Depression	3.3	3.1	3.3	3.2
Depression psychiatric	2.0	2.0	2.0	2.1
Psychiatric	5.1	4.8	5.0	4.9
DMI	2.5	2.5	2.5	2.7
Gastrointestinal bleeding	0.5	0.5	0.5	0.5
Smoking	0.8	0.8	0.8	0.8
Substance abuse	1.1	1.1	1.1	1.2

Alcohol use	0.3	0.3	0.3	0.4
Healthcare utilization				
Cancer screening	12.2	12.0	12.2	11.4
ER visit in past 30 days	1.4	1.6	1.4	1.7
ER visit in past 7 days	0.5	0.7	0.5	0.8
Number of physician visits; mean (SD)	2.6(3.15)	2.4(3.07)	2.6 (3.16)	2.4 (3.04)
Number of acute care hospital days; mean (SD)	4.7(10.33)	4.5(8.21)	4.6 (10.25)	4.7 (11.24)

Abbreviations: SD, standard deviation; IQR, interquartile range; ADHD, attention deficit hyperactivity disorder; SSRIs, selective serotonin reuptake inhibitors; COPD, chronic obstructive pulmonary disease. Covariates are defined in Appendix Table A.1. Baseline characteristics were assessed in the 1 year prior to the index date.

Figure 6.1 Cumulative incidence of prescription opioid initiation by injury patient within 30 days after the injury by injury type (instrumental variable)

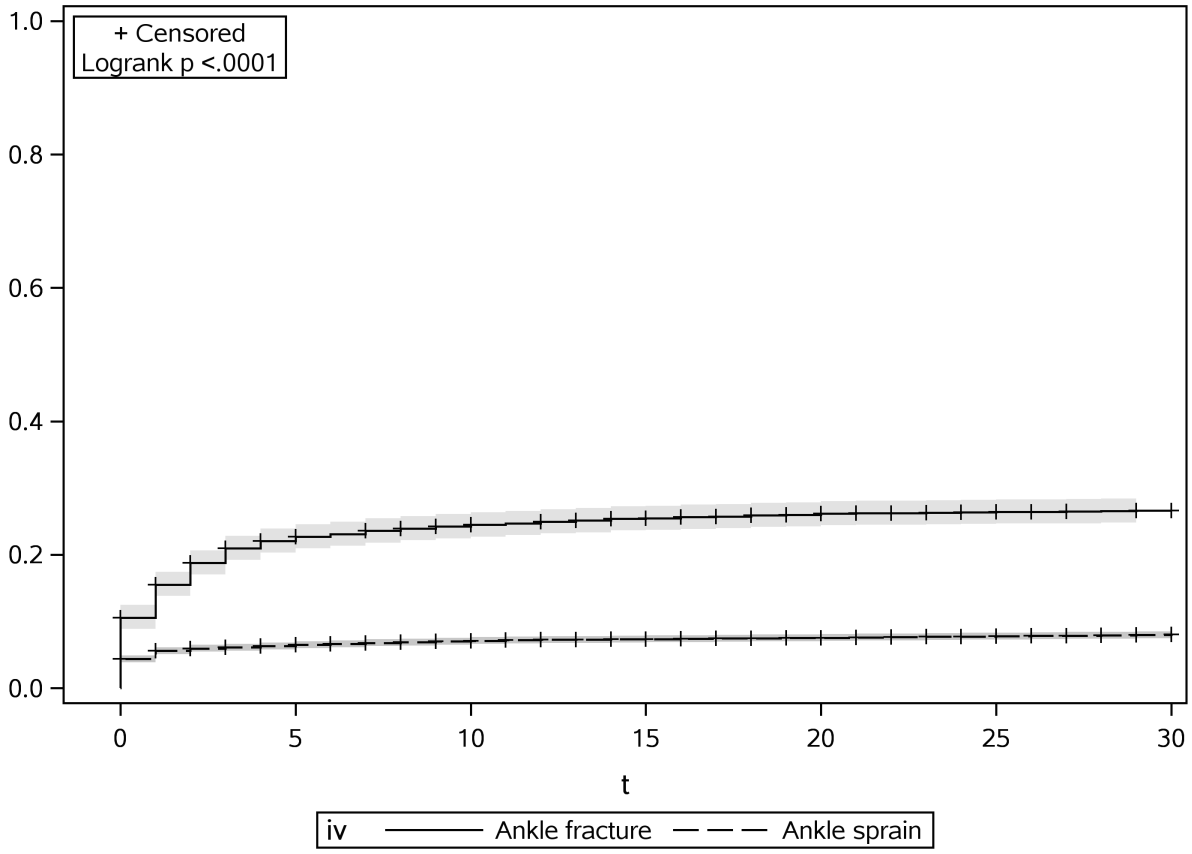


Figure 6.2 Bias component plots unscaled and scaled by instrument strength
Positive values indicate higher prevalence of covariate at baseline among household members of fracture patients than household members of sprain patients

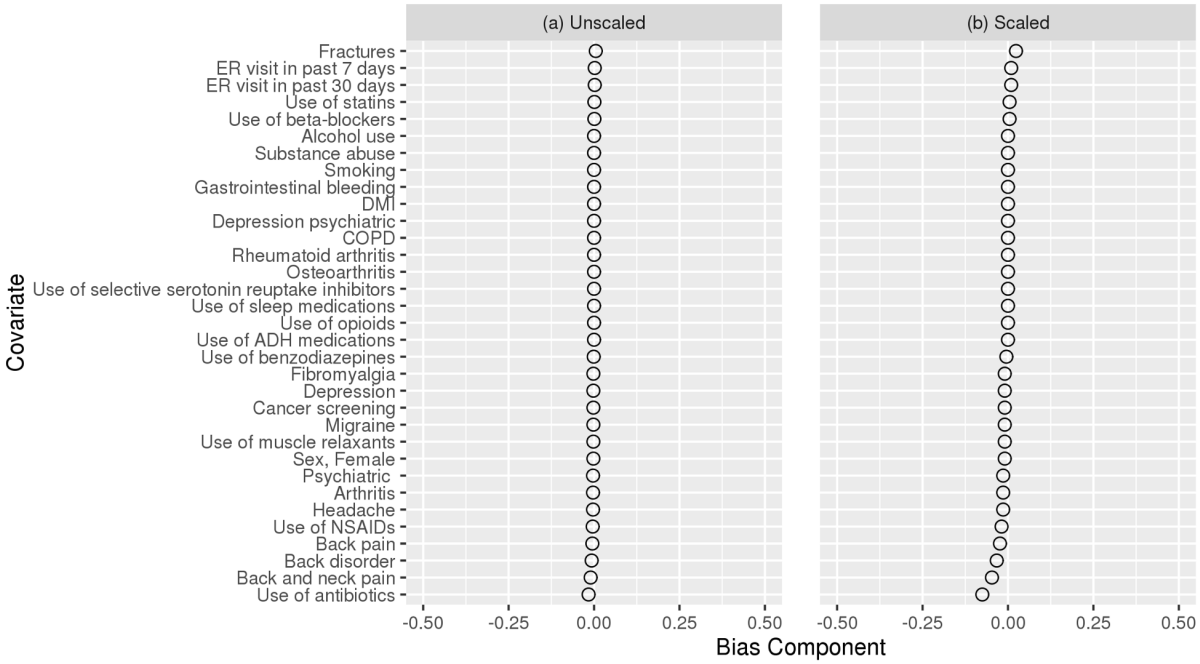


Table 6.2 Events, person-time, and 1-year risk among household members of injury patients by injury type and opioid receipt in injury patient in the full study and adult samples

Injury type	Events	Person Time (Years)	Rate (Per 100 Person-years)	1-Year Risk [a] (%)
Full population (n = 2,822,363)				
Sprain (n = 2,459,122)	236,466	1,900,362	12.4	11.8
Treated	12,690	89,047	14.3	13.2
Untreated	223,776	1,811,315	12.4	11.6
Fracture (n = 363,241)	34,116	280,868	12.1	11.5
Treated	9,710	73,549	13.2	12.3
Untreated	24,406	207,320	11.8	11.1
Adults (n = 1,653,131) [b]				
Sprain (n = 1,438,042)	181,090	1,083,697	16.7	15.5
Treated	9,402	46,760	20.1	18.1
Untreated	171,688	1,036,937	16.6	15.2
Fracture (n = 215,089)	26,261	162,442	16.2	15.0
Treated	7,402	42,284	17.5	16.0
Untreated	18,859	120,158	15.7	14.5

[a] Risks taken from crude cumulative incidence curves estimated using the Kaplan-Meier estimator. Enrollees administratively censored 1 year after index injury or on December 31, 2014.
[b] Adults defined as household members age 18 years or older at baseline.

Figure 6.3 Crude cumulative incidence of opioid initiation among household members of ankle injury patients by injury type

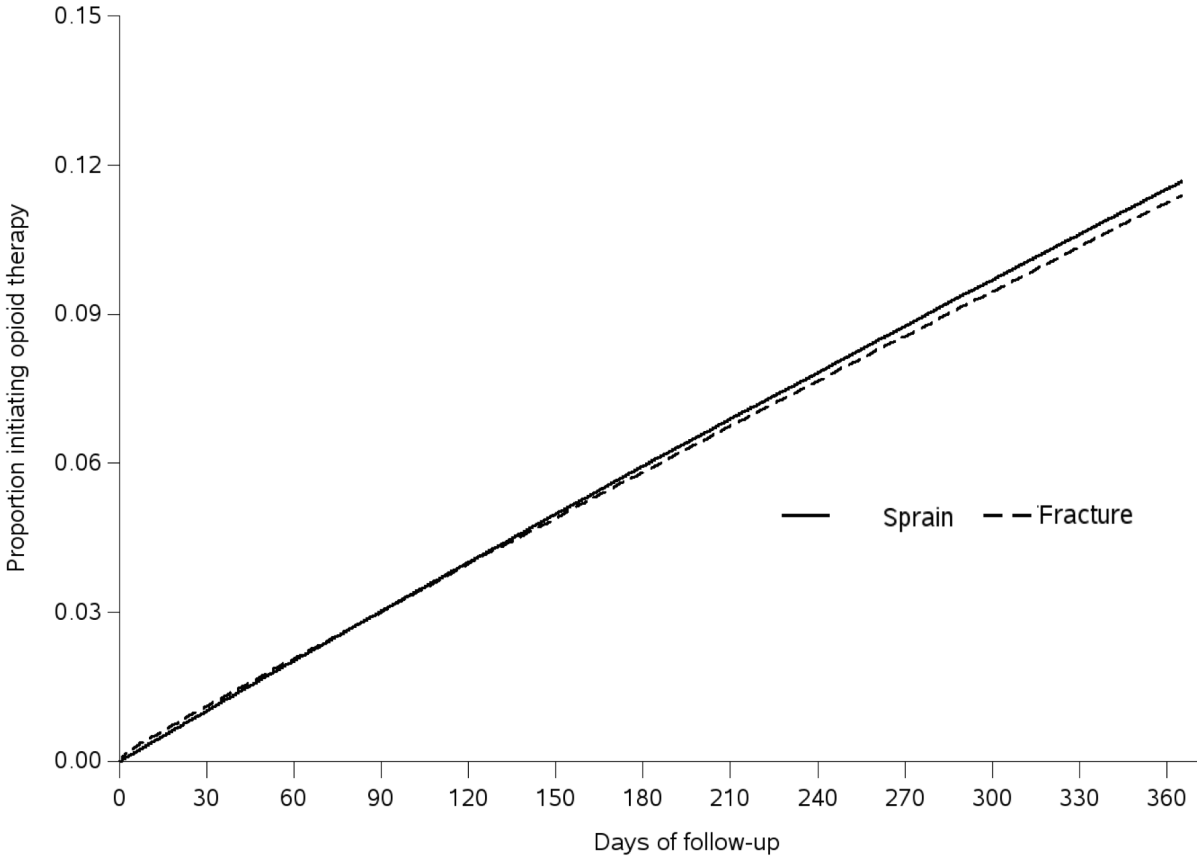


Table 6.3 Risk differences by model type and population

	Overall (n = 2,822,363)		Adults (n = 1,653,131)	
Model	RD [a]	95% CI	RD	95% CI
ITT	-0.26	(-0.30, -0.22)	-0.49	(-0.54, -0.44)
IV[b]	-1.13	(-1.29, -0.97)	-2.13	(-2.36, -1.91)
Adjusted IV	-1.17	(-1.31, -1.02)	-1.84	(-2.38, -1.96)

[a] Risks per 100 enrollees taken from cumulative incidence curves. CIs obtained using nonparametric grouped bootstraps with 250 resamples.
[b] IV estimator is scaled by the compliance percentage (23%). Adjusted estimates obtained from inverse probability treatment and censoring weighted survival functions.
RD, risk difference per 100 enrollees; ITT, intent to treat; IV, instrumental variable.

CHAPTER 7
DISCUSSION

A. SUMMARY OF FINDINGS

This dissertation examined the household context of prescription opioid use in the United States using prospectively collected administrative claims data covering the years 2000-2014.

In Aim 1, we examined and compared household characteristics of patients initiating use of prescription opioids to those initiating prescription NSAIDs. We found that opioid-using and NSAID-using households had similar demographics, but prevalent use of prescription opioids and history of substance abuse tended to cluster within households of opioid new users, whereas COPD and GI bleeding (negative controls) were unassociated with household opioid use. Furthermore, our results suggested that in addition to revealing some baseline differences and potential effect modifiers, identifying households of new opioid users can be used to evaluate prevalent household use of the medication under study and potentially minimize exposure misclassification of “new” users, which could introduce prevalent user (selection) bias.

In Aim 2, we used a novel “new-household” design to examine potential peer effects of prescription opioid use within a heterogeneous population of households of commercial insurance beneficiaries in the US. Our results indicated potentially higher risk of opioid initiation among household members newly exposed to opioids versus NSAIDs through a household member’s prescription. We also found stronger associations among age subgroups, which may help target harm reduction initiatives. However, our results were sensitive to potential unmeasured confounding.

Aim 3 evaluated the novel use of injury type as an instrumental variable for opioid treatment to account for potential unmeasured confounding and homophily bias to estimate peer

effects of opioid use. The injury type instrument compared opioid receipt among ankle fracture patients versus ankle sprain patients, resulting in 23% compliance. Using injury type as an instrument for opioid treatment, we found that the 1-year risk of opioid initiation among household members of treated patients was lower than the risk among household members of untreated patients. However, bounds representing uncertainty of the association crossed the null, suggesting potentially positive or negative peer effects. Nonetheless, the potential use of injury type as instrumental variables for estimating peer effects has not been explored previously and is worth consideration.

Divergent findings from Aims 2 and 3 could be due to different study populations, subpopulations, and assumptions. Aim 2 used a traditional, retrospective new-user, active-comparator cohort study design that we generalized to the household level, which was defined by a heterogeneous population of patients initiating analgesic therapy. In contrast, we considered an instrumental variable approach in Aim 3 in a study population consisting of ankle injury patients and their household members. In addition, the local average treatment effect we estimated in Aim 3 corresponds to a subpopulation of "compliers" within the study cohort, a group that cannot be identified and thus has limited generalizability.[104] Moreover, IV analyses in Aim 3 replace the assumption of no unmeasured confounding of the treatment-outcome relationship in Aim 2 with assumptions about the relationship between the instrument, treatment, and outcome. The fallibility of these assumptions, particularly residual confounding by healthcare-seeking behavior, may have contributed to divergent findings.

B. PUBLIC HEALTH IMPLICATIONS

This research improves understanding of the social context of prescription opioid use in the United States, a concept that has been under-examined in pharmacoepidemiology. Our assessment of household covariates revealed clustering of psychiatric comorbidities within households of patients initiating opioid therapy, as well as prevalent use of prescription drugs

such as benzodiazepines that can be particularly if ingested together with opioids. This information could inform prescribing guidelines to consider the context within which opioids will be used.

This work may also encourage researchers to examine household covariates as potential proxies for unmeasured covariates, effect modifiers, or sources of bias, thereby improving the validity of pharmacoepidemiology studies implementing new-user designs. We identified high levels of prevalent use of the medications under study. Given the high rates of prescription drug sharing, this research urges a social perspective in the design of studies to improve specificity of drug exposure.

To our knowledge, our study is the first to shed light on the potential family risk associated with household opioid exposure. We quantified the extent to which the introduction of opioids into an opioid-naïve household is associated with the risk of opioid initiation among its members. As other researchers have noted,[69] prescribing decisions that focus solely on the intended patient fail to take into account the risks to other individuals in the patient's social network. Understanding these social dynamics of prescription opioid use helps identify points of intervention, such as prescribing therapeutic alternatives to mitigate concerns about opioid overuse.

The proposed use of injury type as an instrumental variable to identify peer effects within social networks in an innovative application of IV methodology. We closely examined the conditions under which identification of peer effects would be possible with the proposed instrument and identified other potential instruments that may be able to disentangle peer effects from homophily in other social network data.

C. STRENGTHS

This dissertation fills an important gap in understanding the social context of prescription drug use in the US by leveraging information about households in large administrative

databases. Large administrative databases are cost-effective, population-based, prospectively collected, and not subject to information or recall bias. In particular, MarketScan is one of the largest and most complete databases available for research, and claims are adjudicated and checked for errors. Experimental studies of this scale would not only be impractical and costly, but potentially unethical given the known risks of opioids.

We investigated a novel hypothesis that prescription opioid use may be driven by peer effects and quantified the risk of opioid initiation due to potential access to household opioids. Previous studies have been qualitative and focused largely on opioid abuse, although much of this stems from legitimate opioid use. Focusing on families in addition to individual patients may be a central unit for addressing the opioid epidemic.

We generalized the new-user design and proposed a "new-household" design to improve specificity of our exposure definition. The new-user design is commonly applied in pharmacoepidemiology,[162] but may have limitations when assessing prior exposure and identifying comorbid conditions.[124] Household clustering is often overlooked in studies using large administrative databases, which may result in anticonservative estimates of precision but also bias, as we have described.

We used bias analyses to assess the robustness of our results to potential unmeasured confounding [116] and quantified the uncertainty of our IV estimates with nonparametric bounds.[105] Transparency of the extent to which inference relies on assumptions, rather than data, helps readers evaluate the magnitude of bias that could affect our conclusions.

D. LIMITATIONS

Considerations for inference specific to the three aims have been described in previous chapters and are summarized below.

Co-residence

MarketScan data are de-identified and lack information on physical address of the enrollees. As a result, we were unable to verify co-residence of household members. In addition, data on other individuals in the household, such as Medicare beneficiaries or persons on another health plan, were unavailable. Misclassification of prior exposure would result in estimates that are biased towards the null.

Potentially incomplete opioid use identification in claims

Enrollees in MarketScan may have had prior exposure to prescription opioids or prescription NSAIDs through other sources, such as in the workplace. Alternatively, prescriptions that were not filed through insurance would not appear in the database, nor would opioids received in inpatient settings. Our first aim sought to identify novel approaches to identifying potential exposure misclassification, whereas the potential for non-differential outcome misclassification will bias the risk difference[112] and presents a limitation of drug utilization research using administrative claims.

Indication and pain severity

MarketScan data lack information on the indication for analgesic therapy and pain severity; this information could improve identification of exchangeable index patient populations. However, covariates of household members were balanced without this information available. Although we do not expect this lack of information to be a source of bias, it would help refine our analyses to better examine the collateral effects of therapeutic alternatives by patient indication.

External validity

Generalizability of our study is limited to individuals with employer-sponsored commercial insurance with prescription drug benefits and exclude individuals covered by

Medicaid or Medicare. Associations may be stronger in households with fewer resources (e.g., publicly insured or uninsured individuals) or among older individuals.

We further assumed treatment version irrelevance (i.e., there may be different versions of household exposure to opioids, but these versions have the same potential outcomes); no interference between households (i.e., the exposure status of one household does not affect outcomes in another household); and no model misspecification in our propensity score models for the calculation of inverse probability of treatment and informative censoring weights.

E. FUTURE RESEARCH

This study has raised a number of questions that we seek to address in future research using the MarketScan databases, as well as other data sources of social networks.

Spillover effects of parental opioid use among children

Our results indicated that the overall risk of opioid initiation was relatively low among children. However, recent increases in the number of pediatric emergencies involving opioids prescribed to adults underscore the harms of proliferating opioid use among US households.[163-165] Previous studies examining pediatric opioid-related adverse events used data from surveillance systems in the United States; however, these data sources have notable limitations. For example, two studies used passive surveillance data from the American Association of Poison Control Centers' National Poison Data System to estimate that over 9000 children have had medical emergencies from unintentional exposure to opioids from 2000-2009.[164] These data lack a meaningful denominator to estimate risk, have insufficient details about the intended patient using opioids, and depend on self-report of a potential poisoning case by the public or health professional. In addition, previous studies have quantified prescription opioid use among adults using adult (age >=20 years) prescription opioid mentions

in the National Ambulatory Medical Survey or the number of unique persons who received a dispensed opioid from retail pharmacies by 3-digit ZIP code during a given quarter, eliminating refills and repeated prescriptions to the individual.[166] These data preclude the possibility of data linkage to obtain information on the joint distribution of exposure, outcome, and covariates to make inferences about the association between adult opioid use and pediatric poisonings.

We hypothesize that parental prescription opioid use increases children's risk of hospitalization and emergency department visits. Parental prescription opioid use may be associated with increased risk of ER visits and hospitalizations via two main pathways involving children's direct exposure to opioids by ingestion and indirect effects, such as through motor vehicle passenger injuries. Although we would not be able to determine the specific type and dose of drug involved in accidental poisonings through insurance claims data, pharmacy dispensing claims most proximal to the time of children's adverse event can be identified. Moreover, stronger opioids based on milligrams of morphine equivalency may be associated with particularly elevated risk of ER visits. Although these events are rare, large databases offer the advantage of being able to identify small differences in risks. Hospitalization and ER visits are coded with high reliability in administrative because their high costs necessitate insurance reimbursement.

Effect heterogeneity by opioid potencies

Understanding heterogeneity of peer effects among opioid households by opioid potency could be another extension of this research. Opioid potencies vary markedly across active ingredients, thus equianalgesic conversion tables are used in clinical practice and epidemiologic studies to standardize opioids to morphine equivalents (Appendix D Table D.1). Future studies could also investigate changes in dosages among household members over time, the frequency of refills, and prescriptions from different providers among individuals in a household.

Household patterns of use of scheduled prescription drugs

Investigating household patterns of other DEA scheduled medications with addiction and diversion potential may also reveal potential peer effects. For instance, stimulants such as attention deficit hyperactivity disorder and narcolepsy medications (e.g., Adderall, Ritalin, and Concerta) act on dopamine receptors in the brain, which activates reward pathways. Ritalin (methylphenidate), in particular, shares the same molecular targets in the brain as cocaine and can lead to euphoric effects when taken intravenously. Similarly, central nervous system depressants increase gammaaminobutyric acid (GABA) levels, which has a sedative effect on the brain. Investigating polypharmacy within households may identify opportunities for misuse or early signs of addiction.

Other endpoints

Another endpoint to consider is the risk of opioid abuse, despite its low sensitivity in claims. A previous study used ICD-9 codes 304.0 (opioid-type dependence), 304.7 (combinations of opioid type with any other), 305.5 (opioid abuse), or 965.0 (poisoning by opiates or related narcotics but excluding 965.01 [heroin poisoning]) to define opioid abuse using medical and pharmaceutical claims data from the Maine Health Data Organization.[167] Associations between household opioid availability and risk of opioid abuse has not been examined using rigorous methods for non-experimental research.[96] Among older adults, one could examine the risk of falls and fractures associated with household opioid availability. For instance, opioid use was associated with increased risk of fractures among Medicare beneficiaries with arthritis, as compared to NSAID use.[88] Whether household opioid availability modifies this association has not been examined.

F. CONCLUSIONS

The availability of household information in databases presents an opportunity to evaluate the social context of prescription drug use, an important factor in addressing the overuse epidemic. Researchers can evaluate prevalent medications within the household to begin to understand the household “medicine cabinet,” and whether the introduction of opioids may put patients and their families at risk for associated adverse events. Additionally, researchers can assess information on household members as potential effect modifiers to improve assessment of the comparative safety of medications.

Household identifiers may be an important, underutilized feature in large administrative healthcare databases to improve specificity of prior exposure and identify potential proxies for unmeasured covariates. Accounting for prior exposure to medications under study and comorbid conditions is critical for valid inference from pharmacoepidemiology studies. For drugs that are commonly shared, additional restrictions to create exposure-free households may improve the validity of estimates. In addition, looking “around” for household covariates instead of looking “further back” in the patient’s health history presents an alternative approach to control confounding.

Households are a simple network structure of individuals who share norms and attitudes towards pain treatment as well as similar environmental exposures and healthcare providers. Within this structure, understanding the role of peer effects in catalyzing opioid use is challenging and requires novel methods that exploit exogenous sources of variation. Instrumental variable methods are a promising alternative to conventional epidemiologic methods, but inference from studies using these methods rests on unverifiable assumptions. Synthesizing results from multiple analyses may be challenging because of different underlying assumptions and target populations, but broader applications of IV methods will catalyze methodological refinement and innovation.

Unlike substance abuse, prescription opioid abuse may result from medical care.[47] Evaluating the household context within which opioids will be used could assist prescribers in identifying at-risk patients. Findings from this research have the potential to positively influence prescribing practice and harm reduction measures for prescription drugs with high abuse and addiction potential.

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APPENDIX A: ADMINISTRATIVE CODES

Table A.1 Administrative codes used for Aims 1-3

Type of Variable	Measurement and other notes
Age	Continuous, modeled using splines [115] or categorized
Sex	Dichotomous
Calendar year	Categorical
Region of residence	Geographic region of employee residence (REGION variable) 1: Northeast 2: North Central 3: South 4: West 5: Unknown
≥1 child under age 18 years	Dichotomous
History of malignancy	ICD-9 codes 140.x-195.x, 196.x-198.x, 199.x, 234.x, 235.x-238.x, 239.x
Use of hospice care	HCPCS code S9126
Back pain	ICD-9: 724.xx
Back and neck pain	ICD-9: 721.xx, 722.xx, 723.xx, 724.xx, 737.1, 737.2, 738.2, 728.4, 738.5, 739.1, 739.2, 739.3, 739.4, 756.1, 846.0, 846.1, 846.2, 846.3, 846.8, 846.9, 847.0, 847.1, 847.2, 847.3, 847.9
Back disorder	ICD-9: 721.xx, 722.xx, 723.xx, 724.xx, 737.xx
Migraine	ICD-9: 346.xx
Headache	ICD-9: 784.0x
Fibromyalgia	ICD-9: 729.1x
Fracture (any)	ICD-9: 800.xx-829.xx, 733.1x
Use of ADHD medication	At least one prescription for amphetamine, dextroamphetamine, lisdexamfetamine dimesylate, or methamphetamine hydrochloride
Use of antibiotics	At least one prescription for tetracyclines, amphenicols, penicillin, beta lactamase inhibitors, macrolides, lincosamides, streptogramins, streptomycins, aminoglycosides, fluoroquinolones, or glycopeptides
Use of benzodiazepine	At least one prescription for alprazolam, amitriptyline hydrochloride/chlordiazepoxide, chlordiazepoxide, chlordiazepoxide hydrochloride/methscopolamine nitrate, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam, or triazolam
Use of Opioids	Hydrocodone, codeine, oxycodone, propoxyphene, tramadol, fentanyl, morphine, hydromorphone, and dhcodeine
Use of NSAIDs	Diclofenac Potassium, Diclofenac Sodium, Diclofenac Sodium/Misoprostol, Esomeprazole Magnesium/Naproxen, Etodolac, Famotidine/Ibuprofen, Fenoprofen Calcium, Flurbiprofen, Ibuprofen (excluding intravenous), Ibuprofen Lysine, Indomethacin and Indomethacin Sodium (excluding rectal suppositories), Ketoprofen, Ketorolac Tromethamine (excluding injection, intramuscular, and nasal routes), Lansoprazole/Naproxen, Meclofenamate Sodium, Mefenamic Acid, Meloxicam, Nabumetone, Naproxen, Naproxen Sodium, Naproxen Sodium/Sumatriptan Succinate, Oxaprozin, Piroxicam, Sulindac, Tolmetin Sodium
Use of muscle relaxants	At least one prescription for aspirin/carisoprodol/codeine phosphate, carisoprodol, cyclobenzaprine, metaxalone, methocarbamol, aspirin/methocarbamol, or aspirin/carisoprodol

Use of selective serotonin reuptake inhibitor	At least one prescription for citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, or venlafaxine
Use of sleep medications	At least one prescription for eszopiclone, ramelteon, trazodone, zaleplon, or zolpidem
Use of statins	At least one prescription for atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin
GI complications	Any ulcer with hemorrhage or hematemesis or procedure to stop bleeding (ICD-9 diagnosis codes 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x ,533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 578.0, ICD 9 procedure code 44.43 OR CPT 43255) – 89% PPV in HealthCore, a generally young, healthy, working, commercially-insured population[113]
History of substance abuse (not illicit drugs)	Diagnoses of drug dependence or abuse not specific to illicit drugs (ICD-9 codes 304.0-304.9, 305.2, , 304.2, 304.3) Sensitivity 61%, Specificity 99%, PPV 70%, NPV 98% in VHA, which has relatively higher prevalence of psychiatric disease and substance abuse than the general population[168]
History of depression	ICD 9 codes 296.2, 296.3, 298.0, 300.4, 309.0, 309.1, 309.28, or 311 validated against the Patient Health Questionnaire (PHQ-9) (Sensitivity = 51.1%, PPV = 66.4%) or an antidepressant claim within 12 months after an emergent medical hospital admission validated against a structured diagnostic interview (sensitivity = 52.6%, PPV = 54.5%) [169]
History of psychiatric disease	ICD-9 codes 295.xx-298.xx
Inpatient admissions	Number of inpatient admissions during the baseline period
Outpatient visits	Number of inpatient outpatient admissions during the baseline period
Ankle injury (Aim 3)	
Fracture	ICD-9: 824.0-824.9 (inpatient or outpatient)
Sprain	ICD-9: 845.00, 845.01, 845.02, 845.03, 845.09 (inpatient or outpatient)

APPENDIX B: BIAS ANALYSES FOR AIM 2

Table B.1 Bias analyses for associations between opioid use within households

Bias analysis examining risk difference of opioid initiation by household opioid availability assuming different distributions of an unmeasured binary confounder.

PD of unmeasured confounder across household exposure	RD of unmeasured confounder-opioid initiation relationship			
	0.6	**0.7**	**0.8**	**0.9**
0.1	0.65 (0.62, 0.68)	0.64 (0.61, 0.67)	0.63 (0.60, 0.66)	0.62 (0.59, 0.65)
0.2	0.59 (0.56, 0.62)	0.57 (0.54, 0.60)	0.55 (0.52, 0.58)	0.53 (0.50, 0.56)
0.3	0.53 (0.50, 0.56)	0.50 (0.47, 0.53)	0.47 (0.44, 0.50)	0.44 (0.41, 0.47)
0.4	0.47 (0.44, 0.50)	0.43 (0.40, 0.46)	0.39 (0.36, 0.42)	0.35 (0.32, 0.38)
0.5	0.41 (0.38, 0.44)	0.36 (0.33, 0.39)	0.31 (0.28, 0.34)	0.26 (0.23, 0.29)
0.6	0.35 (0.32, 0.38)	0.29 (0.26, 0.32)	0.23 (0.20, 0.26)	0.17 (0.14, 0.20)
0.7	0.29 (0.26, 0.32)	0.22 (0.19, 0.25)	0.15 (0.12, 0.18)	0.08 (0.05, 0.11)
0.8	0.23 (0.20, 0.26)	0.15 (0.12, 0.18)	0.07 (0.04, 0.10)	-0.01 (-0.04, 0.02)
0.9	0.17 (0.14, 0.20)	0.08 (0.05, 0.11)	-0.01 (-0.04, 0.02)	-0.10 (-0.13, -0.07)

Prevalence difference (PD) per 100 enrollees of unmeasured confounder across levels of household opioid availability. Risk difference (RD) per 100 enrollees estimating the association between an unmeasured confounder and opioid initiation within all inverse probability weighted strata. Observed inverse probability weighted risk difference of 0.71 per 100 enrollees and confidence limits corrected by bias terms that are the product of the PD and RD

APPENDIX C: CHARACTERISTICS OF FULL IV AND TREATED POPULATIONS IN AIM 3

Table C.1 Baseline characteristics of ankle injury patients

Characteristic	Fracture n = 153,478 (%)	Sprain n = 1,012,374 (%)
Opioid initiation within 30 days of injury	28.1	5.1
Region		
Northeast	17.6	16.8
North Central	28.1	27.6
South	35.2	34.2
West	19.1	21.4
Age; median (IQR)	18 (12-46)	17 (13-38)
Age categories		
<6	5.5	2.1
6-11	15.6	13.8
12-17	28.5	35.0
18-25	8.8	13.1
26-35	4.9	7.5
36-45	11.3	12.7
46-55	15.1	10.8
56+	10.6	5.0
Sex, Female	48.0	53.6
Baseline mediation use		
ADHD medications	1.7	2.0
Antibiotics	38.7	42.0
Beta-blockers	3.5	2.4
Benzodiazepines	3.7	3.4
Muscle relaxants	1.9	2.4
NSAIDs	9.2	13.6
Sleep medications	2.2	2.0
Selective serotonin reuptake inhibitors	6.2	5.5
Statins	6.5	4.3
Pain conditions		
Back disorder	9.9	10.6
Back and neck pain	11.9	13.4
Back pain	6.3	7.0
Headache	3.8	4.5
Migraine	1.4	1.9
Arthritis	37.8	38.0
Osteoarthritis	2.6	2.0
Rheumatoid arthritis	0.8	0.8
Fibromyalgia	1.5	1.8
Comorbidities		
COPD	0.7	0.3
Depression	4.2	4.2
Psychiatric	6.3	6.3
DMI	3.8	2.4
Gastrointestinal bleeding	0.6	0.5
Smoking	2.0	1.1

Substance abuse	2.7	1.5
Alcohol use	1.0	0.4
Healthcare utilization		
Cancer screening	12.8	11.0
ER visit in past 7 days	45.2	25.4
Number of physician visits; mean (SD)	3.5(3.68)	3.8(3.58)
Number of acute care hospital days; mean (SD)	6.7(13.02)	5.2(11.92)

Table C.2 Characteristics of full IV and treated populations

	Sprain			Fracture		
	Total n = 2,459,122	**Untreated n = 2,344,730**	**Treated n = 114,392**	**Total n = 363,241**	**Untreated n = 268,826**	**Treated n = 94,415**
Characteristic	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Household size; mean (SD)	4.4 (1.32)	4.4 (1.32)	4.2 (1.33)	4.3 (1.39)	4.4 (1.38)	4.2 (1.39)
Region						
Northeast	17.3	17.5	12.0	18.3	19.7	14.6
North Central	28.2	28.3	27.8	28.2	27.9	28.9
South	32.8	32.5	39.1	34.1	33.4	36.0
West	21.6	21.7	21.1	19.4	19.0	20.6
Age; median (IQR)	21 (12-44)	22 (12-44)	19 (11-43)	22 (12-44)	23 (12-44)	21 (12-45)
Age categories						
<6	7.7	7.6	9.7	7.3	7.4	7.1
6-11	15.8	15.8	16.9	15.7	15.9	15.1
12-17	18.0	17.9	19.1	17.8	17.4	18.8
18-25	11.9	11.8	13.6	12.0	11.1	14.5
26-35	5.3	5.3	5.1	5.9	6.3	4.8
36-45	19.7	20.0	14.7	19.4	20.8	15.6
46-55	17.3	17.4	15.7	16.1	15.9	16.7
56-65	4.2	4.1	5.2	5.8	5.2	7.5
Sex, Female	48.3	48.2	48.9	48.1	48.0	48.2
Baseline mediation use						
ADHD medications	1.7	1.7	2.0	1.7	1.6	1.8
Antibiotics	37.2	37.1	38.6	35.6	35.7	35.5
Beta-blockers	2.6	2.6	2.8	2.7	2.5	3.2
Benzodiazepines	3.1	3.1	3.3	3.0	3.0	3.2
Muscle relaxants	1.9	1.9	2.0	1.7	1.7	1.9
NSAIDs	6.5	6.5	6.7	6.1	6.0	6.5
Sleep medications	1.8	1.8	2.0	1.8	1.7	1.9
SSRIs	4.8	4.8	5.0	4.8	4.6	5.1
Statins	5.3	5.3	5.4	5.4	5.1	6.2
Pain conditions						
Back and neck pain	10.4	10.4	9.3	9.4	9.7	8.8
Back pain	5.3	5.3	4.7	4.8	4.9	4.4
Back disorder	8.2	8.2	7.2	7.5	7.7	7.0
Headache	3.1	3.1	3.1	2.8	2.9	2.6

Migraine	1.4	1.4	1.4	1.2	1.3	1.1
Arthritis	9.4	9.4	8.8	9.1	9.4	8.2
Osteoarthritis	1.3	1.3	1.2	1.3	1.3	1.3
Rheumatoid arthritis	0.6	0.6	0.6	0.6	0.6	0.5
Fractures	2.5	2.5	2.3	3.0	3.2	2.7
Fibromyalgia	1.3	1.3	1.1	1.1	1.1	1.0
Comorbidities						
COPD	0.3	0.3	0.4	0.3	0.3	0.4
Depression	3.3	3.3	3.3	3.1	3.1	3.2
Depression psychiatric	2.0	2.0	2.1	2.0	1.9	2.1
Psychiatric	5.1	5.1	5.1	4.8	4.8	4.7
DMI	2.5	2.5	2.7	2.5	2.4	2.8
Gastrointestinal bleeding	0.5	0.5	0.5	0.5	0.5	0.5
Smoking	0.8	0.8	0.8	0.8	0.7	0.9
Substance abuse	1.1	1.1	1.2	1.1	1.1	1.3
Alcohol use	0.3	0.3	0.3	0.3	0.3	0.4
Healthcare utilization						
Cancer screening	12.2	12.2	11.1	12.0	12.0	11.8
ER visit in past 30 days	1.4	1.4	1.7	1.6	1.6	1.7
ER visit in past 7 days	0.5	0.5	0.6	0.7	0.6	1.0
Number of physician visits; mean (SD)	2.6 (3.16)	2.6 (3.16)	2.6 (3.12)	2.4(3.07)	2.5 (3.11)	2.3 (2.94)
Number of acute care hospital days; mean (SD)	4.7 (10.62)	4.7 (10.49)	4.7 (12.63)	4.5(8.21)	4.4 (7.94)	4.9 (8.93)

APPENDIX D: OPIOID EQUIANALGESIC TABLE

Table D.1 Opioid equianalgesic table

Prescription Opioid*	Morphine Equivalent Conversion Factor/mg of Opioid [170]
Codeine with Acetaminophen	0.15
Codeine Phosphate	0.15
Fentanyl	2.4
Fentanyl Citrate	0.125
Hydrocodone Bitartrate	1
Hydrocodone Bitartrate/Acetaminophen	1
Hydrocodone Bitartrate/Homatropine	1
Hydromorphone Hydrochloride	4
Methadone Hydrochloride	3
Morphine Sulfate	1
Oxycodone Hydrochloride	1.5
Oxycodone Hydrochloride/Acetaminophen	1.5
Propoxyphene/Acetaminophen	0.23
Tramadol Hydrochloride	0.1
Tramadol Hydrochloride/Acetaminophen	0.1

* OxyContin (Oxycodone HCI) reformulated in August 2010 to be tamper resistant. Propoxyphene withdrawn from market in November 2010 due to cardiac toxicity

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