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Association between Prescribed Opioid Dose and Risk of Motor Vehicle Crashes

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Abstract

Opioid-involved motor vehicle traffic fatalities have increased over the past 2 decades. However, the extent to which prescribed opioids increase risk of motor vehicle crashes remains uncertain. This study used real-world healthcare claims data to examine the association between prescription opioid dose and motor vehicle crash risk. Using nationwide US commercial insurance claims data for 2010-2018, we identified 772,404 adults who received incident, non-cancer opioid therapy. We examined associations between daily prescription opioid dose, calculated in morphine milligram equivalents (MMEs) from filled prescription claims, and risk of motor vehicle crashes, assessed as diagnoses of motor vehicle injuries in claims for emergency visits, inpatient hospitalizations, and ambulance transportation. We estimated associations using a within-individual design, which ruled out all time-stable confounding. We complemented the design with time-varying statistical adjustment for other pharmacotherapies and a negative control pain pharmacotherapy analysis (with incident cyclic antidepressant prescriptions). During 2,150,009 person-years of follow-up, there were 12,123 motor vehicle crashes (5.64 crashes per 1000 person-years). In within-individual comparisons, crash risk was greater during opioid prescription periods involving

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doses ≤60 MME/day (odds ratio [OR], 3.86; 95% confidence interval [CI], 3.54, 4.21), >60-120 MME/day (OR, 5.46; 95% CI, 4.44, 6.73), and >120 MME/day (OR, 3.45; 95% CI, 2.31, 5.15) than during off-treatment periods. The negative control analysis supported the specificity of the results to opioids rather than to other processes associated with pharmacologic pain management. These findings suggest that receipt of prescription opioids, even at doses ≤60 MME/day, is associated with an increased risk of motor vehicle crashes.

1. INTRODUCTION

After decades of growth in US overdoses involving opioids and other drugs, major policy and guideline changes have been implemented to curb the adverse effects of prescription opioids [6,22,39]. There is also increasing recognition of the need to consider harmful opioid outcomes beyond overdose [1,36,41], including accidental injuries [34]. In particular, motor vehicle crashes are a health challenge in the US, leading to 37,595 deaths and more than 2 million emergency department (ED) visits in 2019 alone [10,11], and the prevalence of prescription opioids in traffic fatality toxicology findings increased from 1% to 7% in 1995-2015 [15].

Package inserts included with opioid products advise patients “not to drive or operate dangerous machinery unless they are tolerant to the effects of [the medication] and know how they will react” [57]. Many—though not all [3,5]—experimental opioid-administration studies demonstrate moderate opioid-related impairment of driving performance [9,69]. However, observational studies are needed to understand how acute impairment translates to crash risk among patients in the context of real-world prescribing (e.g., clinically relevant doses, longer-term treatment) [47,75]. Many epidemiologic studies show that individuals with opioid prescriptions or opioid-positive toxicology tests are at greater risk of crash involvement, culpability, injuries, and fatalities than are individuals without prescriptions or with negative toxicology tests [9,16,25,30,43,65]. Although such studies may support the hypothesis of increased crash risk due to prescribed opioids, the threat of confounding from unmeasured factors that differentiate opioid recipients from non-recipients has thus far precluded clear causal inferences [16,25,54,61]. Critically, confounding by indications for pain management is a possible alternative explanation for these associations [55,71,72]. In fact, one recent study of mostly older adults found little difference in crash risk during the first 14 days of opioid or nonsteroidal anti-inflammatory drug treatment [32]. Moreover, opioid recipients may also carry other pre-existing crash risk, particularly given that motor vehicle crashes are themselves often a reason for pain management with opioids [54].

Within-individual methods can help address bias from unmeasured confounding [13,45,59,73]. By comparing risk across treatment and non-treatment periods over time, these approaches consider each patient as their own control, thereby ruling out time-stable confounding. One within-individual study using 1986-2004 United Kingdom primary care data demonstrated that crash risk more than doubled during opioid therapy, depending on the specific opioid and time in treatment [29]. However, we are aware of only two subsequent within-individual studies, using data from Australia and West Virginia, respectively, both of which were limited by small samples [49,64]. Given cross-national differences and secular

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trends in prescribing practices and driving behavior [26,38], it is unclear how well these data will inform current risk evaluations.

The present study used a within-individual design and recent US data to examine the association between prescription opioid receipt and risk of motor vehicle crashes. We complemented our analysis with a negative control comparison that evaluated the specificity of the results to opioids rather than to pharmacologic pain management more broadly [46]. Finally, we examined opioid-dose-related differences given that fewer observational studies have considered dosage [31,43].

2. METHODS

2.1 Data source

As in our prior study of prescription opioids and substance-related morbidity [58], we used the IBM® MarketScan® Commercial database ("MarketScan") for January 1, 2010 through December 31, 2018 in all analyses [33]. MarketScan data derive from nationwide, employer-based healthcare insurance claims for inpatient and outpatient services and filled prescriptions. Thus, the included individuals comprise employees enrolled in included plans who were up to 65 years of age, along with their spouses and dependents. During 2010-2018, the data covered approximately 130 million unique enrollee observations. This study was determined to be exempt human subjects research by the Indiana University and University of Chicago Institutional Review Boards. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies.

2.2 Cohort

Our primary analytic sample was an incident opioid recipient cohort, with initiation defined as the first opioid prescription fill. We required participants to have a wash-in period of at least 12 calendar months of continuous MarketScan enrollment prior to opioid initiation [60] and to be at least 19 years old at initiation [13]. To ensure sufficient time receiving opioids and variability in opioid doses, we required participants to have at least 28 days opioid receipt during follow-up. We excluded individuals with cancer diagnoses or hospice claims in the 1 year prior to initiation, as well as those with invalid, improbable, or difficult-to-calculate opioid prescription data [53]. Complete inclusion criteria and the derivation of the cohort are detailed in Table S1, Supplemental Digital Content. Follow-up ended at first disenrollment from included plans (defined as a month with no enrolled days or prescription drug coverage, according to that year's enrollment records), cancer diagnosis, hospice claim, or December 31, 2018.

2.3 Prescription opioid analgesics

We estimated prescription opioid dose in morphine milligram equivalents (MMEs) for each person-day, using the opioid drugs and morphine equivalence factors compiled by the Centers for Disease Control and Prevention (CDC) [53]. We included opioids typically used by outpatients, excluding buprenorphine and spray products to facilitate dose conversion. We assumed that prescriptions covered the number of days supplied and started on the fill date,

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with the exception that we calculated the covered days for fentanyl patches by assuming that each was worn sequentially for 3 days. We summed doses for prescriptions with overlapping days to obtain total daily dose if the prescriptions were for differing opioid drugs. However, if prescriptions for the same drug (e.g., short-acting hydrocodone) overlapped, we shifted the covered days of later prescriptions such that their start dates occurred immediately after earlier prescriptions ended. To correspond with prior studies [18,24], we categorized daily opioid dose as none, ≤60 MME, >60-120 MME, or >120 MME.

2.4 Motor vehicle crashes

We defined motor vehicle crashes using claims for ED visits, inpatient hospitalizations, and ambulance transportation, which allowed us to assess serious events without capturing subsequent treatment encounters following a previous crash. Diagnoses were recorded using *International Classification of Diseases* (ICD) codes, and we identified crashes from motor vehicle traffic and non-traffic injury diagnoses using the CDC's *ICD-10-CM* external cause-of-injury framework [35]. We included corresponding *ICD-9-CM* codes for motor vehicle traffic injuries, along with non-traffic injuries excluding those of pedestrians, pedal cyclists, or riders of animals or animal-drawn vehicles (Table S2, Supplemental Digital Content). We permitted participants to have multiple motor vehicle crashes during follow-up but required claims to be separated by at least 2 days to count as separate crash events. Otherwise, we assumed claims were related to a single event (e.g., overnight stays) [18,42].

2.5 Covariates

We adjusted for time-varying confounding from other psychoactive prescription medications that could impact crash risk (i.e., pharmacotherapies for substance use disorder, benzodiazepines, gabapentinoids, and z-hypnotic medications; Table S3, Supplemental Digital Content). Specifically, we included dichotomous covariates that indicated whether a given day was covered by a prescription, again assuming that prescriptions started on the fill date and covered the days supplied. We additionally adjusted for sex, time-varying age (in years), and calendar year.

2.6 Statistical analysis

As a preliminary step, we plotted the motor vehicle crash rate across the year prior to and following prescription opioid initiation. For our primary analyses, we structured follow-up time by person-day to examine associations between daily opioid dose and crash risk. We assumed that crashes on the initiation date occurred prior to opioid exposure, and we analyzed only subsequent follow-up days to avoid bias due to prior crashes that led to opioid initiations [48]. We excluded all follow-up days on which participants were admitted into inpatient facilities (other than motor vehicle crash days) [70]. We also excluded days with crash claims that were considered an extension of a prior crash event, as well as the 2 days following all crashes, because new discrete crash events would not be permitted on those dates by design. We managed and analyzed data in SAS, version 9.4 (SAS Institute, Inc).

We first examined population-level associations using discrete-time logistic regression [27], which yielded odds ratios (ORs). To the extent that the motor vehicle crash rate per day is low across exposure/covariate levels, ORs will approximate relative risk [19,20]. These

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models examined differences in risk of motor vehicle crashes across days as a function of opioid dose, allowing participants to experience multiple days with events and using PROC SURVEYLOGISTIC to correct standard errors for the non-independence of days within participants. Although the population models included statistical covariates, they could not rule out unmeasured confounding (e.g., underlying painful conditions, genetic vulnerability to risky driving [4]). We therefore next applied within-individual comparisons [8,27], which ruled out all confounding that did not vary across time within individuals. We estimated these associations using conditional logistic regression with each individual as a separate stratum (PROC LOGISTIC), as has been recommended for fixed effects regression with dichotomous outcomes [2]. As we have described previously [13,14,58,59], this within-individual approach is conceptually similar to a self-controlled case series [73]. However, it differs in that exposure and covariate status are permitted to vary throughout follow-up on a person-day basis, and we focused exclusively on post-initiation time. Only those individuals with variability (i.e., discordance) in motor vehicle crashes and predictors during follow-up contributed information to the within-individual comparisons. That is, the many individuals who did not experience a motor vehicle crash during follow-up did not contribute to the within-individual comparisons, nor did those few individuals who experienced a crash but did not experience change in opioid dose exposure or other covariates during follow-up. We included all of these non-discordant individuals in the population-level analysis, but they were not informative for the within-individual analysis. We restricted the within-individual time-varying covariates to the other psychoactive medications given the limited possible within-individual change in age and calendar year during follow-up.

One assumption of the within-individual design is that there is no reverse causation (i.e., outcomes do not influence the likelihood of subsequent exposure). However, this assumption may be violated given that pain due to injuries sustained in motor vehicle crashes may be managed with prescription opioids [29]. To address this assumption violation, we took two steps. First, as noted above, we only analyzed days after the initial prescription fill. Second, for later follow-up, we constructed a separate exposure category for the time immediately before subsequent discrete treatment periods (Figure 1) [73]. As has been described previously, by excluding this time from the reference (i.e., off-treatment) period, this strategy can help reduce the downward bias induced by event-dependent prescription [63]. Based on our preliminary analysis and prior research [29], we determined the period to be the 30 days up to and including the start of the next treatment. When these before-next-treatment periods overlapped with prior treatment days, the before-next-treatment periods took priority, meaning that these days were defined as before-next-treatment days regardless of other exposure status [74]. We additionally created a separate exposure category for the 30 days after prior treatment periods to account for any potential discontinuation effects or extended exposure beyond the prescribed days supply [13]. All other off-treatment days served as the reference period.

2.6.1 Negative control—The within-individual comparison is susceptible to unmeasured time-varying confounding. It is therefore possible for unmeasured factors that covary with dose changes and influence crash risk to bias our results (e.g., pain severity [72], concomitant treatments). We conducted a negative control analysis to evaluate the specificity

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of the within-individual results to prescription opioids rather than to pain or its management more generally [45,46,59]. In this analysis, we replaced our prescription opioid exposure among the opioid-recipient cohort with another incident pharmacologic pain management therapy (cyclic antidepressants [62]) that would be expected to have less impact on risk of motor vehicle crash [25,29,65].

2.6.2 Sensitivity analyses—Sensitivity analyses evaluated the robustness of our findings across cohort, exposure, outcome, and analysis specifications. First, to examine whether our results would apply to those receiving long-term opioid therapy, we restricted the cohort to individuals with at least 90 days covered by prescription opioids [24,58]. Second, conversely, to examine whether our results would apply to those receiving shorter courses of prescribed opioids, we expanded the cohort to include individuals with at least 14 prescribed days. Third, to further reduce the likelihood that our results were affected by previous motor vehicle crashes, we excluded individuals with any recorded crash diagnosis (at age 18 years or older) prior to or on the initiation date. Fourth, to examine whether our results were affected by our decision to shift prescription start dates to prevent overlapping prescriptions of the same drug, we assumed that all prescription supplies were used as dispensed (i.e., beginning on the fill date). Fifth, to examine the impact of the change in *ICD* versions, we censored follow-up after the transition from *ICD-9-CM* (September 30, 2015). Sixth, to ensure that crash diagnoses reflected acute events, we only counted diagnoses occurring in ED visits as events [13]. Seventh, to ensure that opioid recipients were operating vehicles at the time of injury, we restricted events to those that included at least one *ICD* code indicating injury to driver or motorcyclist. Finally, we examined the impact of the before-next-treatment-period definition by (a) prioritizing other opioid exposure categories when periods overlapped, (b) not including the first day of the next treatment period within the 30-day before-next-treatment period (i.e., counting it as exposed), or (c) omitting the before-next-treatment exposure category altogether.

3. RESULTS

The cohort comprised 772,404 incident opioid recipients, followed for 2,150,009 person-years after initiation (Table 1). Of the 6,146,004 opioid prescriptions filled during follow-up, the most common drugs were hydrocodone (48.4% of prescriptions), tramadol (24.0%), and oxycodone (19.5%). During follow-up, there were 12,123 motor vehicle crashes among 10,983 individuals (5.64 crashes per 1000 person-years).

3.1 Prescription opioid initiation

Figure 2 displays the motor vehicle crash rate across the year before and after prescription opioid initiation. Incidence rates were much greater in the month leading to and including the initiation date, consistent with prescription opioids having been initiated, for some, in response to a recent crash. After initiation, incidence rates stabilized but remained elevated relative to those observed ≥3 months prior to initiation.

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3.2 Association between prescription opioid dose and risk of motor vehicle crashes

Motor vehicle crash risk was greater during opioid treatment at all doses than during off-treatment days (Table 2). Specifically, relative to off-treatment time (2.03 crashes per 1000 person-years), crash risk was greater during treatment periods involving doses of ≤60 MME/day (5.31 per 1000 person-years; population OR, 2.91; 95% confidence interval [CI], 2.68, 3.16), >60-120 MME/day (10.44 per 1000 person-years; OR, 5.54; 95% CI, 4.54, 6.75), and >120 MME/day (8.21 per 1000 person-years; OR, 4.28; 95% CI, 3.04, 6.02).

Moreover, the within-individual comparison produced similar results (Table 2). Relative to a given individual's crash risk during off-treatment time, that same individual's risk was greater during periods of ≤60 MME/day (OR, 3.86; 95% CI, 3.54, 4.21), >60–120 MME/day (5.46; 95% CI, 4.44, 6.73), and >120 MME/day (3.45; 95% CI, 2.31, 5.15). We note that risk was greatest in the middle dose range; the association for >60-120 MME/day periods was statistically significantly stronger than associations for both lower (≤60 MME/day; $P = .002$) and higher (>120 MME/day; $P = .04$) dose periods. To explore this non-linearity, we further split the doses into smaller (30 MME/day) categories (Figure 3). Motor vehicle crash risk appeared greatest during periods involving >60-90 MME/day, although confidence intervals were wider at higher doses. Risk was greater for all categories relative to off-treatment days.

For situations in which participants discontinued and subsequently resumed opioid treatment, we considered the 30 days before next treatment periods as a separate exposure category to avoid bias due to reverse causation. As expected, motor vehicle crash risk was high in these before-next-treatment periods (OR, 18.98; 95% CI, 18.13, 19.87). It remained elevated during the 30 days after the end of prior treatment periods, albeit to a lesser extent than during treatment periods themselves (OR, 1.26; 95% CI, 1.14, 1.40).

3.3 Negative control

We identified 55,428 individuals among the cohort who initiated cyclic antidepressants as a negative control pain management pharmacotherapy. They were followed for 120,876 person-years after cyclic antidepressant initiation. In the within-individual comparison, cyclic antidepressants were associated with little difference in risk of motor vehicle crashes (OR, 0.96; 95% CI, 0.74, 1.24; Table 3).

3.4 Sensitivity analyses

We observed comparable results in analyses testing the sensitivity of the findings to cohort, exposure, and outcome definitions (Table 3). Specifically, we found similar associations when we included only long-term opioid therapy recipients or also included shorter-term recipients, when we excluded individuals with previous crashes, when we assumed that all prescriptions were taken as dispensed, and when we restricted outcomes to ICD-9-CM diagnoses, ED events, or events that included driver diagnoses.

Finally, analyses exploring the before-next-treatment period illustrated the impact of this modeling approach. As shown in Table S4, Supplemental Digital Content, had we considered post-initiation treatment period start dates as exposed (i.e., shifting the before-next-treatment period 1 day earlier), we would have estimated dose associations as much

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stronger (e.g., >60-120 MME/day: OR, 9.96; 95% CI, 8.43, 11.77). Conversely, had we not considered days before next treatment periods as a separate exposure category (i.e., had we included them in the off-treatment reference period), we would have estimated dose associations as null or even negative (e.g., >60-120 MME/day: OR, 1.15; 95% CI, 0.97, 1.36).

4. DISCUSSION

This study followed 772,404 opioid recipients for over 2 million person-years to examine the association between prescription opioid therapy and risk of motor vehicle crashes. Crashes resulting in claims for medical care were rare overall, occurring approximately once every 177 person-years (5.64 crashes per 1000 person-years). However, we found that, compared with the odds during non-treatment periods, the odds of motor vehicle crashes were more than tripled during periods involving opioid doses of ≤60 MME/day or >120 MME/day—and more than 5-fold greater during periods involving doses of >60-120 MME/day. These associations held in within-individual comparisons that ruled out all unmeasured time-stable confounding by design, and they were supported by a negative control analysis and other sensitivity analyses.

Previous research has illustrated that prescription opioid recipients experience greater risk of motor vehicle crashes than do non-recipients, but the difficulty of ruling out unmeasured confounding has posed a challenge for determining the specific contribution of opioid therapy itself [16,25,54]. For example, crash-fatality toxicology data can provide details regarding crash circumstances and permit assessment of prescribed and recreational substance use around the time of a crash. However, they offer limited insight into the health context surrounding opioid use and, in particular, have had difficulty distinguishing prescribed use from illicit use of diverted opioid analgesics [9,54]. Although healthcare record data can help researchers identify prescribed use and crashes resulting in medical care, they may have less detail regarding crash circumstances beyond diagnoses, and the threat of bias from confounding has persisted [25]. Our demonstration of independent within-individual associations after confounding adjustment is similar to the within-individual study by Gibson and colleagues [29] that found increased risk of motor vehicle crashes associated with prescribed opioids in United Kingdom primary care records through 2004, despite differences in countries, time, and data sources. Importantly, our study was able to update and extend those prior findings by additionally considering opioid dose and adjusting for other pharmacotherapies. Thus, the accumulating evidence is consistent with the hypothesis that prescribed opioids increase risk of motor vehicle crashes, perhaps even at doses ≤60 MME/day.

To the extent that this epidemiologic literature reflects a true increase in crash risk due to prescription opioid receipt, the underlying causal process is likely pharmacologic. Experimental studies demonstrate that opioids produce moderate and possibly dose-dependent acute impairment in cognitive functioning and driving performance [9,69]. Cognitive and psychomotor impairment may help explain the increase in fatal crash culpability due to failure to stay in the proper lane and other unsafe driving actions associated with opioid use [17,23]. Interestingly, we found that risk of motor vehicle

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crashes may peak at doses >60-90 MME/day. This non-linear dose-response relationship is consistent with a prior study demonstrating possible attenuation of increased risk at the highest doses (≥200 MME) [31]. One potential explanation that has been proposed is that individuals who receive higher doses would have acquired tolerance to the cognitive and psychomotor effects of opioids [75]. Against this possibility, however, is that studies have demonstrated persisting or even increasing crash risk over the course of opioid treatment [29,50]. Indeed, it may also be that when individuals receive opioid therapy at higher doses they drive less, perhaps because of concerns about impairment or because of generally reduced physical activity due to pain [56]. Given that we could not account for within-individual differences in driving rates associated with higher doses, our results may actually underestimate a true pharmacologic effect [29].

We note that, as has been demonstrated previously [29], risk was high in the period immediately prior to opioid initiation. Moreover, among participants who discontinued and then resumed opioid therapy, we observed high motor vehicle crash risk during the 30 days prior to therapy resumption. This pattern may be unsurprising given that crash injuries may be indications for prescription opioids. We followed methodologic recommendations to address the possible bias towards the null that would be expected because of crash-dependent opioid prescribing, and our sensitivity analyses illustrated the impact of our approach [73].

Our findings underscore the need to assess motor vehicle crashes among the other public health effects of opioid prescribing. In policy efforts to balance efficacy and safety, it may be beneficial to evaluate motor vehicle crash risk along with risk of other adverse outcomes, including misuse, diversion, overdose, opioid use disorder, suicide, and other mental health concerns [1,7,36,37,66]. It is important to stress, however, that despite the large relative risk, motor vehicle crashes resulting in a healthcare insurance claim during opioid therapy in our study were rare. Even during treatment periods involving >60-120 MME/day, the unadjusted rate was 1 in 96 person-years, and 98.6% of opioid recipients had no crashes during included follow-up. Thus, without discounting the magnitude of the potential population-level impact, the absolute risk for individual patients is likely to be limited and should be weighed against any potential benefit (e.g., pain control). The low crash rate during opioid treatment may reflect not only the overall rarity of crashes requiring claims for medical care but also current risk-mitigation efforts, such as product labeling. In one study, more than 4 of 5 opioid-recipient drivers reported having received some warning about driving from a medical provider, label, or both, and more than 1 in 2 reported believing that opioids could impair their driving [56]. Given that warning receipt appears to vary across patient socio-demographics [56]—and that socioeconomic and familial circumstances may make refraining from driving burdensome—the gaps among warning receipt, risk perceptions, and behavior underscore the need for additional means of mitigating health (and legal) risks [55].

Limitations

This study should be considered in the context of its strengths and limitations. First, we combined a within-individual design with time-varying covariates, a negative control, and additional sensitivity analyses. Nevertheless, our study cannot rule out all confounding

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from unmeasured factors that varied with opioid dose over time and influenced crash risk, possibly including pain severity [51,52] or use of non-prescribed substances. Thus, it cannot definitively demonstrate any potential opioid-induced crash risk. For example, 3 in 10 traffic fatalities involve an alcohol-impaired driver [68], and we do not know the extent to which alcohol use would covary with opioid dose during treatment and therefore represent an unmeasured time-varying confounder. Second, we employed statistical covariates to help account for time-varying confounding, and this approach can exacerbate bias if the covariates represent mediators or colliders rather than confounders. However, our adjusted and unadjusted results were quite similar, suggesting that any such bias would likely be minimal. Third, we used large-scale data from commercially insured individuals, but approximately 50% of Americans do not have commercial insurance [40]. We do not know the extent to which our results would generalize to other adults. Motor vehicle crash rates are greater among populations covered by Medicaid or workers' compensation or without insurance than among those with commercial or Medicare coverage [21]. Future research is needed to examine opioid dose associations among those without commercial insurance. Moreover, our analytic approach allowed us to include all available follow-up data. However, informative censoring due to loss of insurance coverage could introduce bias, such as if individuals who developed substance use problems were more likely to lose coverage [76]. Fourth, we assessed opioid exposure from claims for filled prescriptions. Thus, we could not assess medications administered in hospitals [70], prescriptions written by providers but not filled (or used) by patients [44], or prescriptions filled without insurance reimbursement, although such fills appear rare [12]. Given the assumptions required in dose calculations, our categories should be considered illustrative rather than as providing meaningful thresholds [67]. Fifth, our motor vehicle crash outcome would not capture near-misses or crashes that do not require or result in healthcare insurance claims for medical services, nor would it include fatal crashes that do not result in claims, although motor vehicle crashes result in far fewer fatalities than healthcare encounters [10,11]. The effect of any reduction in estimated crash rates on our results is not certain. If crash misclassification is random, our associations would be expected to be attenuated towards the null. However, to the extent that crash misclassification varies by opioid dose, this assumption may not hold. Finally, our analysis focused on crash risk associated with opioid dose during prescribed therapy alone, but further research is warranted on other potentially important treatment considerations, such as interactions with other medications (e.g., concurrent opioid-benzodiazepine receipt [28]).

4.1 Conclusions

This study demonstrated the value of large-scale healthcare data and design-based adjustment for confounding in assessing risk of motor vehicle crashes associated with opioid prescribing. We found that motor vehicle crash risk was elevated even during treatment with relatively lower doses, although it may not monotonically increase along with increasing prescribed dose. Regardless of dose, however, our findings add to existing evidence supporting a need for efforts to reduce opioid-related risk of motor vehicle crashes.

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Supplementary Material

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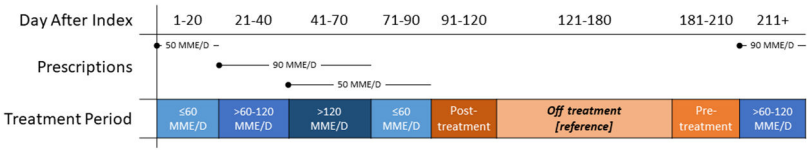

Figure 1.

Illustration of study design for a hypothetical participant. Index refers to day of initial opioid prescription fill. Prescription lines indicate covered days with dose in morphine milligram equivalents per day (MME/D). Treatment periods indicate prescription opioid exposure categories. Dose during treatment could vary on a daily basis. Off-treatment time was classified as days 1-30 after prior treatment (post-treatment), days 1-30 before next treatment (pre-treatment), and other off-treatment time (reference period). Covariates (sex and time varying age, calendar year, and receipt of substance use disorder medications, benzodiazepines, gabapentinoids, and z-hypnotic medications) not shown.

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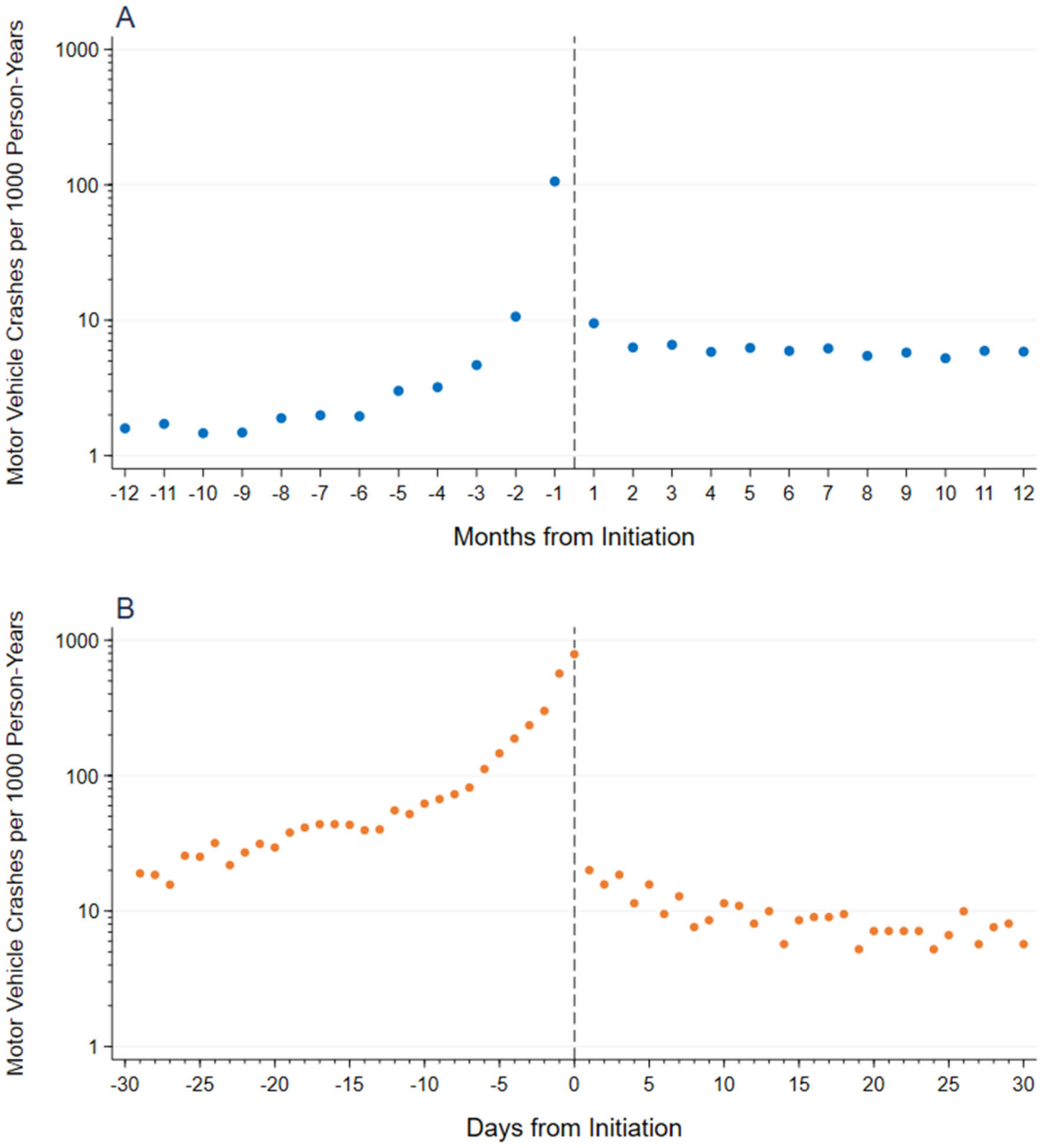

Figure 2.

Prescription opioid initiation and motor vehicle crashes. Motor vehicle crashes per 1000 person-years by month within 1 year of initiation (Panel A) and by day within 30 days of initiation (Panel B).

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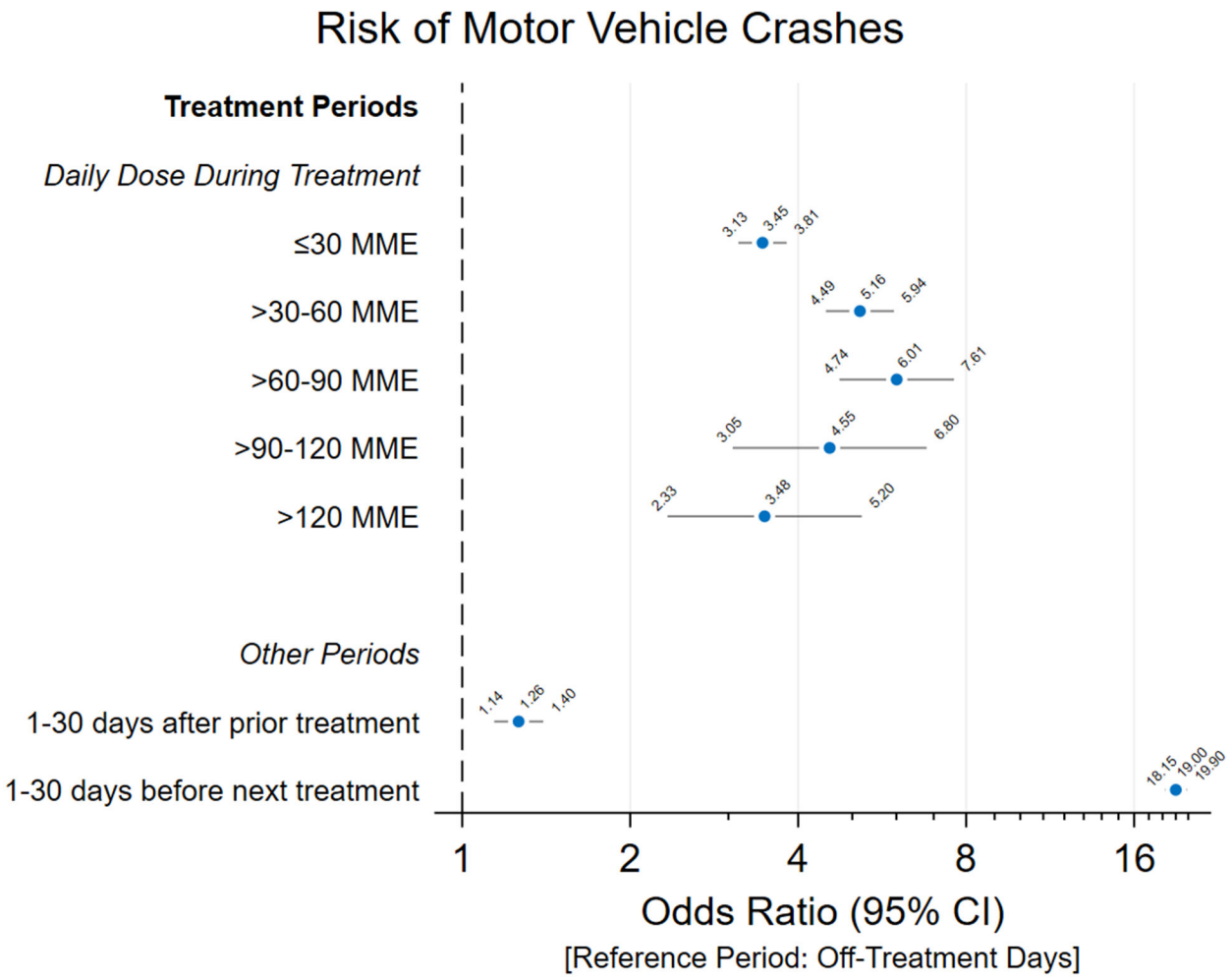

Figure 3.
Risk of motor vehicle crashes as a function of treatment period with smaller (30 morphine milligram equivalents [MME]) dose categories.

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Table 1.

Descriptive Statistics for Included Cohort (N = 772,404)

Variable	n	%
Sex		
Male	366,071	47.4%
Female	406,333	52.6%
Age at Opioid Initiation (years)		
19-25	48,877	6.3%
26-35	109,321	14.2%
36-45	170,436	22.1%
46-55	244,419	31.6%
56-65	199,351	25.8%
Maximum Opioid Dose		
No included prescribed days	6	< 0.1%
≤60 MME	457,485	59.2%
>60-120 MME	233,191	30.2%
>120 MME	81,722	10.6%
Motor Vehicle Crashes		
0	761,421	98.6%
1	10,135	1.3%
2-5	838	0.1%
6-10	10	< 0.1%
Follow-up Days (median [IQR])	836 (389 - 1434)	
Prescribed Days in Follow-Up (median [IQR])	45 (32 - 87)	

Follow-up is the length of time (in days) included in the analysis (i.e., from the day after initiation through first disenrollment and not otherwise excluded). Prescribed days refers to the number of follow-up days covered by an opioid prescription.

IQR, interquartile range. MME, morphine milligram equivalents.

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Table 2.

Motor Vehicle Crashes by Opioid Treatment Period

Treatment Period	Motor Vehicle Crashes	Person-Years	Motor Vehicle Crashes / 1000 Person-Years	Population[a] OR (95% CI)	Within-Individual[b] OR (95% CI)
Off Treatment [reference]	3,143	1,551,421	2.03	[1.00]	[1.00]
Daily Dose during Treatment					
≤60 MME	770	144,903	5.31	2.91 (2.68, 3.16)	3.86 (3.54, 4.21)
>60-120 MME	110	10,532	10.44	5.54 (4.54, 6.75)	5.46 (4.44, 6.73)
>120 MME	33	4,019	8.21	4.28 (3.04, 6.02)	3.45 (2.31, 5.15)
Other Periods					
1-30 days after prior treatment	437	178,612	2.45	1.30 (1.17, 1.44)	1.26 (1.14, 1.40)
1-30 days before next treatment	7,630	260,522	29.29	15.62 (14.92, 16.35)	18.98 (18.13, 19.87)

N = 772,404 individuals, among whom 10,980 were discordant and therefore informative for the within-individual comparisons.

MME, morphine milligram equivalents. OR, odds ratio. CI, confidence interval.

[a]Adjusted for sex, age, calendar year, and receipt of substance use disorder medications, benzodiazepines, gabapentinoids, and z-hypnotic medications.

[b]Adjusted for receipt of substance use disorder medications, benzodiazepines, gabapentinoids, and z-hypnotic medications.

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Table 3.

Results (Odds Ratios with 95% Confidence Intervals) of Within-Individual Sensitivity Analyses

Sensitivity Analysis	Daily Dose During Treatment			Other Periods		Informative N
	≤60 MME	*>60-120 MME*	*>120 MME*	*1-30 days after prior treatment*	*1-30 days before next treatment*	
Negative Control Exposure						
Cyclic antidepressants	0.96 (0.74, 1.24)			0.98 (0.70, 1.38)	1.64 (1.20, 2.24)	714
Cohort						
Long-term opioid therapy only	3.44 (3.03, 3.91)	5.04 (3.88, 6.54)	2.96 (1.88, 4.66)	1.25 (1.04, 1.50)	10.44 (9.50, 11.46)	3,216
Including shorter-term opioid therapy	3.82 (3.54, 4.11)	5.67 (4.73, 6.80)	3.79 (2.62, 5.48)	1.24 (1.15, 1.34)	21.94 (21.23, 22.67)	19,838
No previous crashes	3.69 (3.38, 4.03)	5.30 (4.26, 6.58)	2.94 (1.90, 4.55)	1.21 (1.09, 1.35)	18.58 (17.73, 19.47)	10,444
Exposure						
As-dispensed	3.82 (3.50, 4.18)	6.22 (5.03, 7.70)	4.03 (2.54, 6.39)	1.24 (1.12, 1.37)	18.71 (17.87, 19.60)	10,777
Outcome						
ICD-9-CM only	4.13 (3.69, 4.63)	5.64 (4.32, 7.35)	3.21 (1.92, 5.38)	1.39 (1.22, 1.58)	20.26 (18.98, 21.62)	6,369
Emergency claims only	3.82 (3.48, 4.20)	6.03 (4.73, 7.68)	4.61 (2.93, 7.24)	1.22 (1.09, 1.36)	16.90 (16.06, 17.79)	8,984
Driver diagnoses only	3.65 (3.26, 4.09)	5.14 (3.88, 6.83)	2.25 (1.18, 4.30)	1.21 (1.06, 1.38)	19.30 (18.18, 20.48)	6,838

All models adjusted for receipt of substance use disorder medications, benzodiazepines, gabapentinoids, and z-hypnotic medications. Informative N refers to discordant participants who were informative for the within-individual analyses. Cyclic antidepressant negative control exposure model replaced opioid exposure with cyclic antidepressant exposure (regardless of dose) among incident users in the included cohort. Long-term opioid therapy model restricted to participants with at least 90 prescribed days. Shorter-term opioid therapy model included participants with at least 14 prescribed days. No previous crashes model excluded participants with any crash diagnoses prior to or on the initiation date. As-dispensed model assumed all prescriptions began on fill date, regardless of overlap with prior prescriptions. ICD-9-CM only model ended follow-up at the transition from ICD-9-CM (September 30, 2015). Emergency claims only model counted only claims for emergency department services as motor vehicle crash events. Driver diagnoses only model counted only those motor vehicle crash events in which participants received at least one diagnosis associated with injuries to drivers.

MME, morphine milligram equivalents.

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