

Age-Related Risk of Serious Fall Events and Opioid Analgesic Use

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[+ Supplemental content](#)

IMPORTANCE Opioid analgesics may be associated with increased risk of falls, particularly among older adults.

OBJECTIVE To quantify the age-related risk of serious fall events among adults prescribed opioids by opioid exposure, time from initiation, and daily dose.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study conducted in New South Wales, Australia, used data linking national pharmaceutical claims to national and state datasets, including information on sociodemographic characteristics, clinical characteristics, medicines use, health services utilization, and mortality (POPPY II study). It included adults (18 years or older) who initiated prescription opioid treatment, which was defined as no prior dispensing during the preceding 365 days, between January 1, 2005, and December 31, 2018. Data were analyzed from February to June 2023.

EXPOSURE Time-dependent periods of opioid exposure were evaluated from dispensing records.

MAIN OUTCOME AND MEASURES Serious fall events identified from emergency department, hospitalization, and mortality records. Negative binomial models were used to assess associations between time-dependent opioid exposure (overall, by time from initiation, and by dose), age, and risk of fall events. Models were adjusted for known fall risk factors, including other fall risk-increasing drugs, frailty risk, and prior serious fall events.

RESULTS The cohort comprised 3 212 369 individuals who initiated prescription opioid treatment (1 702 332 women [53%]; median [IQR] age at initiation, 49 [32-65] years). Overall, 506 573 serious fall events were identified, including 5210 fatal falls. During exposure to opioids, the risk of serious fall events was elevated among all age groups; compared with the group aged 18 to 44 years, this risk was highest among those 85 years or older (adjusted incident rate ratio, 6.35; 95% CI, 6.20-6.51). Across all age groups, the first 28 days following opioid initiation was a time of increased serious fall risk; this risk increased with age. Among individuals aged 18 to 84 years, associations were identified between higher daily opioid doses and serious fall events.

CONCLUSIONS AND RELEVANCE The results of this cohort study suggest that prescription opioids were associated with increased risk of serious fall events among adults of all ages, with individuals 85 years or older at greatest risk. These risks should be considered when prescribing opioids, particularly for individuals with preexisting risk factors or when opioids are prescribed at higher doses. Targeted falls prevention efforts may be most effective within the first month following opioid initiation.

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Falls represent a major cause of injury and hospitalization,¹⁻⁵ particularly among older adults, for whom falls represent a major cause of functional decline, loss of independence, and mortality.^{1,2,6,7} The use of opioid analgesics, which may be associated with increased risk of falls due to central nervous system effects,^{8,9} is more common among older populations.¹⁰⁻¹³ This is concerning, as this population is already at higher risk of falls due to other risk factors, including frailty, functional disability, multimorbidity, and polypharmacy.¹⁴⁻¹⁹

Associations have been identified between opioid use and falls among older adults,²⁰⁻²² with the period immediately following initiation identified as a time of heightened risk in 2 new-user studies.^{23,24} To our knowledge, there is limited research specifically examining the age-related risk of falls associated with opioid use, with few population-based studies including adults of all ages, and limited Australian evidence. There is also limited evidence about the effects of opioid doses, and there is a need for research using robust measures of opioid exposure that account for the dynamic nature of clinical opioid use. Furthermore, many studies examine an individual's first fall; however, it is not uncommon for people to have multiple falls,²⁵ and as such, there is a need to quantify risks associated with all fall events. This study extends prior work by quantifying the age-related risk of all serious fall events, or falls resulting in emergency department (ED) presentation, hospitalization, or death, among people using prescription opioids and the association of initiation and opioid dose with fall risk.

Methods

Study Design

This retrospective population-based cohort study used linked data from the POPPY II study,^{26,27} comprising approximately 3.57 million adults (18 years or older) who initiated use of a prescription opioid between 2003 and 2018 in New South Wales (NSW), Australia. This new-user cohort has previously been described.²⁶ Ethical approval and a waiver of informed consent were received from the Australian Institute of Health and Welfare Ethics Committee, NSW Population and Health Services Research Committee, Australian Capital Territory Health Human Research Ethics Committee, and the ACT Calvary Public Hospital Bruce Ethics Committee, and the study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and RECORD-PE statements.²⁸

Setting

Opioid prescribing rates have risen in Australia during the past 30 years, although there is evidence that overall prescribing, and in particular initiation, are decreasing.²⁹ NSW is Australia's most populous state, ranging from 6.6 to 8.0 million residents between 2003 and 2018.³⁰

Individuals were identified from Pharmaceutical Benefits Scheme (PBS) dispensing records. The PBS is Australia's public medicines subsidy program, providing PBS-listed pre-

Key Points

Question What is the association between age-related risk of serious fall events and opioid analgesic use?

Findings In this population-based cohort study of 3.2 million people who initiated prescription opioid treatment, opioid exposure was associated with increased risk of serious fall events among adults of all ages. Risk significantly increased with age and within the first 28 days of commencing opioid use.

Meaning The results of this study suggest that fall risk should be considered when prescribing opioids in adults, particularly in the first 4 weeks of treatment, and among individuals with preexisting risk factors for falls, including older age.

scription medicines priced at, or less than, a set maximum copayment amount to all Australians, as either general or concessional beneficiaries (those receiving government assistance and eligible for a reduced copayment).³¹ Before July 2012, PBS data included all medicines dispensed to concessional beneficiaries and those dispensed to general beneficiaries costing more than the PBS copayment. From July 2012, the data include dispensings for all beneficiaries. Private prescriptions and in-hospital medicines are not included in PBS data; these form a small proportion of opioid use in Australia.³²

Study Procedure

The POPPY II study linked PBS data with 10 national and state health datasets.^{26,27} The current study uses data from the National Death Index, NSW Admitted Patient Data Collection (APDC), NSW Emergency Department Data Collection, and the Australian Cancer Database (eMethods in Supplement 1).

Cohort Definition

All adults who initiated use of a prescription opioid between January 1, 2005, and December 31, 2018, were included, with initiation defined as no opioid dispensing during the previous 365 days.^{26,29} Observation commenced on the date of index opioid dispensing for exposure and covariates; outcomes were counted from the day following index dispensing to exclude events that may have preceded dispensing. Observation ended on December 31, 2018, or the date of death, whichever was earlier. Due to incomplete ascertainment of dispensings to general beneficiaries in PBS data before July 2012, general beneficiaries before July 2013 were excluded to ensure complete data capture. Prior work has shown this exclusion had a limited association with cohort characteristics.²⁶

Opioid Exposure

Opioid dispensings were identified from PBS data using Anatomical Therapeutic Chemical and PBS item codes (eTable 1 in Supplement 1); dispensing data included strengths, formulations, and quantities supplied. As the duration of supply was not recorded, time-varying opioid exposure periods were determined using the Individualised Dispensing Patterns method.³³ This method estimates the duration of supply of each individual dispensing based on the quantity supplied and

number of days between previous dispensings.³³ Exposure periods were categorized as former (ie, no opioid exposure during the past 7 days), current, and recent. The recent period represented a 7-day lag/grace period following the expected duration of supply or until the next dispensing (whichever occurred earlier) and was included to capture periods during which the frequency of use may have been reduced and pharmacological effects may still be experienced, as well as to mitigate the effect of brief interruptions in supply.³³ In the main analyses, current and recent exposure periods were analyzed together. Opioid dose was categorized according to guideline thresholds as 1 to 49, 50 to 89, 90 to 199, and 200 or more oral morphine-equivalent milligrams per day.³⁴

Outcomes

Serious fall events were defined as any hospitalization, ED presentation, or death related to a fall as identified from diagnosis codes. Specifically, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes W00 to W19, *ICD-9* codes E880 to E888, and relevant SNOMED codes were identified from principal/other diagnosis fields in the APDC and Emergency Department Data Collection and underlying/multiple cause of death fields in the National Death Index (eTables 2-4 in [Supplement 1](#)). An event occurring within 7 days of a previous fall-related discharge was considered associated with the same event (eg, a fall-related ED presentation may be followed by hospitalization and/or death).

Covariates

Sociodemographic characteristics at cohort entry included age, sex, year of cohort entry, remoteness (classified using the Australian Bureau of Statistics remoteness areas³⁵), and area-level socioeconomic disadvantage (classified using the Index of Relative Socio-economic Disadvantage³⁶). Fall risk-increasing drugs, as defined by the Swedish National Board of Health and Welfare,^{21,37-39} were identified from PBS dispensing records using Anatomical Therapeutic Chemical codes (eTable 5 in [Supplement 1](#)), with exposure modeled as a time-dependent variable indicating a past 30-day dispensing.

The Hospital Frailty Risk Score⁴⁰ was used to derive frailty risk from hospitalization data (eTable 6 in [Supplement 1](#)). Frailty risk was modeled as a time-dependent variable using *ICD-10* codes from the APDC for all hospitalizations during the previous 2 years, categorized as low (<5), intermediate (5-15), and high (>15) frailty risk.⁴¹

Cancer and receipt of palliative care were identified from the Australian Cancer Database, PBS, and APDC datasets (eTables 7-8 in [Supplement 1](#)). These time-varying covariates were updated daily during follow-up, indicating evidence of the diagnosis and/or associated care during the previous 2 years. Evidence of a prior serious fall during follow-up was modeled as a time-dependent variable from the day after the first on-study event to the end of follow-up.

Statistical Analyses

Crude fall rates and 95% Poisson CIs were calculated by dividing the total number of serious fall events by the total person-

years (PYs) contributed by each person. To examine age-related risk of opioid exposure, models included time-varying opioid exposure, age group, and their interaction, with opioid exposure defined in 3 ways. First, exposure was defined as current/recent and former. Second, intervals of current/recent exposure were divided into the first 28 days following initial dispensing and the remainder (≥ 29 days) of opioid-exposed person-time. Third, intervals of current/recent exposure were divided according to dose thresholds.

Negative binomial regression models were used to estimate incident rate ratios (IRRs) using a generalized estimating equation approach to account for multiple observations per person due to time-varying covariate use. To account for differential follow-up between individuals, an offset for the log of person-time was included. Models were adjusted for sex, year of cohort entry, remoteness, fall risk-increasing drugs, frailty, cancer, palliative care, and previous falls; socioeconomic disadvantage was excluded due to an association with remoteness. Analyses were conducted using SAS, version 9.4 (SAS Institute), with significance set at $P < .05$.

Sensitivity Analyses

First, to assess the association of combining recent and current opioid exposure periods, analyses were replicated with current and recent exposure periods modeled separately. Second, to assess the association of using different periods to assess recent medicine use, the look-back period for fall risk-increasing drug dispensing was extended to 90 days. Third, to assess the association of different intervals in identifying discrete fall events, analyses were replicated in which overlapping events were defined as those occurring with a 1-day or 3-day gap. Finally, E values were calculated to assess the minimum strength of the independent association (after controlling for measured covariates) that an unmeasured confounder would require with opioid exposure and falls to explain our observed associations.⁴²

Results

Of 3 212 369 individuals who initiated prescription opioids (eFigure 1 in [Supplement 1](#)), 1 702 332 (53.0%) were female and 2 253 144 (70.7%) lived in major cities (Table 1^{35-37,40}). At cohort entry, the median age was 49 years (IQR, 32-65 years), and 936 836 (28.9%) were 65 years or older. There was a total of 16 894 229 PY of follow-up (median per person, 4.3 PY [IQR, 2.3-7.9 PY]).

Serious Fall Events

A total of 315 054 individuals (9.8%) experienced a serious fall event, with a crude rate (CR) of 299.85 per 10 000 PY (95% CI, 299.02-300.68; Table 2). CRs increased with age and were highest among individuals 85 years or older (CR, 1748.11 per 10 000 PY; 95% CI, 1739.99-1756.25). There were 5210 fatal events (CR, 3.08 per 10 000 PY; 95% CI, 3.00-3.17); among people 85 years or older, the crude fatal fall rate was 30.94 per 10 000 PY (95% CI, 29.87- 32.04).

Table 1. Characteristics of the 3 212 369 Cohort Individuals at the Time of Cohort Entry

Characteristic	No. (%)
Sex	
Female	1 702 332 (53.0)
Male	1 510 037 (47.0)
Age group at cohort entry, y	
18-44	1 307 130 (40.7)
45-64	968 403 (30.1)
65-84	799 551 (24.9)
≥85	137 285 (4.3)
Year of cohort entry	
2005-2007	609 603 (19.0)
2008-2010	399 190 (12.4)
2011-2013	486 964 (15.2)
2014-2016	1 147 501 (35.7)
2017-2018	569 111 (17.7)
Remoteness^{a,b}	
Major city	2 253 144 (70.7)
Inner regional	710 975 (22.3)
Outer regional	206 405 (6.5)
Remote/very remote	17 585 (0.6)
Relative socioeconomic disadvantage^{c,d}	
Experienced most disadvantage	585 723 (18.4)
Second quintile	593 282 (18.6)
Third quintile	742 191 (23.3)
Fourth quintile	640 225 (20.1)
Experienced least disadvantage	624 758 (19.6)
Exposed to any fall risk-increasing drug^e	
1 147 344 (35.7)	
Frailty risk^f	
Low frailty risk (<5)	3 012 236 (93.8)
Moderate frailty risk (5-15)	144 591 (4.5)
High frailty risk (>15)	55 542 (1.7)
Evidence of cancer^g	
155 171 (4.8)	
Receipt of palliative care^g	
26 641 (0.8)	

^a Classified using 2016 Australian Statistical Geographic Standard—Remoteness Structure.³⁵

^b Excludes 24 260 individuals with missing values.

^c Classified using Socio-Economic Indexes for Areas Index of Relative Socio-economic Disadvantage 2011.³⁶

^d Excludes 26 190 individuals with missing values.

^e Fall risk-increasing drug dispensing during previous 30 day.³⁷

^f Calculated from hospitalizations during the previous 2 years using the Hospital Frailty Risk Score.⁴⁰

^g Evidence during previous 2 years.

Serious Fall Events by Opioid Exposure

Within all age groups, crude fall rates were higher during periods of current opioid exposure (eTable 9 in Supplement 1). Among individuals 85 years or older, the crude fall rate during current opioid exposure was 2475.57 per 10 000 PY (95% CI, 2455.39-2495.88). After adjusting for covariates, current opioid exposure was associated with increased risk of serious fall events in all age groups (Figure). This association ranged from 1.31 (95% CI, 1.29-1.32) for individuals 85 years or older to 2.53 (95% CI, 2.47-2.59) for individuals aged 18 to 44 years.

The magnitude of these associations decreasing with increasing age reflected the higher baseline (former opioid exposure) fall risk among older age groups. This was evident in comparisons between age groups in which during periods of current opioid exposure, increased age was associated with increased fall risk. Compared with individuals aged 18 to 44 years, those 85 years or older had a more than 6-fold increase in risk of serious fall events (IRR, 6.35; 95% CI, 6.20-6.51) during periods of opioid exposure (eTable 10 in Supplement 1).

Serious Fall Events by Time From Initiation

For all age groups, the risk of serious fall events was higher during the first 28 days following opioid initiation compared with the remainder of exposed time (eTable 11 in Supplement 1). Among individuals aged 18 to 44 years, the rate of serious fall events was 5.50 (95% CI, 5.31-5.70) times higher during the first 28 days and 1.90 (95% CI, 1.85-1.96) times higher during later opioid-exposed periods compared with periods of former exposure (Figure). All comparisons between age groups showed an association of increasing fall risk with increasing age regardless of the type of opioid exposure. Within the first 28 days, the risk of serious fall events was highest for individuals 85 years or older (compared with those aged 18-44 years; IRR, 5.97; 95% CI, 5.74-6.21; eTable 12 in Supplement 1).

Serious Fall Events by Opioid Dose

The risk of serious fall events was higher with increasing opioid doses for the groups aged 18 to 44, 45 to 64, and 65 to 84 years (Figure). The crude falls rate among individuals 85 years or older was larger than for any other age group (eTable 13 in Supplement 1); after adjusting for confounders, higher opioid doses were associated with decreased fall risk for this age group. Compared with individuals aged 18 to 44 years, a daily opioid dose of 1 to 49 mg was associated with an increased fall risk, ranging from 1.54 (95% CI, 1.49-1.58) for individuals aged 45 to 64 years to 9.14 (95% CI, 8.88-9.41) for individuals 85 years or older (eTable 14 in Supplement 1).

Sensitivity Analyses

Modeling current and recent exposure periods separately, extending capture of fall risk-increasing drugs, and modifying the gap between episodes to define discrete fall events generated associations that aligned with the main analyses (eTables 15-22 in Supplement 1). E values ranged from 1.59 to 10.47 (eTables 9, 11, and 13 in Supplement 1), suggesting our findings were moderately robust; there would need to be substantial unmeasured confounders to negate the observed associations between opioid exposure and fall risk.

Discussion

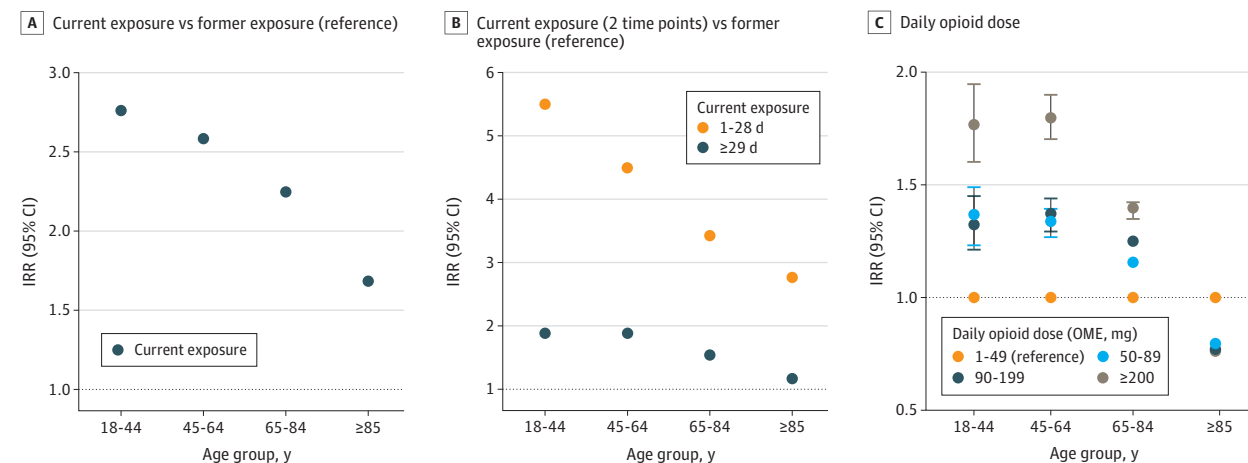
In what is to our knowledge the first Australian population-level study of this kind, current opioid exposure was significantly associated with the risk of a fall-related ED presentation, hospitalization, and/or death. This study examined serious fall events among all adults, and the results sug-

Table 2. Crude Fall Event Rates by Age Group

Age, y	No. of people with an event	No. of serious fall events	PYs	Crude falls rate per 10 000 PY (95% CI)
Any serious fall event	315 054	506 573	16 894 228.65	299.85 (299.02-300.68)
18-44	28 270	33 627	5 654 179.19	59.47 (58.84-60.11)
45-64	43 497	60 296	4 920 548.08	122.54 (121.56-123.52)
65-84	141 387	234 726	5 301 691.98	442.74 (440.95-444.53)
≥85	101 900	177 924	1 017 809.41	1748.11 (1739.99-1756.25)
Nonfatal serious fall event	309 844	501 363	16 894 228.65	296.77 (295.94-297.59)
18-44	28 204	33 561	5 654 179.19	59.36 (58.72-59.99)
45-64	43 277	60 076	4 920 548.08	122.09 (121.12-123.07)
65-84	139 612	232 951	5 301 691.98	439.39 (437.61-441.18)
≥85	98 751	174 775	1 017 809.41	1717.17 (1709.13-1725.24)
Fatal serious fall event	5210	5210	16 894 228.65	3.08 (3.00-3.17)
18-44	66	66	5 654 179.19	0.12 (0.09-0.15)
45-64	220	220	4 920 548.08	0.45 (0.39-0.51)
65-84	1775	1775	5 301 691.98	3.35 (3.19-3.51)
≥85	3149	3149	1 017 809.41	30.94 (29.87-32.04)

Abbreviation: PY, person-years.

Figure. Adjusted Associations Between Opioid Exposure and Serious Fall Events Within Age Groups



Data for the Figure are presented in eTables 9, 11, and 13 in Supplement 1. IRR indicates incident rate ratio; OME mg, oral morphine-equivalent milligrams.

gested that the fall risk-increasing effects of opioids were not exclusively experienced by older adults.

Within age groups, the association of opioid exposure with fall risk appeared highest for younger individuals, likely due to their lower baseline risk (periods of former exposure). Falls are a leading cause of injury-related hospitalization among younger/middle-aged adults^{3,4,43}; however, most research and fall prevention efforts are aimed at older adults. Although older individuals may be more predisposed to serious negative consequences, such as hip or vertebral fractures,⁴⁴ we identified many younger people who experienced falls necessitating an ED presentation or hospitalization, suggesting a need to consider fall prevention education and strategies for younger people who are prescribed opioids.

Although the risk of a serious fall event was consistently increased during periods of opioid exposure across all age

groups, when comparing between age groups, the incidence of serious fall events was considerably higher for older individuals. The markedly high rates of serious falls among older individuals highlight a need for further work to prevent falls and associated serious consequences, including mortality, among older adults.^{2,6} A major component of many community-based falls prevention efforts includes the review of medicines, prevention of polypharmacy, and cessation of drugs known to be associated with increased fall risk.⁴⁵⁻⁴⁷ However, many of these drugs are essential medicines, and there is a need to balance individual clinical need against potential risk. Additionally, there is mixed evidence regarding deprescribing as a single intervention for preventing falls,^{45,47-49} highlighting the value of multifactorial strategies. Conversely, these findings highlight that the risks may outweigh the benefits of opioid therapy for certain groups, particularly

given the limited evidence for the effectiveness of long-term opioid therapy for chronic pain. Accordingly, clinicians should consider approaches that maximize nonopioid therapies and the time-limited use of opioids when these are deemed necessary in keeping with guideline recommendations and principles of rational medicine use.

Among all age groups, the first 28 days following opioid initiation were identified as a higher-risk period for serious fall events, indicating a period during which fall prevention efforts may be of greatest benefit. Prior work has identified the initial 7 days as a time of high risk^{23,24}; we extended this finding and demonstrated that the entire first month of exposure is associated with increased risk compared with the remainder of exposed time. The mechanisms by which this period may be associated with increased risk may be 2-fold. First, the central nervous system effects of opioids may be experienced most acutely at treatment commencement due to the absence of tolerance in opioid-naïve individuals.⁸ Second, opioids may be prescribed for an indication that itself limits mobility (eg, injury); indications could not be determined using the included datasets. Opioid initiation may also coincide with a return to mobility and daily activities, which may be associated with an increase in an individual's risk of falling.

Among individuals aged 18 to 84 years, there was evidence of an association between increased opioid dose and serious fall events. Given associations between opioid dose and other adverse effects,^{8,9} these findings reinforce the need for caution when considering prescribing higher opioid doses. The negative associations identified among the oldest age group may have several explanations. CRs for this group were high among all dose categories, including the reference category, and covariates included in models likely disproportionately affected older individuals. Older people prescribed higher opioid doses may also be less mobile due to the sedating effects of opioids or the conditions for which these doses are indicated; moderate to severe pain and opioid use are associated with reduced mobility in older adults,⁵⁰⁻⁵² potentially translating to fewer opportunities for falling.

Strengths and Limitations

The strengths of this study included an extensive population-based capture of NSW residents who were dispensed opioids during a 14-year period,²⁶ with multiple datasets used to identify serious fall events. Opioid exposure and covariates were assessed in a time-dependent manner using validated measures, reflecting dynamic clinical changes over time.^{33,37,40}

The limitations included underestimation of the true incidence of falls, particularly among younger people who may be less likely to experience injury or seek medical attention^{4,5,53}; associations between opioid use and noninjurious falls require further investigation. Nevertheless, we observed a higher risk of serious fall events associated with opioid exposure in younger individuals. As opioid exposure was determined from the PBS dataset, it is possible that opioid use may have been underestimated, or exposure periods misclassified due to the lack of information on private dispensings or medicines used in public hospitals. However, previous research has shown that PBS data account for almost 90% of all prescription opioid use in Australia.³² Additionally, inclusion of the 7-day lag/grace period potentially reduces the risk of potential opioid exposure misclassification as former during short-term hospitalizations of 7 days or less, which accounted for approximately 90% of hospitalizations for the cohort. During longer hospitalizations, potential exposure misclassification will be associated with a more conservative estimate of the overall risk of serious fall events. Indications for opioid prescribing could not be determined; accordingly, pain and prior injury represented unmeasured confounding that could not be assessed. Additional unmeasured confounders, such as residing in residential care for older adults, were unable to be determined accurately from the included datasets. E values suggested that unmeasured confounders would need to be significantly associated with opioid exposure and falls after adjusting for measured confounders to fully negate our findings. Finally, although validated evidence-based tools were used to assess fall risk-increasing drug use and frailty, not all factors associated with falling are captured in these tools.

Conclusions

In this cohort study, among adults of all ages, opioid exposure was associated with increased risk of fall-related ED presentation, hospitalization, or death. The incidence of serious fall events during periods of opioid exposure increased with age, with individuals 85 years or older at greatest risk. These risks should be considered when prescribing opioids, particularly for individuals with preexisting risk factors for falls, including frailty and older age, or when opioids are prescribed at higher doses. The first month following opioid initiation represents a period during which targeted prevention efforts may be most effective.

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Concept and design: Hopkins, Bharat, Ivers, Draper, Pearson, Gisev.

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