Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
eFigure 1. Study design and sample selection for the yearly cohort 2006-2015

Study design

- Select beneficiaries enrolled in traditional Medicare in the 1-year selection period
- Select beneficiaries with Medicare Part D stand-alone plans in the calendar year
- Select beneficiaries aged above 65
- Exclude beneficiaries developed ESRD or died in the 1-year selection period

Diagram of sample selection

|                          | 2006   | 2007   | 2008   | 2009   | 2010   | 2011   | 2012   | 2013   | 2014   | 2015   |
|--------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| All Medicare beneficiaries without ESRD | 1,497,282 | 1,448,250 | 1,425,400 | 1,413,026 | 1,412,821 | 1,430,802 | 1,439,659 | 1,441,563 | 1,480,857 | 1,470,831 |
| Continuously enrolled in Part D in the 1-year selection period | 752,610 | 749,280 | 757,816 | 758,574 | 769,683 | 797,519 | 730,077 | 946,390 | 982,336 | 986,898 |
| Exclude Medicare beneficiaries covered by Medicare Advantage plans and aged below 65 | 553,862 | 562,952 | 569,260 | 573,495 | 582,654 | 607,080 | 536,601 | 738,294 | 759,012 | 777,244 |
eFigure 2. Study design and sample selection for the longitudinal cohort

Study design

- Continuously enrolled in Part D during the 1-year selection period during 2006-2015.
- Select beneficiaries enrolled in traditional Medicare in the 1-year selection period.
- Select beneficiaries aged above 65.
- Exclude beneficiaries who developed ESRD or died in the 1-year selection period.

Diagram of sample selection

Select Medicare beneficiaries with Part D coverage in 2006-2015. The first observed date of Part D enrollment is the start date of 1-year selection period.
N=1,653,978

Exclude Medicare beneficiaries covered by Medicare Advantage plans
N=1,093,611

Exclude Medicare beneficiaries aged below 65
N=697,122

Exclude Medicare beneficiaries who died or got ESRD in the 1-year selection period
N=649,339

1-year selection period—assess demographics, CKD stages, comorbidities and analgesic use.
|                                    | ICD-9-CM codes                                                                 |
|-----------------------------------|-------------------------------------------------------------------------------|
| Chronic kidney disease (CKD)      | 016.0; 095.4; 189.0, 189.9; 223.0; 236.91; 250.4; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 477.3; 572.4; 581-583; 585-588; 591; 642.1; 646.2; 753.12-753.19; 753.2; 794.4 |
| Staging of chronic kidney disease |                                                                                |
| Stage 1                           | 585.1                                                                         |
| Stage 2                           | 585.2                                                                         |
| Stage 3                           | 585.3                                                                         |
| Stage 4                           | 585.4                                                                         |
| Stage 5                           | 585.5 or 585.6 with no CMS 2728 form                                          |
| Stage unknown or unspecified      | Patient has no claims with codes 585.1-585.6 but has: 016.0; 095.4; 189.0, 189.9; 223.0; 236.91; 250.4; 271.4; 274.1; 283.11; 403; 404; 440.1; 442.1; 477.3; 572.4; 581-583; 585.9; 586-588; 591; 642.1; 646.2; 753.12-753.19; 753.2; 794.4 |
| Hypertension (HTN)                | 362.11; 401-405; 437.2                                                        |
| Cardiovascular disease (CVD)      | 398.91; 402.01, 402.11, 402.91; 404.01, 404.03, 404.11, 404.13, 404.91, 404.93; 410-414; 422; 425-428; 430-438; 440-444; 447; 451-453; 557; V42.1, V45.0, V45.81, V45.82, V53.3 |
| Diabetes mellitus (DM)            | 250; 357.2; 362.0; 366.41                                                      |
| Cancer                            | 140-172; 174-208; 230-231; 233-234                                           |
| Depression                        | 296.2, 311                                                                   |
| Back pain                         | 721.3x - 721.9x, 722.2x, 722.30, 722.70, 722.80, 722.90, 722.32, 722.72, 722.82, 722.92, 722.33, 722.73, 722.83, 722.93, 724.xx, 737.1, 737.3, 738.4, 738.5, 739.2, 739.3, 739.4, 756.10, 756.11, 756.12, 756.13, 756.19, 805.4, 805.8, 839.2, 839.42, 846, 846.0, 847.1, 847.3, 847.2, 847.9 |
| Neck pain                         | 721.0X, 721.1X, 722.0X, 722.31, 722.71, 722.81, 722.91, 723.XX, 839.0, 839.1, 847.0 |
| Arthritis/joint pain              | 710≤codes <720,725≤codes <740                                                |
| Headache/migraine                 | 346≤codes <347, 307.81                                                        |
| Human immunodeficiency virus (HIV)| 042                                                                           |

**Source:** ICD-9-CM, International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification. ICD-9-CM diagnosis codes can have up to five digits with a decimal point between the 3rd and 4th digits, while ICD-10-CM codes have seven digits. Codes listed with three digits include all existing 4th and 5th digits, and those listed with four digits include all existing 5th digits.
## eTable 2. Baseline characteristics of the yearly cohort by year (2006-2015)

| Characteristics          | 2006 (n=553862) | 2007 (n=562952) | 2008 (n=569260) | 2009 (n=573495) | 2010 (n=582654) | 2011 (n=607080) | 2012 (n=536601) | 2013 (n=738294) | 2014 (n=759012) | 2015 (n=777244) |
|--------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Use of Opioids**       |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Ever use                 | 431408 (77.9%)  | 421469 (74.9%)  | 418249 (73.5%)  | 411971 (71.8%)  | 405495 (69.6%)  | 407323 (67.1%)  | 360214 (67.1%)  | 488980 (66.2%)  | 502040 (66.1%)  | 521256 (67.1%)  |
| Total annual days' supply (mean, sd) | 122454 (22.1%)  | 141483 (25.1%)  | 151011 (26.5%)  | 161524 (28.2%)  | 171759 (30.4%)  | 199757 (32.9%)  | 176387 (32.9%)  | 249314 (33.8%)  | 256972 (33.9%)  | 259898 (32.9%)  |
| Total annual days' supply categories | 14.4 (54.4%)   | 17.6 (62.9%)    | 20.8 (70.5%)    | 23.0 (75.4%)    | 25.7 (80.1%)    | 30.4 (89.6%)    | 30.6 (91.6%)    | 33.7 (97.1%)    | 34.7 (99.9%)    | 33.0 (97.6%)    |
| **Use of NSAIDs**        |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Ever use                 | 478843 (86.5%)  | 481372 (85.9%)  | 481856 (84.6%)  | 472941 (82.5%)  | 471047 (80.8%)  | 481754 (79.4%)  | 427219 (79.6%)  | 578502 (78.4%)  | 594501 (78.3%)  | 613266 (78.9%)  |
| Total annual days' supply (mean, sd) | 75019 (13.5%)   | 81580 (14.5%)   | 87404 (15.4%)   | 100554 (17.5%)  | 111607 (19.2%)  | 125326 (20.6%)  | 109382 (20.4%)  | 159792 (21.6%)  | 164511 (21.7%)  | 163978 (21.1%)  |
| Total annual days' supply categories | 15.5 (56.1%)   | 17.1 (61.3%)    | 18.5 (64.2%)    | 20.7 (67.6%)    | 22.8 (71.3%)    | 24.4 (74.1%)    | 23.9 (73.1%)    | 26.4 (78.1%)    | 26.2 (77.8%)    | 25.7 (77.2%)    |
| **Demographics**         |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Age (mean, sd)           | 77.0 (7.7)      | 77.1 (7.7)      | 77.1 (7.8)      | 77.0 (7.8)      | 76.9 (7.8)      | 76.2 (7.5)      | 76.6 (7.8)      | 76.5 (7.8)      | 76.3 (7.7)      |                 |
| Age group                |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| 65-75                    | 249860 (45.1%)  | 253740 (45.1%)  | 259829 (45.6%)  | 266329 (46.4%)  | 273995 (47.0%)  | 288781 (47.6%)  | 277622 (51.7%)  | 362293 (49.1%)  | 380186 (50.1%)  | 397497 (51.1%)  |
| 75-85                    | 210653 (38.0%)  | 210865 (37.5%)  | 209221 (36.8%)  | 206290 (36.0%)  | 205963 (35.3%)  | 212086 (34.9%)  | 180203 (33.6%)  | 251728 (34.1%)  | 254286 (33.5%)  | 256060 (32.9%)  |
| 85 and above             | 93349 (16.9%)   | 98347 (17.5%)   | 100210 (17.6%)  | 100876 (17.6%)  | 102696 (17.6%)  | 106213 (17.5%)  | 78776 (14.7%)   | 124273 (16.8%)  | 124540 (16.4%)  | 123687 (15.9%)  |
| Male                     | 187892 (33.9%)  | 194271 (34.5%)  | 199913 (35.1%)  | 203910 (35.6%)  | 201089 (36.1%)  | 222959 (43.4%)  | 233077 (43.4%)  | 285926 (38.7%)  | 298723 (39.4%)  | 309943 (39.9%)  |
| Race                     |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |

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| Disease          | 2006 Cohort (n=28430) | 2016 Cohort (n=674930) |
|------------------|-----------------------|------------------------|
| CKD stage 1      | 57.7%                 | 9.3%                   |
| CKD stage 2      | 52.3%                 | 90.7%                  |
| CKD stage 3      | 18.6%                 | 18.6%                  |
| CKD stage 4      | 11.3%                 | 11.3%                  |
| Unknown/other    | 8.6%                  | 8.6%                   |
| Cancer           | 7.4%                  | 7.4%                   |
| Depression       | 3.5%                  | 3.5%                   |
| Back pain        | 4.2%                  | 4.2%                   |
| Neck pain        | 4.5%                  | 4.5%                   |
| Arthritis        | 4.9%                  | 4.9%                   |
| Headache         | 4.6%                  | 4.6%                   |
| HIV              | 4.6%                  | 4.6%                   |

*CKD status was not reported in the 2006 cohort as the stage-specific ICD-9-CM CKD codes were introduced in October 2015. Abbreviations: Chronic kidney disease (CKD), hypertension (HTN), cardiovascular disease (CVD), diabetes (DM) and human immunodeficiency virus (HIV)
eTable 3. Baseline characteristics of the yearly cohort by prescription analgesics use status and CKD status (2006-2015)

| Characteristics | Opioids All (n=601,718) | Prescription NSAIDs All (n=4013358) | Non-CKD (n=5,658,736) | Prescription NSAIDs Non-CKD (n=4571866) |
|-----------------|------------------------|-------------------------------------|----------------------|-----------------------------------------|
| **Use of Opioids** |                        |                                    |                      |                                         |
| Ever used       | 246671 (40.99%)        | 246671(100.00%)                    | 20319(30.2%)         | 20319(100.00%)                          |
| Total annual days' supply (mean, sd) | 42.88 (90.32)          | 42.88(90.32)                       | 24.96(5.50)          |                                         |
| **Use of NSAIDs** |                        |                                    |                      |                                         |
| Ever used       | 554992 (92.23%)        | 554992(92.23%)                     | 491202(81.63%)       |                                          |
| Total annual days' supply (mean, sd) | 50.94 (90.99)          | 50.94(90.99)                       | 28.65(7.41)          |                                         |
| **Demographics** |                        |                                    |                      |                                         |
| Age (mean, sd)  | 79.22(7.96)            | 79.22(7.96)                        | 73.27(7.89)          |                                          |
| **Race**        |                        |                                    |                      |                                         |
| White           | 491202(81.63%)         | 491202(81.63%)                     | 372375(66.09%)       |                                          |
| **Other**       |                        |                                    |                      |                                         |
| Asian           | 13650(2.27%)           | 13650(2.27%)                       | 10173(1.77%)         |                                          |
| Black           | 70579(11.73%)          | 70579(11.73%)                      | 6860(1.18%)          |                                          |
| Unknown         | 14090(2.39%)           | 14090(2.39%)                       | 11455(1.90%)         |                                          |
| HTN             | 554992(92.23%)         | 554992(92.23%)                     | 509437(84.66%)       |                                          |

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### Table

| Condition          | Value    | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value | Value |
|--------------------|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| **CVD**            | 445316(74.01%) | 189484(76.82%) | 255832(72.06%) | 65379(70.85%) | 2311062(40.84%) | 793029(48.20%) | 1518033(37.82%) | 431366(39.69%) | 284467(26.17%) | 1025958(22.44%) |
| **DM**             | 295996(49.19%) | 126868(51.43%) | 169128(47.64%) | 47153(51.10%) | 248843(48.85%) | 1310425(23.16%) | 448284(27.25%) | 862141(21.48%) | 1025958(22.44%) |
| **CKD status**     | 601718(100.00%) | 246671(100.00%) | 355047(100.00%) | 92283(100.00%) | 509435(100.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 5658736(100.00%) | 2086570(100.00%) | 4971866(100.00%) |
| **non-CKD**        | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 2311062(40.84%) | 793029(48.20%) | 1518033(37.82%) | 431366(39.69%) | 284467(26.17%) | 1025958(22.44%) |
| **CKD stage 1-2**  | 52087(8.66%) | 21167(8.58%) | 30920(8.71%) | 9559(10.36%) | 42528(8.35%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) |
| **CKD stage 3**    | 220362(36.62%) | 93273(37.81%) | 127089(35.79%) | 32977(35.73%) | 187385(36.78%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) |
| **CKD stage 4-5**  | 65823(10.94%) | 28140(11.41%) | 37683(10.61%) | 6966(7.55%) | 58857(11.55%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) | 0(0.00%) |
| **Unknown/other**  | 263446(43.78%) | 104091(42.20%) | 159355(44.88%) | 3658736(100.00%) | 144578(100.00%) | 401358(100.00%) | 1086870(100.00%) | 4571866(100.00%) |
| **Cancer**         | 104766(17.41%) | 45152(18.30%) | 59614(16.79%) | 89884(17.63%) | 533743(9.79%) | 190384(11.57%) | 363405(28.58%) | 780191(17.07%) | 453340(9.92%) |
| **Depression**     | 85945(14.28%) | 44035(17.85%) | 41910(11.80%) | 14150(15.33%) | 368371(6.51%) | 164776(10.01%) | 82464(7.59%) | 285907(6.25%) | 433340(9.92%) |
| **Back pain**      | 149061(24.77%) | 85033(34.47%) | 64028(18.03%) | 31778(34.44%) | 117283(19.28%) | 50219(8.05%) | 588160(28.58%) | 780191(17.07%) | 70403(9.24%) |
| **Neck pain**      | 40434(6.72%) | 22554(9.14%) | 17880(6.04%) | 32786(6.03%) | 14725(8.83%) | 194027(19.28%) | 240845(5.27%) |
| **Arthritis**      | 418400(69.53%) | 192896(76.20%) | 225568(63.51%) | 72236(78.28%) | 346164(67.95%) | 294626(52.04%) | 1095780(66.60%) | 1848846(46.07%) | 720721(66.44%) | 222254(48.61%) |
| **Headache**       | 4423(0.74%) | 2775(1.12%) | 1648(0.46%) | 1136(1.23%) | 3287(0.65%) | 35964(0.64%) | 18489(1.12%) | 17475(0.44%) | 11528(1.06%) | 24436(0.53%) |
| **HIV**            | 1697(0.28%) | 822(0.33%) | 875(0.25%) | 325(0.35%) | 13720(2.73%) | 6961(0.12%) | 2764(0.17%) | 41970(0.10%) | 1704(0.16%) | 5257(0.11%) |

**Abbreviations**: Chronic kidney disease (CKD), hypertension (HTN), cardiovascular disease (CVD), diabetes (DM) and human immunodeficiency virus (HIV)

Significant group differences were observed in all of characteristics, assessed by t-test and chi-square test (p<0.0001)
eFigure 3. Trends in total annual days' supply of opioids and prescription NSAIDs by CKD status, the yearly cohort 2006-2015

(a) Opioids
(b) Prescription NSAIDs

(a) The average number of days/year of opioid analgesics prescribed among users rose from 75 days/year in 2006 to 114 days/year in 2014, with a slight decline after 2014. (b) The average days of NSAIDs prescribed per user remained stable during 2006-2015, ranging from 93-101 days per person.
eFigure 4. Trends in proportion of prescribed opioids and NSAIDs by CKD and race, the yearly cohort 2006-2015
eFigure 5. Trends in use of opioids and prescription NSAIDs by CKD and selected comorbidities, the yearly cohort 2006-2015*

*Solid line represented patients with the specified disease, and dash lines represented those without the specified disease.
Abbreviations: hypertension (HTN), cardiovascular disease (CVD), diabetes (DM) and human immunodeficiency virus (HIV)
eTable 4. Results of trend analyses for opioid and prescription NSAID use according to CKD status, the yearly cohort 2006-2015

| Measures                        | Time               | Non-CKD       | CKD stage1-2 | CKD stage3 | CKD stage4-5 | CKD stage unknown/other |
|---------------------------------|--------------------|---------------|--------------|------------|--------------|------------------------|
| **Ever used opioids**           |                    |               |              |            |              |                        |
| Model1                          | 1.06, (1.06,1.07)  |               |              |            |              |                        |
| Model2                          | 1.06, (1.06,1.06)  | ref           | 1.27, (1.25,1.30) | 1.33, (1.32,1.34) | 1.43, (1.41,1.45) | 1.26, (1.25,1.28) |
| Model3                          | 1.06, (1.06,1.06)  | ref           | 1.44, (1.37,1.52) | 1.53, (1.48,1.57) | 1.63, (1.56,1.71) | 1.37, (1.34,1.40) |
| Model4                          | 1.07, (1.06,1.07)  | ref           | 1.46, (1.38,1.53) | 1.55, (1.50,1.59) | 1.67, (1.60,1.75) | 1.38, (1.34,1.41) |
| **Prescribed opioids >90 days** |                    |               |              |            |              |                        |
| Model1                          | 1.12, (1.11,1.12)  |               |              |            |              |                        |
| Model2                          | 1.12, (1.11,1.12)  | ref           | 1.08, (1.03,1.12) | 1.07, (1.05,1.10) | 1.05, (1.00,1.09) | 1.08, (1.06,1.10) |
| Model3                          | 1.12, (1.12,1.12)  | ref           | 1.24, (1.08,1.43) | 1.27, (1.17,1.37) | 1.30, (1.13,1.49) | 1.23, (1.16,1.32) |
| Model4                          | 1.12, (1.11,1.12)  | ref           | 1.24, (1.07,1.43) | 1.26, (1.16,1.36) | 1.29, (1.12,1.47) | 1.22, (1.15,1.31) |
| **Ever used prescription NSAIDs** |                    |               |              |            |              |                        |
| Model1                          | 1.04, (1.04,1.05)  |               |              |            |              |                        |
| Model2                          | 1.05, (1.05,1.05)  | ref           | 0.80, (0.78,0.82) | 0.67, (0.66,0.68) | 0.52, (0.50,0.53) | 0.82, (0.81,0.83) |
| Model3                          | 1.05, (1.05,1.05)  | ref           | 0.90, (0.84,0.97) | 0.87, (0.83,0.90) | 0.68, (0.64,0.73) | 0.92, (0.89,0.94) |
| Model4                          | 1.06, (1.06,1.06)  | ref           | 0.92, (0.86,0.99) | 0.88, (0.84,0.92) | 0.70, (0.65,0.75) | 0.95, (0.92,0.98) |
| **Prescribed NSAIDs >90 days**  |                    |               |              |            |              |                        |
| Model1                          | 1.02, (1.02,1.02)  |               |              |            |              |                        |
| Model2                          | 1.02, (1.02,1.03)  | ref           | 0.86, (0.81,0.91) | 0.68, (0.66,0.71) | 0.61, (0.56,0.67) | 0.88, (0.85,0.90) |
| Model3                          | 1.02, (1.02,1.03)  | ref           | 1.07, (0.89,1.28) | 0.84, (0.74,0.95) | 0.97, (0.77,1.23) | 1.03, (0.95,1.12) |
| Model4                          | 1.02, (1.02,1.03)  | ref           | 1.08, (0.89,1.31) | 0.84, (0.73,0.96) | 0.91, (0.71,1.17) | 1.04, (0.96,1.13) |

Note: Odds ratio (95% confidence intervals) in opioids and prescription NSAIDs use, compared to non-CKD population as reference. Model 1 adjusted for time; Model 2 adjusted for time and CKD status; Model 3 adjusted for time, CKD status, and interaction CKD status×time. Model 4 adjusted for time, CKD status, interaction CKD status×time, age, race and gender. P value for interaction CKD status×time <0.05 except for Model 3 and Model 4 in prescribed opioids >90 days.

Abbreviations: Chronic kidney disease (CKD)
eFigure 6. Changes in proportion of prescribed opioids among CKD and without CKD from year 2006-2015*  

CKD  
2006-2008  
(c)  
2009-2011  
(d)  
2012-2015  
(e)  
(f)  

Non-CKD  
2006-2008  
(b)  
2009-2011  
(h)  
2012-2015  
(g) 

*Value below 15 and above 50 were coded as 15 and 50.
eFigure 7. Changes in proportion of prescribed NSAIDs among CKD and without CKD from year 2006-2015*

CKD

2006-2008

Non-CKD

2009-2011

2012-2015

*Value below 5 and above 25 were coded as 5 and 25

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*Figure 8. Changes in proportion of prescribed opioids greater than 90 days among users with CKD and without CKD from 2006-2015*

*Value below 10 and above 40 were coded as 10 and 40*
eFigure 9. Changes in proportion of prescribed NSAIDs greater than 90 days among users with CKD and without CKD from 2006-2015*

*Value below 10 and above 40 were coded as 10 and 40

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eFigure 10. Changes in total annual days' supply of opioids among users with CKD and without CKD from 2006-2015*

*Value below 50 and above 150 were coded as 50 and 150
eFigure 11. Changes in total annual days' supply of prescription NSAIDs among users with CKD and without CKD from 2006-2015*

*Value below 55 and above 120 were coded as 55 and 120
eTable 5. Results of generalized linear models for the relationship of patients’ baseline characteristics to opioid and prescription NSAID use (as prescribed greater than 90 days), the yearly cohort 2006-2015

| Characteristics | Opioids >90 days | Prescription NSAIDs >90 days |
|-----------------|------------------|-----------------------------|
|                 | OR               | 95%CI | P value | OR               | 95%CI | P value |
| Age group       |                  |       |         |                  |       |         |
| 65-75           | ref              | ref   | ref     | ref              | ref   | ref     |
| 75-85           | 1.36             | 1.34-1.38 | <.0001 | 1.05             | 1.03-1.06 | <.0001 |
| 85 and above    | 1.80             | 1.76-1.83 | <.0001 | 1.11             | 1.09-1.14 | <.0001 |
| Gender          |                  |       |         |                  |       |         |
| Male            | ref              | ref   | ref     | ref              | ref   | ref     |
| Female          | 1.32             | 1.30-1.33 | <.0001 | 1.20             | 1.19-1.22 | <.0001 |
| Race            |                  |       |         |                  |       |         |
| White           | ref              | ref   | ref     | ref              | ref   | ref     |
| Asian           | 0.52             | 0.49-0.55 | <.0001 | 1.07             | 1.04-1.10 | <.0001 |
| Other           | 0.92             | 0.88-0.97 | 0.0006 | 0.87             | 0.83-0.90 | <.0001 |
| Black           | 1.17             | 1.15-1.20 | <.0001 | 0.96             | 0.94-0.98 | 0.0001 |
| Unknown         | 1.01             | 0.92-1.10 | 0.8947 | 1.22             | 1.13-1.33 | <.0001 |
| HTN             | 1.08             | 1.07-1.10 | <.0001 | 1.04             | 1.03-1.06 | <.0001 |
| CVD             | 1.09             | 1.08-1.10 | <.0001 | 0.95             | 0.94-0.96 | <.0001 |
| DM              | 1.16             | 1.14-1.18 | <.0001 | 1.07             | 1.05-1.08 | <.0001 |
| CKD status      |                  |       |         |                  |       |         |
| non-CKD         | ref              | ref   | ref     | ref              | ref   | ref     |
| CKD stage 1-2   | 1.15             | 1.11-1.19 | <.0001 | 0.86             | 0.81-0.91 | <.0001 |
| CKD stage 3     | 1.19             | 1.16-1.21 | <.0001 | 0.68             | 0.65-0.70 | <.0001 |
| CKD stage 4-5   | 1.16             | 1.12-1.21 | <.0001 | 0.59             | 0.54-0.64 | <.0001 |
| Unknown/other   | 1.08             | 1.06-1.10 | <.0001 | 0.86             | 0.84-0.89 | <.0001 |
| Cancer          | 1.09             | 1.07-1.10 | <.0001 | 0.93             | 0.92-0.95 | <.0001 |
| Depression      | 1.10             | 1.08-1.11 | <.0001 | 1.04             | 1.02-1.06 | <.0001 |
| Back pain       | 1.26             | 1.24-1.27 | <.0001 | 1.08             | 1.07-1.09 | <.0001 |
| Neck pain       | 1.03             | 1.02-1.05 | <.0001 | 1.02             | 1.00-1.04 | 0.0137 |
| Arthritis       | 1.20             | 1.19-1.22 | <.0001 | 1.20             | 1.18-1.21 | <.0001 |
| Headache        | 1.04             | 1.00-1.09 | 0.0495 | 0.99             | 0.94-1.04 | 0.6516 |
| HIV             | 1.15             | 1.04-1.28 | 0.0062 | 0.86             | 0.74-1.01 | 0.0591 |

Abbreviations: Chronic kidney disease (CKD), hypertension (HTN), cardiovascular disease (CVD), diabetes (DM) and human immunodeficiency virus (HIV)
etTable 6. Results of multivariable-adjusted Cox models for the association of opioid and prescription NSAID use (as total annual days' supply) with CKD outcomes

| Characteristics                      | ESRD* | All-cause mortality |
|--------------------------------------|-------|---------------------|
|                                      | HR    | 95%CI   | P value | HR    | 95%CI   | P value |
| Total annual days' supply of opioids |       |         |         |       |         |         |
| 0 days                               | ref   | ref     | ref     | ref   | ref     | ref     |
| 1-90 days                            | 1.07  | 1.00-1.14 | 0.0393  | 1.07  | 1.06-1.08 | <.0001 |
| 91-180 days                          | 1.26  | 1.11-1.44 | 0.0004  | 1.42  | 1.39-1.45 | <.0001 |
| >180 days                            | 1.17  | 1.05-1.31 | 0.0057  | 1.70  | 1.68-1.73 | <.0001 |
| Total annual days' supply of NSAIDs  |       |         |         |       |         |         |
| 0 days                               | ref   | ref     | ref     | ref   | ref     | ref     |
| 1-90 days                            | 0.98  | 0.91-1.06 | 0.6322  | 0.81  | 0.80-0.82 | <.0001 |
| 91-180 days                          | 0.77  | 0.65-0.91 | 0.0018  | 0.82  | 0.80-0.84 | <.0001 |
| >180 days                            | 0.97  | 0.85-1.11 | 0.6324  | 0.92  | 0.90-0.94 | <.0001 |
| Age group                            |       |         |         |       |         |         |
| 65-75                                | 0.83  | 0.78-0.87 | <.0001  | 2.14  | 2.12-2.16 | <.0001 |
| 75-85                                | 0.43  | 0.39-0.49 | <.0001  | 5.22  | 5.17-5.28 | <.0001 |
| 85 and above                         |       |         |         |       |         |         |
| Gender                               |       |         |         |       |         |         |
| Male                                 | ref   | ref     | ref     | ref   | ref     | ref     |
| Female                               | 0.75  | 0.71-0.79 | <.0001  | 0.79  | 0.78-0.80 | <.0001 |
| Race                                 |       |         |         |       |         |         |
| White                                | ref   | ref     | ref     | ref   | ref     | ref     |
| Asian                                | 1.69  | 1.51-1.90 | <.0001  | 0.66  | 0.64-0.67 | <.0001 |
| Other                                | 1.49  | 1.27-1.74 | <.0001  | 0.84  | 0.82-0.87 | <.0001 |
| Black                                | 2.08  | 1.95-2.22 | <.0001  | 1.06  | 1.05-1.07 | <.0001 |
| Unknown                              | 0.83  | 0.45-1.55 | 0.5619  | 0.92  | 0.85-1.00 | 0.0559 |
| HTN                                  | 1.50  | 1.38-1.62 | <.0001  | 0.97  | 0.96-0.98 | <.0001 |
| CVD                                  | 1.31  | 1.24-1.40 | <.0001  | 1.63  | 1.62-1.65 | <.0001 |
| DM                                   | 2.24  | 2.11-2.37 | <.0001  | 1.25  | 1.24-1.26 | <.0001 |
| CKD status                           |       |         |         |       |         |         |
| non-CKD                              | ref   | ref     | ref     | ref   | ref     | ref     |
| CKD stage 1-2                        | 6.56  | 5.41-7.94 | <.0001  | 1.35  | 1.29-1.41 | <.0001 |
| CKD stage 3                          | 10.78 | 9.85-11.80 | <.0001  | 1.41  | 1.37-1.44 | <.0001 |
| CKD stage 4-5                        | 51.02 | 47.47-54.83 | <.0001  | 2.04  | 1.98-2.09 | <.0001 |
| Unknown/other                        | 5.68  | 5.22-6.18 | <.0001  | 1.55  | 1.53-1.57 | <.0001 |
| Cancer                               | 1.01  | 0.93-1.10 | 0.7678  | 1.31  | 1.29-1.33 | <.0001 |
| Depression                           | 0.81  | 0.71-0.91 | 0.0005  | 1.63  | 1.61-1.65 | <.0001 |
| Back pain                            | 0.87  | 0.81-0.94 | 0.0006  | 0.83  | 0.82-0.84 | <.0001 |
| Neck pain                            | 0.92  | 0.80-1.04 | 0.1864  | 0.82  | 0.80-0.83 | <.0001 |
| Arthritis                            | 0.82  | 0.78-0.87 | <.0001  | 1.11  | 1.10-1.12 | <.0001 |

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| Condition | HR   | 95% CI   | p-value | HR   | 95% CI   | p-value |
|-----------|------|----------|---------|------|----------|---------|
| Headache  | 0.72 | 0.47-1.10| 0.1292  | 0.72 | 0.67-0.76| <.0001  |
| HIV       | 1.33 | 0.73-2.40| 0.3494  | 1.64 | 1.45-1.85| <.0001  |

* A competing risk model (accounting for death) was used to estimate the hazard ratio (HR) for development of ESRD.

Abbreviations: Chronic kidney disease (CKD), hypertension (HTN), cardiovascular disease (CVD), diabetes (DM) and human immunodeficiency virus (HIV)