

Supplementary Table S1. International Classification of Diseases codes for the diseases analyzed in this study

| Diseases                                | ICD-9-CM  | ICD-10-CM        |
|---|-----------|------------------|
| Natural causes of death                 |           |                  |
| Infection and parasitic diseases        | 001–139   | A010–B99         |
| Neoplasms                               | 140–239   | C00–D48          |
| Metabolic and immunity diseases         | 249–279   | E00–E90          |
| Hematological diseases                  | 280–289   | D50–D89          |
| Mental disorders                        | 290–319   | F00–F99          |
| Diseases of the nervous system and      | 320–389   | G00–G99          |
| sensory organs                          |           |                  |
| Circulatory diseases                    | 390–459   | I00–I99          |
| Respiratory diseases                    | 460–519   | J00–J99          |
| Digestive diseases                      | 520–579   | K00–K93          |
| Genitourinary diseases                  | 580–629   | N00–N99          |
| Complications during pregnancy,         | 630–676   | O00–O99          |
| childbirth, or the puerperium           |           |                  |
| Skin and subcutaneous tissue diseases   | 680–709   | L00–L99          |
| Musculoskeletal and connective tissue   | 710–739   | M00–M99          |
| diseases                                |           |                  |
| Congenital anomalies                    | 740–759   | Q00–Q99          |
| Conditions originating in the perinatal | 760–799   | P96              |
| period                                  |           |                  |
| Symptoms/signs not classified           | 780–799   | R00–R99          |
| elsewhere                               |           |                  |
| Unnatural causes of death               |           |                  |
| Accidents and violence                  | E800–E949 | V01–X59, Y85–Y86 |
| Suicide                                 | E950–E959 | X60–X84, Y87     |
| Homicide                                | E960–E969 | X85–Y09, Y87.1   |
| Unspecified cause of death              | NA        | NA               |

Abbreviations: NA, not applicable; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification

Supplementary Table S2. Comparison of opioid analgesics consumed by patients enrolled in different calendar years

| Opioid<br>analgesics | Total  | <u>2001–2003</u> |       | <u>2004–2006</u> |       | <u>2007–2009</u> |       | <u>2010–2012</u> |       |
|----------------------|--------|------------------|-------|------------------|-------|------------------|-------|------------------|-------|
|                      |        | <i>n</i>         | %     | <i>n</i>         | %     | <i>n</i>         | %     | <i>n</i>         | %     |
| Fentanyl             | 14     | 4                | 0.7   | 4                | 0.5   | 3                | 0.1   | 3                | 0.0   |
| Morphine             | 33     | 4                | 0.7   | 10               | 1.3   | 14               | 0.4   | 5                | 0.1   |
| Tramadol             | 11,553 | 229              | 40.9  | 423              | 53.6  | 3473             | 91.4  | 7428             | 94.7  |
| Codeine              | 1390   | 323              | 57.7  | 352              | 44.6  | 308              | 8.1   | 407              | 5.2   |
|                      | 12,990 | 560              | 100.0 | 789              | 100.0 | 3798             | 100.0 | 7843             | 100.0 |

Supplementary Table S3. Comparison of underlying causes of death between male and female users of long-term opioid analgesics

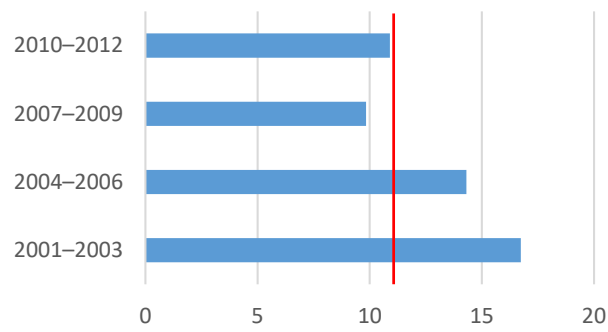
| Underlying cause of death | Males    |       | Females  |       | <i>p</i> value <sup>a</sup> |
|---------------------------|----------|-------|----------|-------|-----------------------------|
|                           | <i>n</i> | %     | <i>n</i> | %     |                             |
| Natural causes            | 308      | 85.1  | 173      | 88.3. | 0.234                       |
| Unnatural causes          | 42       | 11.6  | 21       | 10.7  |                             |
| Unspecified causes        | 12       | 3.3   | 2        | 1.0   |                             |
| Total                     | 362      | 100.0 | 196      | 100.0 |                             |

<sup>a</sup> Based on a  $\chi^2$  test

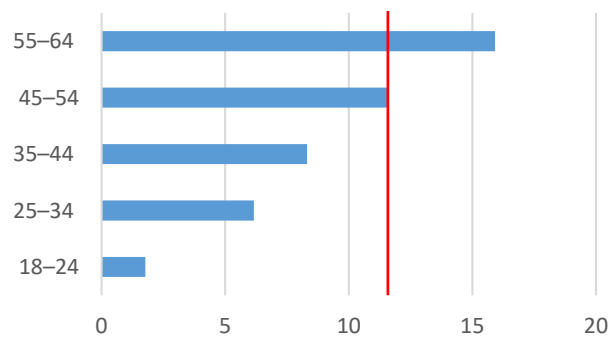
Supplementary Table S4. Comparison of underlying causes of death among long-term users of opioid analgesics with respect to their age at cohort enrollment

| Underlying cause of death | 18–24 years |       | 25–34 years |       | 35–44 years |       | 45–54 years |       | 55–64 years |       | <i>p</i> value |
|---------------------------|-------------|-------|-------------|-------|-------------|-------|-------------|-------|-------------|-------|----------------|
|                           | <i>n</i>    | %     | <i>n</i>    | %     | <i>n</i>    | %     | <i>n</i>    | %     | <i>n</i>    | %     |                |
| Natural causes            | 20          | 74.1  | 78          | 83.0  | 80          | 86.0  | 124         | 86.1  | 179         | 89.5  | 0.519          |
| Unnatural causes          | 5           | 18.5  | 13          | 13.8  | 11          | 11.8  | 17          | 11.8  | 17          | 8.5   |                |
| Unspecified causes        | 2           | 7.4   | 3           | 3.2   | 2           | 2.2   | 3           | 2.1   | 4           | 2.0   |                |
| Total                     | 27          | 100.0 | 94          | 100.0 | 93          | 100.0 | 144         | 100.0 | 200         | 100.0 |                |

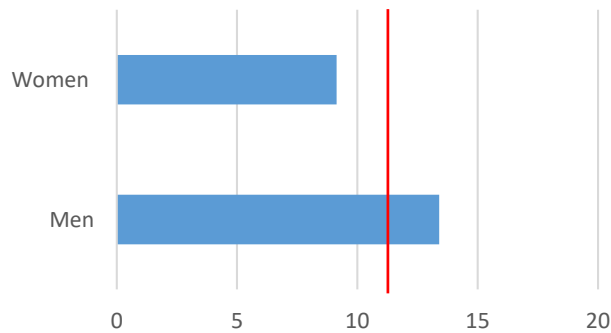
<sup>a</sup> Based on a  $\chi^2$  test



Mortality rate (*per* 10<sup>3</sup> person-years)



Mortality rate (*per* 10<sup>3</sup> person-years)



Mortality rate (*per* 10<sup>3</sup> person-years)

Supplementary Figure S1. Mortality rate according to calendar year of enrollment (upper), age (years) at cohort enrollment (middle), or sex (lower). The red bar indicates the overall mortality (11.62 *per* 10<sup>3</sup> person-years) of all long-term users of opioid analgesics users.