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Increased risk of death with codeine use in the elderly over 85 years old and patients with respiratory disease

A case-control study using retrospective insurance claims database

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Abstract

To investigate the risk of mortality associated with exposure to codeine, considering various risk groups, using population-based national insurance claims data.

National sample cohort data from the National Health Insurance Service of South Korea (2002–2013) was used in this case-control study. Cases were defined as patients with a death record between January 1, 2002 and December 31, 2013. Each case was matched to 10 controls based on age, sex, baseline comorbidities, and year of death. Definition of exposure was codeine prescription in 30 days prior to death and sensitivity analyses were performed for 15 and 60-day exposures. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were estimated using conditional logistic regression adjusting for benzodiazepine, other opioids, anesthetics, hypnotics, CYP2D6 inducer, CYP3A4 inducer, and the Charlson comorbidity index.

A total of 19,341 cases and 185,700 matched controls were included. The overall risk associated with codeine use and mortality risk was not significant (aOR 1.08, 95% CI 1.00–1.16). Sensitivity analyses with different exposure time window also presented similar insignificant results. However, in the subgroup analyses, codeine use was associated with an increased risk of mortality in the >85-year-old age group (aOR 2.38, 95% CI 1.26–4.48) and patients with respiratory disease (aOR 1.29, 95% CI 1.17–1.42).

Although no statistically significant association was found in codeine exposure and mortality risk between cases and controls, we demonstrated that the elderly over 85 years old and patients with respiratory disease are associated with a higher risk with codeine exposure. Therefore, a more cautious practice of codeine prescription in these groups might be needed.

Abbreviations: aOR = adjusted odd ratio, ATC = anatomic therapeutic chemical, CCI = Charlson comorbidity index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, FDA = Food And Drug Administration.

Keywords: case-control study, mortality, opioids, pharmacoepidemiology, safety

1. Introduction

Opioid analgesics are frequently prescribed for patients to treat cancer or non-cancer-related pain[1,2] Opioid therapy for acute pain such as post-operative pain is necessary, and chronic therapy is applicable for palliative care and cancer pain.[3] Codeine is a commonly prescribed weak opioid, second only to morphine, and is a widely used narcotic for its analgesic and antitussive properties.[4] Despite most codeine preparations (single-ingredient codeine) requires a prescription, there are no requirements to keep controlled registers.[4] Usually, combination preparations containing low dose of codeine with acetaminophen or ibuprofen is available without prescriptions.[4] Healthcare professionals and the public generally consider codeine to be safe, based on that over-the-counter products are widely available for self-medication in many countries.[5] In the UK, the lower strength codeine phosphate 15 mg/5 mL oral solution is available for purchase in pharmacies after consultation with a pharmacist for dry cough in patients over 18 years old without a prescription.[6] However, the potential for combination analgesic misuse, along with their easy accessibility, and the rates of over-the-counter and prescription medication abuse have resulted in a growing public health concern worldwide.[7–10] Moreover, deaths have been reported involving codeine and codeine–ibuprofen combinations.[7,8,10] The misuse may cause respiratory depression leading to bronchopneumonia or aspiration pneumonia, central nervous

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system depression, and coma.[11] In addition, in case reports and post-mortem analysis described the rapid metabolism of codeine into morphine, in fast metabolizers.[12–16]

From 1969 to 2012, 13 children in the U.S died after taking codeine and, of these, 8 children had undergone a tonsillectomy or adenoidectomy. These deaths prompted the Food and Drug Administration (FDA) to issue a boxed warning in 2013 to contraindicate codeine use in adolescents under the age of 18 with obstructive sleep apnea, or those who have either tonsillectomy or adenoidectomy.[17] In 2013, the European Medicine Agency prohibited the use of codeine-containing products for children under the age of 12.[18] Additionally, in April 2017, the FDA updated their warnings to contraindicate codeine in patients under the age of 12.[18–20]

However, aside from children, an Australian study concerning self-reported codeine misusers indicated that the proportion of female users was high (70%).[10] Burr et al (2018)[21] conducted a retrospective 24-year cohort study exploring trends in all opiate prescriptions, using a primary care database. There was a statistically significant association between premature mortality and the heavy use of any opiate or codeine alone in patients with ulcerative colitis.

Since opioid analgesic use has increased in recent years in developed countries, with a rise in misuse of prescription opioids and related fatalities, an assessment of death risk associated with codeine use both in children and adult groups is required.[22] In this context, we aimed to evaluate the risk of death associated with codeine use including analgesic and cold remedies using population-based national insurance claims data.

2. Materials and methods

2.1. Database

We used national sample cohort data from the National Health Insurance Service. To assess its validity, average total annual medical expenses, distribution of residential area, and the mean and standard deviation of health insurance premiums of the sample cohort were compared to the entire population. All differences were negligible for the duration of the sampling period.[23] Comprehensive demographic data for the sample cohort were available, including sex, age recorded in 5-year intervals, income level, and date of death; as well as healthcare data, including clinical diagnoses, medical procedures, expenditures, and drug prescriptions. The information on prescribed drugs included the generic name, prescription date, duration of use, and route of administration. All diagnoses and classifications of comorbidities were coded according to the International Classification of Disease, Tenth Revision, Clinical Modification codes (Supplementary Table 1, http://links.lww.com/MD/E855)

This study was approved by the Institutional Review Board of the Sungkyunkwan University in South Korea (SKKU-IRB-2016–10-013). All personal identifying information for patients was anonymous; therefore, informed consent was waived by the Institutional Review Board for this study.

2.2. Case definition and control selection

A case-control design was used to assess the association between codeine exposure and mortality risk[24] this study design was selected due to the rarity of outcome, death, induced through medication.

Cases were identified by the death record data was retrieved from the Statistics Korea database. The index date was defined as the date of a death that occurred between January 2002 and December 2013. Cases included patients with or without codeine exposure prior to the index date. Patients who died between January 2002 and February 2002 or those who had a prescription of codeine on the index date were excluded because those patients did not have enough survival time to have a month of codeine exposure. The inclusion criteria for controls were patients who did not die during the follow-up period of this case-control study. Patients included as controls regardless of their exposure status to codeine. For each case, 10 controls were randomly selected after being matched according to age, sex, baseline comorbidities and year of death. The individuals exposed and not exposed to codeine in the case and the control group was compared.

2.3. Exposure assessment

Codeine and dihydrocodeine were the main exposures in this study, and combinations with other medications including acetaminophen, ibuprofen, aspirin, ammonium chloride, chlorpheniramine maleate, methylephedrine HCl, guaifenesin, bromhexine hydrochloride, and carbinoxamine maleate. In South Korea, codeine and dihydrocodeine are not classified as opioids but require a prescription, and they are commonly available in the oral administration form in either tablets or cough syrups.[25] The cumulative dose and duration of exposure was not taken into account, as the dose of codeine was assumed to be within commonly prescribed doses, and the mechanism leading to death was assumed to occur acutely after exposure.

Patient medication history was collected 1 year prior to the index date, based on Anatomic Therapeutic Chemical (ATC) classification codes and generic codes (Supplementary Table 2, http://links.lww.com/MD/E856).[26] The main time window was 30 days, assuming that death would have occurred acutely after codeine exposure, as the mechanism of death after codeine use is suggested to occur through rapid metabolism of codeine into morphine in fast metabolizers.[12–15] According to a study conducted in 2010, all-cause mortality was 2 times higher after only 30 days of codeine use (RR 2.05, 95% confidence interval [CI] 1.22–3.45).[27] The prescriptions from both inpatient and outpatient settings were assessed. To confirm the robustness of our main results, we conducted a sensitivity analysis by repeating our analyses with multiple time windows of 15- and 60-day exposures prior to the index date.

2.4. Potential confounders

Age, sex, cause of treatment (analgesic or antitussive), comorbidities (obstructive sleep apnea, respiratory disease, renal disease, hepatic disease, cardiovascular disease, and malignant neoplasm), and co-medication (other types of opioids, benzodiazepines, anesthetics, hypnotics, selective serotonin reuptake inhibitors, and serotonin–norepinephrine reuptake inhibitors]) are all possible confounders of the association between codeine exposure and death.[11] The following disorders that presented prior to the index date were assessed: obstructive sleep apnea, respiratory disease (bronchial asthma and chronic obstructive pulmonary disease [COPD]), renal disease, cardiovascular disease, and malignant neoplasms (Supplementary Tables 1, http://links.lww.com/MD/E855 and 3, http://links.lww.com/MD/E857). We used the

Charlson comorbidity index (CCI), a weight index of 19 chronic comorbid diseases (e.g., cancer, diabetes, myocardial infarction, moderate, or severe renal disease, hemiplegia, liver disease, and COPD), according to previous diagnoses during 1 year prior to the index date.[28]

The main confounding co-medications considered were benzodiazepines, anesthetics, hypnotics, antidepressants, and opioid analgesics. The prescription histories presented prior to the index date were assessed using the following ATC codes: benzodiazepines (ATC code: N03AE, N05BA, and N05CD), antidepressants (ATC code: N06AA, N06AB, N06AG, and N06AX), and opioid analgesics (ATC code: N02AA, N02AB, N02AD, N02AE, N02AF, N02AX, and N01AH).

2.5. Results of codeine use and risk of mortality

The main results compared the odds of death with the exposure of codeine 30 days prior to death. We conducted a subgroup analyses according to the indication of codeine prescription (analgesic or antitussive), age group, sex, comorbidities (obstructive sleep apnea, respiratory disease, renal disease, hepatic disease, cardiovascular disease, and malignant neoplasm) and the CCI level (0, 1–2, 3+). Age groups were categorized as the following: <10, 10 to 14, 15 to 19, 20 to 64, 65 to 84, ≥85 years.

In addition, the Secondary outcome was odds of death within the case group based on the cause of death, whether it was a respiratory failure or other causes.

2.6. Statistical analysis

We conducted a *t* test for continuous variables and a Chi-squared test for categorical variables to estimate crude and adjusted odds ratios (aORs) through comparing the odds of codeine exposure between the case and the control groups. Stratified analyses were performed to assess the strength of association according to age group, comorbidities (including obstructive sleep apnea, respiratory disease (bronchial Asthma and COPD), renal disease, hepatic disease, cardiovascular disease, and malignant neoplasm) (Supplementary Table 1, http://links.lww.com/MD/E855), other types of opioids, benzodiazepines, anesthetics, hypnotics, CYP enzyme 2D6, and CYP3A4 inducers and inhibitors (Supplementary Table 3, http://links.lww.com/MD/E857). Adjustments for covariates (the use of benzodiazepine, other opioids, anesthetics, hypnotics, CYP2D6 inducer, CYP3A4 inducer, and CCI level) were performed by standard unconditional logistic regression to examine whether differences in effect size were statistically significant depending on age group, sex, CCI, and the presence or absence of conditions with a high-risk of death (comorbidities) due to codeine use. All tests were 2-sided, with a significance level of 0.05. The cut-off *P*-value was .05. All data transformations and statistical analyses were conducted using SAS version 9.4 for Windows (SAS Institute, Cary, NC).

3. Results

The source (national sample cohort from NHIS-NSC) data consisted of 1,113,656 population. After application of the exclusion criteria, 19,341 cases and 185,700 controls were included in our analysis (Fig. 1). There were differences in the baseline characteristics, cases were more likely to have comorbidities such as obstructive sleep apnea, renal disease and malignant neoplasm, and the CCI score was significantly higher. In addition, cases had more concomitant medications prescribed such as benzodiazepines, opioid analgesics anesthetics, and hypnotics (Table 1).

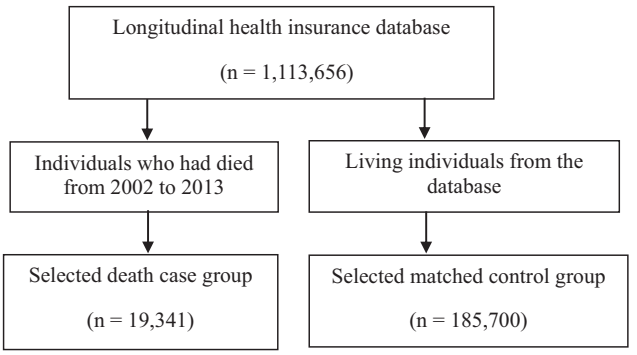

Figure 1. The case-control study patient selection process.

In the primary analysis, the use of codeine within the 30-day time window was associated with an increased mortality risk (OR 1.99, 95% CI 1.89–2.09). After adjustment for other major potential confounders, such as age, sex, baseline comorbidities, and year of death, the aOR decreased to 1.08 (95% CI 1.00–1.16) and showed a null association (Table 2).

Subgroup analyses stratified by sex, age group, comorbidities, CCI score, and type of administration were conducted (Table 3). There was a significantly increased risk of death in patients using codeine as an analgesic (aOR 3.91, 95% CI 2.91–5.26). However, the number was small, only 11.20% of the case and 6.07% of the control group had an analgesic use indication in the database, which needs careful interpretation. Moreover, patients exposed to codeine and aged >85 years showed an increased risk of death (aOR 2.38, 95% CI 1.26–4.48) (Table 3), whereas other age groups did not show any significant associations. Among the 15 to 19-year age group and the 10 to 14-year age group, there was a tendency towards increased risk but this was not significant (aOR 1.36, 95% CI 0.61–3.06 and aOR 1.36, 95% CI 0.34–5.46, respectively). For comorbidities, only patients with respiratory disease had a moderately increased risk (aOR 1.29, 95% CI 1.17–1.42). There was no significant association with CCI scores and mortality risk (Table 3).

In the secondary analysis, the risk of mortality associated with the use of codeine was compared within the case group, based on the cause of death. The risk of a respiratory related death compared with other causes was substantially higher in patients who were over 85 years (aOR 2.65; 95% CI 1.05–6.67). There was a moderately elevated risk of respiratory related death in males (aOR 1.30, 95% CI 1.11–1.51). Antitussive use of codeine was associated with increased respiratory failure attributable death (aOR 1.29, 95% CI 1.14–1.45), Patients with respiratory disease, hepatic disease, cardiovascular disease, and malignant neoplasm were associated with higher respiratory related deaths, and a CCI score of >3 was associated with a higher rate of death due to respiratory depression (Table 4).

Sensitivity analysis was performed by varying the time windows for codeine exposure to include 15 to 60-day exposures (exposure at 15, 30, and 60 days). The aORs for the 0 to 30 days and 0 to 60 days' time window were 1.08 (95% CI 1.00–1.16) and 1.07 (95% CI 1.00–1.14), respectively. The association between mortality and codeine use showed similar insignificant results in 3 different time windows (Table 5).

Table 1

A comparison of demographic status and comorbidity between the control and case groups.

Characteristics	Cases (n = 19,341)	Controls (n = 185,700)	*P*
Age (yr), n (%)			
≥85	269 (1.39)	1821 (0.98)	<.0001
65–84	8172 (42.25)	76,918 (41.42)	
20–64	10,534 (54.46)	103,478 (55.72)	
15–19	138 (0.71)	1374 (0.74)	
10–14	58 (0.30)	531 (0.29)	
<10	170 (0.88)	1578 (0.85)	
Sex, n (%)			
Male	11,073 (57.25)	106,391 (57.29)	.9138
Yr of death, n (%)			
2003	2620 (13.55)	25,510 (13.74)	.9992
2004	2051 (10.60)	19,825 (10.68)	
2005	1840 (9.51)	17,812 (9.59)	
2006	1695 (8.76)	16,307 (8.78)	
2007	1639 (8.47)	15,730 (8.47)	
2008	1966 (10.16)	18,873 (10.16)	
2009	1590 (8.22)	15,226 (8.20)	
2010	1441 (7.45)	13,771 (7.42)	
2011	1567 (8.10)	14,801 (7.97)	
2012	1516 (7.84)	14,394 (7.75)	
2013	1416 (7.32)	13,451 (7.24)	
Concomitant medication, n (%)			
Benzodiazepine			
No	13,259 (68.55)	168,734 (90.86)	<.0001
Yes	6082 (31.45)	16,966 (9.14)	
Other opioids			
No	13,319 (68.86)	169,270 (91.15)	<.0001
Yes	6022 (31.14)	16,430 (8.85)	
Anesthetics			
No	19,211 (99.33)	185,613 (99.95)	<.0001
Yes	130 (0.67)	87 (0.05)	
Hypnotics			
No	18,916 (97.80)	185,088 (99.67)	<.0001
Yes	425 (2.20)	612 (0.33)	
CYP2D6 inducer			
No	18,911 (97.78)	184,916 (99.58)	<.0001
Yes	430 (2.22)	784 (0.42)	
CYP3A4 inducer			
No	19,005 (98.26)	18,5087 (99.67)	<.0001
Yes	336 (1.74)	613 (0.33)	
Comorbidities, n (%)*			
Obstructive sleep apnea	15 (0.08)	399 (0.21)	<.0001
Respiratory disease	6526 (33.74)	62,046 (33.41)	.3548
Renal disease	315 (1.63)	1807 (0.97)	<.0001
Hepatic disease	6965 (36.01)	66,231 (35.67)	.3392
Cardiovascular disease	11,024 (57.00)	105,858 (57.00)	.9856
Malignant neoplasm	4905 (25.36)	44,212 (23.81)	<.0001
CCI (mean, SD)	4.84 (4.08)	1.35 (1.89)	<.0001
0	2684 (13.88)	85,285 (45.93)	<.0001
1–2	4497 (23.25)	63,611 (34.25)	
>3	12,160 (62.87)	36,804 (19.82)	

* Overlapping between comorbidities is possible. Diseases included in comorbidities (Supplementary Table 2, http://links.lww.com/MD/E856).

CCI = Charlson comorbidity index, SD = standard deviation.

4. Discussion

This is the first population-based study to investigate codeine use and associated death risk. This study demonstrated a moderate trend of increased but statistically not significant mortality risk associated with codeine use (aOR 1.08, 95% CI 1.00–1.16).

Our results corroborate a recent study that examined the overdosed opioid prescriptions and risk factors for severe respiratory depression. In adult patients who were presented with acute opioid overdose between 2009 and 2013, the unadjusted relative risk of severe respiratory depression(SRD) was the highest for fentanyl (83.3% SRD) and the lowest for codeine (3.6% SRD).[29] Since opioids are known to have an increased death risk by respiratory depression,[30] the lowest respiratory depression risk with codeine use could explain the null association in this research.

However, in the subgroup analysis, a significantly increased mortality risk was observed in elderly patients >85 years (aOR 2.38, 95% CI 1.26–4.48) with the exposure of codeine. In the group aged between 10 and 19 years of age, the result showed an increased but not statistically significant mortality risk (10–14 years: aOR, 1.36, 95% CI 0.34–5.46; 15–19 years: aOR, 1.36, 95% CI 0.61–3.06). Due to a lack of power (N = 196), no robust conclusions could be drawn concerning this group. Concurrent comorbidities did not affect the mortality risk except for respiratory disease, which showed a moderately increased risk (aOR 1.29, 95% CI 1.17–1.42).

Increased mortality risk in relation to the elderly population was consistent with that of a cohort study using the US beneficiary data from 1996 to 2005 where all-cause mortality was nearly 2 times higher after 30 days of codeine use (RR 2.05, 95% CI 1.22–3.45), compared with hydrocodone users, where the mean age of the study participants were 79.[27] In addition, the increased risk of fatal respiratory depression as a cause of death after codeine use is consistent with a series of case reports that have appeared in the literature since 2004.[31] Similar results on the increased risk of death associated with codeine use were reported in a cohort study using ResearchOne data from primary care in England in 2018. In their research, in patients with Crohn disease and ulcerative colitis, there was a significant association between heavy codeine use and ulcerative colitis patients (ulcerative colitis: moderate use, Hazard Ratio 0.72, 95% CI 0.3–1.47; and heavy use, HR 1.83, 95% CI 1.10–3.05).[21]

Many case reports have linked codeine exposure with pediatric deaths.[32,33] In a case series published in 2012 in the U.S has reported 2 deaths and 1 case of respiratory depression in children following codeine use for tonsillectomy and for adenoidectomy to treat obstructive sleep apnea.[33] In a review by the FDA using data from the Adverse Event Reporting System from 1965 to 2015, results revealed a total of 64 cases of severe respiratory depression and 24 codeine-related deaths and, among these, 12 patients were children under the age of 12 years.[31]

Postmortem redistribution may affect the interpretation of drug concentrations in the different postmortem matrices especially when identifying the cause of death from adverse drug events or drug abuse.[34] Usually, opioids are thought to have a tendency of undergoing PMR due to their physiochemical properties (e.g., large Volume of distribution). However, codeine has a less extensive PMR compared to morphine.[35,36] So, it may be more interpretable to determine the cause of death from codeine use.[37]

Our findings show similar results as those who died were more likely to have obstructive sleep apnea. Due to the lack of power, we were not able to demonstrate significant death risk in younger patients, but there was a trend of increased risk observed (Table 3).

Through these findings, we must be aware that specific vulnerable population (the elderly and patients with respiratory disease) should use codeine with caution. In addition, codeine use as antitussives in patients with respiratory disease should be avoided if possible since codeine used as antitussive had a slightly

Table 2

Mortality risk in patients with codeine exposure (30-day exposure period).

Comparators	Cases (n = 19,341)	Controls (n = 185,700)	Crude OR (95% CI)*	Adjusted OR (95% CI)*,†
codeine exposure, n (%)				
Yes	2168 (11.21)	11,273 (6.07)	2.00 (1.89, 2.09)	1.08 (1.00, 1.16)
No	17,173 (88.79)	174,427 (93.93)		

* Cases and controls were matched according to age groups, sex, baseline comorbidities, and year of death.

† Matched (conditional logistic regression) analysis adjusted for the use of benzodiazepine, other opioids, anesthetics, hypnotics, CYP2D6 inducer, CYP3A4 inducer, and the Charlson comorbidity index level.
CI = confidence interval, OR = odds ratio.

higher risk of death classified as respiratory depression. (Table 4) Antitussive use of codeine for young children has been banned from 2015 by FDA[38] to protect children against codeine exposure. Likewise, based on these results, similar regulation or precaution seems to be required for the elderly especially for those over 85 years of age and people with respiratory disease.

The biological mechanism of death after codeine use may be due to the rapid metabolism of codeine into morphine. Codeine is a prodrug that requires conversion in the liver by the cytochrome P450 2D6 (CYP2D6) enzyme, approximately 0% to 15% of codeine is converted into its metabolite morphine.[16,39] The CYP2D6 enzyme has clinical significance as it exhibits the greatest genetic polymorphism.[2] Types of polymorphism include poor metabolizers (low or zero activity variants), normal metabolizers (high or normal activity variants, also called extensive metabolizers), intermediate metabolizers and ultra-rapid metabolizers (multiple gene copy variants).[39,40] Ultrarapid metabolizers of the CYP2D6 genotype have a faster rate of conversion into morphine, leading to life-threatening opiate overdose.[15,41] On the other hand, poor metabolizers have little

Table 3

Mortality risk in codeine users stratified according to age, sex, cause of treatment, comorbidities, and the Charlson comorbidity index.

Current exposure group	Cases (n = 19,341)	Controls (n = 185,700)	Crude OR (95% CI)*	Adjusted OR (95% CI)*,†
Age (yr), n (%)				
≥85	269 (1.39)	1821 (0.98)	4.17 (2.48, 7.00)	2.38 (1.26, 4.48)
65–84	8172 (42.25)	76,918 (41.42)	1.64 (1.52, 1.76)	1.10 (0.99, 1.21)
20–64	10,534 (54.46)	103,478 (55.72)	2.46 (2.29, 2.63)	1.04 (0.93, 1.17)
15–19	138 (0.71)	1374 (0.74)	1.66 (0.85, 3.22)	1.36 (0.61, 3.06)
10–14	58 (0.30)	531 (0.29)	2.02 (0.79, 5.17)	1.36 (0.34, 5.46)
<10	170 (0.88)	1578 (0.85)	0.55 (0.30, 1.01)	0.53 (0.24, 1.18)
Sex, n (%)				
Male	11,073 (57.25)	106,391 (57.29)	2.14 (2.00, 2.29)	1.09 (0.99, 1.21)
Female	8268 (42.75)	79,309 (42.71)	1.84 (1.71, 1.98)	1.05 (0.95, 1.17)
Cause of treatment				
Pain	372	199	18.25 (15.28, 21.78)	3.91 (2.91, 5.26)
Antitussive	1796	11,074	1.64 (1.55, 1.73)	0.99 (0.92, 1.06)
Comorbidities, n (%)				
Obstructive Sleep Apnea				
Yes	15 (0.08)	399 (0.21)		
No	19,326 (99.92)	185,301 (99.79)	1.99 (1.89, 2.09)	1.07 (1.00, 1.16)
Respiratory disease				
Yes	6526 (33.74)	62,046 (33.41)	2.24 (2.10, 2.40)	1.29 (1.17, 1.42)
No	12,815 (66.26)	123,654 (66.59)	1.70 (1.58, 1.84)	0.89 (0.80, 1.00)
Renal disease				
Yes	315 (1.63)	1807 (0.97)	2.13 (1.44, 3.15)	1.20 (0.62, 2.29)
No	19,026 (98.37)	183,893 (99.03)	1.99 (1.89, 2.09)	1.07 (1.00, 1.16)
Hepatic disease				
Yes	6965 (36.01)	66,231 (35.67)	2.04 (1.88, 2.20)	1.02 (0.90, 1.16)
No	12,376 (63.99)	119,469 (64.33)	1.96 (1.84, 2.09)	1.11 (1.01, 1.21)
Cardiovascular disease				
Yes	11,024 (57.00)	105,858 (57.00)	1.73 (1.62, 1.84)	1.00 (0.91, 1.09)
No	8317 (43.00)	79,842 (43.00)	2.49 (2.30, 2.70)	1.19 (1.06, 1.33)
Malignant neoplasms				
Yes	4905 (25.36)	44,212 (23.81)	3.32 (3.04, 3.61)	1.18 (1.00, 1.40)
No	14,436 (74.64)	141,488 (76.19)	1.57 (1.47, 1.67)	1.04 (0.96, 1.13)
Charlson comorbidity index level				
0	2684	85,285	1.44 (1.18, 1.77)	1.18 (0.95, 1.46)
1–2	4497	63,611	1.47 (1.29, 1.68)	1.08 (0.93, 1.25)
>3	12,160	36,804	1.93 (1.80, 2.08)	1.09 (0.99, 1.22)

* Cases and controls were matched according to age group, sex, baseline comorbidities, and year of death.

† Matched (conditional logistic regression) analysis adjusted for the use of benzodiazepine, other opioids, anesthetics, hypnotics, CYP2D6 inducer, CYP3A4 inducer, and the Charlson comorbidity index level.
CI = confidence interval, OR = odds ratio.

Table 4

A comparison of the cause of death between respiratory failure (depression) versus other causes of death.

	All cause of mortality (n = 19,341)			
	Respiratory failure (n = 3,337)	Other causes of death (n = 16,004)	Crude OR (95% CI)	Adjusted OR (95% CI)*
Age (yr), n (%)				
≥85	38 (1.14)	231 (1.44)	3.10 (1.30, 7.42)	2.65 (1.05, 6.67)
65–84	1520 (45.55)	6652 (41.56)	1.49 (1.27, 1.74)	1.21 (1.02, 1.42)
20–64	1718 (51.48)	8816 (55.09)	1.57 (1.35, 1.82)	1.18 (1.01, 1.39)
15–19	21 (0.63)	117 (0.73)	3.70 (0.98, 13.99)	4.46 (1.00, 19.88)
10–14	10 (0.30)	48 (0.30)	2.75 (0.43, 17.61)	3.64 (0.39, 34.39)
<10	30 (0.90)	140 (0.87)	1.62 (0.41, 6.37)	1.41 (0.34, 5.80)
Sex, n (%)				
Male	1884 (56.46)	9189 (57.42)	1.66 (1.44, 1.92)	1.30 (1.11, 1.51)
Female	1453 (43.54)	6815 (42.58)	1.45 (1.24, 1.70)	1.14 (0.96, 1.35)
Cause of treatment				
Pain	84	288	1.41 (1.10, 1.80)	0.91 (0.71, 1.18)
Antitussive	426	1,370	1.56 (1.39, 1.76)	1.29 (1.14, 1.45)
Comorbidities, n (%)				
Obstructive sleep apnea				
Yes	2 (0.06)	13 (0.08)	-	-
No	3335 (99.94)	15,991 (99.92)	1.56 (1.40, 1.74)	1.23 (1.10, 1.38)
Respiratory disease				
Yes	1451 (43.48)	5075 (31.71)	1.47 (1.29, 1.69)	1.29 (1.11, 1.49)
No	1886 (56.52)	10,929 (68.29)	1.13 (0.93, 1.37)	0.89 (0.73, 1.09)
Renal disease				
Yes	97 (2.91)	218 (1.36)	1.65 (0.87, 3.13)	1.54 (0.79, 2.98)
No	15,786 (97.09)	3240 (98.64)	1.55 (1.39, 1.73)	1.22 (1.08, 1.36)
Hepatic disease				
Yes	1487 (44.56)	5478 (34.23)	1.43 (1.22, 1.68)	1.24 (1.05, 1.46)
No	1850 (55.44)	10,526 (65.77)	1.60 (1.39, 1.85)	1.24 (1.06, 1.44)
Cardiovascular disease				
Yes	2238 (67.07)	8786 (54.90)	1.41 (1.23, 1.61)	1.18 (1.02, 1.36)
No	1099 (32.93)	7218 (45.10)	1.86 (1.57, 2.22)	1.37 (1.13, 1.65)
Malignant neoplasm				
Yes	828 (24.81)	4077 (25.47)	1.70 (1.43, 2.03)	1.35 (1.12, 1.62)
No	2509 (75.19)	11,927 (74.53)	1.52 (1.32, 1.74)	1.18 (1.02, 1.37)
Charlson comorbidity index level				
0	210	2474	0.88	0.69
1–2	686	3811	1.24	0.98
>3	2441	9719	1.48	1.30

* Standard (unconditional logistic regression) analysis adjusted for the use of benzodiazepine, other opioids, anesthetics, hypnotics, CYP2D6 inducer, CYP3A4 inducer, and the Charlson comorbidity index level.
CI = confidence interval, OR = odds ratio.

Table 5

Sensitivity analysis of codeine use by different time window.

Current exposure period	Cases (n = 19,341)	Controls (n = 185,700)	Crude OR (95% CI)*	Adjusted OR (95% CI)*,†
0–15 d				
Yes	1213 (6.27)	6364 (3.43)	1.91 (1.79–2.03)	1.02 (0.92–1.12)
No	18,128 (93.73)	179,336 (96.57)		
P for trend			<.0001	.76
0–30 d				
Yes	2168 (11.21)	11,273 (6.07)	1.99 (1.89–2.09)	1.08 (1.00–1.16)
No	17,173 (88.79)	174,427 (93.93)		
P for trend			<.0001	.049
0–60 days				
Yes	3411 (17.64)	18,962 (10.21)	1.93 (1.85–2.02)	1.07 (1.01–1.14)
No	15,930 (82.36)	166,738 (89.79)		
P for trend			<.0001	.031

* Cases and controls were matched according to age group, sex, baseline comorbidities, and year of death.
† Matched (conditional logistic regression) analysis adjusted for the use of benzodiazepine, other opioids, anesthetics, hypnotics, CYP2D6 inducer, CYP3A4 inducer, and the Charlson comorbidity index level.
CI = confidence interval, OR = odds ratio.

or no effect. [42] There are ethnic differences in the CYP2D6 genotype of ultrarapid metabolizers that are estimated to be 1% to 2% for those of Chinese, Japanese and Hispanic descent, 3% to 4% in African Americans and 1% to 10% in Caucasians.[13] This could provide a possible explanation to the null association of codeine use and death risk of the total population (Asian) of this study.

Therefore, codeine is contraindicated in all patients of any age known to be CYP2D6 ultra-rapid metabolizers.[16] This was described in a case published in 2009 concerning a 2-year-old child who died following an adenotonsillectomy after having codeine prescription the following day, and who was later confirmed as an ultra-rapid metabolizer.[12] In a case series reporting the deaths of 2 children who were later confirmed ultra-rapid metabolizers, developed toxicity within 1 to 2 days after a typical dose of codeine treatment as well.[33]

The strengths of this study are that it used a representative, nationwide population-based sample, with a relatively low risk of selection and recall bias, containing diagnosis, treatment, birth, death, and health promotion data provided by the National Health Insurance Service. This is the single insurer operated by Korean government, which is compulsory for all residents to enroll by law and to have any medical services insured.[23] In addition, this study controlled confounders through matching and statistical adjustment, and had overall sufficient statistical power to analyze the data robustly. Finally, this study provided information on the risk of death associated with codeine use in various subgroups, in relation to age, sex, underlying disease, concomitant medication, and cause of death.

This study has several limitations. First, the exact date of death was not available (only the month and year were reported). Since we assumed that the date of death was the 15th day of the month, this may have affected the 30-day time window for codeine exposure used in the analysis. However, to overcome this limitation, we conducted a sensitivity analysis by varying the time window by 15 and 60 days and obtained similar results. Second, the mortality risk associated with codeine use has been attributed to respiratory depression especially with over dose; however, we were not able to evaluate codeine dose concerning death risk. However, due to the large body of codeine products were prescribed for antitussive cough medications which contains low dose of codeine, we assumed that most of the codeine prescriptions were within the normal dose range. Also, due to the characteristics of secondary information from population-based data, our study was dependent on the context and structure of national health claims database which did not indicate the exact cause of death, drug indication or did not include the information of over the counter drugs. Another limitation was that we could not evaluate the effect of concomitant drugs which alter the metabolism of codeine via hepatic CYP enzyme activities, due to the small number of patients with concomitant use of these drugs.

However, these findings are potentially important requiring further studies to confirm our novel findings and reveal mechanisms of the effects of codeine in increased mortality associated with certain risk groups.

In conclusion, this study demonstrated that though no statistically significant associations were found between codeine exposure and mortality among the total population, the elderly and patients with respiratory disease had a slight but significant increase in mortality with codeine exposure.

Author contributions

Ju-Young Shin and Sohyun Jeong had the original idea for the study, all co-authors, carried out the design. Ha jin Tchoe and Sohyun Jeong drafted the original manuscript, which was revised by all authors. Jin Hyun Nam provided advanced statistical methods. All authors read and approved the final manuscript.

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