

Online Supplement 2

Results of long-term care resident cohort analysis

Community-dwelling older adults and older adults living in long-term care facilities were examined separately for several reasons: long-term care residents tend to be more frail than the general population; long-term care residents have different provider care access; and, opioids are more frequently used in suboptimal ways among individuals with COPD in long-term care versus the community [1]. We used the same methods to examine adverse respiratory outcomes in the long-term care cohort as we did for the community-dwelling cohort.

A total of 14,749 long-term care residents with COPD who were 66 years and older were identified between April 1, 2007 and March 31, 2012, 61.1% of whom received a new opioid (Table 1 in this supplement). Baseline demographic and health characteristics associated with new opioid users and controls are described in Table 1. Baseline characteristics were well-balanced among new opioid users and controls following propensity score weighting, with standardized differences below 10% for all variables.

In the overall cohort, compared to controls, new users were associated with significantly increased risk for ER visits for COPD or pneumonia (HR 2.13, 95% CI 1.35-3.38), COPD or pneumonia-related mortality (HR 2.32, 95% CI 1.74-3.11) and all-cause mortality (HR 3.18, 95% CI 2.77-3.66) (Table 2 in this Supplement). No significant associations between new opioid use and other adverse outcomes were observed. These results are similar to the community-dwelling cohort, with the exception that the association with outpatient respiratory exacerbations was not significantly reduced among new users living in long-term care.

Among users of combination opioid/non-opioid agents versus controls, significantly increased associations with ER visits (HR 2.70, 95% CI 1.70-4.27) and hospitalizations (HR 1.35, 95% CI 1.04-1.76) for COPD or pneumonia were found, as well as COPD or pneumonia-

related mortality (HR 1.95, 95% CI 1.43-2.66) and all-cause mortality (HR 2.47, 95% CI 2.13-2.87) (Table 3 in this Supplement). Among users of opioid-only agents compared to controls, increased associations with COPD or pneumonia-related mortality (HR 2.94, 95% CI 2.11-4.10) and all-cause mortality (HR 4.72, 95% CI 4.06-5.48) were observed, but no significant associations were identified for any of our other adverse respiratory outcomes. This pattern of results among long-term care residents stands in contrast to what was observed for the community-dwelling cohort, where adverse respiratory outcomes were predominantly observed among users of opioid-only agents and less so for combination opioid/non-opioid formulations. However, this discrepancy may be explained by the fact that residents of long-term care homes are frailer than community-dwelling older adults, and therefore, may be more vulnerable to potential adverse effects of the generally less potent combination opioid/non-opioid agents. Since about 75% of new opioid use among older long-term care residents with COPD is in the form of combination opioid/non-opioid agents [1], and the overall cohort size of the long-term care resident group was substantially smaller than the community-dwelling group (about one-tenth the size), our long-term care resident group analysis was possibly under-powered to detect adverse respiratory effects associated with generally more potent opioid-only agent use.

No significant associations were observed between use of either shorter-acting or long-acting opioid-only agents and outpatient or inpatient-related respiratory exacerbations (Table 4 in this Supplement). Both short-acting and longer-acting opioid-only drugs were associated with greater COPD and pneumonia-related mortality (shorter-acting agents: HR 2.69, 95% CI 1.88-3.84); longer-acting agents: HR 4.09, 95% CI 2.34-7.16) and all-cause mortality (shorter-acting agents: HR 4.23, 95% CI 3.60-4.97; longer-acting agents: HR 7.48; 95% CI 5.99-9.32). Although in the community-dwelling cohort, shorter-acting and long-acting opioid-only agents

were associated with increased respiratory exacerbations, as a result of its substantially smaller cohort size, the long-term care resident analysis was possibly under-powered to detect a similar pattern of results.

Among recipients of caffeine-containing opioids, there were associations with increased outpatient exacerbations (HR 1.23; 95% CI 1.01-1.49), ER visits for COPD or pneumonia (HR 2.75; 95% CI 1.72-4.38), and hospitalizations for COPD and pneumonia (HR 1.32; 95% CI 1.01-1.74) relative to controls (Table 5 in this Supplement). These morbidity outcomes were not significantly elevated among users of non-caffeine-containing opioids. Although in the community-dwelling cohort associations with increased adverse respiratory morbidity outcomes were identified among non-caffeine-containing opioid recipients, frailer long-term care residents may be more vulnerable to the potential adverse effects of the generally less potent combination opioid/non-opioid formulations than community-dwelling older adults, and these combination agents are the most frequently used opioid type among long-term care residents [1]. Associations with increased COPD or pneumonia-related and all-cause mortality were observed with use of both caffeine-containing (HR 1.93; 95% CI 1.40-2.66 and HR 2.46; 95% CI 2.12-2.86, respectively) and non-caffeine-containing (HR 2.69; 95% CI 1.96-3.70 and HR 4.12, 95% CI 3.55-4.79, respectively) opioids relative to controls, with the hazard ratios for mortality being relatively higher among the subgroup of opioid recipients lacking the potentially protective effect of added caffeine.

Compared to controls, users of longer-acting opioid-only agents of ≤ 30 mg of morphine equivalents per day were associated with significantly decreased risk for outpatient exacerbations (HR 0.37; 95% CI 0.15-0.97), but increased risk for COPD or pneumonia-related mortality (HR

2.74; 95% CI 1.23-6.11) and all-cause mortality (HR 6.65; 95% CI 4.94-8.97) (Table 6 in this Supplement). Similarly, among users of longer-acting of opioid-only agents of >30 mg of morphine equivalents per day, there were associations with decreased outpatient exacerbations (HR 0.34; 95% CI 0.16-0.73), but greater COPD or pneumonia-related mortality (HR 6.69; 95% CI 3.03-14.78) and all-cause mortality (HR 8.44; 95% CI 6.10-11.68). Associations with other adverse outcomes were non-significant among longer-acting opioid-only agent users, regardless of dose. Compared to controls, users of shorter-acting opioid-only agents of \leq 30 mg of morphine equivalents per day were associated with significantly increased risk for COPD or pneumonia-related mortality (HR 2.47; 95% CI 1.66-3.69) and all-cause mortality (HR 4.18; 95% CI 3.47-5.03). Users of shorter-acting opioid-only agents of >30 mg of morphine equivalents per day also were associated with greater COPD or pneumonia-related mortality (HR 3.21; 95% CI 1.91-5.38) and all-cause mortality (HR 4.64; 95% CI 3.76-5.72). Associations with other adverse outcomes were non-significant among shorter-acting opioid-only agent users, regardless of dose. A possible explanation for why non-mortality adverse respiratory outcomes were either decreased or non-significant in these dosing sensitivity analyses is because of the increased and competing risk of death, in the setting of small sample sizes.

In the subgroup of individuals with 0 exacerbations in the year prior to index, new users relative to controls were associated with significantly increased risk for ER visits for COPD or pneumonia (HR 3.47, 95% CI 1.50-8.04) (Table 7 in this Supplement). No other significant associations were observed between opioid use and non-mortality outcomes, distinguishing by COPD exacerbation history. Across all COPD exacerbation frequency subgroups, new versus non-users were associated with significantly increased COPD or pneumonia-related mortality (0 exacerbations in the year prior to index: HR 3.00; 95% CI 1.87-4.80; \geq 1 outpatient

exacerbation in the year prior to index: HR 2.64; 95% CI 1.11-6.28; ≥ 1 exacerbation requiring presentation to hospital: HR 1.80; 95% CI 1.20-2.70). The association with all-cause mortality was also greater among new versus non-users across all COPD exacerbation frequency subgroups (0 exacerbations in the year prior to index: HR 3.94, 95% CI 3.24-4.80; ≥ 1 outpatient exacerbation in the year prior to index: HR 4.54, 95% CI 2.86-7.20; ≥ 1 exacerbation requiring presentation to hospital: HR 2.20, 95% CI 1.77-2.73). The findings of increased ER visits for COPD or pneumonia and mortality in the healthiest subgroup of individuals with COPD supports that our overall findings are robust.

After having excluded individuals with comorbid lung cancer, among new opioid users versus controls, significantly increased associations were observed for ER visits (HR 2.07; 95% CI 1.30-3.29) and hospitalizations (HR 1.31; 95% CI 1.02-1.67) for COPD or pneumonia, as well as COPD or pneumonia-related mortality (HR 2.27; 95% CI 1.69-3.03) and all-cause mortality (HR 3.24; 95% CI 2.82-3.72) (Table 8 in this Supplement). Significant associations were not found with other adverse outcomes. After excluding individuals with any cancer, significantly increased associations with ER visits (HR 1.97; 95% CI 1.23-3.16) and hospitalizations (HR 1.35; 95% CI 1.05-1.74) for COPD or pneumonia, as well as COPD or pneumonia-related mortality (HR 2.27; 95% CI 1.69-3.06) and all-cause mortality (HR 3.29; 95% CI 2.86-3.80) remained among new opioid users compared to controls (Table 9 in this Supplement). Significant associations were not found with other adverse outcomes.

References

1. Vozoris NT, Wang X, Fischer HD, Gershon AS, Bell CM, Gill SS, O'Donnell DE, Austin PC, Stephenson AL, Rochon PA. Incident opioid drug use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. *Br J Clin Pharmacol* 2016; 81: 161-70.

	Before propensity score weighting			After propensity score weighting		
	New opioid users	Controls	Standardized difference	New opioid users	Controls	Standardized difference
	N=9012	N=5737		N=9009	N=5738	
Age (mean + standard deviation)	84.2 ± 7.2	85.0 ± 7.4	0.11	84.5 ± 7.2	84.5 ± 7.5	0.007
Female (%)	60.4	58.5	0.04	59.7	59.4	0.005
Low income based on ODB flag within 1 yr prior to the index date (%)	39.5	39.4	0.00	39.4	39.2	0.003
Income quintile (%)						
1 (lowest)	26.0	26.1	0.00	26.0	26.1	0.001
2	19.3	19.7	0.01	19.5	19.6	0.0002
3	19.6	18.7	0.02	19.2	19.5	0.006
4	18.2	18.6	0.01	18.4	18.2	0.005
5 (highest)	16.4	16.4	0.00	16.3	16.3	0.002
Missing data	0.5	0.5	0.00	0.5	0.5	0.002
Rural setting (%)	18.8	16.1	0.07	17.7	17.8	0.002

COPD exacerbation frequency past year (%)							
0 exacerbations	63.6	62.6	0.02	63.3	62.9	0.006	
>=1 outpatient exacerbations	10.3	11.7	0.05	10.8	10.7	0.005	
>=1 exacerbations requiring presentation to hospital	26.1	25.7	0.01	25.9	26.4	0.01	
COPD exacerbation in past 30 days (%)	8.3	9.4	0.04	8.6	8.9	0.01	
(Table 1 continued)	Before propensity score weighting			After propensity score weighting			
Baseline characteristics	New opioid users	Controls	Standardized difference	New opioid users	Controls	Standardized difference	
Duration of COPD prior to index date (%)							
< 2 years	21.7	31.7	0.23	25.7	26.4	0.02	
2-5 years	19.4	17.1	0.06	18.5	18.5	0.001	
> 5 years	59.0	51.2	0.16	55.8	55.1	0.01	
Medications in past 180 days (%)							
Short/long-acting beta agonists	39.0	37.0	0.04	38.2	38.9	0.01	
Short/long-acting anticholinergics	41.2	39.2	0.04	40.5	40.8	0.007	
Inhaled corticosteroids	17.0	16.4	0.02	16.7	17.0	0.008	
Combination inhaled corticosteroid-long acting beta agonist inhalers	25.9	22.3	0.08	24.5	24.6	0.003	
Oral corticosteroids	12.7	11.2	0.04	12.1	12.2	0.005	
Theophylline	1.8	1.7	0.01	1.8	1.8	0.005	
Respiratory antibiotics	53.4	52.1	0.03	53.0	53.4	0.01	
Any outpatient visits past 12 months (%)	95.3	92.6	0.12	94.2	94.2	0.001	
Any hospitalizations past 12 months (%)	52.6	46.8	0.12	50.5	51.4	0.02	

Any ICU admissions past 12 months (%)	7.8	6.5	0.05	7.4	8.0	0.03	
Any surgery past 12 months (%)	16.1	4.8	0.36	11.7	11.7	0.0001	
Total number of non-opioid drugs received in the past year (mean + standard deviation)	15.1 ± 6.9	14.4 ± 6.4	0.11	14.9 ± 6.8	15.1 ± 6.6	0.03	
Incident benzodiazepine receipt past 30 days (%)	5.9	4.5	0.06	5.4	5.1	0.01	
(Table 1 continued)	Before propensity score weighting			After propensity score weighting			
Baseline characteristics	New opioid users	Controls	Standardized difference	New opioid users	Controls	Standardized difference	
Prevalent benzodiazepine receipt past 30 days (%)	29.2	23.1	0.14	26.9	26.9	0.001	
Charlson score (%)							
0	12.8	11.1	0.05	12.1	11.8	0.01	
1	18.3	18.6	0.01	18.4	18.3	0.002	
2	18.4	19.2	0.02	18.7	18.8	0.001	
> 3	41.4	38.3	0.06	40.3	40.9	0.01	
Missing data	9.2	12.9	0.12	10.5	10.2	0.008	
Ischemic heart disease† (%)	49.7	43.8	0.12	47.5	47.8	0.007	
Congestive heart failure† (%)	47.4	44.5	0.06	46.2	46.3	0.003	
Any malignancy† (%)	8.1	5.2	0.12	7.0	7.1	0.005	
Musculoskeletal/connective tissue disease† (%)	85.3	79.3	0.16	83.2	83.1	0.0007	

Osteoporosis† (%)	16.6	14.5	0.06	15.9	15.9	0.002	
Psychotic psychiatric disease† (%)	21.8	23.6	0.04	22.5	22.6	0.002	
Non-psychotic psychiatric disease† (%)	59.6	58.8	0.02	59.3	59.2	0.003	
Sleep disorder† (%)	50.5	48.7	0.04	49.8	50.3	0.009	
Dementia† (%)	73.7	81.9	0.20	76.8	76.8	0.0009	
Cohort entry in flu season (%)	38.8	35.5	0.07	37.4	37.8	0.008	

* Standardized differences of > 0.10 are thought to indicate potentially meaningful differences.

† Presence of all comorbidities was based on 5-year look-back from the index date.

Table 2. Hazard ratios and confidence intervals for adverse respiratory outcomes among propensity score weighted long-term care resident cohort

Outcomes	Status of opioid use	Number (%) of events	HR (95% CI)	p-value	
Outpatient respiratory exacerbations	New opioid users	397 (4.4%)	1.06 (0.89-1.27)	0.52	
	Controls	238 (4.2%)	referent		
ER visits for COPD or pneumonia	New opioid users	96 (1.1%)	2.13 (1.35-3.38)	0.001	
	Controls	29 (0.5%)	referent		
Hospitalizations for COPD or pneumonia	New opioid users	226 (2.5%)	1.28 (1.00-1.65)	0.05	
	Controls	112 (2.0%)	referent		
ICU admissions during hospitalizations or COPD or pneumonia	New opioid users	19 (0.2%)	0.92 (0.40-2.12)	0.84	
	Controls	13 (0.2%)	referent		
COPD or pneumonia-related mortality	New opioid users	210(2.3%)	2.32(1.74-3.11)	<.0001	

	Controls	61(1.1%)			
All-cause mortality	New opioid users	1265 (14.0%)	3.18 (2.77-3.66)	<.0001	
	Controls	268 (4.7%)	referent		

Opioid drug type	Opioid use status	Outpatient respiratory exacerbations			ER visits for COPD or pneumonia			Hospitalizations for COPD or pneumonia			ICU admissions during hospitalizations for COPD or pneumonia			COPD or pneumonia-related mortality			All-cause mortality		
		Number (% of events)	HR(95% CI)	p-value	Number (% of events)	HR(95% CI)	p-value	Number (% of events)	HR(95% CI)	p-value	Number (% of events)	HR(95% CI)	p-value	Number (% of events)	HR(95% CI)	p-value	Number (% of events)	HR(95% CI)	p-value
Opioid-only formulation	New users	116(4.1%)	0.98(0.76,1.26)	0.87	16(0.6%)	1.10(0.59,2.06)	0.77	64(2.2%)	1.16(0.84,1.61)	0.37	8(0.3%)	1.26(0.47,3.42)	0.64	87(3.1%)	2.94(2.11,4.10)	<.0001	595(20.9%)	4.72(4.06,5.48)	<.0001
	Controls	238(4.1%)	referent		29(0.5%)	referent		112(1.9%)	referent		12(0.2%)	referent		66(1.1%)	referent		281(4.9%)	referent	
Combination opioid/non-opioid formulation	New users	287(4.7%)	1.14(0.94,1.38)	0.17	78(1.3%)	2.70(1.70,4.27)	<.0001	157(2.6%)	1.35(1.04,1.76)	0.03	10(0.2%)	0.78(0.31,1.92)	0.58	121(2.0%)	1.95(1.43,2.66)	<.0001	675(11.0%)	2.47(2.13,2.87)	<.0001
	Controls	234(4.1%)	referent		27(0.5%)	referent		109(1.9%)	referent		12(0.2%)	referent		60(1.0%)	referent		264(4.6%)	referent	

Opioid drug half-life type	Opioid use status	Outpatient respiratory exacerbations			ER visits for COPD or pneumonia			Hospitalizations for COPD or pneumonia			ICU admissions during hospitalizations for COPD or pneumonia			COPD or pneumonia-related mortality			All-cause mortality		
		Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value
Shorter-acting opioid-only formulation	New users	102(4.5%)	1.08(0.82,1.43)	0.56	13(0.6%)	1.17(0.61,2.25)	0.63	46(2.0%)	1.05(0.73,1.51)	0.80	6(0.3%)	1.37(0.50,3.78)	0.54	64(2.9%)	2.69(1.88,3.84)	<.0001	428(19.0%)	4.23(3.60,4.97)	<.0001
	Controls	240(4.2%)	referent		29(0.5%)	referent		111(1.9%)	referent		12(0.2%)	referent		67(1.2%)	referent		282(4.9%)	referent	
Longer-acting opioid-only formulation	New users	10(1.6%)	0.40(0.23,0.69)	0.001	<6*	0.38(0.08,1.70)	0.21	18(2.9%)	1.60(0.86,2.98)	0.14	<6*	0.64(0.08,5.03)	0.67	24(4.0%)	4.09(2.34,7.16)	<.0001	184(30.6%)	7.48(5.99,9.32)	<.0001
	Controls	228(4.0%)	referent		27(0.5%)	referent		104(1.8%)	referent		10(0.2%)	referent		66(1.1%)	referent		279(4.9%)	referent	

*Percentages are not presented, according to Institute of Clinical Evaluative Sciences reporting rules, because of small cell size.

Opioid drug type	Opioid use status	Outpatient respiratory exacerbations			ER visits for COPD or pneumonia			Hospitalizations for COPD or pneumonia			ICU admissions during hospitalization for COPD or pneumonia			COPD or pneumonia-related mortality			All-cause mortality		
		Number (%) of events	HR (95% CI)	p-value	Number (%) of events	HR (95% CI)	p-value	Number (%) of events	HR (95% CI)	p-value	Number (%) of events	HR (95% CI)	p-value	Number (%) of events	HR (95% CI)	p-value	Number (%) of events	HR (95% CI)	p-value
Caffeine-containing opioid	New users	251(5.0%)	1.23(1.01,1.49)	0.04	65(1.3%)	2.75(1.72,4.38)	<.0001	124(2.5%)	1.32(1.01,1.74)	0.04	8(0.2%)	0.79 (0.31-2.04)	0.62	99(2.0%)	1.93(1.40,2.66)	<.0001	551(10.9%)	2.46(2.12,2.86)	<.0001
	Controls	232(4.0%)	referent		27(0.5%)	referent		107(1.9%)	referent		11(0.2%)			60(1.1%)	referent		264(4.6%)	referent	
Non-caffeine-containing opioid	New users	151(3.8%)	0.91(0.72,1.14)	0.40	30(0.8%)	1.47(0.85,2.54)	0.16	98(2.5%)	1.24(0.93,1.67)	0.15	10(0.3%)	1.11 (0.43-2.87)	0.82	111(2.8%)	2.69(1.96,3.70)	<.0001	730(18.5%)	4.12(3.55,4.79)	<.0001
	Controls	242(4.2%)	referent		30(0.5%)	referent		115(2.0%)	referent		11(0.2%)			65(1.1%)	referent		281(4.9%)	referent	

Table 6. Hazard ratios and confidence intervals for adverse respiratory outcomes among propensity score weighted long-term care resident cohort, distinguishing by opioid drug dose																			
Opioid drug dose category	Opioid use status	Outpatient respiratory exacerbations			ER visits for COPD or pneumonia			Hospitalizations for COPD or pneumonia			ICU admissions during hospitalizations for COPD or pneumonia			COPD or pneumonia-related mortality			All-cause mortality		
		Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value	Number (%) of events	HR(95% CI)	p-value
Longer-acting opioid-only agents*																			
<= 30 mg of morphine equivalents per day	New users	<6‡	0.37(0.15,0.97)	0.04	<6‡	0.27(0.04,2.01)	0.20	12(4.2%)	2.36(0.95,5.88)	0.06	<6‡	0.00(0.00,0.00)	<.0001	8(2.7%)	2.74(1.23,6.11)	0.01	79(27.5%)	6.65(4.94,8.97)	<.0001
	Controls	228(4.0%)	referent		27(0.5%)	referent		104(1.8%)	referent		10(0.2%)	referent		66(1.2%)	referent		280(4.9%)	referent	
> 30 mg of morphine equivalents per day	New users	<6‡	0.34(0.16,0.73)	0.005	<6‡	0.28(0.04,2.09)	0.22	6(1.8%)	1.02(0.39,2.66)	0.98	<6‡	0.80(0.10,6.31)	0.83	23(6.5%)	6.69(3.03,14.78)	<.0001	117(33.9%)	8.44(6.10,11.68)	<.0001
	Controls	228(4.0%)	referent		27(0.5%)	referent		104(1.8%)	referent		10(0.2%)	referent		66(1.2%)	referent		278(4.9%)	referent	
Shorter-acting opioid-only agents†																			
<= 30 mg of morphine equivalents per day	New users	65(4.8%)	1.16(0.80,1.67)	0.44	9(0.6%)	1.28(0.61,2.69)	0.51	28(2.1%)	1.09(0.70,1.72)	0.70	<6‡	1.29(0.42,3.99)	0.65	36(2.6%)	2.47(1.66,3.69)	<.0001	254(18.7%)	4.18(3.47,5.03)	<.0001
	Controls	228(4.0%)	referent		27(0.5%)	referent		104(1.8%)	referent		10(0.2%)	referent		66(1.2%)	referent		278(4.9%)	referent	

>=1 outpatient respiratory exacerbations in the year prior to index	New users	116(12.5%)	1.25(0.90,1.73)	0.18	12(1.3%)	1.58(0.57,4.38)	0.38	30(3.3%)	1.25(0.64,2.46)	0.51	<6*	1.10(0.10,12.16)	0.94	30(3.2%)	2.64(1.11,6.28)	0.03	138(15.0%)	4.54(2.86,7.20)	<.0001
	Controls	68(10.1%)	referent		6(0.8%)	referent		18(2.6%)	referent		<6*	referent		9(1.3%)	referent		24(3.5%)	referent	
>=1 exacerbations requiring presentation to hospital in the year prior to index	New users	144(6.1%)	0.90(0.68,1.20)	0.47	45(1.9%)	1.80(0.94,3.42)	0.07	106(4.5%)	1.14(0.80,1.62)	0.47	10(0.4%)	1.23(0.33,4.56)	0.76	90(3.8%)	1.80(1.20,2.70)	0.004	384(16.3%)	2.20(1.77,2.73)	<.0001
	Controls	100(6.8%)	referent		16(1.1%)	referent		58(4.0%)	referent		<6*	referent		33(2.2%)	referent		116(7.9%)	referent	

*Percentages are not presented, according to Institute of Clinical Evaluative Sciences reporting rules, because of small cell size.

Table 8. Hazard ratios and confidence intervals for adverse respiratory outcomes among propensity score weighted long term care resident cohort, excluding individuals with pre-existing lung cancer					
Outcomes	Status of opioid use	Number (%) of events	HR (95% CI)	p-value	
Outpatient respiratory exacerbations	New opioid users	390(4.4%)	1.07(0.90,1.28)	0.44	
	Controls	233(4.1%)	referent		
ER visits for COPD or pneumonia	New opioid users	94(1.1%)	2.07(1.30,3.29)	0.002	
	Controls	29(0.5%)	referent		
Hospitalizations for COPD or pneumonia	New opioid users	221(2.5%)	1.31(1.02,1.67)	0.03	
	Controls	109(1.9%)	referent		
ICU admissions during hospitalizations for COPD or pneumonia	New opioid users	19(0.2%)	0.96(0.42,2.18)	0.93	
	Controls	12(0.2%)	referent		
COPD or pneumonia-related mortality	New opioid users	206(2.3%)	2.27(1.69,3.03)	<.0001	
	Controls	62(1.1%)	referent		
All-cause mortality	New opioid users	1238(13.9%)	3.24(2.82,3.72)	<.0001	
	Controls	259(4.6%)	referent		

Table 9. Hazard ratios and confidence intervals for adverse respiratory outcomes among propensity score weighted long term care resident cohort, excluding individuals with any pre-existing malignancy					
Outcomes	Status of opioid use	Number (%) of events	HR (95% CI)	p-value	
Outpatient respiratory exacerbations	New opioid users	365(4.4%)	1.06(0.88,1.28)	0.51	
	Controls	225(4.1%)	referent		
ER visits for COPD or pneumonia	New opioid users	86(1.0%)	1.97(1.23,3.16)	0.005	
	Controls	29(0.5%)	referent		
Hospitalizations for COPD or pneumonia	New opioid users	209(2.5%)	1.35(1.05,1.74)	0.02	
	Controls	102(1.9%)	referent		
ICU admissions during hospitalizations for COPD or pneumonia	New opioid users	17(0.2%)	1.04(0.44,2.48)	0.92	
	Controls	10(0.2%)	referent		
COPD or pneumonia-related mortality	New opioid users	196(2.4%)	2.27(1.69,3.06)	<.0001	
	Controls	60(1.1%)	referent		
All-cause mortality	New opioid users	1148(13.9%)	3.29(2.86,3.80)	<.0001	
	Controls	242(4.5%)	referent		

