Appendix
Association Between Buprenorphine for Opioid Use Disorder and Mortality Risk
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<u>**Supplemental Online Content**</u>
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Appendix Methods 1. ICD-10 Diagnostic Codes Used in Classifying Cause-Specific Mortality Outcomes	
Cause-Specific Outcome	ICD-10 Codes
Opioid-specific	T40.0, T40.1, T40.2, T40.3, T40.4, and T40.6
Overdose	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6, X40, X41, X42, X43, X44, X60, X61, X62, X63, X64, X85, Y10, Y11, Y12, Y13, or Y14
Suicide	X60-X84

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Appendix Table 1. Baseline Characteristics of Veterans Treated for OUD with Buprenorphine and Associations with Mortality in the VHA, 2008-2017

Demographics and Clinical Measures	Suicide/Overdose		Suicide		Overdose		Opioid-Related Death		All-Cause Death	
	uHR	95% CI	uHR	95% CI	uHR	95% CI	uHR	95% CI	uHR	95% CI
Gender										
Female	Ref		Ref		Ref		Ref		Ref	
Male	1.39	1.04, 1.87	1.76	0.72, 4.31	1.31	0.97, 1.76	1.50	1.03, 2.19	1.67	1.36, 2.06
Age (Years)										
18-24	1.70	1.09, 2.66	0.99	0.37, 2.67	1.84	1.12, 3.02	2.06	1.14, 3.73	0.25	0.19, 0.32
25-44	1.37	0.94, 2.01	0.81	0.37, 1.76	1.55	1.01, 2.39	1.66	0.99, 2.79	0.25	0.21, 0.89
45-64	1.12	0.76, 1.65	0.48	0.21, 1.07	1.31	0.85, 2.01	1.32	0.78, 2.23	0.51	0.44, 0.59
≥65	Ref		Ref		Ref		Ref		Ref	
Race										
White	Ref		Ref		Ref		Ref		Ref	
Black	0.60	0.47, 0.75	0.05	0.01, 0.38	0.67	0.53, 0.85	0.80	0.62, 1.03	1.24	1.11, 1.40
Other	0.74	0.46, 1.20	0.60	0.15, 2.44	0.73	0.44, 1.22	0.71	0.38, 1.32	0.82	0.60, 1.12
Unknown/Missing	1.08	0.79, 1.47	1.07	0.47, 2.43	1.10	0.79, 1.52	1.29	0.90, 1.85	1.54	1.28, 1.84
Ethnicity										
Hispanic	Ref		Ref		Ref		Ref		Ref	
Non-Hispanic	1.49	1.04, 2.08	1.19	0.52, 2.70	1.62	1.12, 2.33	1.56	1.02, 2.38	1.10	0.91, 1.33
Unknown/Missing	1.78	1.10, 2.89	1.07	0.27, 4.27	1.99	1.19, 3.34	2.14	1.18, 3.86	1.54	1.16, 2.04
Indication for Homelessness/Unstable Housing										
No	Ref		Ref		Ref		Ref		Ref	
Yes	1.76	1.55, 2.00	0.86	0.58, 1.27	1.92	1.68, 2.19	1.94	1.66, 2.28	1.55	1.43, 1.69
Residential Designation										
Urban	Ref		Ref		Ref		Ref		Ref	
Rural	0.76	0.61, 0.95	0.60	0.30, 1.18	0.77	0.61, 0.98	0.76	0.58, 1.00	0.83	0.73, 0.96
Unknown/Missing	2.61	1.71, 3.99	3.53	1.30, 9.56	2.38	1.49, 3.79	1.66	0.86, 3.21	3.64	2.87, 4.61
Distance to Closest Primary Care Facility										
0-19 miles	Ref		Ref		Ref		Ref		Ref	
≥20 miles	0.86	0.73, 1.00	1.39	0.95, 2.05	0.80	0.66, 0.93	0.74	0.60, 0.92	0.84	0.75, 0.93
Unknown/Missing	19.63	12.29, 31.37	26.06	8.22, 82.68	18.10	10.84, 30.22	11.63	5.51, 24.55	26.32	20.11, 34.45

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Appendix Table 1. Baseline Characteristics of Veterans Treated for OUD with Buprenorphine and Associations with Mortality in the VHA, 2008-2017

Demographics and Clinical Measures	Suicide/Overdose		Suicide		Overdose		Opioid-Related Death		All-Cause Death	
	uHR	95% CI	uHR	95% CI	uHR	95% CI	uHR	95% CI	uHR	95% CI
Distance to Closest Secondary Care Facility										
0-19 miles	Ref		Ref		Ref		Ref		Ref	
≥20 miles	0.85	0.75, 0.96	1.10	0.77, 1.57	0.80	0.70, 0.92	0.77	0.66, 0.90	0.85	0.78, 0.92
Unknown/Missing	9.25	5.85, 14.65	12.26	3.82, 39.32	8.47	5.14, 13.96	5.04	2.38, 10.67	12.24	9.39, 15.95
Drive Time to Closest Primary Care Facility										
0-29 minutes	Ref		Ref		Ref		Ref		Ref	
≥ 30 minutes	0.79	0.66, 0.95	1.14	0.74, 1.77	0.75	0.62, 0.91	0.74	0.59, 0.93	0.83	0.74, 0.93
Unknown/Missing	19.54	12.23, 31.21	24.55	7.76, 77.72	18.18	10.89, 30.36	11.77	5.58, 24.84	26.49	20.24, 34.66
Drive Time to Closest Secondary Care Facility										
0-29 minutes	Ref		Ref		Ref		Ref		Ref	
≥ 30 minutes	0.85	0.75, 0.97	0.92	0.65, 1.31	0.83	0.73, 0.95	0.80	0.69, 0.94	0.87	0.80, 0.94
Unknown/Missing	9.36	5.92, 14.80	11.17	3.50, 35.49	8.71	5.29, 14.34	5.22	2.47, 10.04	12.49	9.60, 16.27
Treatment Initiation Era										
2008-2009	Ref		Ref		Ref		Ref		Ref	
2010-2011	1.11	0.90, 1.36	0.77	0.46, 1.31	1.18	0.94, 1.47	1.23	0.93, 1.63	0.87	0.77, 0.98
2012-2013	1.34	1.10, 1.64	0.82	0.49, 1.37	1.43	1.15, 1.77	1.68	1.29, 2.19	0.98	0.87, 1.11
2014-2015	1.75	1.41, 2.16	1.11	0.64, 1.92	1.88	1.50, 2.36	2.34	1.77, 3.09	1.04	0.91, 1.19
2016-2017	1.91	1.44, 2.54	1.47	0.73, 2.97	2.03	1.50, 2.76	2.51	1.74, 3.61	1.23	1.02, 1.48
Clinical Characteristics (Ref = No)										
Co-morbidities										
AIDS/HIV	1.30	0.74, 2.30	***	***	1.15	0.82, 2.56	1.53	0.79, 2.95	2.27	1.71, 3.01
Cardiac arrhythmia	0.98	0.76, 1.27	0.82	0.38, 1.76	1.05	0.80, 1.36	0.99	0.72, 1.37	1.51	1.32, 1.74
Chronic obstructive pulmonary disease	1.18	0.99, 1.41	0.62	0.34, 1.15	1.26	1.05, 1.52	1.22	0.98, 1.52	1.97	1.79, 2.18
Congestive heart failure	1.29	0.85, 1.95	0.41	0.06, 2.95	1.44	0.95, 2.18	1.41	0.86, 2.32	3.49	2.94, 4.14
Diabetes (with complications)	1.36	0.95, 1.94	0.96	0.31, 3.03	1.47	1.02, 2.11	1.37	0.88, 2.14	2.81	2.37, 3.32
Diabetes (without	1.08	0.86, 1.35	0.83	0.42, 1.63	1.12	0.89, 1.41	1.08	0.82, 1.42	2.01	1.79, 2.25

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Demographics and Clinical Measures	Suicide/Overdose		Suicide		Overdose		Opioid-Related Death		All-Cause Death	
	uHR	95% CI	uHR	95% CI	uHR	95% CI	uHR	95% CI	uHR	95% CI
complications)										
Hypertension (without complications)	1.08	0.94, 1.23	0.89	0.60, 1.30	1.12	0.97, 1.28	1.09	0.92, 1.29	2.00	1.84, 2.17
Hypertension (with complications)	1.62	0.97, 2.70	2.39	0.76, 7.52	1.45	0.82, 2.56	1.36	0.68, 2.72	2.93	2.28, 3.77
Liver disease	1.35	1.14, 1.59	0.87	0.52, 1.48	1.38	1.16, 1.64	1.52	1.25, 1.85	2.09	1.90, 2.30
Malignancy	0.86	0.56, 1.33	1.24	0.46, 3.37	0.77	0.48, 1.25	0.77	0.43, 1.36	2.26	1.89, 2.70
Myocardial infarction	0.77	0.37, 1.63	***	***	0.86	0.41, 1.81	1.22	0.58, 2.56	2.44	1.84, 3.21
Non-metastatic cancer	0.84	0.53, 1.35	1.06	0.34, 3.34	0.78	0.47, 1.30	0.81	0.45, 1.47	2.33	1.93, 2.82
Obesity	1.14	0.94, 1.37	0.89	0.50, 1.57	1.18	0.96, 1.43	1.14	0.90, 1.44	1.21	1.07, 1.36
Peripheral vascular disease	1.47	1.02, 2.13	2.32	1.02, 5.26	1.41	0.95, 2.10	1.10	0.65, 1.87	2.87	2.40, 3.43
Renal disease	1.20	0.75, 1.91	1.50	0.48, 4.72	1.19	0.73, 1.95	1.36	0.79, 2.36	2.72	2.21, 3.34
Weight loss	0.82	0.56, 1.21	0.47	0.12, 1.89	0.84	0.56, 1.27	0.79	0.48, 1.30	1.94	1.63, 2.30
Psychiatric Co-morbidities										
Attention-deficit/ Hyperactivity disorder	1.41	1.11, 1.81	2.07	1.17, 3.67	1.39	1.07, 1.81	1.45	1.07, 1.96	0.89	0.74, 1.09
Adjustment	1.26	1.07, 1.48	0.96	0.58, 1.58	1.30	1.09, 1.55	1.25	1.02, 1.54	1.06	0.95, 1.19
Anxiety disorder	1.47	1.28, 1.68	1.24	0.87, 1.78	1.50	1.30, 1.73	1.57	1.32, 1.85	1.08	0.99, 1.17
Bipolar disorder	1.51	1.31, 1.75	0.78	0.49, 1.26	1.61	1.39, 1.87	1.60	1.34, 1.91	1.16	1.05, 1.29
Depression	1.55	1.33, 1.82	1.60	1.03, 2.47	1.50	1.31, 1.83	1.47	1.21, 1.78	1.24	1.13, 1.37
Personality disorder	1.49	1.22, 1.81	1.77	1.06, 2.94	1.47	1.19, 1.82	1.43	1.11, 1.84	1.36	1.19, 1.55
Post-traumatic stress disorder	1.32	1.16, 1.50	1.39	0.98, 1.97	1.32	1.15, 1.51	1.36	1.16, 1.59	1.05	0.96, 1.14
Schizophrenia	1.34	1.06, 1.70	0.91	0.42, 1.95	1.40	1.10, 1.78	1.30	0.96, 1.75	1.36	1.17, 1.58
Other Substance Use Dependence										
Alcohol	1.50	1.32, 1.71	1.16	0.81, 1.65	1.52	1.33, 1.74	1.48	1.26, 1.74	1.43	1.32, 1.55
Stimulants	1.27	1.09, 1.47	0.68	0.42, 1.11	1.37	1.15, 1.56	1.43	1.20, 1.71	1.13	1.02, 1.24
Cannabis	1.14	0.94, 1.37	0.77	0.43, 1.40	1.15	0.94, 1.40	1.14	0.90, 1.43	0.98	0.87, 1.12
Cocaine	1.50	1.30, 1.73	0.44	0.24, 0.80	1.63	1.41, 1.89	1.72	1.44, 2.05	1.37	1.25, 1.51
Hallucinogen	1.71	0.81-3.60	***	***	1.91	0.91, 4.01	2.30	1.03, 5.15	0.83	0.41, 1.66
Nicotine	1.28	1.13, 1.45	1.01	0.71, 1.43	1.30	1.14, 1.49	1.27	1.08, 1.49	1.28	1.18, 1.40
Sedative	1.70	1.42, 2.05	1.01	0.54, 1.87	1.79	1.48, 2.17	1.74	1.39, 2.19	1.35	1.19, 1.54

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Demographics and Clinical Measures	Suicide/Overdose		Suicide		Overdose		Opioid-Related Death		All-Cause Death	
	uHR	95% CI	uHR	95% CI	uHR	95% CI	uHR	95% CI	uHR	95% CI
Recent Medication Use										
Antidepressants	1.41	1.23, 1.62	1.61	1.08, 2.39	1.39	1.20, 1.61	1.37	1.15, 1.63	1.27	1.16, 1.39
Antipsychotics	1.62	1.41, 1.85	1.48	1.02, 2.15	1.64	1.43, 1.90	1.55	1.31, 1.84	1.33	1.21, 1.46
Anxiolytics	1.29	1.14, 1.47	1.63	1.15, 2.30	1.27	1.11, 1.45	1.20	1.02, 1.41	1.27	1.17, 1.38
Mood Stabilizers	1.57	1.38, 1.78	1.27	0.89, 1.82	1.58	1.38, 1.80	1.48	1.26, 1.74	1.32	1.21, 1.43
Opioids	1.05	0.93, 1.20	0.97	0.68, 1.39	1.09	0.95, 1.24	1.02	0.87, 1.20	1.24	1.14, 1.35
Stimulants	1.45	1.08, 1.96	1.98	0.97, 4.05	1.48	1.08, 2.02	1.31	0.88, 1.94	0.89	0.70, 1.14
Healthcare Utilization										
Inpatient Admission										
Any reason	1.71	1.50, 1.94	1.32	0.94, 1.87	1.74	1.52, 1.99	1.71	1.46, 2.01	1.72	1.58, 1.87
Mental Health	1.71	1.50, 1.94	1.30	0.92, 1.84	1.75	1.53, 2.00	1.71	1.46, 2.01	1.64	1.51, 1.78
Suicide or Self harm	1.59	1.33, 1.90	2.18	1.40, 3.39	1.53	1.27, 1.86	1.45	1.15, 1.83	1.36	1.21, 1.54
Substance Use	1.70	1.50, 1.93	1.33	0.94, 1.88	1.74	1.53, 1.99	1.72	1.46, 2.01	1.55	1.43, 1.68
Urgent Care Use	1.45	1.25, 1.70	1.04	0.65, 1.66	1.51	1.29, 1.77	1.50	1.24, 1.81	1.15	1.04, 1.29
Emergency Department Use										
Suicide or Self harm	1.58	1.29, 1.94	2.00	1.20, 3.33	1.55	1.25, 1.93	1.36	1.04, 1.78	1.28	1.11, 1.48
Substance Use	1.44	1.26, 1.64	1.89	1.33, 2.67	1.40	1.22, 1.61	1.44	1.23, 1.70	1.25	1.15, 1.37

Appendix Table 1. Baseline Characteristics of Veterans Treated for OUD with Buprenorphine and Associations with Mortality in the VHA, 2008-2017

VHA = Veterans Health Administration; uHR = unadjusted hazard ratio; *** = Unable to compute hazard ratios due to small sample size

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Appendix Table 2. Follow-up Time, Deaths, and Incidence Rates by Type of MOUD among Veterans Initiating Buprenorphine Pharmacotherapy in the VHA, 2008-2017 (N=29,054)						
Type of Death	**Methadone** Total Person-Days = 258,355		**Naltrexone** Total Person-Days = 177,339		**Buprenorphine** Total Person-Days = 15,094,978	
	n	IR	n	IR	n	IR
Suicide/Overdose	11	4.26	13	7.33	142	0.94
Suicide	1	0.39	2	1.13	25	0.17
Overdose	10	3.87	11	6.20	121	0.80
Opioid-Related	7	2.71	10	5.64	87	0.58
All Cause Death	28	10.84	19	10.71	380	2.52

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; MOUD = Medications for OUD

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Appendix Table 3. Association between Treatment Status and Death with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)					
Treatment Status and Suicide/Overdose (n=964 Deaths)					
Treatment Status	Person Days at Risk	n	IR	uHR (95% CI)	aHR (95% CI)[a]
Treated	15,094,978	142	0.94	Ref	Ref
Not Treated Overall	20,191,645	822	4.07	4.61 (3.84, 5.54)	4.33 (3.60, 5.21)
Treated	15,094,978	142	0.94	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	543,673	28	5.15	5.13 (3.40, 7.75)	4.56 (3.01, 6.90)
8-14 days since last treatment	388,091	28	7.21	7.47 (4.95, 11.28)	6.54 (4.32, 9.91)
15-30 days since last treatment	708,080	26	3.67	3.95 (2.59, 6.04)	3.45 (2.25, 5.29)
>30 days since last treatment	18,551,801	740	3.99	4.51 (3.74, 5.43)	4.29 (3.55, 5.17)
Treatment Status and Suicide (n=128 Deaths)					
Treatment Status	Person Days at Risk	n	IR	uHR (95% CI)	aHR (95% CI)[b]
Treated	15,094,978	25	0.17	Ref	Ref
Not Treated Overall	20,191,645	103	0.51	3.53 (2.24, 5.58)	3.57 (2.25, 5.66)
Treated	15,094,978	25	0.17	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	543,673	3	0.55	2.95 (0.88, 9.95)	2.79 (0.82, 9.46)
8-14 days since last treatment	388,091	5	1.29	6.11 (2.26, 16.54)	5.83 (2.15, 15.85)
15-30 days since last treatment	708,080	3	0.42	2.78 (0.83, 9.32)	2.56 (0.76, 8.70)
>30 days since last treatment	18,551,801	92	0.50	3.46 (2.16, 5.55)	3.55 (2.21, 5.70)
Treatment Status and Overdose (n=867 Deaths)					
Treatment Status	Person Days at Risk	n	IR	uHR (95% CI)	aHR (95% CI)[c]
Treated	15,094,978	121	0.80	Ref	Ref
Not Treated Overall	20,191,645	746	3.69	4.83 (3.97, 5.89)	4.58 (3.75, 5.59)
Treated	15,094,978	121	0.80	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	543,673	25	4.60	5.40 (3.49, 8.38)	4.82 (3.10, 7.49)
8-14 days since last treatment	388,091	24	6.18	7.73 (4.96, 12.04)	6.81 (4.35, 10.65)
15-30 days since last treatment	708,080	24	3.39	4.24 (2.72, 6.61)	3.73 (2.38, 5.83)
>30 days since last treatment	18,551,801	673	3.63	4.73 (3.87, 5.78)	4.53 (3.70, 5.55)
Treatment Status and Opioid-Related Death (n=616 Deaths)					
Treatment Status	Person Days at Risk	n	IR	uHR (95% CI)	aHR (95% CI)[d]
Treated	15,094,978	87	0.58	Ref	Ref
Not Treated Overall	20,191,645	529	2.62	4.84 (3.84, 6.12)	4.59 (3.62, 5.80)
Treated	15,094,978	87	0.58	Ref	Ref

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Appendix Table 3. Association between Treatment Status and Death with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

Not Treated Stratified					
≤7 days since last treatment	543,673	20	3.68	5.95 (3.62, 9.76)	5.18 (3.14, 8.52)
8-14 days since last treatment	388,091	19	4.90	8.70 (5.27, 14.39)	7.46 (4.49, 12.39)
15-30 days since last treatment	708,080	15	2.12	3.60 (2.07, 6.28)	3.08 (1.76, 5.40)
>30 days since last treatment	18,551,801	475	2.56	4.72 (3.72, 5.99)	4.54 (3.57, 5.77)
Treatment Status and All-Cause Death (n=2,274 Deaths)					
Treatment Status	Person Days at Risk	n	IR	uHR (95% CI)	aHR (95% CI)[e]
Treated	15,094,978	380	2.52	Ref	Ref
Not Treated Overall	20,191,645	1,894	9.38	3.81 (3.40, 4.27)	3.82 (3.41, 4.28)
Treated	15,094,978	380	2.52	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	543,673	57	10.48	4.21 (3.18, 5.58)	4.25 (3.20, 5.65)
8-14 days since last treatment	388,091	65	16.75	6.90 (5.28, 9.01)	6.94 (5.30, 9.07)
15-30 days since last treatment	708,080	71	10.03	4.16 (3.22, 5.38)	4.17 (3.22, 5.41)
>30 days since last treatment	18,551,801	1,701	9.17	3.67 (3.27, 4.12)	3.68 (3.28, 4.14)

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

[a] Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[b] Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)

[c] Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median dose of buprenorphine, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[d] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)

[e] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median dose of buprenorphine, other MOUD, healthcare utilization (urgent care visit, overdose in ED)

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Appendix Table 4. Association between Treatment Status and Death with up to 1 Year of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)					
Treatment Status and Suicide/Overdose (n=265 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[a]
Treated	5,663,738	50	0.88	Ref	Ref
Not Treated Overall	4,163,150	215	5.16	6.31 (4.58, 8.69)	6.01 (4.34, 8.30)
Treated	5,663,738	50	0.88	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	296,722	19	6.40	6.75 (3.93, 11.60)	6.03 (3.50, 10.40)
8-14 days since last treatment	209,264	14	6.69	7.52 (4.10, 13.79)	6.62 (3.59, 12.21)
15-30 days since last treatment	380,269	9	2.37	2.85 (1.39, 5.88)	2.52 (1.22, 5.21)
>30 days since last treatment	3,276,895	173	5.28	6.67 (4.75, 9.36)	6.53 (4.63, 9.21)
Treatment Status and Suicide (n=40 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[b]
Treated	5,663,738	9	0.16	Ref	Ref
Not Treated Overall	4,163,150	31	0.74	5.87 (2.65, 13.01)	5.64 (2.52, 12.63)
Treated	5,663,738	9	0.16	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	296,722	3	1.01	5.89 (1.52, 22.75)	5.02 (1.28, 19.70)
8-14 days since last treatment	209,264	3	1.43	6.79 (1.73, 26.67)	5.85 (1.47, 23.23)
15-30 days since last treatment	380,269	1	0.26	2.17 (0.27, 17.73)	1.70 (0.20, 14.18)
>30 days since last treatment	3,276,895	24	0.73	6.28 (2.63, 15.04)	6.43 (2.66, 15.56)
Treatment Status and Overdose (n=229 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[c]
Treated	5,663,738	42	0.74	Ref	Ref
Not Treated Overall	4,163,150	187	4.49	6.40 (4.52, 9.04)	5.95 (4.19, 8.46)
Treated	5,663,738	42	0.74	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	296,722	16	5.39	6.68 (3.70, 12.03)	5.86 (3.24, 10.61)
8-14 days since last treatment	209,264	12	5.73	7.93 (4.12, 15.26)	6.89 (3.56, 13.32)
15-30 days since last treatment	380,269	8	2.10	2.90 (1.34, 6.25)	2.54 (1.17, 5.50)
>30 days since last treatment	3,276,895	151	4.61	6.79 (4.71, 9.81)	6.48 (4.46, 9.42)
Treatment Status and Opioid-Related Death (n=162) Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[d]
Treated	5,663,738	32	0.56	Ref	Ref

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Appendix Table 4. Association between Treatment Status and Death with up to 1 Year of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)					
Not Treated Overall	4,163,150	130	3.12	6.08 (4.07, 9.09)	5.55 (3.68, 8.35)
Treated	5,663,738	32	0.56	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	296,722	12	4.04	6.50 (3.29, 12.81)	5.56 (2.81, 11.02)
8-14 days since last treatment	209,264	10	4.78	9.11 (4.41, 18.83)	7.69 (3.69, 16.00)
15-30 days since last treatment	380,269	4	1.05	1.82 (0.64, 5.23)	1.54 (0.54, 4.45)
>30 days since last treatment	3,276,895	104	3.17	6.51 (4.24, 10.01)	6.12 (3.95, 9.47)
Treatment Status and All-Cause Death (n=542 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)e
Treated	5,663,738	124	2.19	Ref	Ref
Not Treated Overall	4,163,150	418	10.04	4.93 (4.00, 6.09)	4.75 (3.84, 5.88)
Treated	5,663,738	124	2.19	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	296,722	30	10.11	4.59 (3.05, 6.89)	4.43 (2.94, 6.67)
8-14 days since last treatment	209,264	29	13.86	6.60 (4.36, 9.99)	6.29 (4.14, 9.55)
15-30 days since last treatment	380,269	24	6.31	3.08 (1.97, 4.81)	2.92 (1.86, 4.57)
>30 days since last treatment	3,276,895	335	10.22	5.12 (4.10, 6.40)	4.94 (3.94, 6.20)

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

[a] Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[b] Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)

[c] Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median dose of buprenorphine, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[d] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)

[e] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte

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Appendix Table 4. Association between Treatment Status and Death with up to 1 Year of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median dose of buprenorphine, other MOUD, healthcare utilization (urgent care visit, overdose in ED)

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Appendix Table 5. Association between Treatment Status and Death with up to 2 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)					
Treatment Status and Suicide/Overdose (n=488 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[a]
Treated	9,187,970	77	0.84	Ref	Ref
Not Treated Overall	8,948,410	411	4.59	5.90 (4.58, 7.58)	5.61 (4.35, 7.22)
Treated	9,187,970	77	0.84	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	401,255	22	5.48	6.01 (3.70, 9.75)	5.44 (3.35, 8.85)
8-14 days since last treatment	284,364	17	5.98	6.90 (4.04, 11.79)	6.19 (3.61, 10.60)
15-30 days since last treatment	517,880	18	3.48	4.28 (2.54, 7.23)	3.85 (2.27, 6.51)
>30 days since last treatment	7,744,911	354	4.57	5.98 (4.61, 7.76)	5.77 (4.44, 7.50)
Treatment Status and Suicide (n=65 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[b]
Treated	9,187,970	15	0.16	Ref	Ref
Not Treated Overall	8,948,410	50	0.56	4.17 (2.27, 7.67)	4.15 (2.24, 7.68)
Treated	9,187,970	15	0.16	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	401,255	3	0.75	3.98 (1.12, 14.17)	3.58 (1.00, 12.84)
8-14 days since last treatment	284,364	3	1.05	4.74 (1.32, 17.12)	4.33 (1.20, 15.69)
15-30 days since last treatment	517,880	2	0.39	2.75 (0.61, 12.31)	2.36 (0.52, 10.76)
>30 days since last treatment	7,744,911	42	0.54	4.28 (2.24, 8.17)	4.39 (2.28, 8.45)
Treatment Status and Overdose (n=434 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[c]
Treated	9,187,970	64	0.70	Ref	Ref
Not Treated Overall	8,948,410	370	4.13	6.25 (4.76, 8.22)	5.96 (4.53, 7.86)
Treated	9,187,970	64	0.70	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	401,255	19	4.74	6.24 (3.70, 10.52)	5.69 (3.37, 9.63)
8-14 days since last treatment	284,364	15	5.27	7.60 (4.29, 13.46)	6.90 (3.88, 12.25)
15-30 days since last treatment	517,880	17	3.28	4.77 (2.76, 8.23)	4.34 (2.51, 7.52)
>30 days since last treatment	7,744,911	319	4.12	6.33 (4.77, 8.39)	6.11 (4.59, 8.13)
Treatment Status and Opioid-Related Death (n=310 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[d]
Treated	9,187,970	46	0.50	Ref	Ref
Not Treated Overall	8,948,410	264	2.95	6.37 (4.61, 8.80)	6.07 (4.38, 8.42)
Treated	9,187,970	46	0.50	Ref	Ref

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Appendix Table 5. Association between Treatment Status and Death with up to 2 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)					
Not Treated Stratified					
≤7 days since last treatment	401,255	14	3.49	6.27 (3.40, 11.57)	5.67 (3.06, 10.48)
8-14 days since last treatment	284,364	12	4.22	8.77 (4.60, 16.74)	7.86 (4.10, 15.07)
15-30 days since last treatment	517,880	10	1.93	3.78 (1.88, 7.59)	3.40 (1.68, 6.85)
>30 days since last treatment	7,744,911	228	2.94	6.54 (4.67, 9.15)	6.33 (4.51, 8.90)
Treatment Status and All-Cause Death (N=1,092 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)
Treated	9,187,970	210	2.29	Ref	Ref
Not Treated Overall	8,948,410	882	9.86	4.49 (3.84, 5.25)	4.49 (3.83, 5.26)
Treated	9,187,970	210	2.29	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	401,255	41	10.22	4.48 (3.19, 6.30)	4.53 (3.22, 6.37)
8-14 days since last treatment	284,364	42	14.77	6.71 (4.79, 9.41)	6.73 (4.79, 9.45)
15-30 days since last treatment	517,880	47	9.08	4.20 (3.05, 5.80)	4.20 (3.04, 5.81)
>30 days since last treatment	7,744,911	752	9.71	4.39 (3.74, 5.16)	3.73 (5.17)

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

[a] Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[b] Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)

[c] Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median dose of buprenorphine, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[d] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)

[e] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median buprenorphine dose, other MOUD, healthcare utilization (urgent care visit, overdose in ED)

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Appendix Table 6. Association between Treatment Status and Death with up to 3 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)					
Treatment Status and Suicide/Overdose (n=684 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[a]
Treated	11,753,066	111	0.94	Ref	Ref
Not Treated Overall	13,328,049	573	4.30	4.84 (3.92, 5.96)	4.59 (3.72, 5.67)
Treated	11,753,066	111	0.94	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	467,075	25	5.35	5.35 (3.44, 8.32)	4.80 (3.08, 7.48)
8-14 days since last treatment	332,087	26	7.83	8.17 (5.29, 12.63)	7.25 (4.68, 11.25)
15-30 days since last treatment	605,231	22	3.63	3.96 (2.49, 6.30)	3.51 (2.20, 5.60)
>30 days since last treatment	11,923,656	500	4.19	4.70 (3.79, 5.83)	4.52 (3.65, 5.62)
Treatment Status and Suicide (n=92 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[b]
Treated	11,753,066	21	0.18	Ref	Ref
Not Treated Overall	13,328,049	71	0.53	3.46 (2.07, 5.76)	3.47 (2.07, 5.81)
Treated	11,753,066	21	0.18	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	467,075	3	0.64	3.19 (0.93, 10.94)	2.94 (0.85, 10.12)
8-14 days since last treatment	332,087	4	1.20	5.20 (1.72, 15.74)	4.87 (1.60, 14.78)
15-30 days since last treatment	605,231	2	0.33	2.06 (0.48, 8.93)	1.84 (0.42, 8.06)
>30 days since last treatment	11,923,656	62	0.52	3.45 (2.02, 5.87)	3.54 (2.07, 6.05)
Treatment Status and Overdose (n=611 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[c]
Treated	11,753,066	93	0.79	Ref	Ref
Not Treated Overall	13,328,049	518	3.89	5.13 (4.09, 6.44)	4.89 (3.89, 6.15)
Treated	11,753,066	93	0.79	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	467,075	22	4.71	5.63 (3.51, 9.03)	5.08 (3.16, 8.17)
8-14 days since last treatment	332,087	23	6.93	8.90 (5.60, 14.15)	7.97 (5.00, 12.72)
15-30 days since last treatment	605,231	21	3.47	4.45 (2.75, 7.21)	3.99 (2.46, 6.47)
>30 days since last treatment	11,923,656	452	3.79	4.98 (3.95, 6.28)	4.80 (3.80, 6.07)
Treatment Status and Opioid-Related Death (n=435 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[d]
Treated	11,753,066	65	0.55	Ref	Ref
Not Treated Overall	13,328,049	370	2.78	5.36 (4.08, 7.03)	5.13 (3.90, 6.75)
Treated	11,753,066	65	0.55	Ref	Ref

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Appendix Table 6. Association between Treatment Status and Death with up to 3 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)					
Not Treated Stratified					
≤7 days since last treatment	467,075	17	3.64	6.11 (3.54, 10.54)	5.48 (3.17, 9.48)
8-14 days since last treatment	332,087	18	5.42	10.23 (6.02, 17.37)	9.09 (5.33, 15.52)
15-30 days since last treatment	605,231	13	2.15	3.85 (2.10, 7.05)	3.42 (1.86, 6.28)
>30 days since last treatment	11,923,656	322	2.70	5.21 (3.94, 6.88)	5.06 (3.82, 6.71)
Treatment Status and All-Cause Death (n=1,538 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[e]
Treated	11,753,066	289	2.46	Ref	Ref
Not Treated Overall	13,328,049	1,249	9.37	3.94 (3.45, 4.50)	3.96 (4.47, 4.53)
Treated	11,753,066	289	2.46	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	467,075	46	9.85	4.03 (2.94, 5.52)	4.07 (2.96, 5.59)
8-14 days since last treatment	332,087	56	16.86	7.11 (5.32, 9.51)	7.15 (5.33, 9.58)
15-30 days since last treatment	605,231	56	9.25	3.94 (2.95, 5.27)	3.95 (2.95, 5.29)
>30 days since last treatment	11,923,656	1,091	9.15	3.81 (3.32, 4.36)	3.83 (3.34, 4.39)

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

[a] Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[b] Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)

[c] Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median buprenorphine dose, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[d] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)

[e] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median buprenorphine dose, other MOUD, healthcare utilization (urgent care visit, overdose in ED)

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Appendix Table 7. Association between Treatment Status and Death with up to 4 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)

Treatment Status and Suicide/Overdose (n=847 Deaths)

Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[a]
Treated	13,660,680	130	0.95	Ref	Ref
Not Treated Overall	17,099,344	717	4.19	4.67 (3.85, 5.66)	4.41 (3.64, 5.36)
Treated	13,660,680	130	0.95	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	511,921	28	5.47	5.43 (3.58, 8.23)	4.83 (3.18, 7.34)
8-14 days since last treatment	364,604	27	7.41	7.64 (5.01, 11.65)	6.72 (4.39, 10.27)
15-30 days since last treatment	665,247	25	3.76	4.04 (2.62, 6.23)	3.54 (2.28, 5.48)
>30 days since last treatment	15,557,572	637	4.09	4.54 (3.73, 5.52)	4.35 (3.47, 5.30)

Treatment Status and Suicide (n=111 Deaths)

Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[b]
Treated	13,660,680	23	0.17	Ref	Ref
Not Treated Overall	17,099,344	88	0.51	3.54 (2.19, 5.73)	3.56 (2.20, 5.79)
Treated	13,660,680	23	0.17	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	511,921	3	0.59	3.05 (0.90, 10.37)	2.86 (0.84, 9.76)
8-14 days since last treatment	364,604	4	1.10	5.00 (1.67, 14.98)	4.73 (1.57, 14.22)
15-30 days since last treatment	665,247	3	0.45	2.95 (0.87, 9.98)	2.68 (0.78, 9.18)
>30 days since last treatment	15,557,572	78	0.50	3.52 (2.14, 5.79)	3.60 (2.18, 5.95)

Treatment Status and Overdose (n=758 Deaths)

Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[c]
Treated	13,660,680	110	0.81	Ref	Ref
Not Treated Overall	17,099,344	648	3.79	4.91 (3.99, 6.04)	4.68 (3.80, 5.77)
Treated	13,660,680	110	0.81	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	511,921	25	4.88	5.75 (3.70, 8.95)	5.15 (3.30, 8.04)
8-14 days since last treatment	364,604	24	6.58	8.27 (5.28, 12.94)	7.33 (4.67, 11.51)
15-30 days since last treatment	665,247	23	3.46	4.34 (2.75, 6.84)	3.84 (2.42, 6.08)
>30 days since last treatment	15,557,572	576	3.70	4.77 (3.86, 5.89)	4.60 (3.72, 5.70)

Treatment Status and Opioid-Related Death (n=542 Deaths)

Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[d]
Treated	13,660,680	78	0.57	Ref	Ref
Not Treated Overall	17,099,344	464	2.71	5.04 (3.94, 6.45)	4.82 (3.76, 6.18)
Treated	13,660,680	78	0.57	Ref	Ref

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Appendix Table 7. Association between Treatment Status and Death with up to 4 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017 (N=29,054)					
Not Treated Stratified					
≤7 days since last treatment	511,921	20	3.91	6.42 (3.89, 10.59)	5.64 (3.41, 9.34)
8-14 days since last treatment	364,604	19	5.21	3.64 (2.04, 6.48)	8.20 (4.91, 13.71)
15-30 days since last treatment	665,247	14	2.10	9.46 (5.69, 15.72)	3.16 (1.76, 5.65)
>30 days since last treatment	15,557,572	411	2.64	4.88 (3.79, 6.27)	4.75 (3.68, 6.12)
Treatment Status and All-Cause Death (n=1,951 Deaths)					
Treatment Status	Person Days at Risk	N	IR	uHR (95% CI)	aHR (95% CI)[e]
Treated	13,660,680	346	2.53	Ref	Ref
Not Treated Overall	17,099,344	1,605	9.39	3.79 (3.34, 4.28)	3.81 (3.38, 4.30)
Treated	13,660,680	346	2.53	Ref	Ref
Not Treated Stratified					
≤7 days since last treatment	511,921	52	10.16	4.05 (3.01, 5.34)	4.08 (3.03, 5.49)
8-14 days since last treatment	364,604	59	16.18	6.62 (5.00, 8.76)	6.64 (5.01, 8.80)
15-30 days since last treatment	665,247	64	9.62	3.97 (3.03, 5.21)	3.97 (3.02, 5.22)
>30 days since last treatment	15,557,572	1,430	9.19	3.67 (3.25, 4.15)	3.69 (3.26, 4.18)

VHA = Veterans Health Administration; N = Total Sample Population; n = number of deaths; IR = Incidence rate (deaths per 100,000 person days); uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio; ED = emergency department; MOUD = Medications for OUD

[a] Adjusted for: Demographics (age, gender, race, rural, homelessness, year initiating buprenorphine), clinical co-morbidities (depression, peripheral vascular disease, liver disease), concurrent substance dependence (alcohol, cannabis), medications (antipsychotics, mood stabilizers), other MOUD, and healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[b] Adjusted for: Demographics (age, gender, race, rural), clinical co-morbidities (hypertension w/ complications, cardiovascular disease, bipolar, anxiety, depression, history of suicide, ADHD, personality disorders), concurrent substance dependence (cannabis, stimulants, cocaine), medications (antipsychotics), other MOUD, and healthcare utilization (overdose in ED)

[c] Adjusted for: Demographics (age, gender, race, ethnicity, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, peripheral vascular disease, fluid and electrolyte disorders, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers), median dose of buprenorphine, other MOUD, healthcare utilization (overdose in ED, inpatient admission for substance use or dependence)

[d] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (arrythmia, pulmonary circulation disorders, liver disease, bipolar, anxiety), concurrent substance dependence (cannabis, sedative, cocaine), medications (antipsychotics), median buprenorphine dose, other MOUD, and healthcare utilization (overdose in ED)

[e] Adjusted for: Demographics (age, gender, race, ethnicity, homelessness, rural, year initiating buprenorphine), clinical co-morbidities (HIV/AIDS, pulmonary circulation disorders, peripheral vascular disease, hypertension without complications, other neurological disorders, fluid and electrolyte disturbances, deficiency anemia, bipolar), concurrent substance dependence (cannabis, sedatives, cocaine), medications (antipsychotics, mood stabilizers, opioids), median buprenorphine dose, other MOUD, healthcare utilization (urgent care visit, overdose in ED)

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Appendix Table 8. Comparison of Results between Main and Sensitivity Analyses for the Association between Treatment Status and Mortality with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017

Outcome	Main Analysis[a] N=29,054	SA 1: Excluding Low Utilizers[b] N=26,404	SA 2: Excluding Infrequent Buprenorphine Utilizers[c] N=24,405	SA 3: E-Values[d]
Suicide/Overdose Deaths	**n=964**	**n=899**	**n=731**	
Treatment Status	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	E-Value/CI
Treated	Ref	Ref	Ref	Ref
Not Treated Overall	4.33 (3.60, 5.21)	4.15 (3.44, 5.02)	3.92 (3.23, 4.76)	8.15/6.66
Treated	Ref	Ref	Ref	Ref
Not Treated Stratified				
≤7 days since last treatment	4.56 (3.01, 6.90)	4.23 (2.75, 6.50)	4.16 (2.53, 6.83)	8.59/5.47
8-14 days since last treatment	6.54 (4.32, 9.91)	6.30 (4.12, 9.63)	6.66 (4.18, 10.62)	12.56/8.11
15-30 days since last treatment	3.45 (2.25, 5.29)	3.19 (2.05, 4.98)	3.27 (2.01, 5.32)	6.36/3.93
>30 days since last treatment	4.29 (3.55, 5.17)	4.12 (3.40, 5.00)	3.87 (3.18, 4.71)	8.05/6.56
Suicide Deaths	**n=128**	**n=120**	**n=97**	
Treatment Status	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	E-Value/CI
Treated	Ref	Ref	Ref	Ref
Not Treated Overall	3.57 (2.25, 5.66)	3.61 (2.23, 5.83)	3.05 (1.87, 4.96)	6.60/3.93
Treated	Ref	Ref	Ref	Ref
Not Treated Stratified				
≤7 days since last treatment	2.79 (0.82, 9.46)	2.89 (0.85, 9.88)	2.87 (0.67, 12.31)	5.02/1.00
8-14 days since last treatment	5.83 (2.15, 15.85)	4.77 (1.58, 14.35)	3.92 (0.91, 16.88)	11.14/3.72
15-30 days since last treatment	2.56 (0.76, 8.70)	2.71 (0.79, 9.29)	2.10 (0.49, 9.08)	4.56/1.00
>30 days since last treatment	3.55 (2.21, 5.70)	3.64 (2.22, 5.99)	3.08 (1.88, 5.05)	6.56/3.85
Overdose Deaths	**n=867**	**n=807**	**n=657**	
Treatment Status	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	E-Value/CI
Treated	Ref	Ref	Ref	Ref
Not Treated Overall	4.58 (3.75, 5.59)	4.34 (3.54, 5.31)	4.20 (3.40, 5.17)	8.63/6.96
Treated	Ref	Ref	Ref	Ref
Not Treated Stratified				
≤7 days since last treatment	4.82 (3.10, 7.49)	4.39 (2.78, 6.93)	4.39 (2.59, 7.45)	9.11/5.65

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Appendix Table 8. Comparison of Results between Main and Sensitivity Analyses for the Association between Treatment Status and Mortality with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017			
8-14 days since last treatment	6.81 (4.35, 10.65)	6.76 (4.31, 10.59)	7.18 (4.38, 11.75)	13.10/8.17
15-30 days since last treatment	3.73 (2.38, 5.83)	3.39 (2.13, 5.41)	3.68 (2.22, 7.45)	6.90/4.13
>30 days since last treatment	4.53 (3.70, 5.55)	4.30 (3.50, 5.29)	4.13 (3.34, 5.11)	8.53/6.86
Opioid-Related Deaths	**n=616**	**n=578**	**n=459**	
Treatment Status	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	E-Value/CI
Treated	Ref	Ref	Ref	Ref
Not Treated Overall	4.59 (3.62, 5.80)	4.27 (3.36, 5.41)	4.03 (3.14, 5.16)	8.89/6.86
Treated	Ref	Ref	Ref	Ref
Not Treated Stratified				
≤7 days since last treatment	5.18 (3.14, 8.52)	4.53 (2.69, 7.63)	4.46 (2.42, 8.24)	8.65/6.70
8-14 days since last treatment	7.46 (4.49, 12.39)	7.27 (4.37, 12.10)	7.61 (4.34, 13.33)	14.40/8.45
15-30 days since last treatment	3.08 (1.76, 5.40)	2.61 (1.44, 4.73)	2.76 (1.42, 5.37)	5.61/2.92
>30 days since last treatment	4.54 (3.57, 5.77)	4.25 (3.33, 5.42)	3.98 (3.09, 5.11)	8.55/6.60
All-Cause Deaths	**n=2,274**	**n=2,138**	**n=1,737**	
Treatment Status	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	E-Value/CI
Treated	Ref	Ref	Ref	Ref
Not Treated Overall	3.82 (3.41, 4.28)	3.74 (3.32, 4.20)	3.58 (3.17, 4.04)	7.10/6.28
Treated	Ref	Ref	Ref	Ref
Not Treated Stratified				
≤7 days since last treatment	4.25 (3.20, 5.65)	3.73 (2.75, 5.05)	4.17 (3.03, 5.74)	7.97/5.85
8-14 days since last treatment	6.94 (5.30, 9.07)	6.88 (5.23, 9.05)	7.19 (5.37, 9.62)	13.36/10.07
15-30 days since last treatment	4.17 (3.22, 5.41)	4.04 (3.09, 5.27)	4.13 (3.10, 5.49)	7.81/5.89
>30 days since last treatment	3.68 (3.28, 4.14)	3.62 (3.21, 4.08)	3.43 (3.04, 3.88)	6.82/6.01

VHA = Veterans Health Administration; N = Total Sample Population; n = Number of deaths; IR = Incidence rate (deaths per 100,000 person days); SA = Sensitivity analysis; uHR = unadjusted hazard ratio; aHR = adjusted hazard ratio

[a] Main Analysis: Represents the results from the final models for each mortality outcome over five years of follow-up, as seen in Table 3.

[b] SA 1: Represents results from excluding Veterans who had ≤14 outpatient encounters within the VHA system in the two years preceding initial buprenorphine prescription. The purpose of this analysis was to assess whether there was potential unmeasured confounding from those who might not have had the opportunity to have co-morbidities documented to the same extent as routine VHA users.

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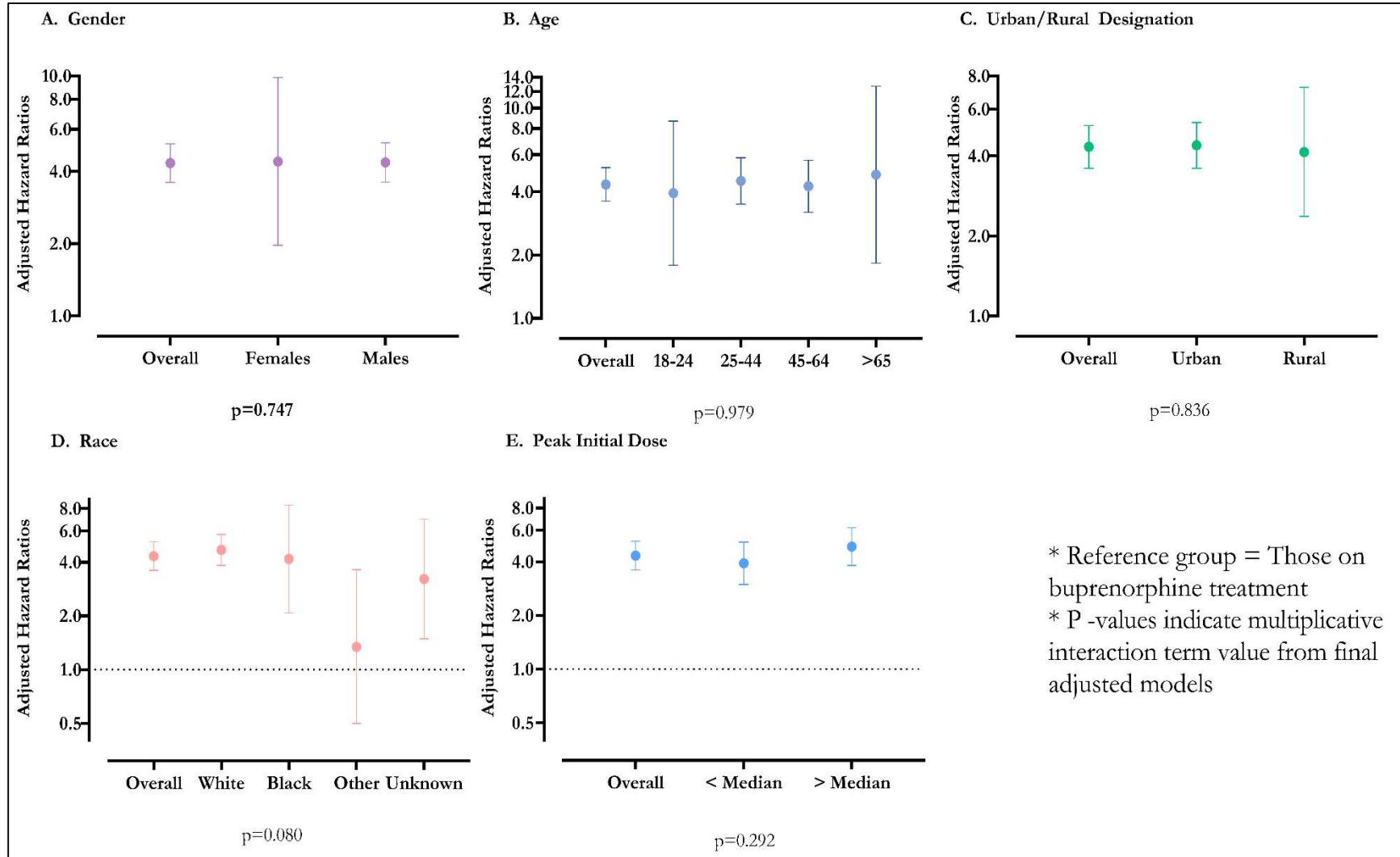**Vakkalanka et al.**

Appendix Table 8. Comparison of Results between Main and Sensitivity Analyses for the Association between Treatment Status and Mortality with up to 5 Years of Follow-Up from Buprenorphine Treatment Initiation among Veterans Treated in the VHA, 2008-2017

[c] SA 2: Represents results from excluding Veterans who had a total of ≤30 days on buprenorphine treatment over five years of follow up from the initial buprenorphine prescription. The purpose of this analysis was to account for potential misclassification of exposure, specifically among those who might have received treatment outside of the VHA but have been documented as not being on treatment in our main analysis.

[d] SA 3: Represents an assessment of unmeasured confounding and bias by evaluating the E-values, the minimum strength of association that an unmeasured confounder would need to fully explain away the observed association, conditioned on covariates that are measured. For example, for the primary suicide/overdose composite outcome over 5 years of follow-up, the observed hazard ratio of 4.34 could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a hazard ratio of 8.15-fold each, above and beyond the measured confounders, but weaker confounding could not do so. The confidence interval could be moved to include the null by an unmeasured confounder that was associated with both the treatment and the outcome by a hazard ratio of 6.66-fold each, above and beyond the measured confounders, but weaker confounding could not do so.

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Appendix Figure 1. Evaluation of Multiplicative Effect Modification of Buprenorphine Pharmacotherapy and Mortality by Select Variables

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Appendix Figure 2. Association between Receipt of Buprenorphine Pharmacotherapy and Morality by Year of Follow-Up