

Supplemental Materials

Supplemental Table 1: ICD-10 Codes Utilized in this Study

ICD-10 Codes for Sepsis deaths
A40 Streptococcal Septicemia
A40.0 Septicaemia due to streptococcus, group A
A40.1 Septicaemia due to streptococcus, group B
A40.2 Septicaemia due to streptococcus, group D
A40.3 Septicaemia due to Streptococcus pneumoniae
A40.8 Other streptococcal septicaemia
A40.9 Streptococcal septicaemia, unspecified
A41 Other Septicemia
A41.0 Septicaemia due to Staphylococcus aureus
A41.1 Septicaemia due to other specified staphylococcus
A41.2 Septicaemia due to unspecified staphylococcus
A41.3 Septicaemia due to Haemophilus influenzae
A41.4 Septicaemia due to anaerobes
A41.5 Septicaemia due to other Gram-negative organisms
A41.8 Other specified septicaemia
A41.9 Septicaemia, unspecified
ICD-10 codes for most common associated causes of deaths
COVID-19 (U07.1)
Influenza and pneumonia (J09-J18)
N39.0 (Urinary tract infection, site not specified)
N30 (Cystitis)
N15.1 (Renal and perinephric abscess)
N13.6 (Pyonephrosis)
F03 (Unspecified dementia)
F01 (Vascular dementia)
G30 (Alzheimer disease)
F05.1 (Delirium superimposed on dementia)
Pneumonitis due to solids and liquids (J69)
Chronic lower respiratory diseases (J40-J47)
A04.7 (Enterocolitis due to Clostridium difficile)
COVID-19 (U07.1)
Influenza and pneumonia (J09-J18)
N39.0 (Urinary tract infection, site not specified)
N30 (Cystitis)
N15.1 (Renal and perinephric abscess)

Supplemental Table 2: Number of sepsis-related deaths overall and by gender in the United States from 1999-2022.

Year	Overall	Male	Female
1999	136812	63180	73632
2000	135322	62184	73138
2001	137787	63293	74494
2002	141063	65167	75896
2003	143225	66347	76878
2004	143621	66899	76722
2005	150432	70465	79967
2006	150318	70677	79641
2007	150389	71106	79283
2008	157284	74114	83170
2009	155441	73949	81492
2010	157780	75486	82294
2011	163118	77710	85408
2012	163495	78867	84628
2013	172068	83168	88900
2014	180677	87995	92682
2015	193580	94881	98699
2016	196328	96862	99466
2017	202135	100085	102050
2018	204402	102183	102219
2019	199628	100504	99124

2020	240718	124379	116339
2021	259410	135582	123828
2022	242038	123966	118072
Total	4177071	2029049	2148022

Supplemental Table 3: Age adjusted mortality rates of sepsis from 1999-2022 in the United States overall, and for males and females with joinpoint analysis.

Year	Overall	Female	Male
1999	77.5	69.2	89.6
2000	75.7	67.9	86.9
2001	75.8	68.4	86.4
2002	76.4	68.9	87.2
2003	76.3	68.9	86.8
2004	75.3	68	85.7
2005	77.3	69.7	88.2
2006	75.8	68.4	86.2
2007	74.3	66.9	84.7
2008	76.2	69.1	86.1
2009	73.8	66.7	83.7
2010	73.7	66.2	83.9
2011	74.1	67.2	83.6
2012	72.5	65.3	82.4
2013	74.6	67.4	84.4
2014	76.5	68.9	86.7
2015	80.2	71.9	91.3
2016	79.7	71.3	90.9
2017	80.3	71.6	91.6
2018	79.4	70.5	91.2
2019	76.1	67.3	87.6
2020	90.3	78.3	105.6
2021	99.1	86	115.6
2022	89	78.2	103.2

Supplemental Table 4: Sepsis age adjusted mortality rates stratified by race from 1999-2022.

Year	NH American Indian or Alaska Native	NH Black or African American	NH White	Hispanic or Latino	NH Asian or Pacific Islander	NH Asian	NH Native Hawaiian or Other Pacific Islander
1999	94.29	159.74	68.51	83.47	57.93		
2000	85.98	154.44	67.49	77.67	53.95		
2001	82.4	151.9	67.82	80.28	52.65		
2002	89.1	150.59	68.64	79.72	54.93		
2003	93.31	148.4	68.86	78.36	52		
2004	85.79	143.66	68.35	77.81	53.73		
2005	91.97	144.89	70.4	81.04	54.27		
2006	88.51	139.77	69.11	78.12	54.64		
2007	96.26	136.87	67.86	75.98	53.91		
2008	101.83	134.5	70.15	77.5	55.22		
2009	109.83	126.92	68.3	74.68	52.23		
2010	100.56	124.1	68.45	74.59	52.37		
2011	102.38	121.94	69.5	72.87	50.42		
2012	101.65	115.96	68.17	71.23	49.66		
2013	102.21	118.89	70.33	72.02	51.44		
2014	109.7	117.73	72.84	72.85	49.12		
2015	112.21	121.67	76.79	73.56	50.65		
2016	111.57	119.58	76.57	73.42	50.23		
2017	114.05	117.82	77.23	74.76	50.8		
2018	104.29	117.78	76.57	73.24	49.09	47.95	91.85
2019	99.91	111.45	73.81	69.1	46.81	45.41	97.33
2020	135.86	142.22	83.18	99.8	59.31	57.54	124.13
2021	146.99	149.44	93.8	103.29	62.46	60.46	132.45
2022	131.09	135.42	85.73	83.65	55.52	53.85	114.97

Supplemental Table 5: Crude mortality rates for sepsis in 10-year age groups from 1999-2022.

Year	Young (25-44)	Middle age (45-74)	Elderly (≥75)
1999	8.48	65.73	474.58
2000	7.24	64.85	465.66
2001	7.17	65.47	463.88
2002	7.27	65.71	469.11
2003	7.44	65.49	467.77
2004	7.02	65.31	460.12
2005	7.07	66.34	477.12
2006	7.14	65.48	464.42
2007	6.76	64.7	453.98
2008	7.05	65.85	466.76
2009	7.47	64.6	445.65
2010	6.8	64.14	449.59
2011	7.05	64.85	449.85
2012	6.84	63.45	440.48
2013	7.24	65.74	450.12
2014	7.54	68.72	454.83
2015	7.72	71.2	481.14
2016	8.29	71.82	470.58
2017	8.34	72.17	474.25
2018	8.4	72.29	464.47
2019	8.44	70.11	439.27
2020	10.82	88.23	492.76
2021	13.81	98.79	522.38
2022	11.1	86.38	486.3

Supplemental Table 6: Age Adjusted Mortality rate stratified by census region between 1999 and 2022.

Year	Census Region 1: Northeast	Census Region 2: Midwest	Census Region 3: South	Census Region 4: West
1999	85.21	69.57	87.24	61.69
2000	84.41	67.53	85.28	59.36
2001	83.68	67.34	85.57	60.29
2002	83.55	68.48	86.35	60.9
2003	81.17	68.09	86.6	62.73
2004	81.65	66.88	84.83	61.87
2005	83.8	69.65	86.81	63.23
2006	81.11	67.5	84.89	64.07
2007	78.69	66.99	83.07	63.04
2008	78.48	70.23	84.79	65.52
2009	73.46	68.08	83.04	64.43
2010	73.9	67.18	82.29	65.55
2011	74.29	69.4	81.59	66.14
2012	71.83	66.88	81.18	64.26
2013	74.6	68.04	83.39	66.36
2014	76.39	70.64	85.44	67.12
2015	78.25	74.9	89.69	70.83
2016	76.72	73.39	89.68	71.53
2017	73.86	74.67	91.02	72.6
2018	73.77	75.13	90.57	69.26
2019	70.86	73.21	85.96	66.32
2020	82.43	86.62	102.43	79.36
2021	83.99	90.52	116.72	89.64
2022	81.23	83.66	100.2	80.97

Supplemental Table 7: Most common sepsis associated causes of deaths. Crude number and Percentage contributed in 1999 to 2001, 2017 to 2019 and 2019 to 2021

Crude Number			
	1999 to 2001	2017-2019	2020-2022
Sepsis	409921	606165	742166
Heart failure	33104	58454	73286

Pneumonia (Including Influenza)	85144	143703	205042
Pneumonitis due to solids and liquids	14456	37008	42418
Urinary tract infections	31775	68282	81768
Dementia (including Alzheimer and vasuclar)	29797	13144	47894
Chronic lower respiratory diseases	29289	45425	11157
Enterocolitis due to Clostridium difficile	2028	13144	11157
COVID 19	-	-	112331
Percentage			
	1999 to 2001 (%)	2017-2019 (%)	2020-2022 (%)
Heart failure	8.08	9.64	9.87
Pneumonia (Including Influenza)	20.77	23.71	27.63
Pneumonitis due to solids and liquids	3.53	6.11	5.72
Urinary tract infections	7.75	11.26	11.02
Dementia (including Alzheimer and vasuclar)	7.27	2.17	6.45
Chronic lower respiratory diseases	7.15	7.49	1.50
Enterocolitis due to Clostridium difficile	0.49	2.17	1.50
COVID 19	-	-	15.14

Supplemental Table 8: AAMR for sensitivity analysis using sepsis as underlying cause of death, Sepsis + COVID-19 deaths and sepsis excluding COVID-19 deaths

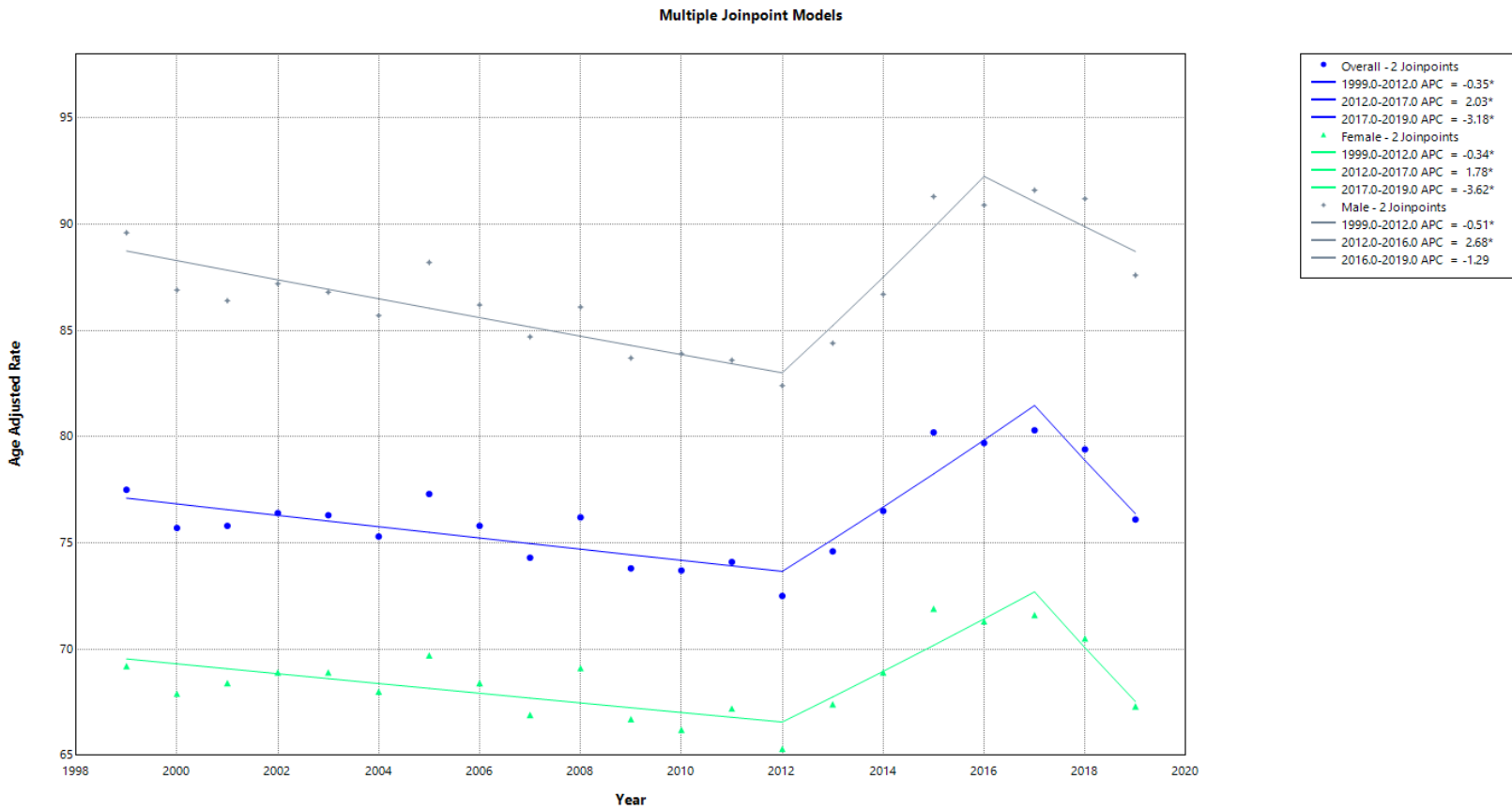
Year	Sepsis as underlying or contributing cause of death	Sepsis as underlying cause of death (sensitivity analysis)	Sepsis +COVID 19 related deaths	Sepsis deaths excluding COVID-19
1999	77.5	17.08	-	-
2000	75.7	17.17	-	-
2001	75.8	17.39	-	-
2002	76.4	18.06	-	-
2003	76.3	17.86	-	-
2004	75.3	17.21	-	-
2005	77.3	17.26	-	-
2006	75.8	16.98	-	-
2007	74.3	16.93	-	-
2008	76.2	17.14	-	-
2009	73.8	16.71	-	-
2010	73.7	16.07	-	-
2011	74.1	16.05	-	-
2012	72.5	15.76	-	-
2013	74.6	16.39	-	-
2014	76.5	16.31	-	-
2015	80.2	16.71	-	-
2016	79.7	16.31	-	-
2017	80.3	16.13	-	-
2018	79.4	15.67	-	-
2019	76.1	14.49	-	-
2020	90.3	14.89	13.29	77.01
2021	99.1	15.66	18.98	80.12
2022	89	15.4	9.88	79.12

Supplemental Table 9: Crude number of deaths for sensitivity analysis using sepsis as underlying cause of death, Sepsis + COVID-19 deaths and sepsis excluding COVID-19 deaths

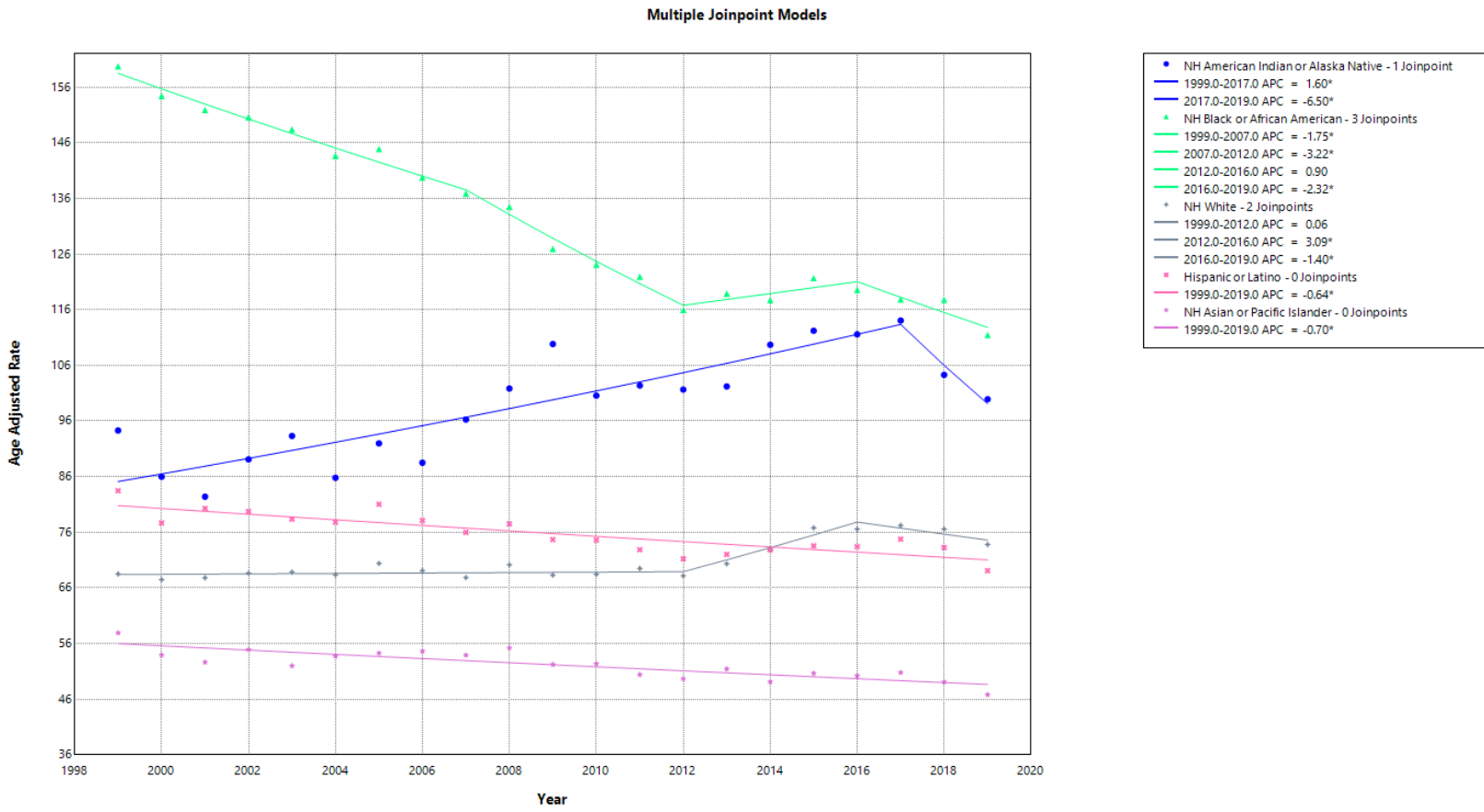
Year	Sepsis as underlying or contributing cause of death	Sepsis as underlying cause of death (sensitivity analysis)	Sepsis + COVID-19 related deaths	Sepsis deaths excluding COVID-19
1999	136812	30112	-	-
2000	135322	30687	-	-
2001	137787	31616	-	-
2002	141063	33274	-	-
2003	143225	33472	-	-
2004	143621	32814	-	-
2005	150432	33517	-	-
2006	150318	33654	-	-
2007	150389	34231	-	-
2008	157284	35345	-	-
2009	155441	35132	-	-
2010	157780	34326	-	-
2011	163118	35305	-	-
2012	163495	35426	-	-
2013	172068	37758	-	-

2014	180677	38538	-	-
2015	193580	40341	-	-
2016	196328	40134	-	-
2017	202135	40547	-	-
2018	204402	40350	-	-
2019	199628	38068	-	-
2020	240718	39747	35632	205086
2021	259410	40982	49741	209669
2022	242038	41905	26958	215080

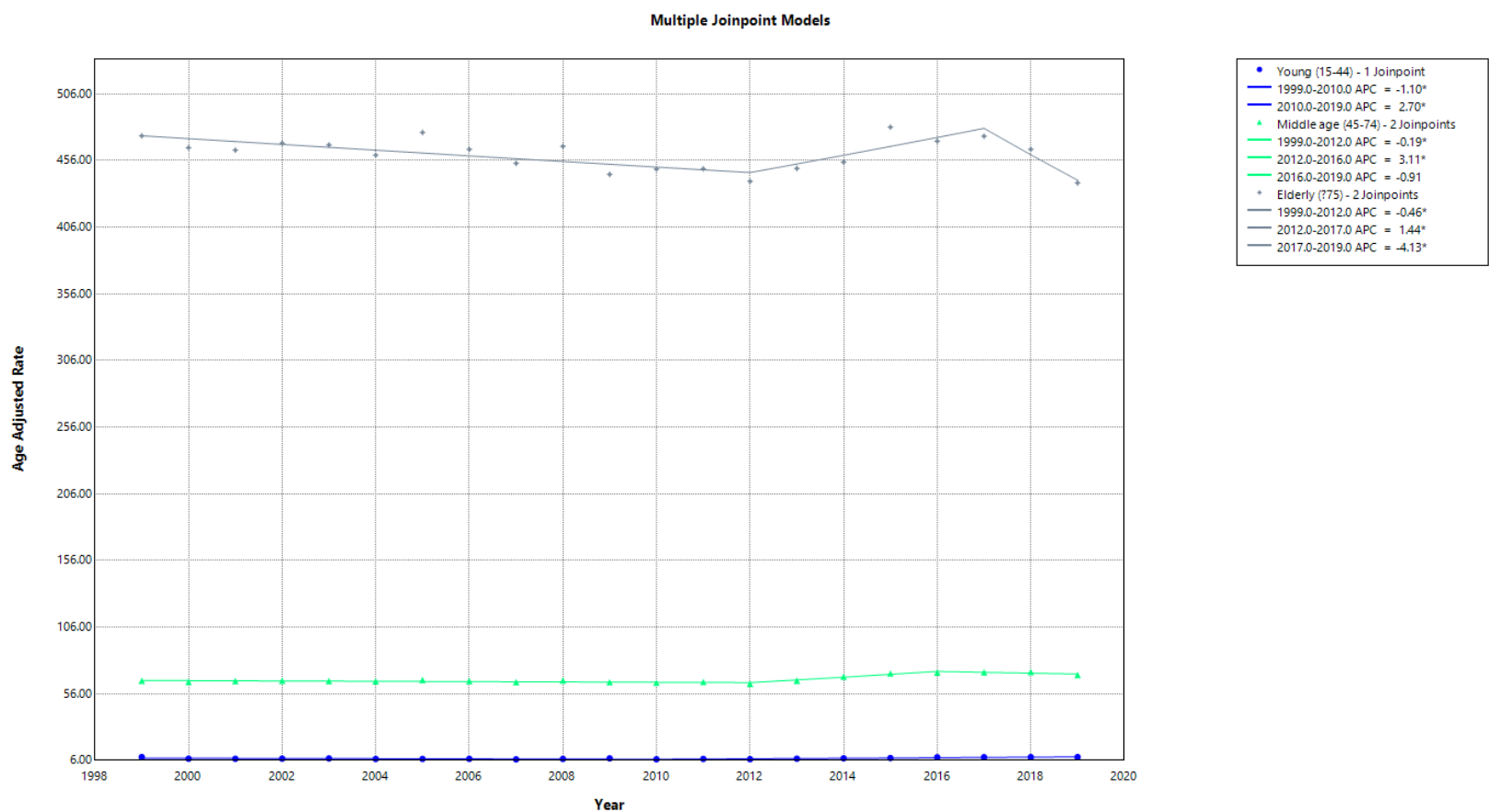
Supplemental Figure 1: Joinpoint models stratified by gender for sepsis age adjusted mortality rates from 1999-2019. *Indicates the APC is significantly different from 0.



Supplemental Figure 2: Age adjusted mortality rates with inflection points for data regarding race from 1999-2019. *Indicates the APC is significantly different from 0.



Supplemental Figure 3: Age adjusted mortality rates with inflection points for data regarding age groups from 1999-2019. *Indicates the APC is significantly different from 0.



Supplemental Figure 4: Age adjusted mortality rates with inflection points for data regarding United States census regions from 1999-2019. *Indicates the APC is significantly different from 0.

