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Supplemental Material

Warm Season and Emergency Department Visits to U.S. Children's Hospitals

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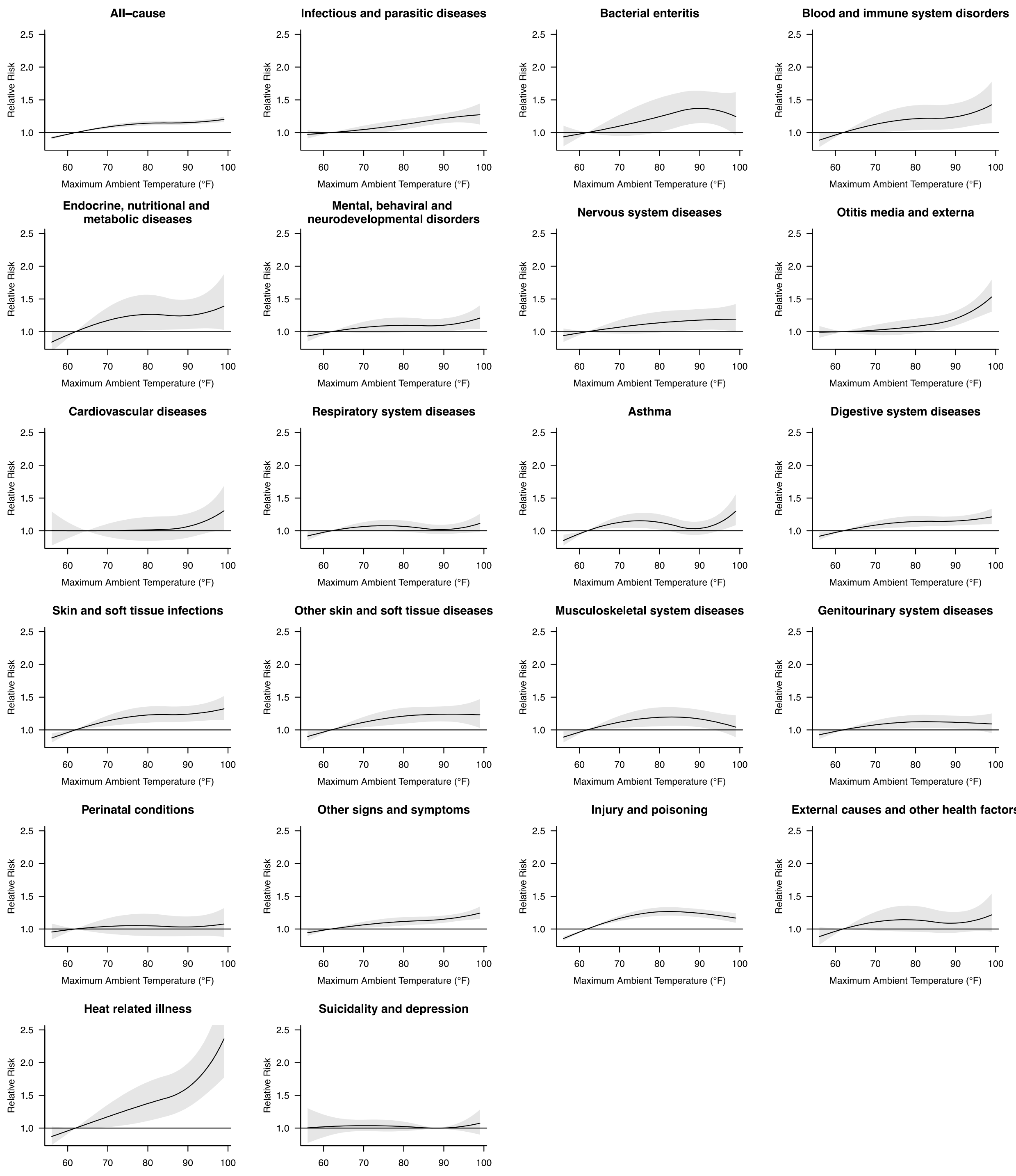

Figure S1. Estimated exposure-response functions and 95% confidence intervals of the association between daily maximum temperature and relative risk of emergency department visits for all causes and specific causes, summed over all lags (0-7 days), and fitted using a quadratic B-spline with 3 degrees of freedom. The temperature-ED visit association was modeled with a quasi-Poisson regression with distributed lag nonlinear model for each hospital, controlling for temporal trends, seasonality, relative humidity, federal holidays, and day of the week. Relative risks were then pooled across the 47 participating hospitals using multivariate random-effect meta-analyses with hospital-specific mean and range of temperatures as the predictors. The mean minimum morbidity daily maximum temperature across the 47 children's hospitals was the reference temperature.

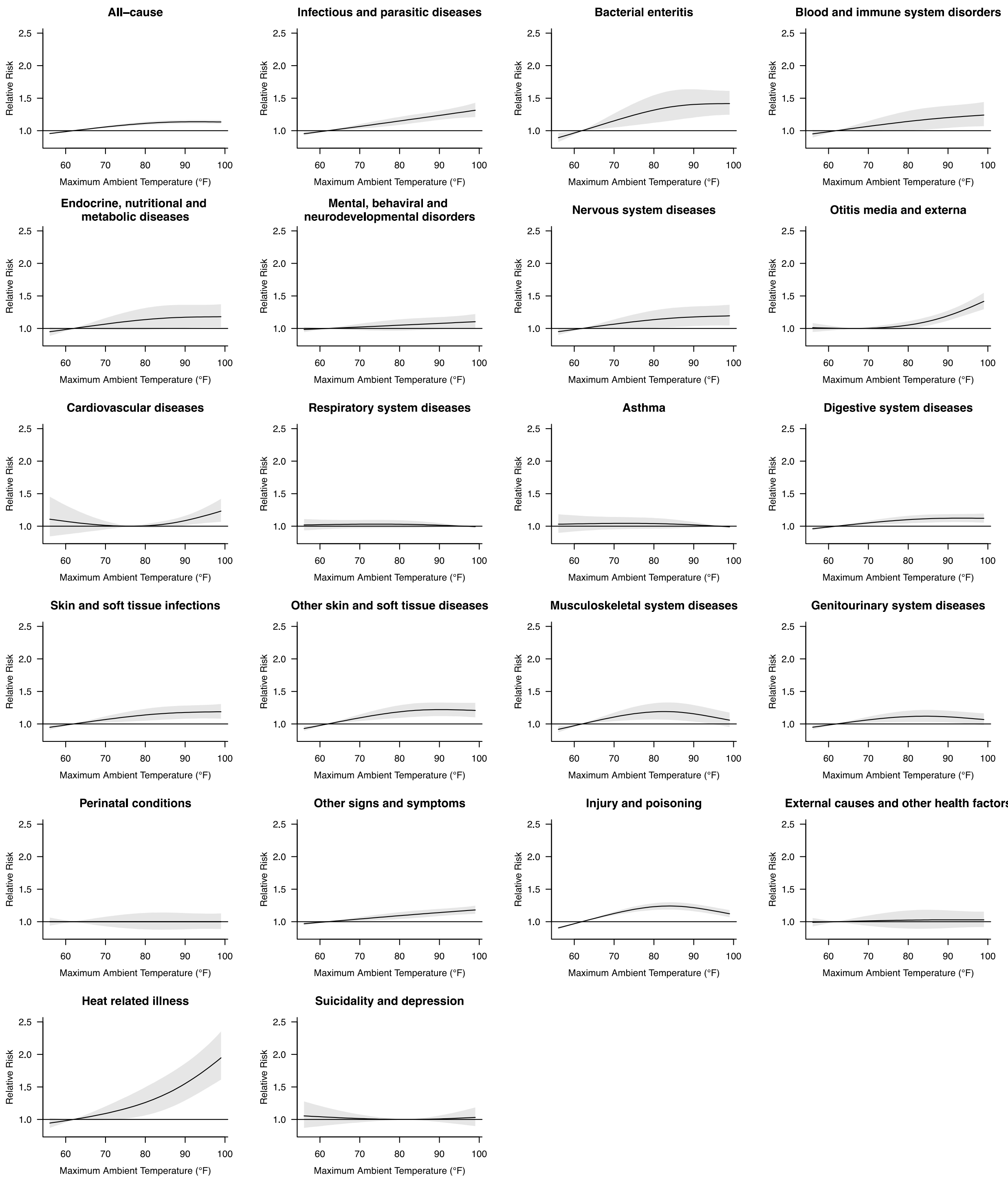

Figure S2. Estimated exposure-response functions and 95% confidence intervals as in Figure S1 but fitted with a natural cubic spline with 3 degrees of freedom for ambient temperature.

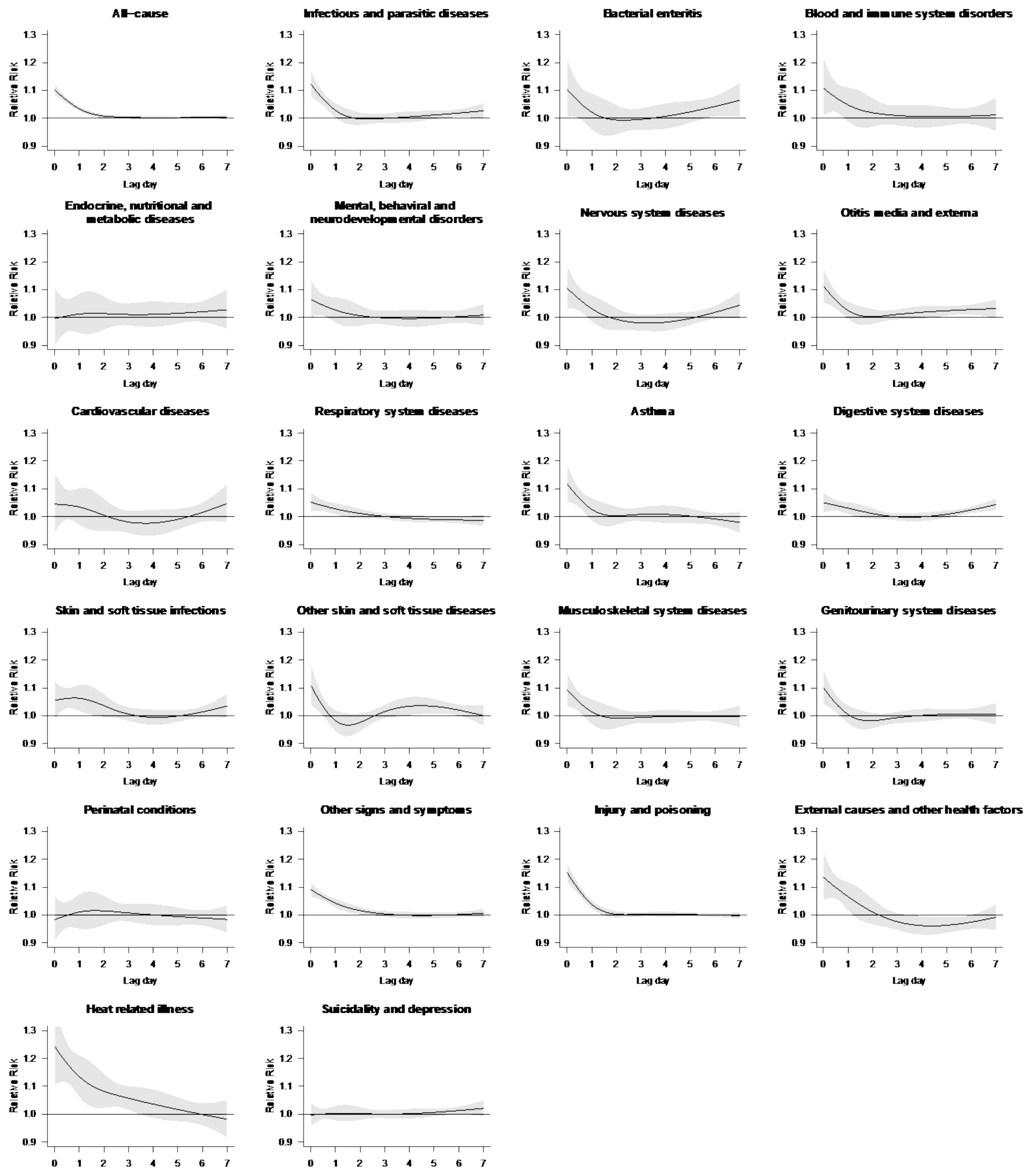

Figure S3. Estimated lag-response functions and 95% confidence intervals depicting the time course of the association between daily maximum temperature at the 95th percentile and relative risk of emergency department visits for all causes and specific causes, May through September of 2016-2018. The temperature-ED visit association was modeled with a quasi-Poisson regression with a distributed lag nonlinear model for each hospital, controlling for temporal trends, seasonality, relative humidity, federal holidays, and day of the week. The relationship between ambient temperature and emergency department visits was fitted using a quadratic B-spline with 3 degrees of freedom and the time-response function was fitted using a natural cubic B-spline with 2 knots placed at equal intervals on the log scale of lags up to 7 days. Relative risks are then pooled across the 47 participating hospitals using multivariate random-effect meta-analyses with hospital-specific mean and range of temperatures as the predictors. The mean minimum morbidity daily maximum temperature across the 47 children's hospitals was the reference temperature.

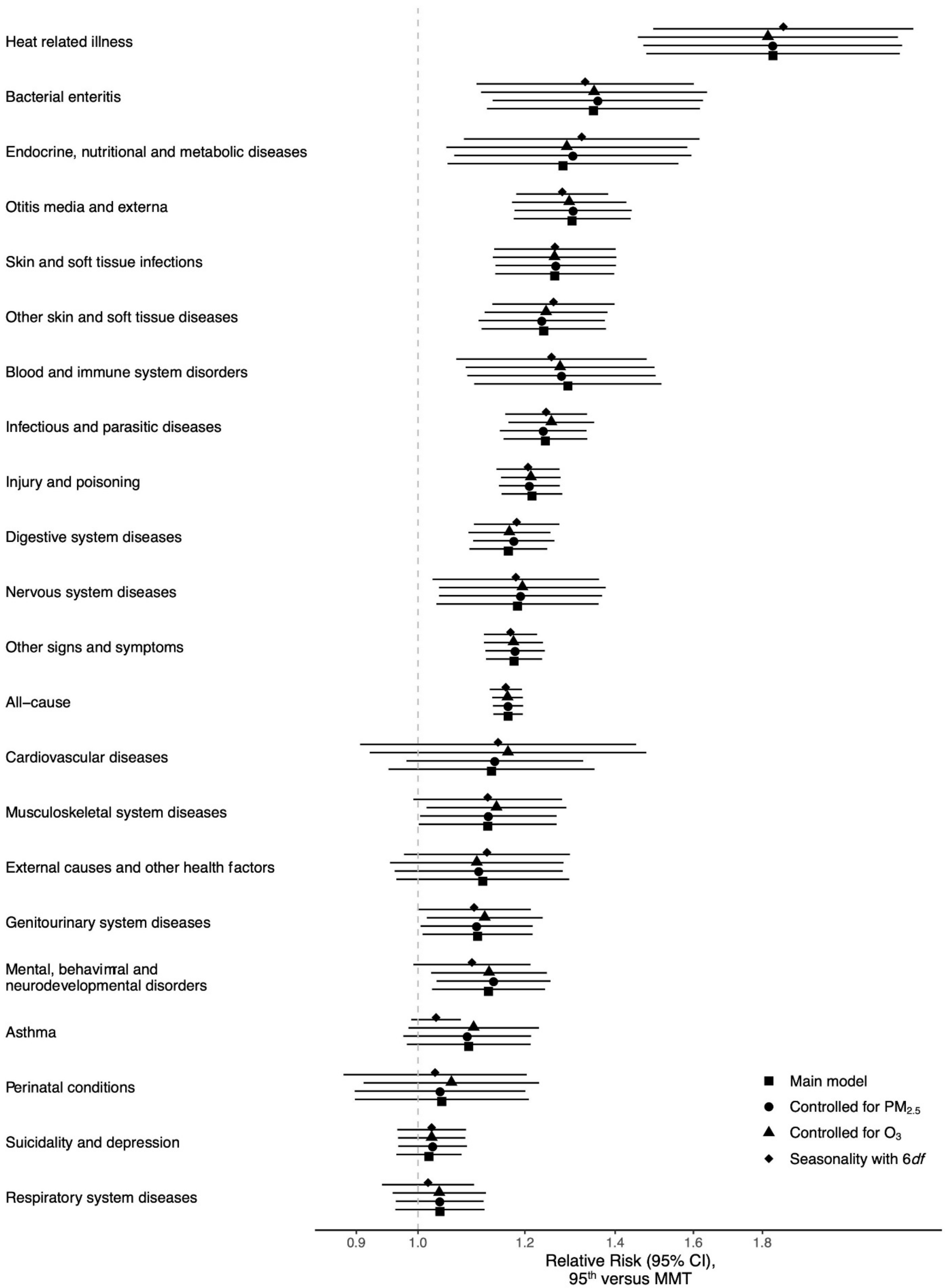

Figure S4. Sensitivity analyses controlling for air pollutants and seasonality on the association of specific causes of emergency department visits with daily maximum warm season (May to September) temperature among 47 participating children's hospitals, 2016-2018. Relative risks contrast the 95th percentile of the hospital-specific warm season (May to September) daily maximum temperature distribution to the hospital-specific minimum morbidity temperature (MMT) over lag 0-7 days among 47 participating children's hospitals from May to September, 2016-2018. The temperature-ED visit association was modeled with a quasi-Poisson regression with distributed lag nonlinear model for each hospital, controlling for temporal trends, seasonality, relative humidity, federal holidays, and day of the week. Relative risks are then pooled across the 47 participating hospitals using multivariate random-effect meta-analyses with hospital-specific mean and range of daily maximum temperatures as the predictors

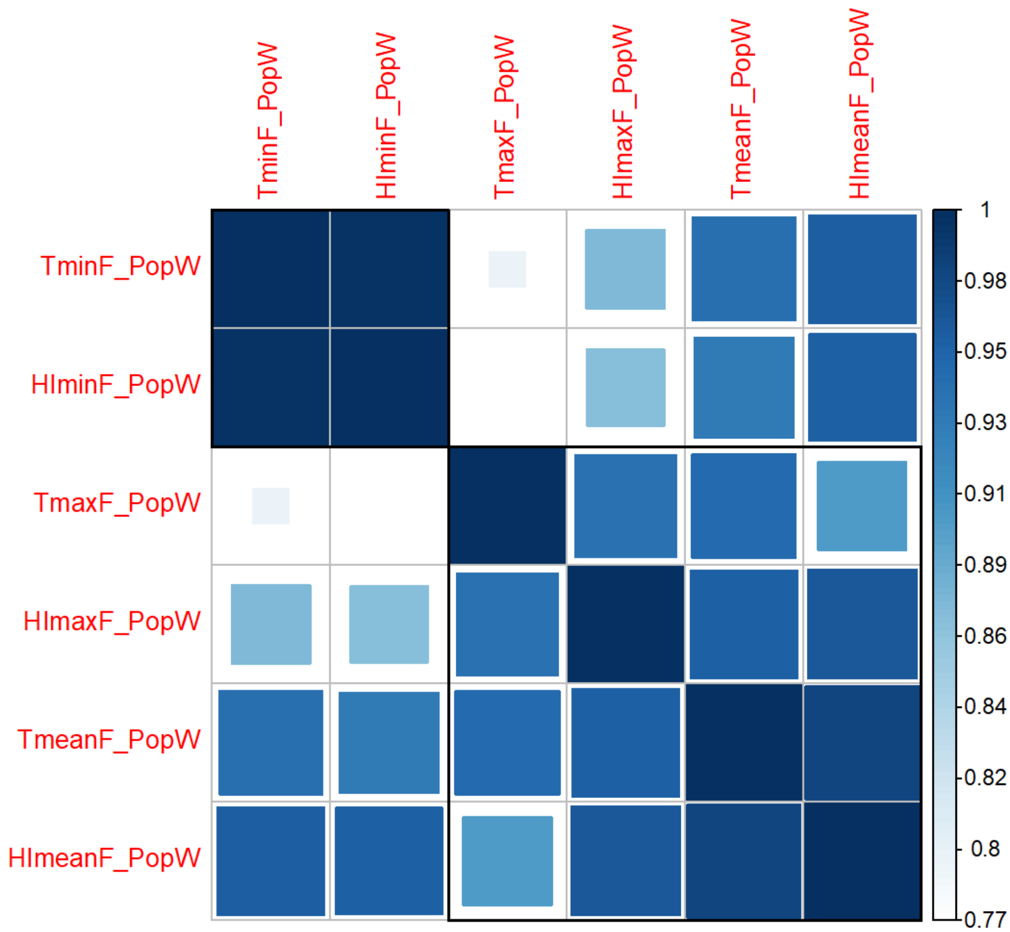

Figure S5. Pearson correlation between temperature metrics. Size and shading of the square is proportional to the correlation coefficients.

Note: TminF_PopW, population-weighted daily minimum ambient temperature; TmeanF_PopW, population-weighted daily mean ambient temperature; TmaxF_PopW, population-weighted daily maximum ambient temperature; HIminF_PopW, population-weighted daily minimum heat index; HImeanF_PopW, population-weighted daily mean heat index; HImaxF_PopW, population-weighted daily maximum heat index. Calculation of heat index was based upon the National Weather Service regression model (https://www.wpc.ncep.noaa.gov/html/heatindex_equation.shtml).

Table S1. Personal characteristics of the subjects for all causes and heat-related illness, 2016-2018.

Personal characteristics	All-cause N (%) (N=3,812,395)	Heat-related illness N (%) (N=28,729)
Age		
0-5 y	2,075,518 (54.4)	17,297 (60.2)
6-12 y	1,058,161 (27.8)	6,319 (22.0)
13-18 y	678,716 (17.8)	5,113 (17.8)
Sex		
Male	2,024,190 (53.1)	14,647 (51.0)
Female	1,787,677 (46.9)	14,077 (49.0)
Race[A]		
White	1,839,315 (48.2)	17,244 (60.0)
Black	1,072,037 (28.1)	5,647 (19.7)
Asian	104,615 (2.7)	889 (3.1)
Pacific Islander	14,506 (0.4)	110 (0.4)
American Indian	13,348 (0.4)	95 (0.3)
Other	597,996 (15.7)	3,734 (13.0)
Unknown	225,061(5.9)	1,413 (4.9)
Ethnicity		

Hispanic or Latino	1,057,184 (27.7)	6,519 (22.7)
Not Hispanic or Latino	2,509,678 (65.8)	20,260 (70.5)
Unknown	245,533 (6.4)	1,950 (6.8)
Insurance Status		
Public	2,445,946 (64.2)	16,882 (58.8)
Private	1,026,164 (26.9)	10,028 (34.9)
Other/unknown	340,285 (8.9)	1,819 (6.3)

[A] Some patients were identified with multiple race categories, which results in some totals greater than 100%.

Table S2. The attributable number and fraction for specific causes of emergency department visits attributable to moderate and extreme heat exposure over lag 0-7 days during May to September from 2016 to 2018 in 47 participating US children's hospitals.

Causes of emergency department visits	Moderate heat		Extreme heat	
	Attributable fraction (95% eCI) (%)	Attributable number (95% eCI)	Attributable fraction (95% eCI) (%)	Attributable number (95% eCI)
Heat related illness	28.3 (15.6, 33.8)	8135 (4478, 9719)	2.6 (1.9, 2.9)	760 (547, 837)
Otitis media and externa	12.0 (7.2, 15.3)	16241 (9750, 20670)	1.5 (1.1, 1.7)	1964 (1536, 2237)
Bacterial enteritis	23.7 (12.1, 29.2)	9843 (5010, 12119)	1.4 (0.8, 1.7)	599 (338, 720)
Infectious and parasitic diseases	12.7 (10.6, 14.4)	34092 (28644, 38623)	1.2 (1.0, 1.4)	3208 (2563, 3694)
Blood and immune system disorders	15.8 (10.0, 19.9)	5210 (3282, 6562)	1.2 (0.9, 1.5)	404 (289, 486)
Nervous system diseases	13.6 (5.9, 18.0)	9176 (4011, 12180)	0.9 (0.5, 1.2)	624 (310, 800)
Skin and soft tissue infections	16.6 (14.1, 18.6)	16002 (13609, 17940)	1.2 (0.9, 1.3)	1117 (884, 1278)
Other skin and soft tissue diseases	15.7 (12.5, 18.1)	14467 (11463, 16633)	1.1 (0.7, 1.3)	971 (616, 1189)
Other signs and symptoms	10.5 (7.5, 12.8)	78415 (56547, 96051)	0.9 (0.7, 1.0)	6379 (5042, 7360)
Endocrine, nutritional and metabolic diseases	18.0 (7.7, 22.7)	4604 (1982, 5801)	1.3 (0.5, 1.6)	322 (126, 406)
Cardiovascular diseases	9.6 (-4.1, 15.8)	1758 (-757, 2896)	1.1 (0.6, 1.5)	209 (101, 266)
Digestive system diseases	11.0 (7.2, 13.9)	28722 (18812, 36387)	0.8 (0.5, 0.9)	2016 (1377, 2474)
All-cause	11.0 (9.4, 12.6)	420745 (357890, 480468)	0.7 (0.6, 0.8)	27351 (23866, 30357)
Mental, behavioral and neurodevelopmental disorders	9.3 (5.6, 11.9)	6477 (3941, 8349)	0.7 (0.5, 0.8)	460 (336, 563)
Injury and poisoning	17.0 (14.0, 19.3)	157737 (13034, 179733)	0.8 (0.6, 0.9)	7206 (5485, 8479)
Genitourinary system diseases	9.1 (5.9, 11.5)	9806 (6345, 12459)	0.5 (0.2, 0.7)	546 (186, 775)
External causes and other health factors	11.2 (2.7, 15.8)	9384 (2274, 13216)	0.8 (0.4, 1.1)	710 (302, 936)

Respiratory system diseases	8.1 (4.5, 10.7)	47596 (26176, 62729)	0.6 (0.4, 0.7)	3380 (2084, 4281)
Musculoskeletal system diseases	10.2 (4.3, 14.0)	10503 (4391, 14380)	0.4 (0.0, 0.6)	441 (25, 655)
Asthma	10.9 (5.5, 14.6)	12848 (6497, 17211)	0.8 (0.5, 1.0)	969 (571, 1218)
Perinatal conditions	6.3 (-1.6, 10.9)	2922 (-730, 5084)	0.4 (-0.0, 0.7)	199 (-6.4, 340)
Suicidality and depression	3.5 (-1.4, 6.6)	1155 (-460, 2202)	0.3 (0.0, 0.5)	108 (12, 177)

Note: We fitted a time-series Poisson regression for each hospital, controlling for temporal trends, seasonality, relative humidity, federal holiday, and day of the week. We estimated temperature-ED visits associations with a distributed lag nonlinear model with 7 days of lag, and then pooled them in a multivariate random-effect meta-analyses with hospital-specific mean and range of daily maximum temperatures as the predictors. We then calculated the attributable number and fraction of ED visits based on the best linear unbiased prediction of the overall cumulative exposure-response association in each hospital. Moderate heat was defined as ambient temperature between cause-specific, hospital-specific minimum morbidity temperature (MMT) and the 95th percentile of the cause-specific, hospital-specific warm season daily maximum temperature distribution; and extreme heat was defined as ambient temperature at or above the 95th percentile of the cause-specific, hospital-specific warm season daily maximum temperature distribution. Points and whiskers denote the fraction and number of ED visits (and 95% confidence intervals). eCI, empirical confidence interval.

Table S3. Stratified pooled relative risk and 95% confidence interval of the association of cause-specific emergency department visits associated with days of extreme heat by age and sex.

Disease	Age				Sex		
	0-5y	6-12 y	13-18 y	p-value for heterogeneity	Male	Female	p-value for heterogeneity
Otitis media and externa	1.24 (1.1, 1.39)	1.7 (1.5, 1.93)	1.68 (1.39, 2.04)	<0.001	1.31 (1.17, 1.47)	1.3 (1.12, 1.51)	0.87
Bacterial enteritis	1.31 (1.02, 1.67)	1.49 (1.09, 2.04)	1.51 (0.97, 2.34)	0.70	1.47 (1.18, 1.82)	1.24 (1.09, 1.4)	0.12
Infectious and parasitic diseases	1.32 (1.21, 1.44)	1.11 (1.01, 1.22)	1.09 (0.89, 1.32)	0.01	1.31 (1.19, 1.43)	1.19 (1.1, 1.3)	0.14
Nervous system diseases	1.26 (1, 1.6)	1.13 (0.94, 1.36)	1.21 (1.06, 1.39)	0.73	1.33 (1.08, 1.63)	1.1 (0.94, 1.28)	0.14
Blood and immune system disorders	1.47 (1.13, 1.91)	1.17 (0.89, 1.54)	1.43 (1.04, 1.97)	0.39	1.51 (1.21, 1.9)	1.16 (0.91, 1.48)	0.10
Skin and soft tissue infections	1.22 (1.06, 1.4)	1.32 (1.11, 1.58)	1.42 (1.12, 1.79)	0.48	1.34 (1.16, 1.54)	1.21 (1.06, 1.38)	0.31
Endocrine, nutritional, and metabolic diseases	1.55 (1.07, 2.26)	1.16 (0.85, 1.58)	1.34 (0.97, 1.85)	0.48	1.24 (0.91, 1.69)	1.36 (1.04, 1.79)	0.63
Other signs and symptoms	1.22 (1.16, 1.29)	1.12 (1.05, 1.21)	1.15 (1.04, 1.27)	0.17	1.16 (1.1, 1.23)	1.19 (1.12, 1.27)	0.53
Cardiovascular diseases	1.15 (0.78, 1.71)	1.52 (0.95, 2.44)	1.28 (1.07, 1.53)	0.20	1.4 (1.02, 1.91)	1.12 (0.97, 1.3)	0.19
Other skin and soft tissue diseases	1.25 (1.09, 1.44)	1.2 (1, 1.43)	1.36 (1.04, 1.78)	0.73	1.27 (1.11, 1.45)	1.26 (1.1, 1.46)	0.69
Digestive system diseases	1.14 (1.05, 1.25)	1.27 (1.15, 1.41)	1.07 (0.94, 1.23)	0.10	1.21 (1.12, 1.3)	1.12 (1.02, 1.23)	0.24
Mental, behavioral and neurodevelopmental disorders	1.11 (0.91, 1.35)	1.1 (0.94, 1.29)	1.18 (1.04, 1.33)	0.76	1.17 (1.01, 1.36)	1.11 (0.97, 1.28)	0.61
Injury and poisoning	1.19 (1.12, 1.25)	1.2 (1.11, 1.3)	1.29 (1.17, 1.42)	0.30	1.24 (1.16, 1.31)	1.19 (1.12, 1.26)	0.34
Genitourinary system diseases	1.22 (1.07, 1.38)	1.08 (0.9, 1.28)	1.04 (0.88, 1.22)	0.24	1.15 (1, 1.33)	1.08 (0.97, 1.2)	0.43
Musculoskeletal system diseases	1.1 (0.92, 1.32)	1.07 (0.91, 1.26)	1.13 (0.97, 1.3)	0.79	1.08 (0.95, 1.23)	1.12 (0.97, 1.3)	0.53
External causes and other health factors	1.19 (1.12, 1.25)	1.2 (1.11, 1.3)	1.29 (1.17, 1.42)	0.30	1.24 (1.16, 1.31)	1.19 (1.12, 1.26)	0.34
Perinatal conditions	1.04 (0.9, 1.21)	NA	NA	NA	1.01 (0.94, 1.07)	1.21 (0.98, 1.49)	0.08

Respiratory system diseases	1.02 (0.94, 1.11)	1.09 (0.97, 1.22)	1.11 (0.98, 1.26)	0.37	1.05 (0.97, 1.14)	1.02 (0.93, 1.12)	0.61
Asthma	1.1 (0.97, 1.24)	1.13 (0.98, 1.3)	1.1 (0.87, 1.4)	0.87	1.16 (1.03, 1.3)	1.03 (0.98, 1.09)	0.03
Suicidality and depression	NA	1.01 (0.89, 1.14)	1.02 (0.95, 1.09)	0.90	1.07 (0.84, 1.37)	1.01 (0.93, 1.08)	0.60

[A]: Relative risks contrast the 95th percentile of the county-specific warm season (May to September) daily maximum temperature distribution to the county-specific minimum morbidity temperature (MMT), over lag 0-7 days among 47 participating children's hospitals from May to September, 2016-2018. The temperature-ED visit association was modeled with a quasi-Poisson regression with distributed lag nonlinear model for each hospital, controlling for temporal trends, seasonality, relative humidity, federal holidays, and day of the week. Relative risks are then pooled across the 47 participating hospitals using multivariate random-effect meta-analyses with hospital-specific mean and range of temperatures as the predictors. The temperature-ED visit association was modeled with a quasi-Poisson regression with distributed lag nonlinear model for each hospital, controlling for temporal trends, seasonality, relative humidity, federal holidays, and day of the week. Relative risks are then pooled across the 47 participating hospitals using multivariate random-effect meta-analyses with hospital-specific mean and range of temperatures as the predictors.

[B] NA=not applicable

Table S4. Stratified pooled relative risk and 95% confidence interval of the association of cause-specific emergency department visits associated with days of extreme heat by race and insurance status.

Disease	Race			Insurance Status			
	White	Other groups	p-value for heterogeneity	Public	Private	Other/unknown	p-value for heterogeneity
Otitis media and externa	1.16 (0.96, 1.41)	1.36 (1.17, 1.57)	0.21	1.26 (1.17, 1.36)	1.47 (1.19, 1.82)	1.48 (1.1, 1.98)	0.24
Bacterial enteritis	1.11 (0.99, 1.25)	1.57 (1.31, 1.87)	<0.001	1.6 (1.36, 1.89)	1.33 (0.96, 1.83)	NA	0.04
Infectious and parasitic diseases	1.26 (1.1, 1.45)	1.25 (1.12, 1.39)	0.81	1.25 (1.13, 1.39)	1.21 (1.04, 1.39)	1.21 (1.06, 1.37)	0.83
Nervous system diseases	1.05 (0.99, 1.12)	1.26 (1.02, 1.55)	<0.001	1.2 (1.01, 1.43)	1.27 (1.02, 1.58)	1.15 (0.73, 1.8)	0.81
Blood and immune system disorders	1.24 (0.91, 1.7)	1.25 (1.01, 1.55)	0.71	1.3 (1.03, 1.63)	1.32 (1.01, 1.73)	NA	0.04
Skin and soft tissue infections	1.12 (0.91, 1.39)	1.37 (1.19, 1.58)	0.12	1.25 (1.09, 1.44)	1.25 (1.02, 1.53)	1.51 (0.98, 2.34)	0.71
Endocrine, nutritional and metabolic diseases	1.08 (0.97, 1.21)	1.5 (1.14, 1.98)	0.001	1.19 (0.88, 1.62)	1.46 (1.08, 1.97)	NA	0.33
Other signs and symptoms	1.16 (1.07, 1.25)	1.22 (1.13, 1.31)	0.32	1.19 (1.1, 1.28)	1.09 (1.02, 1.16)	1.22 (0.96, 1.54)	0.04
Cardiovascular diseases	1.29 (0.81, 2.06)	1.41 (1.01, 1.96)	0.17	1.2 (0.86, 1.68)	1.19 (0.93, 1.51)	NA	0.90
Other skin and soft tissue diseases	1.25 (1, 1.58)	1.25 (1.09, 1.44)	0.88	1.18 (1.02, 1.36)	1.63 (1.24, 2.15)	NA	0.06
Digestive system diseases	1.17 (1.05, 1.3)	1.24 (1.12, 1.38)	0.22	1.19 (1.07, 1.33)	1.19 (1.05, 1.35)	1.19 (0.9, 1.57)	0.86
Mental, behavioral and neurodevelopmental disorders	1.01 (0.96, 1.05)	1.26 (1.08, 1.46)	<0.001	1.14 (0.97, 1.33)	1.12 (0.97, 1.31)	NA	0.54
Injury and poisoning	1.11 (1.03, 1.19)	1.29 (1.21, 1.38)	0.002	1.26 (1.16, 1.37)	1.16 (1.1, 1.22)	1.37 (1.12, 1.67)	0.07
Genitourinary system diseases	1.06 (0.99, 1.13)	1.1 (0.97, 1.24)	0.21	1.09 (0.95, 1.25)	1.16 (0.99, 1.37)	1.17 (0.84, 1.63)	0.76
Musculoskeletal system diseases	1.29 (1.08, 1.55)	1.2 (1.03, 1.39)	0.09	1.18 (1.01, 1.39)	1.04 (0.98, 1.1)	1.22 (0.88, 1.69)	0.01
External causes and other health factors	1.11 (1.03, 1.19)	1.29 (1.21, 1.38)	0.002	1.26 (1.16, 1.37)	1.16 (1.1, 1.22)	1.37 (1.12, 1.67)	0.07
Perinatal conditions	1.06 (0.77, 1.45)	1.13 (0.9, 1.43)	0.47	1.06 (0.85, 1.32)	1.02 (0.93, 1.13)	NA	0.93

Respiratory system diseases	1.05 (1, 1.09)	1.06 (0.98, 1.16)	0.51	1.05 (0.95, 1.15)	1.04 (0.92, 1.17)	1.08 (0.93, 1.26)	0.85
Asthma	1.05 (0.96, 1.15)	1.18 (1.03, 1.34)	0.16	1.11 (0.98, 1.26)	1.09 (0.88, 1.35)	1.1 (0.89, 1.35)	0.96
Suicidality and depression	1.23 (0.97, 1.57)	1.05 (0.93, 1.18)	0.11	1.01 (0.94, 1.09)	1.16 (0.94, 1.45)	NA	0.09

[A]: Relative risks contrast the 95th percentile of the hospital-specific warm season (May to September) daily maximum temperature distribution to the hospital-specific minimum morbidity temperature (MMT), over lag 0-7 days among 47 participating children's hospitals from May to September, 2016-2018. The temperature-ED visit association was modeled with a quasi-Poisson regression with distributed lag nonlinear model for each hospital, controlling for temporal trends, seasonality, relative humidity, federal holidays, and day of the week. Relative risks are then pooled across the 47 participating hospitals using multivariate random-effect meta-analyses with hospital-specific mean and range of temperatures as the predictors. The temperature-ED visit association was modeled with a quasi-Poisson regression with distributed lag nonlinear model for each hospital, controlling for temporal trends, seasonality, relative humidity, federal holidays, and day of the week. Relative risks are then pooled across the 47 participating hospitals using multivariate random-effect meta-analyses with hospital-specific mean and range of temperatures as the predictors.
[B] NA=not applicable

Table S5. Sample sizes for stratified analyses shown in tables S3 and S4

	0-5y	6-12y	13-18y	Male	Female	White	Minority race	Public insurance	Private insurance	Other insurance
Infectious and parasitic diseases	202980	46440	19725	142261	126875	108536	160232	196220	49235	23690
Endocrine, nutritional, and metabolic diseases	5956	8831	10798	11892	13688	15124	10474	14566	9542	1477
Blood and immune system disorders	13023	9991	9894	17199	15709	10930	21890	20482	10609	1817
Mental, behavioral and neurodevelopmental	2739	24326	42930	33615	36330	40682	29139	39556	26581	3858
Nervous system diseases	19491	22249	25787	31646	35865	38482	28832	38997	24124	4406
Otitis media and externa	99459	27703	8147	73481	61827	57740	77768	99913	21959	13437
Cardiovascular diseases	6305	5782	6223	10126	8146	10304	7954	10368	6409	1533
Respiratory system diseases	396829	137569	51844	330639	255586	234210	351510	414447	121922	49873
Digestive system diseases	132363	82198	47254	136371	125439	132492	129291	171256	69350	21209
Genitourinary system diseases	46666	30579	31073	40332	67983	55856	52055	68381	29782	10155
Musculoskeletal system diseases	25615	39598	37404	50570	52034	48684	53820	63126	30645	8846
Perinatal conditions	46474	30	10	24998	21507	24078	22469	28219	13424	4871
Other signs and symptoms	422008	191122	136007	377626	371457	381054	368204	476021	203217	69899
Injury and poisoning	416942	324516	188196	533132	396272	498704	430337	524118	321725	83811
External causes and other health factors	52380	19224	12116	43236	40438	37020	46397	54303	18565	10852
Heat related illness	17297	6319	5113	14647	14077	17214	11485	16882	10028	1819
Asthma	59858	44216	13523	73506	44088	36220	81261	82450	25998	9149
Bacterial enteritis	28365	9192	3913	22238	19230	18210	23112	28846	9796	2828
Skin and soft tissue infections	51004	28039	17437	49099	47378	45934	50266	64970	22212	9298

Other skin and soft tissue diseases	54900	24617	12518	46689	45344	36202	55889	67339	15341	9355
Suicidality and depression	573	8583	24073	12489	20738	20398	12915	16948	14537	1744
Total	2075518	1058161	678716	2024190	1787677	1836806	1973080	2445946	1026164	340285

References

Gasparrini A, Guo Y, Hashizume M, Kinney PL, Petkova EP, Lavigne E, et al. 2015. Temporal variation in heat–mortality associations: A multicountry study. Environ Health Perspect 123:1200–1207; doi:10.1289/ehp.1409070.

Gasparrini A, Guo Y, Hashizume M, Lavigne E, Tobias A, Zanobetti A, et al. 2016. Changes in Susceptibility to Heat during the Summer: A Multicountry Analysis. Am J Epidemiol 183:1027–1036; doi:10.1093/aje/kwv260.

R Code

```
### (c) Antonio Gasparrini 2015-2017
################################################################################
# FUNCTION FOR COMPUTING ATTRIBUTABLE MEASURES FROM DLNM
#   REQUIRES dlnm VERSION 2.2.0 AND ON
################################################################################
#
# Version: 25 January 2017
#
################################################################################
#
#   - x: AN EXPOSURE VECTOR OR (ONLY FOR dir="back") A MATRIX OF LAGGED EXPOSURES
#   - basis: THE CROSS-BASIS COMPUTED FROM x
#   - cases: THE CASES VECTOR OR (ONLY FOR dir="forw") THE MATRIX OF FUTURE CASES
#   - model: THE FITTED MODEL
#   - coef AND vcov: COEF AND VCOV FOR basis IF model IS NOT PROVIDED
#   - type: EITHER "an" OR "af" FOR ATTRIBUTABLE NUMBER OR FRACTION
#   - dir: EITHER "back" OR "forw" FOR BACKWARD OR FORWARD PERSPECTIVES
#   - tot: IF TRUE, THE TOTAL ATTRIBUTABLE RISK IS COMPUTED
#   - cen: THE REFERENCE VALUE USED AS COUNTERFACTUAL SCENARIO
#   - range: THE RANGE OF EXPOSURE. IF NULL, THE WHOLE RANGE IS USED
#   - sim: IF SIMULATION SAMPLES SHOULD BE RETURNED. ONLY FOR tot=TRUE
#   - nsim: NUMBER OF SIMULATION SAMPLES
################################################################################
attrdl <- function(x,basis,cases,model=NULL,coef=NULL,vcov=NULL,type="af",
                   dir="back",tot=TRUE,cen,range=NULL,sim=FALSE,nsim=5000) {
  ################################################################################
  #
  # CHECK VERSION OF THE DLNM PACKAGE
  if(packageVersion("dlnm")<"2.2.0")
    stop("update dlnm package to version >= 2.2.0")
  #
  # EXTRACT NAME AND CHECK type AND dir
  name <- deparse(substitute(basis))
  type <- match.arg(type,c("an","af"))
  dir <- match.arg(dir,c("back","forw"))
  #
  # DEFINE CENTERING
  if(missing(cen) && is.null(cen <- attr(basis,"argvar")$cen))
    stop("'cen' must be provided")
  if(!is.numeric(cen) && length(cen)>1L) stop("'cen' must be a numeric scalar")
```

```
attributes(basis)$argvar$cen <- NULL
#
# SELECT RANGE (FORCE TO CENTERING VALUE OTHERWISE, MEANING NULL RISK)
if(!is.null(range)) x[x<range[1]|x>range[2]] <- cen
#
# COMPUTE THE MATRIX OF
#   - LAGGED EXPOSURES IF dir="back"
#   - CONSTANT EXPOSURES ALONG LAGS IF dir="forw"
lag <- attr(basis,"lag")
if(NCOL(x)==1L) {
  at <- if(dir=="back") tsModel:::Lag(x,seq(lag[1],lag[2])) else
    matrix(rep(x,diff(lag)+1),length(x))
} else {
  if(dir=="forw") stop("'x' must be a vector when dir='forw'")
  if(ncol(at <- x)!=diff(lag)+1)
    stop("dimension of 'x' not compatible with 'basis'")
}
#
# NUMBER USED FOR THE CONTRIBUTION AT EACH TIME IN FORWARD TYPE
#   - IF cases PROVIDED AS A MATRIX, TAKE THE ROW AVERAGE
#   - IF PROVIDED AS A TIME SERIES, COMPUTE THE FORWARD MOVING AVERAGE
#   - THIS EXCLUDES MISSING ACCORDINGLY
# ALSO COMPUTE THE DENOMINATOR TO BE USED BELOW
if(NROW(cases)!=NROW(at)) stop("'x' and 'cases' not consistent")
if(NCOL(cases)>1L) {
  if(dir=="back") stop("'cases' must be a vector if dir='back'")
  if(ncol(cases)!=diff(lag)+1) stop("dimension of 'cases' not compatible")
  den <- sum(rowMeans(cases,na.rm=TRUE),na.rm=TRUE)
  cases <- rowMeans(cases)
} else {
  den <- sum(cases,na.rm=TRUE)
  if(dir=="forw")
    cases <- rowMeans(as.matrix(tsModel:::Lag(cases,-seq(lag[1],lag[2]))))
}
#
################################################################################
#
# EXTRACT COEF AND VCOV IF MODEL IS PROVIDED
if(!is.null(model)) {
  cond <- paste0(name,"[[:print:]]*v[0-9]{1,2}\\.l[0-9]{1,2}")
  if(ncol(basis)==1L) cond <- name
  model.class <- class(model)
  coef <- dlnm:::getcoef(model,model.class)
  ind <- grep(cond,names(coef))
  coef <- coef[ind]
  vcov <- dlnm:::getvcov(model,model.class)[ind,ind,drop=FALSE]
  model.link <- dlnm:::getlink(model,model.class)
  if(model.link!="log") stop("'model' must have a log link function")
}
#
```

```
# IF REDUCED ESTIMATES ARE PROVIDED
typebasis <- ifelse(length(coef)!=ncol(basis),"one","cb")
#
################################################################################
#
# PREPARE THE ARGUMENTS FOR TH BASIS TRANSFORMATION
predvar <- if(typebasis=="one") x else seq(NROW(at))
predlag <- if(typebasis=="one") 0 else dlnm:::seqlag(lag)
#
# CREATE THE MATRIX OF TRANSFORMED CENTRED VARIABLES (DEPENDENT ON typebasis)
if(typebasis=="cb") {
  Xpred <- dlnm:::mkXpred(typebasis,basis,at,predvar,predlag,cen)
  Xpredall <- 0
  for (i in seq(length(predlag))) {
    ind <- seq(length(predvar))+length(predvar)*(i-1)
    Xpredall <- Xpredall + Xpred[ind,,drop=FALSE]
  }
} else {
  basis <- do.call(onebasis,c(list(x=x),attr(basis,"argvar")))
  Xpredall <- dlnm:::mkXpred(typebasis,basis,x,predvar,predlag,cen)
}
#
# CHECK DIMENSIONS
if(length(coef)!=ncol(Xpredall))
  stop("arguments 'basis' do not match 'model' or 'coef'-'vcov'")
if(any(dim(vcov)!=c(length(coef),length(coef))))
  stop("arguments 'coef' and 'vcov' do no match")
if(typebasis=="one" && dir=="back")
  stop("only dir='forw' allowed for reduced estimates")
#
################################################################################
#
# COMPUTE AF AND AN
af <- 1-exp(-drop(as.matrix(Xpredall%*%coef)))
an <- af*cases
#
# TOTAL
#   - SELECT NON-MISSING OBS CONTRIBUTING TO COMPUTATION
#   - DERIVE TOTAL AF
#   - COMPUTE TOTAL AN WITH ADJUSTED DENOMINATOR (OBSERVED TOTAL NUMBER)
if(tot) {
  isna <- is.na(an)
  af <- sum(an[!isna])/sum(cases[!isna])
  an <- af*den
}
#
################################################################################
#
# EMPIRICAL CONFIDENCE INTERVALS
if(!tot && sim) {
```

```
    sim <- FALSE
    warning("simulation samples only returned for tot=T")
  }
  if(sim) {
    # SAMPLE COEF
    k <- length(coef)
    eigen <- eigen(vcov)
    X <- matrix(rnorm(length(coef)*nsim),nsim)
    coefsim <- coef + eigen$vectors %*% diag(sqrt(eigen$values),k) %*% t(X)
    # RUN THE LOOP
    # pre_afsim <- (1 - exp(- Xpredall %*% coefsim)) * cases # a matrix
    # afsim <- colSums(pre_afsim,na.rm=TRUE) / sum(cases[!isna],na.rm=TRUE)
    afsim <- apply(coefsim,2, function(coefi) {
      ani <- (1-exp(-drop(Xpredall%*%coefi)))*cases
      sum(ani[!is.na(ani)])/sum(cases[!is.na(ani)])
    })
    ansim <- afsim*den
  }
  #
  ################################################################################
  #
  res <- if(sim) {
    if(type=="an") ansim else afsim
  } else {
    if(type=="an") an else af
  }
  #
  return(res)
}

#
#=====================================================================
# This is the sample R code for two-stage-time-series analysis
# ==================================================================
library(tidyverse)
library(lubridate)
library(dlnm)
library(splines)
library(mvmeta)

load('phis.rda') # phis is the dataset

hospital_number <- as.character(unique(phis$Hospital_Number)) # get hospital unique number
dlist <- lapply(hospital_number, function(x) dset[dset$Hospital_Number==x,])
names(dlist) <- hospital_number

dis <- names(dlist[[1]])[5:26] # get the name of the diseases that are interested
tab <- matrix(NA,22,4) # create a matrix to store results
colnames(tab) <- c('dis', 'allRRfit', 'allRRlow', 'allRRhigh')
tab[1:22,1] <- dis
```

```
coef  <- matrix(NA, length(hospital_number), 3, dimnames=list(hospital_number))
vcov <- vector("list", length(hospital_number))
names(vcov) <- hospital_number
pert <- matrix(NA, length(hospital_number), 119, # create a matrix to store temperature percentiles
               dimnames = list(hospital_number, c("min", paste0('p', 1:9/10),
                                              paste0('p', 1:99), paste0('p99.',1:9), "max")))

avgtmean <- sapply(dlist, function(x) mean(x$TmaxF_PopW, na.rm = T)) # hospital-specific average
        temperature
rangetmean <- sapply(dlist, function(x) diff(range(x$TmaxF_PopW, na.rm = T)))
#hospital-specific range of temperature

cities <- data.frame(city = hospital_number)
datanew <- data.frame(avgtmean=mean(tapply(avgtmean, cities$city, mean)), # a new dataset for prediction
                  rangetmean=mean(tapply(rangetmean, cities$city, mean)))

for (j in seq_along(dis)) {
  for (i in seq_along(hospital_number)) {
    cat(i, '')
    data <- dlist[[i]] %>%
      mutate(dow=wday(Admit_Date),
           year=year(Admit_Date),
           ymonth=format(Admit_Date,"%Y-%m"))

    data$dos <- sequence(tapply(data$Admit_Date, data$year, length))

    # create the cross-basis term for temperature
    cb <- crossbasis(data$TmaxF_PopW, lag = 7, argvar = list(fun='bs', degree=2,
        knots=median(data$TmaxF_PopW),
                arglag = list(knots = logknots(7, 2)), group = data$year)

    eval(parse(text=paste0("model <- glm(", dis[j],"~ cb + factor(dow) + factor(holid) +
    ns(dos, 4) + ns(Admit_Date, 3/10) + ns(RHmax_PopW, 4),
                    family = quasipoisson, data = data, na.action = 'na.exclude')")))

    red <- crossreduce(cb, model, cen = median(data$TmaxF_PopW))
    coef[i,] <- coef(red)
    vcov[[i]] <- vcov(red)
    pert[i,] <- quantile(data$TmaxF_PopW, c(0:9/10, 1:99, 991:1000/10)/100,
                    na.rm = TRUE)
  }

  pmean <- as.data.frame(pert) %>% rownames_to_column(var = "fips_code") %>%
    select(-fips_code) %>% summarise_all(mean)

  mvall <- mvmeta(coef ~ avgtmean + rangetmean, vcov, method = "reml") # random-effects meta-regression

blup <- blup(mvall,vcov=T)
```

```
    bvar <- onebasis(unlist(pmean),fun="bs", degree=2,knots=pmean$p50)

    pmeanB <- pmean %>% select(p1:p99)
    cpall <- crosspred(bvar, coef=coef(mvall), vcov=vcov(mvall),
                    model.link = 'log',at=pmeanB)
    pmin <-  names(pmeanB[which.min((cpall$allfit))])


cpall <- crosspred(bvar, coef=coef(mvall), vcov=vcov(mvall),
                    model.link = 'log',  cen = pmeanB[pmin], at=pmean$p95, ci.level=(1-0.05/44)) # correct for
        multiple comparisons

    tab2[j,2] <- cpall$allRRfit
    tab2[j,3] <- cpall$allRRlow
    tab2[j,4] <- cpall$allRRhigh}

  tab <-  tab %>% as_tibble() %>% mutate(allRRfit=as.numeric(allRRfit),
                                    allRRlow=as.numeric(allRRlow),
                                    allRRhigh=as.numeric(allRRhigh)) %>%
  mutate(sig=case_when(allRRlow>1|allRRhigh<1~'sig',TRUE~'not')) %>%
  mutate(dis_f1=case_when(dis=='total'~'All-cause',
                        dis=='symptom'~
                          'Other signs and symptoms',
                        dis=='suic_depress'~'Suicidality and depression',
                        dis=='skin_soft'~ 'Skin and soft tissue infections',
                        dis=='skin_soft_other'~'Other skin and soft tissue diseases',
                        dis=='rd'~'Respiratory system diseases',
                        dis=='otitis'~'Otitis media and externa',
                        dis=='perinatal'~'Perinatal conditions',
                        dis=='nervous'~'Nervous system diseases',
                        dis=='muscul'~'Musculoskeletal system diseases',
                        dis=='mental'~'Mental, behaviral and \nneurodevelopmental disorders',
                        dis=='injury'~'Injury and poisoning',
                        dis=='infect_parasite'~'Infectious and parasitic diseases',
                        dis=='heat_deplet'~'Heat related illness',
                        dis=='genit'~'Genitourinary system diseases',
                        dis=='external'~'External causes and other health factors',
                        dis=='endo_nutri_metab'~'Endocrine, nutritional and metabolic diseases',
                        dis=='digest'~'Digestive system diseases',
                        dis=='cvd'~'Cardiovascular diseases',
                        dis=='blood'~'Blood and immune system disorders',
                        dis=='bact_ent'~'Bacterial enteritis',
                        dis=='asthma'~'Asthma')) %>%
    mutate(dis_f1 = fct_reorder(dis_f1, desc(allRRfit)))

### ==============================================
# This is the sample R code to calculate AN/AF
#===============================================

avgtmean <- sapply(dlist, function(x) mean(x$TmaxF_PopW, na.rm = T))
```

```
rangetmean <- sapply(dlist, function(x) diff(range(x$TmaxF_PopW, na.rm = T)))
cities <- data.frame(city = hospital_number)
datanew <- data.frame(avgtmean = mean(tapply(avgtmean, cities$city, mean)),
                      rangetmean = mean(tapply(rangetmean, cities$city, mean)))
set.seed(12345678)
hospital_number <- as.character(unique(phis$Hospital_Number))
dlist <- lapply(hospital_number, function(x) phis[phis$Hospital_Number == x, ])
names(dlist) <- hospital_number
dis <- names(dlist[[1]])[5:26]

tab2b <- matrix(NA,22,7) # Create a matrix to store results
colnames(tab2b) <- c('dis', 'antot','antotlow','antothigh','aftot','aftotlow','aftothigh')
tab2b[1:22,1] <- dis
source("attrdl.R") # source the 'attrdl.R' function

for (j in seq_along(dis)) {
   toted <- rep(NA, length(hospital_number))
   names(toted) <- hospital_number

   # store results for point AN
   matsim <- matrix(NA, length(hospital_number), 1,
                    dimnames=list(hospital_number, c('total_heat')))

   nsim <- 5000 # define number of simulation

   # store results for simulated AN
   arraysim <- array(NA, dim = c(length(hospital_number), 1, nsim),
                     dimnames = list(hospital_number, c('total_heat')))

    # store coefficients and covariates
   coef  <- matrix(NA, length(hospital_number), 1, dimnames = list(hospital_number))
   vcov <- vector("list", length(hospital_number))
   names(vcov) <- hospital_number
   pert <- matrix(NA, length(hospital_number), 119, # create a matrix to store temperature percentiles
                  dimnames = list(hospital_number, c("min", paste0('p', 1:9/10), paste0('p', 1:99),
                                               paste0('p99.',1:9), "max")))

   for (k in seq_along(hospital_number)) {
     data <- dlist[[k]] %>%
       mutate(dow = wday(Admit_Date), year = year(Admit_Date), ymonth = format(Admit_Date, "%Y-%m"))

     data$dos <- sequence(tapply(data$Admit_Date, data$year, length))

     # create the cross-basis term for temperature
     cb <- crossbasis(data$TmaxF_PopW, lag = 7, argvar = list(fun='bs', degree=2,
          knots=median(data$TmaxF_PopW),  arglag = list(knots = logknots(7, 2)), group = data$year)

     eval(parse(text=paste0("model <- glm(", dis[j], " ~ cb + factor(dow) +
     factor(holid) + ns(dos, 4) + ns(Admit_Date, 3/10) + ns(RHmax_PopW, 4),
                        family = quasipoisson, data = data, na.action = 'na.exclude')")))
```

```
    red <- crossreduce(cb, model, cen = median(data$TmaxF_PopW))
    coef[k, ] <- coef(red)
    vcov[[k]] <- vcov(red)
    pert[k, ] <- quantile(data$TmaxF_PopW, c(0:9/10, 1:99, 991:1000/10)/100,
                          na.rm = TRUE)
  }
  mvall <- mvmeta(coef ~ avgtmean + rangetmean, vcov, method = "reml") # random-effects meta-regression
  blup <- blup(mvall, vcov=T) # blup


 bvar <- onebasis(unlist(pmean),fun="bs", degree=2,knots=pmean$p50)

  pmeanB <- pmean %>% select(p1:p99)
  cpall <- crosspred(bvar, coef=coef(mvall), vcov=vcov(mvall),
                     model.link = 'log',at=pmeanB)
  pmin <-  names(pmeanB[which.min((cpall$allfit))])

####################################################################################
  # RE-CENTERING

  # GENERATE THE MATRIX FOR STORING THE RESULTS
  minperchosp <- mintemphosp <- rep(NA,length(dlist))
  names(mintemphosp) <- names(minperchosp) <- hospital_number

  # DEFINE MINIMUM MORTALITY VALUES: EXCLUDE LOW AND VERY HOT TEMPERATURE
  for(l in seq(length(dlist))) {
    data <- dlist[[l]]
    argvar=list(fun='bs',degree=2, knots=median(data$TmaxF_PopW,0.5))
    predvar <- quantile(data$TmaxF_PopW,1:99/100,na.rm=T)
    # REDEFINE THE FUNCTION USING ALL THE ARGUMENTS (BOUNDARY KNOTS INCLUDED)
    argvar <- list(x=predvar,fun='bs', degree=2,
                   knots=quantile(data$TmaxF_PopW,0.5,na.rm=T),
                   Bound=range(data$TmaxF_PopW,na.rm=T))
    bvar <- do.call(onebasis,argvar)
    minperchosp[l] <- (1:99)[which.min((bvar%*%blup[[l]]$blup))]
    mintemphosp[l] <- quantile(data$TmaxF_PopW,minperchosp[l]/100,na.rm=T)
    #      print(minperchosp[l])
  }


  for (i in seq_along(hospital_number)) {
    cat(i, '')
    data <- dlist[[i]] %>%
      mutate(dow = wday(Admit_Date), year = year(Admit_Date), ymonth = format(Admit_Date, "%Y-%m"))

    data$dos <- sequence(tapply(data$Admit_Date, data$year, length))

    cb <- crossbasis(data$TmaxF_PopW, lag = 7, argvar = list(fun='bs', degree=2,
        knots=median(data$TmaxF_PopW),  arglag = list(knots = logknots(7, 2)), group = data$year)
```

```
    # for point AN
    eval(parse(text=paste0("matsim[i,'total_heat'] <- attrdl(data$TmaxF_PopW, cb, data$", dis[j],
    ', coef=blup[[i]]$blup, vcov=blup[[i]]$vcov, type = "an", dir = "forw", cen= mintemphosp[i],
                        range = c(mintemphosp[i],2000))')))
    # for simulated AN
    eval(parse(text=paste0('arraysim[i,"total_heat",] <- attrdl(data$TmaxF_PopW,cb, data$', dis[j],
    ',coef=blup[[i]]$blup, vcov=blup[[i]]$vcov,type="an",dir="forw", cen= mintemphosp[i],
                   range = c(mintemphosp[i],2000),sim=T,nsim=nsim)')))
    # total recorded ED visits
    eval(parse(text=paste0('toted[i] <- sum(data$', dis[j],',na.rm = T)')))
  }

  # total AN
  antot <- colSums(matsim)
  antotlow <- apply(apply(arraysim,c(2,3),sum),1,quantile, 0.05/44) # correct for multiple comparisons
  antothigh <- apply(apply(arraysim,c(2,3),sum),1,quantile,(1-0.05/44))
  totedtot <- sum(toted) # sum of the observed ED visits

  #=========================================
  # ATTRIBUTABLE FRACTION
  # TOTAL
  aftot <- antot/totedtot*100
  aftotlow <- antotlow/totedtot*100
  aftothigh <- antothigh/totedtot*100

  if(heat=='total_heat'){
    tab2b[j,2] <- antot[1]; tab2b[j,3] <- antotlow[1]; tab2b[j,4] <- antothigh[1]
    tab2b[j,5] <- aftot[1]; tab2b[j,6] <- aftotlow[1]; tab2b[j,7] <- aftothigh[1]
  }
}

tab2b <- tab2b %>% as_tibble() %>%
  mutate(antot=as.numeric(antot),antotlow=as.numeric(antotlow),antothigh=as.numeric(antothigh),
       aftot=as.numeric(aftot),aftotlow=as.numeric(aftotlow),aftothigh=as.numeric(aftothigh)) %>%
  mutate(dis_f1=case_when(dis=='total'~'All-cause',
                        dis=='symptom'~
                          'Other signs and symptoms',
                        dis=='suic_depress'~'Suicidality and depression',
                        dis=='skin_soft'~ 'Skin and soft tissue infections',
                        dis=='skin_soft_other'~'Other skin and soft tissue diseases',
                        dis=='rd'~'Respiratory system diseases',
                        dis=='otitis'~'Otitis media and externa',
                        dis=='perinatal'~'Perinatal conditions',
                        dis=='nervous'~'Nervous system diseases',
                        dis=='muscul'~'Musculoskeletal system diseases',
                        dis=='mental'~'Mental, behaviral and \nneurodevelopmental disorders',
                        dis=='injury'~'Injury and poisoning',
                        dis=='infect_parasite'~'Infectious and parasitic diseases',
                        dis=='heat_deplet'~'Heat related illness',
```

```
dis=='genit'~'Genitourinary system diseases',
dis=='external'~'External causes and other health factors',
dis=='endo_nutri_metab'~'Endocrine, nutritional and metabolic diseases',
dis=='digest'~'Digestive system diseases',
dis=='cvd'~'Cardiovascular diseases',
dis=='blood'~'Blood and immune system disorders',
dis=='bact_ent'~'Bacterial enteritis',
dis=='asthma'~'Asthma'))
```