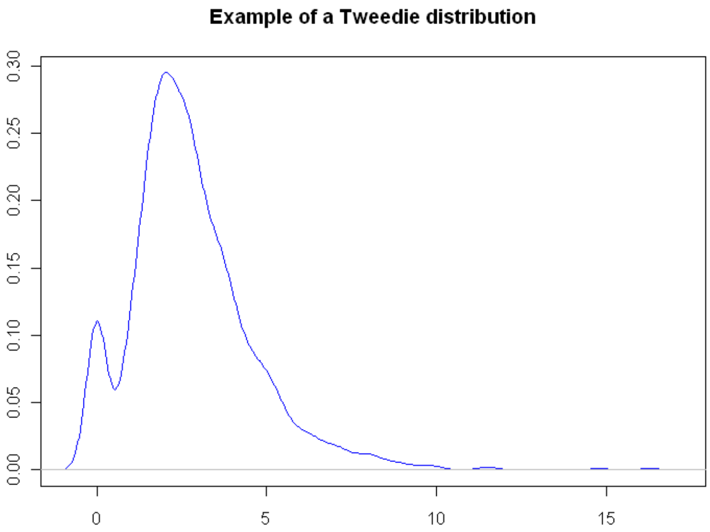
eAppendix 1: Location of the gene promoter and region amplified

Gene	Chromo-some	Promoter *Start* *end*	Amplicon *Start* *end*	Location	Promoter	CpGs (position)
F3	1	94779671 94780502	94779878 94780068	CpG island	Yes	94779947 (pos1) 94779950 (pos2) 94779956 (pos3) 94779958 (pos4) 94779974 (pos5)
ICAM	19	10242017 10242937	10242034 10242283	CpG island	Yes	10242236 (pos1) 10242225 (pos2) 10242218 (pos3)
TLR2	4	154824391 154824991	154824566 154824754	CpG island	Yes	154824709 (pos1) 154824713 (pos2) 154824715 (pos3) 154824723 (pos4) 154824727 (pos5)
CRAT	9	130912702 130913404	130912776 130912862	CpG island	Yes	130912824 (pos1) 130912806 (pos2)
OGG1	3	9766128 9766775	9766288 9766514	CpG island	Yes	9766356 (pos1) 9766366 (pos2) 9766373 (pos3) 9766380 (pos4)
IFNγ	12	66839561 66840293	66840120 66840260	non-CpG island		66840192 (pos1) 66840186 (pos2)
IL6	7	22732791 22733685	22733758 22733893	non-CpG island	No	22733847 (pos1) 22733841 (pos2)
iNOS	17	23149861 23150461	23149873 23149990	non-CpG island	Yes	23149929 (pos1) 23149936 (pos2)
GCR	5	142760496 142761097	142760531 142760806	non-CpG island	Yes	142760565

eAppendix 2: Tweedie distribution



eAppendix 3: Blood count characteristics of the NAS participants across visits

	Percent of neutrophils	**Percent of lymphocytes**	**Percent of monocytes**	**Percent of basophils**
Baseline (n=777)	[48, 62, 74]	[15, 26, 38]	[6, 8, 12]	[0, 1, 1]
$N_{missing}$	22	22	29	29
Among participants having one visit (n_1=221)				
Visit 1	[48, 63, 77]	[13, 25, 37]	[5, 8, 12]	[0, 1, 1]
Among participants having two visits (n_1=217)				
Visit 1	[47, 62, 74]	[15, 25, 40]	[6, 9, 13]	[0, 1, 1]
Visit 2	[48, 64, 75]	[14, 24, 37]	[6, 9, 13]	[0, 1, 1]
Among participants having three visits (n_3=216)				
Visit 1	[47, 62, 72]	[16, 26, 39]	[6, 9, 12]	[0, 1, 1]
Visit 2	[48, 62, 74]	[15, 26, 38]	[6, 9, 12]	[0, 1, 1]
Visit 3	[48, 62, 76]	[13, 25, 39]	[5, 8, 12]	[0, 1, 1]
Among participants having four visits (n_4=120)				
Visit 1	[49, 61, 74]	[15, 26, 36]	[6, 8, 12]	[0, 1, 1]
Visit 2	[46, 62, 78]	[13, 25, 40]	[5, 9, 12]	[0, 1, 1]
Visit 3	[47, 61, 76]	[13, 26, 37]	[5, 9, 12]	[0, 1, 1]
Visit 4	[50, 63, 76]	[12, 25, 37]	[5, 8, 12]	[0, 1, 1]
Among participants having five visits (n_5=3)				
Visit 1	[49, 58, 67]	[18, 25, 33]	[9, 10, 11]	[1, 1, 1]
Visit 2	[59, 64, 70]	[18, 22, 26]	[8, 9, 10]	[0, 0, 1]
Visit 3	[16, 54, 68]	[18, 29, 78]	[3, 9, 11]	[1, 1, 1]
Visit 4	[14, 60, 67]	[17, 18, 83]	[2, 10, 14]	[0, 0, 1]
Visit 5	[15, 55, 75]	[13, 24, 82]	[2, 9, 11]	[0, 1, 1]

eAppendix 4: Distributions of the weather and air pollution variables

	$n_{observations}$	$n_{missing}$	IQR	Percentiles		
				5th	50th	95th
Temperature (ºC)						
1 week	1,798	0	13ºC	-1ºC	13ºC	24ºC
2 weeks	1,798	0	13ºC	-1ºC	13ºC	24ºC
3 weeks	1,798	0	13ºC	-1ºC	13ºC	23ºC
Relative humidity (%)						
1 week	1,798	0	12%	53%	68%	82%
2 weeks	1,798	0	10%	56%	68%	80%
3 weeks	1,798	0	9%	56%	68%	78%
$PM_{2.5}$ (μg/m^3)						
1 week	1,798	0	4.3	5.8	9.5	16.0
2 weeks	1,798	0	3.8	6.2	9.5	15.2
3 weeks	1,798	0	3.5	6.3	9.6	14.8

eAppendix 5: Spearman correlations between weather variables and $PM_{2.5}$ (1-week moving average)

	Temperature	**Relative humidity**	**Absolute humidity**	**Barometric pressure**	**$PM_{2.5}$**
Temperature	1	0.22*	0.96*	-0.06*	0.30*
Relative humidity		1	0.46*	0.05*	0.10*
Absolute humidity			1	-0.04	0.30*
Barometric pressure				1	0.08*
$PM_{2.5}$					1

*p-value<0.05

eAppendix 6a: Gene specific DNA methylation (% 5mC) across visits [5th, 50th, and 95th percentiles]

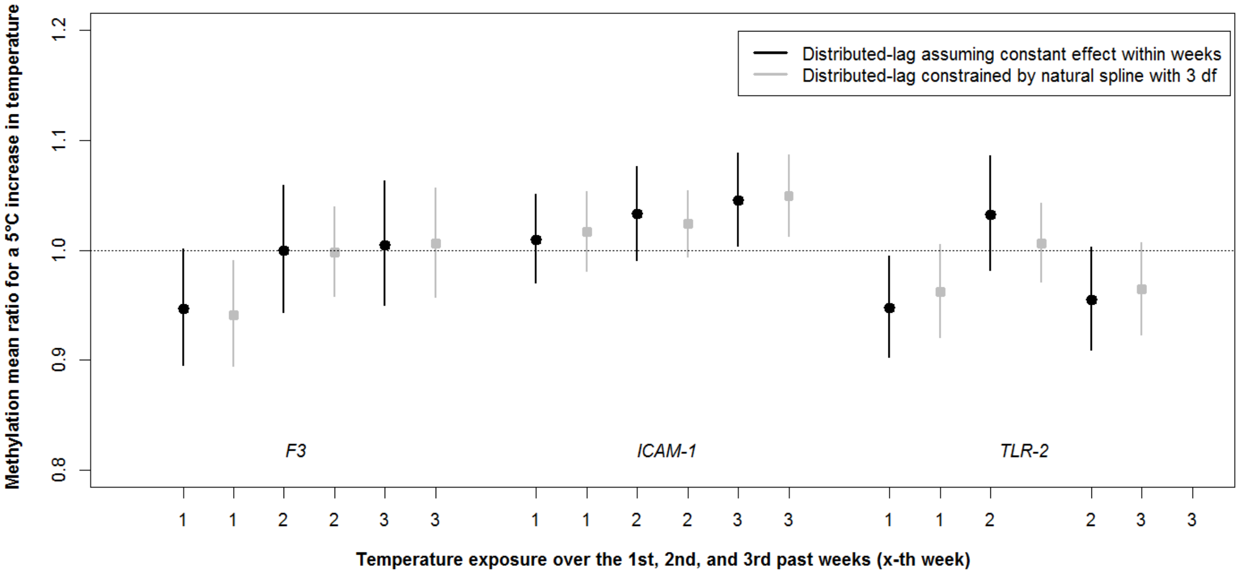
Gene	***F3***	***ICAM-1***	***TLR-2***	***CRAT***	***OGG***
$n_{observations}$	1,533	1,424	1,424	1,669	1,159
$n_{missing}$	265	374	374	129	639
Baseline (n=777)	[1.0, 2.0, 4.5]	[2.2, 4.1, 8.2]	[1.5, 2.8, 5.3]	[1.7, 3.1, 5.0]	[0.8, 1.8, 4.1]
Participants having one visit (n=221)					
Visit 1	[1.1, 1.9, 3.5]	[2.6, 4.3, 7.7]	[1.4, 2.8, 5.0]	[2.0, 3.2, 4.6]	[0.8, 1.6, 4.1]
Participants having two visits (n=217)					
Visit 1	[1.0, 2.0, 4.2]	[2.2, 4.1, 8.4]	[1.5, 2.6, 5.1]	[1.7, 3.1, 5.1]	[0.8, 1.8, 4.1]
Visit 2	[0.8, 2.3, 4.4]	[2.2, 3.9, 8.2]	[1.0, 2.6, 5.7]	[1.6, 3.2, 5.2]	[0.5, 1.7, 4.5]
Participants having three visits (n=216)					
Visit 1	[1.0, 2.0,4.5]	[2.1, 3.8, 7.6]	[1.3, 2.8, 5.2]	[1.6, 3.0, 5.1]	[1.0, 2.0, 4.1]
Visit 2	[0.9, 2.5, 4.5]	[2.1, 3.6, 7.8]	[1.5, 2.6, 5.3]	[1.5, 2.9, 5.6]	[0.8, 2.0, 4.4]
Visit 3	[0.9, 1.8, 4.3]	[2.9, 4.2, 6.7]	[0.9, 2.1, 4.9]	[1.9, 3.3, 5.2]	[0.3, 1.3, 6.0]
Participants having four visits (n=120)					
Visit 1	[0.4, 2.3, 5.2]	[2.1,4.0, 9.8]	[1.9, 3.3, 5.9]	[1.6, 3.0, 5.5]	[0.9, 2.0, 5.3]
Visit 2	[1.0, 2.4, 4.8]	[2.0, 3.3, 9.9]	[1.7, 3.1, 6.0]	[1.6, 2.9, 5.1]	[0.6, 1.5, 4.3]
Visit 3	[1.8, 2.9, 4.5]	[2.5, 4.4, 6.1]	[1.5, 3.0, 6.3]	[2.4, 3.5, 5.3]	[0.7, 2.9, 6.0]
Visit 4	[0.7, 1.3, 3.1]	[2.8, 4.0, 8.3]	[0.9, 1.6, 4.0]	[1.9, 3.3, 5.7]	[0.4, 0.7, 4.3]
Participants having five visits (n=3)					
Visit 1	[NA*, 3.0, 3.2]	[3.0, 3.3, 4.5]	[2.3, 3.1, 3.9]	[2.6, 2.6, 2.6]	[1.0, 2.4, 3.8]
Visit 2	[2.6, 2.9, 3.3]	[NA*, 2.6, 2.7]	[NA*, 1.9, 2.8]	[4.1, 4.6, 5.7]	[1.3, 1.7, 2.2]
Visit 3	[2.4, 3.6, 8.5]	[NA*, 3.5, 3.7]	[NA*, NA*, 4.9]	[3.3, 4.6, 5.8]	[5.2, 5.2, 5.2]
Visit 4	[NA*, NA*, 2.2]	[2.5, 4.2, 7.1]	[NA*, NA*, 2.9]	[2.6, 2.9, 3.2]	[0.7, 1.4, 2.9]
Visit 5	[0.7, 1.6, 34.6]	[3.2, 5.2, 6.0]	[1.4, 2.1, 3.5]	[2.6, 2.7, 2.8]	[0.3, 0.6, 0.9]

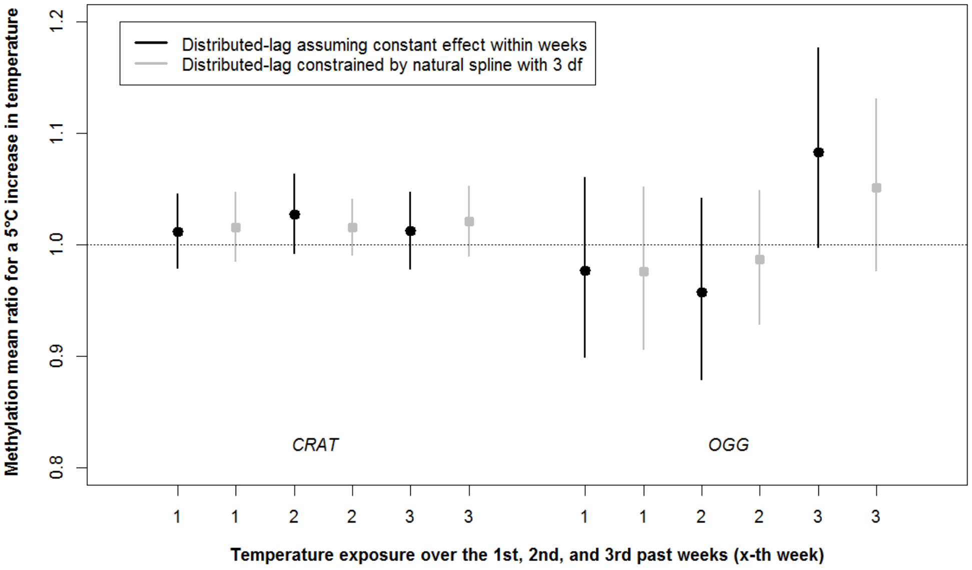
*NA=missing data

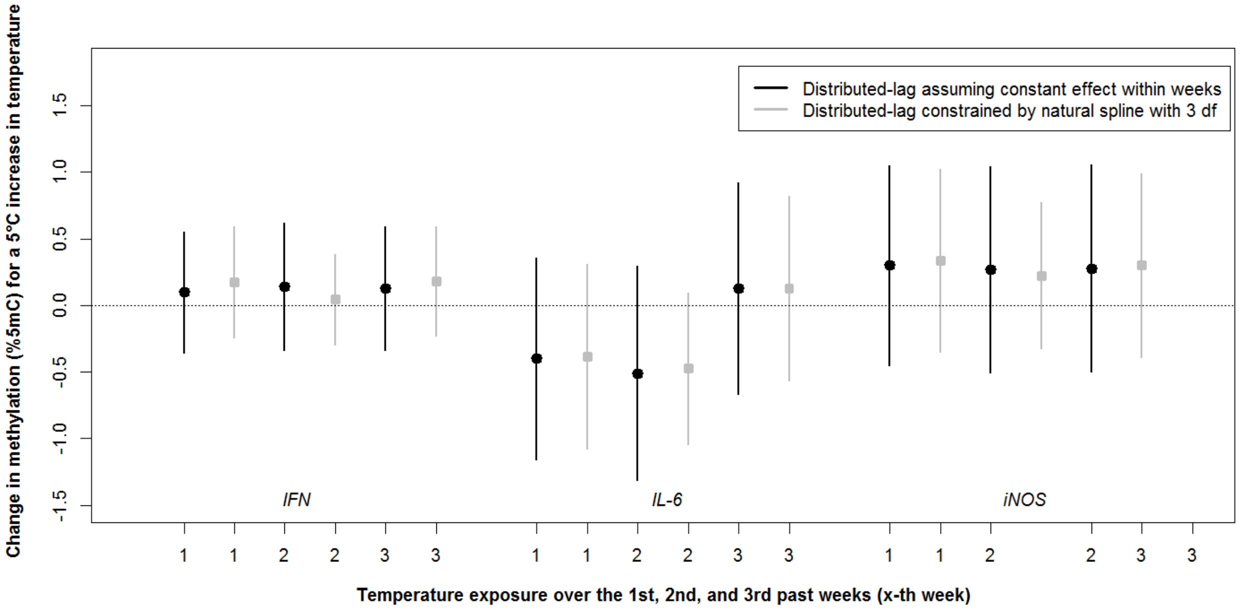
eAppendix 6b: Gene-specific, *LINE-1*, and *Alu* DNA methylation (% 5mC) across visits [5th, 50th, and 95th percentiles]

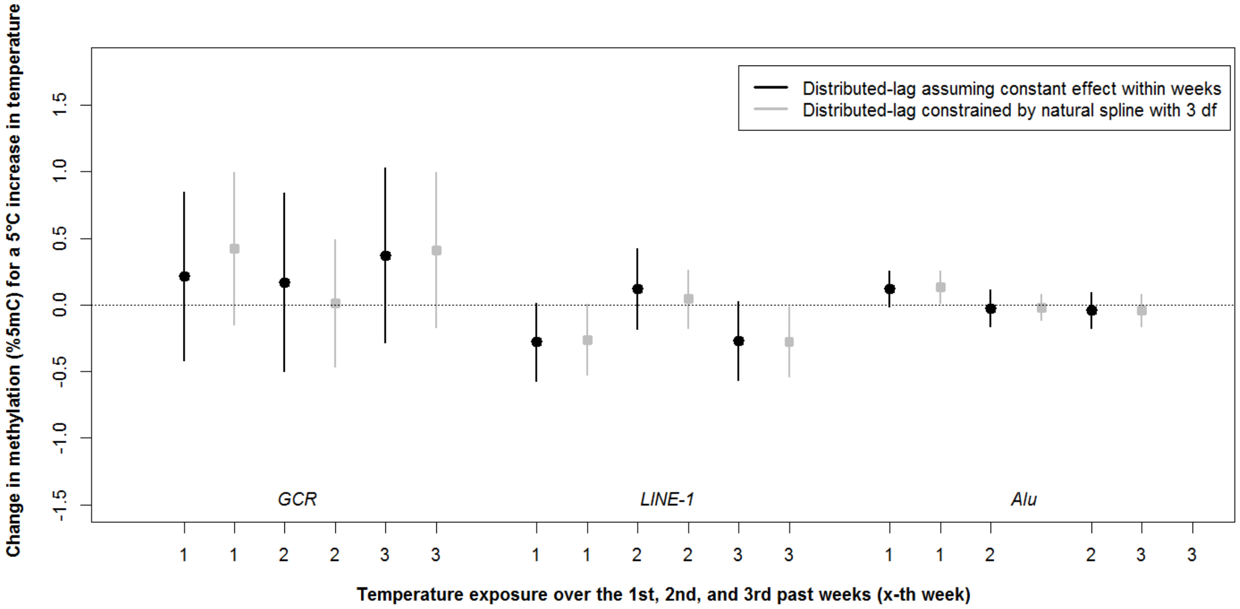
Gene or elements	***IFN-γ***	***IL-6***	***iNOS***	***GCR***	***LINE-1***	***Alu***
$\mathbf{n_{observations}}$	1,736	1,749	1,273	1,549	1,761	1,779
$\mathbf{n_{missing}}$	62	49	525	249	37	19
Baseline (n=777)	[75.4, 85.2, 91.1]	[25.4, 43.7, 62.1]	[57.6, 70.6, 79.8]	[37.6, 47.0, 55.8]	[74.0, 77.3, 82.8]	[24.5, 26.1, 28.1]
Participants having one visit (n=221)						
Visit 1	[72.4, 85.2, 91.8]	[23.7, 43.8, 61.6]	[55.4, 70.3, 80.9]	[37.3, 46.3, 54.8]	[74.0, 77.1, 83.6]	[24.6, 26.0, 27.9]
Participants having two visits (n=217)						
Visit 1	[75.4, 85.5, 90.9]	[23.7, 43.1, 65.3]	[60.9, 71.0, 80.0]	[39.7, 47.0, 57.6]	[74.1, 77.3, 83.0]	[24.2, 26.0, 28.5]
Visit 2	[75.8, 86.2, 91.4]	[24.7, 42.8, 59.8]	[54.1, 68.2, 78.2]	[33.4, 47.0, 55.0]	[75.1, 81.0, 84.7]	[23.3, 25.9, 28.8]
Participants having three visits (n=216)						
Visit 1	[75.8, 84.7, 91.1]	[28.9, 43.7, 59.8]	[59.4, 70.4, 78.6]	[37.3, 46.8, 54.5]	[73.7, 77.4, 82.7]	[24.6, 26.1, 28.2]
Visit 2	[76.4, 86.8, 90.7]	[28.4, 43.0, 57.5]	[56.8, 68.9, 78.5]	[37.3, 47.5, 54.7]	[75.4, 79.1, 83.9]	[24.1, 25.6, 27.4]
Visit 3	[76.3, 86.2, 91.1]	[24.9, 42.9, 59.7]	[56.8, 68.9, 78.5]	[34.3, 46.4, 54.6]	[76.0, 82.6, 85.4]	[22.9, 26.2, 29.7]
Participants having four visits (n=120)						
Visit 1	[76.9, 84.4, 90.7]	[28.9, 43.8, 61.8]	[59.9, 71.6, 79.1]	[38.9, 47.4, 60.6]	[74.2, 77.3, 81.7]	[24.6, 26.2, 28.4]
Visit 2	[76.9, 85.6, 91.4]	[25.3, 43.4, 58.4]	[58.7, 70.5, 77.9]	[36.9, 48.2, 56.9]	[74.7, 78.9, 84.3]	[24.7, 25.9, 27.9]
Visit 3	[75.0, 86.4, 89.3]	[28.7, 44.4, 62.9]	[57.6, 70.5, 77.9]	[41.4, 48.3, 54.1]	[74.8, 79.0, 83.7]	[22.6, 25.6, 27.6]
Visit 4	[77.5, 86.2, 92.7]	[26.3, 44.9, 60.5]	[55.3, 65.2, 78.5]	[37.4, 48.0, 56.9]	[81.8, 83.9, 86.0]	[25.6, 27.6, 30.5]
Participants having five visits (n=3)						
Visit 1	[82.0,85.6, 93.9]	[NA*, 44.2, 51.8]	[69.6, 70.5, 71.4]	[31.3, 38.1, 45.0]	[78.9, 79.4, 82.4]	[23.7, 24.8, 27.5]
Visit 2	[84.2, 86.2, 89.9]	[36.8, 44.8, 50.1]	[64.1, 66.5, 69.0]	[40.9, 43.7, 46.5]	[81.1, 81.7, 82.3]	[25.8, 25.9, 27.7]
Visit 3	[83.9, 85.0, 86.2]	[39.0, 42.8, 50.1]	[71.9, 74.0, 76.2]	[42.9, 45.9, 49.0]	[78.0, 78.9, 80.0]	[26.3, 26.5, 27.1]
Visit 4	[87.7, 89.2, 89.7]	[13.8, 30.4, 47.9]	[45.9, 56.8, 67.8]	[15.7, 42.5, 44.8]	[75.0, 78.1, 78.5]	[20.4, 26.4, 26.8]
Visit 5	[80.1, 86.8, 92.1]	[17.0, 28.6, 44.3]	[62.3, 66.4, 70.5]	[24.1, 45.4, 50.6]	[82.7, 83.3, 84.9]	[27.0, 27.5, 30.4]

eAppendix 7: Associations between a 5ºC increase in temperature and gene-specific methylation across the 1st, 2nd, and 3rd weeks of exposure (Estimates and associated 95% CI)

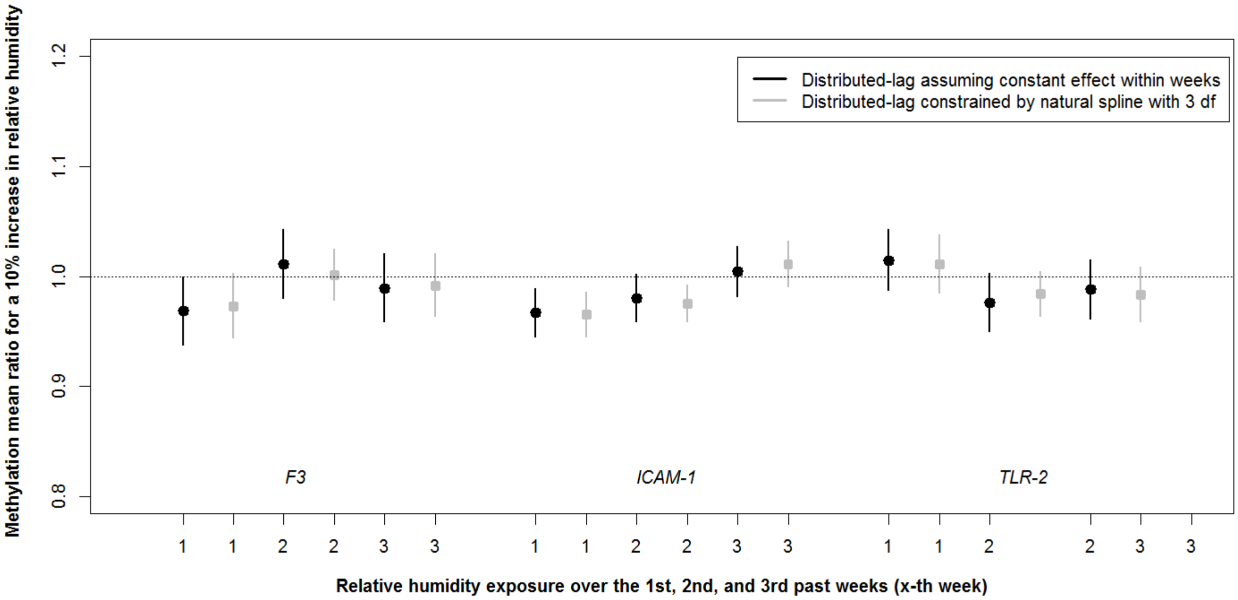


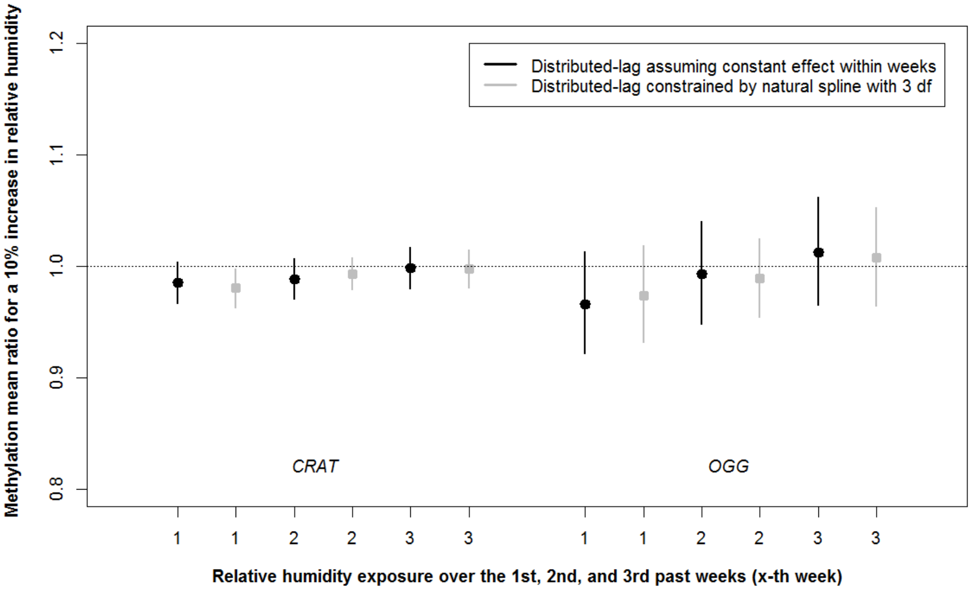


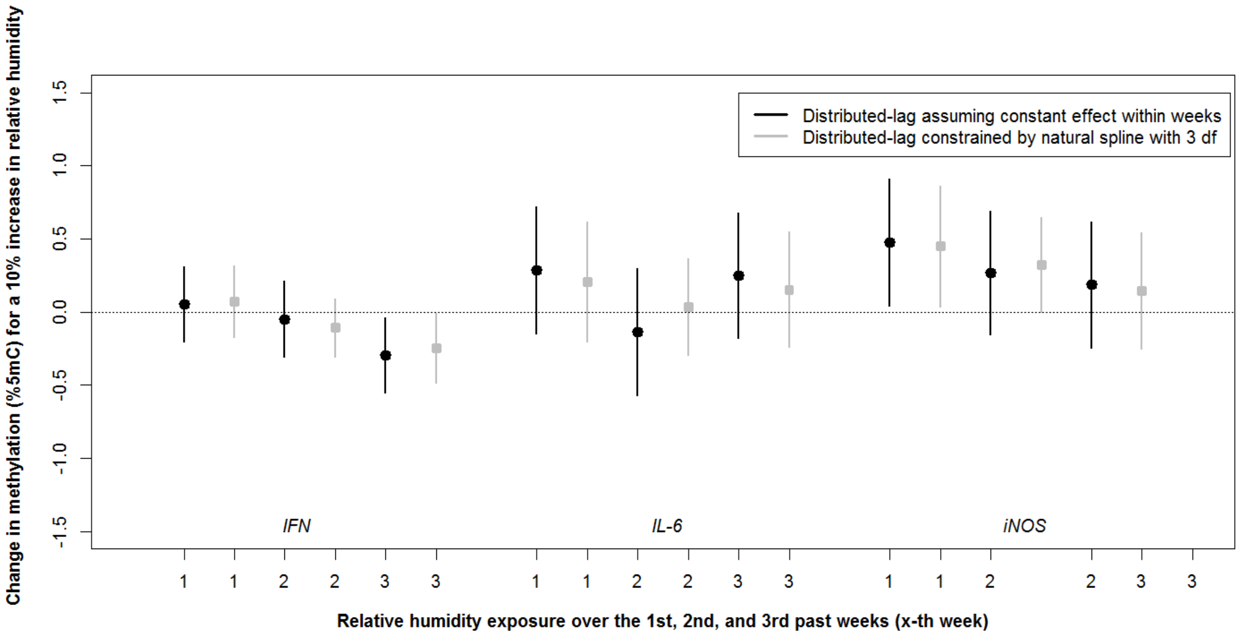

Distributed-lag assuming constant effect within weeks
Distributed-lag constrained by natural spline with 3 df
Change in methylation (%5mC) for a 5°C increase in temperature
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
IFN
IL-6
iNOS
1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3
Temperature exposure over the 1st, 2nd, and 3rd past weeks (x-th week)

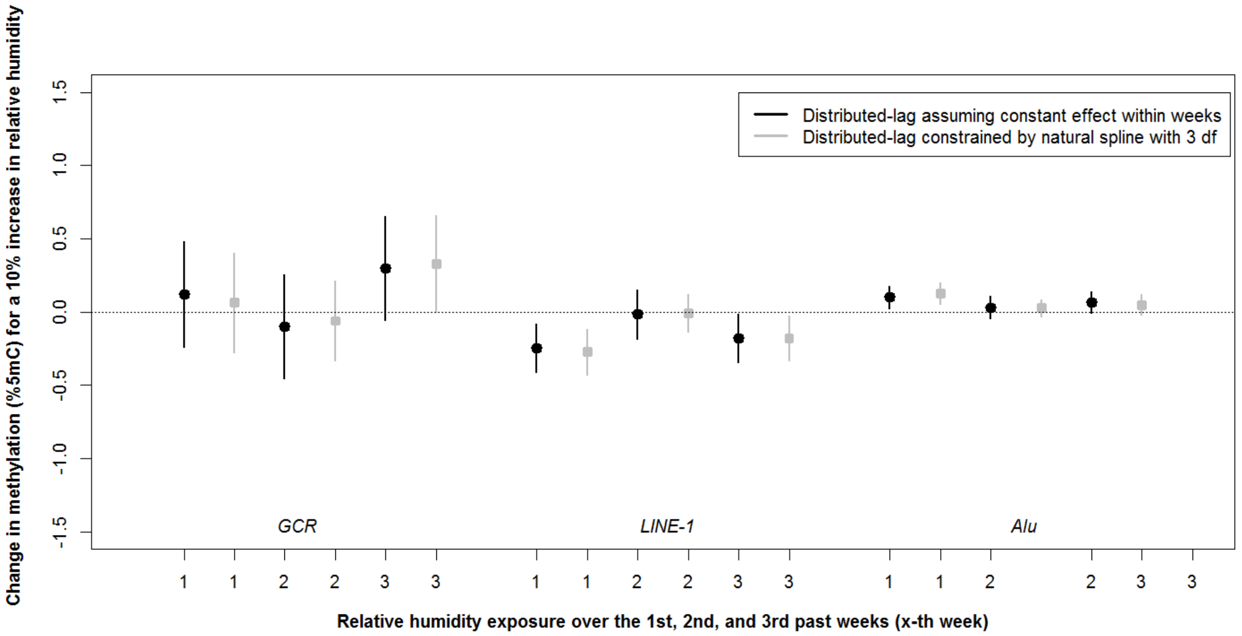

Distributed-lag assuming constant effect within weeks
Distributed-lag constrained by natural spline with 3 df
Change in methylation (%5mC) for a 5°C increase in temperature
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
GCR
LINE-1
Alu
1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3
Temperature exposure over the 1st, 2nd, and 3rd past weeks (x-th week)

eAppendix 8: Associations between a 10% increase in relative humidity and methylation on specific genes, *LINE-1*, and *Alu* across the 1st, 2nd, and 3rd weeks of exposure (Estimates and associated 95% CI)






Change in methylation (%5mC) for a 10% increase in relative humidity
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Distributed-lag assuming constant effect within weeks
Distributed-lag constrained by natural spline with 3 df
IFN
IL-6
iNOS
1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3
Relative humidity exposure over the 1st, 2nd, and 3rd past weeks (x-th week)


Change in methylation (%5mC) for a 10% increase in relative humidity
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Distributed-lag assuming constant effect within weeks
Distributed-lag constrained by natural spline with 3 df
GCR
LINE-1
Alu
1 1 2 2 3 3 1 1 2 2 3 3 1 1 2 2 3 3
Relative humidity exposure over the 1st, 2nd, and 3rd past weeks (x-th week)

eAppendix 9a: Associations between temperature and relative humidity exposure (over the 3-week period preceding medical examination) and gene-specific methylation (sensitivity analysis)

Methylation mean ratio for a Δ increase in temperature and relative humidity [95% CI]

F3	Model 1 (Main model)	Model 2	Model 3
Temperature	0.945 [0.874 to 1.021]	0.951 [0.879 to 1.029]	0.970 [0.890 to 1.058]
Relative humidity	0.967 [0.921 to 1.015]	0.970 [0.923 to 1.019]	0.967 [0.920 to 1.016]
ICAM-1	Model 1 (Main model)	Model 2	Model 3
Temperature	**1.092 [1.034 to 1.154]**	**1.090 [1.031 to 1.152]**	**1.115 [1.050 to 1.185]**
Relative humidity	**0.952 [0.920 to 0.985]**	**0.951 [0.918 to 0.984]**	**0.949 [0.917 to 0.983]**
***TLR*-2**	Model 1 (Main model)	Model 2	Model 3
Temperature	**0.933 [0.872 to 0.999]**	**0.930 [0.868 to 0.996]**	0.929 [0.862 to 1.001]
Relative humidity	0.978 [0.938 to 1.020]	0.978 [0.937 to 1.020]	0.974 [0.933 to 1.017]
CRAT	Model 1 (Main model)	Model 2	Model 3
Temperature	**1.053 [1.004 to 1.104]**	**1.062 [1.012 to 1.114]**	**1.095 [1.040 to 1.153]**
Relative humidity	0.966 [0.920 to 1.014]	0.977 [0.949 to 1.006]	0.977 [0.949 to 1.006]
OGG	Model 1 (Main model)	Model 2	Model 3
Temperature	1.013 [0.904 to 1.134]	1.038 [0.925 to 1.164]	0.989 [0.872 to 1.122]
Relative humidity	0.971 [0.903 to 1.043]	0.971 [0.903 to 1.044]	0.967 [0.898 to 1.042]

Δ* corresponds to increments of 5ºC and 10% for temperature and relative humidity, respectively

a) Variables included in model 1: f_1(temperature)[d], f_2(relative humidity)[d], age, body mass index, smoking status, diabetes status, statin use, % neutrophils in blood count, % lymphocytes in blood count, % monocytes in blood count, % basophils in blood count, seasonal sine and cosine, season, and batch

b) Variables included in model 2: variables included in model 1 and f_3(barometric pressure)[d]

c) Variables included in model 3: variables included in model 1 and f_3($PM_{2.5}$)[d]

d) f_1(temperature), f_2(relative humidity), f_3(barometric pressure) represent the distributed-lag functions with sets of coefficients constrained by a natural spline (with 3 degrees of freedom) that correspond to the temperature and relative humidity effects at lags 0 and 20 days.

eAppendix 9b: Associations between temperature and relative humidity exposure (over the 3-week period preceding medical examination) and gene-specific, *LINE-1*, and *Alu* methylation (sensitivity analysis)

Change in methylation (% 5mC) for a Δ increase in temperature and relative humidity [95% CI]

IFN-γ	Model 1 (Main model)	Model 2	Model 3
Temperature	0.396 [-0.256 to 1.048]	0.352 [-0.311 to 1.016]	0.479 [-0.244 to 1.202]
Relative humidity	-0.289 [-0.684 to 0.106]	-0.246 [-0.649 to 0.156]	-0.284 [-0.691 to 0.124]
***IL*-6**	Model 1 (Main model)	Model 2	Model 3
Temperature	-0.736 [-1.810 to 0.338]	-0.865 [-1.955 to 0.224]	-1.044 [-2.237 to 0.149]
Relative humidity	0.390 [-0.264 to 1.043]	0.264 [-0.401 to 0.930]	0.367 [-0.317 to 1.050]
iNOS	Model 1 (Main model)	Model 2	Model 3
Temperature	0.863 [-0.174 to 1.900]	0.936 [-0.122 to 1.994]	**1.681 [0.530 to 2.831]**
Relative humidity	**0.913 [0.253 to 1.572]**	**0.911 [0.237 to 1.585]**	**0.997 [0.316 to 1.677]**
GCR	Model 1 (Main model)	Model 2	Model 3
Temperature	0.845 [-0.053 to 1.743]	0.806 [-0.106 to 1.718]	**1.192 [0.199 to 2.186]**
Relative humidity	0.328 [-0.222 to 0.877]	0.305 [-0.255 to 0.865]	0.373 [-0.193 to 0.938]
LINE-1	Model 1 (Main model)	Model 2	Model 3
Temperature	**-0.497 [-0.915 to -0.080]**	**-0.503 [-0.927 to -0.079]**	-0.109 [-0.567 to 0.349]
Relative humidity	**-0.464 [-0.719 to -0.210]**	**-0.473 [-0.731 to -0.214]**	**-0.451 [-0.710 to -0.192]**
Alu	Model 1 (Main model)	Model 2	Model 3
Temperature	0.074 [-0.114 to 0.262]	0.065 [-0.125 to 0.256]	-0.039 [-0.248 to 0.170]
Relative humidity	**0.199 [0.083 to 0.314]**	**0.177 [0.060 to 0.294]**	**0.167 [0.049 to 0.286]**

Δ* corresponds to increments of 5°C and 10% for temperature and relative humidity, respectively

a) Variables included in model 1: f_1(temperature)[d], f_2(relative humidity)[d], age, body mass index, smoking status, diabetes status, statin use, % neutrophils in blood count, % lymphocytes in blood count, % monocytes in blood count, % basophils in blood count, seasonal sine and cosine, season, and batch

b) Variables included in model 2: variables included in model 1 and f_3(barometric pressure)[d]

c) Variables included in model 3: variables included in model 1 and f_3($PM_{2.5}$)[d]

d) f_1(temperature), f_2(relative humidity), f_3(barometric pressure) represent the distributed-lag functions with sets of coefficients constrained by a natural spline (with 3 degrees of freedom) that correspond to the temperature and relative humidity effects at lags 0 and 20 days.