

## **Supplemental Material to:**

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**Air pollution and gene-specific methylation in the  
Normative Aging Study: association, effect modification,  
and mediation analysis**

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**Supplementary material:** Air pollution is associated with gene-specific DNA methylation in the Normative Aging Study

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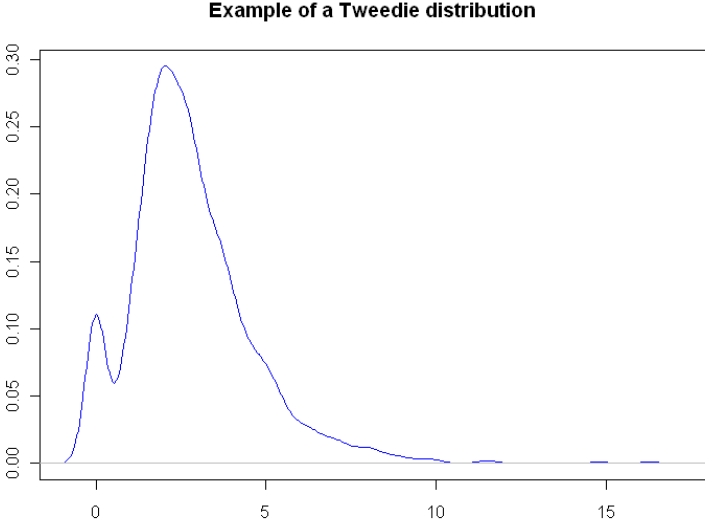
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**Web Figure 1: Tweedie distribution**



**Web Table 1: Distributions of the weather and air pollution variables**

	<b>n<sub>observations</sub></b>	<b>n<sub>missing</sub></b>	<b>IQR</b>	<b>5<sup>th</sup></b>	<b>Percentiles 50<sup>th</sup></b>	<b>95<sup>th</sup></b>
<b>Temperature (°C)</b>						
1-week moving average	1,798	0	13°C	-1°C	13°C	24°C
2-week moving average	1,798	0	13°C	-1°C	13°C	24°C
3-week moving average	1,798	0	13°C	-1°C	13°C	23°C
4-week moving average	1,798	0	13°C	-1°C	14°C	23°C
<b>Relative humidity(%)</b>						
1-week moving average	1,798	0	12%	53%	68%	82%
2-week moving average	1,798	0	10%	56%	68%	80%
3-week moving average	1,798	0	9%	56%	68%	78%
4-week moving average	1,798	0	8%	58%	69%	77%
<b>Particle number per cm<sup>3</sup></b>						
1-week moving average	1,369	429	15,020	9,024	18,353	42,547
2-week moving average	1,369	429	14,795	9,219	18,092	42,749
3-week moving average	1,365	433	14,559	9,273	18,356	42,621
4-week moving average	1,365	433	14,599	9,352	18,426	42,291
<b>Black carbon (µg/m<sup>3</sup>)</b>						
1-week moving average	1,798	0	0.33	0.42	0.73	1.16
2-week moving average	1,798	0	0.28	0.43	0.73	1.07
3-week moving average	1,798	0	0.25	0.45	0.74	1.05
4-week moving average	1,798	0	0.26	0.46	0.74	1.04
<b>Sulfate (µg/m<sup>3</sup>)</b>						
1-week moving average	1,555	243	1.47	1.16	2.56	5.49
2-week moving average	1,553	245	1.29	1.38	2.65	5.03
3-week moving average	1,535	263	1.27	1.45	2.70	4.87
4-week moving average	1,555	243	1.22	1.57	2.69	4.88
<b>Ozone (ppm)</b>						
1-week moving average	1,796	2	0.014	0.011	0.024	0.038
2-week moving average	1,798	0	0.013	0.012	0.025	0.036
3-week moving average	1,798	0	0.013	0.012	0.026	0.036
4-week moving average	1,798	0	0.013	0.012	0.026	0.035

Abbreviation : Interquartile range (IQR)

**Web Table 2: Spearman correlations between weather and air pollution variables (1-week moving average)**

	Temperature	Relative humidity	Particle number	Black carbon	Sulfate	Ozone
Temperature	1	0.22*	-0.69*	0.39*	0.35*	0.49*
Relative humidity		1	-0.07*	0.39*	0.16*	-0.22*
Particle number			1	-0.03	-0.06*	-0.39*
Black carbon				1	0.57*	-0.14*
Sulfate					1	0.26*
Ozone						1

\*  $P < 0.05$

**Web Table 3: Spearman correlations between air pollutant concentrations (1<sup>st</sup> week, 2<sup>nd</sup> week, 3<sup>rd</sup> week, and 4<sup>th</sup> week moving averages preceding participant's visit)**

<b>PN</b>	<b>1<sup>st</sup> week</b>	<b>2<sup>nd</sup> week</b>	<b>3<sup>rd</sup> week</b>	<b>4<sup>th</sup> week</b>
<b>1<sup>st</sup> week</b>	1	0.90*	0.88*	0.86*
<b>2<sup>nd</sup> week</b>		1	0.91*	0.88*
<b>3<sup>rd</sup> week</b>			1	0.90*
<b>4<sup>th</sup> week</b>				1
<b>Black carbon</b>	<b>1<sup>st</sup> week</b>	<b>2<sup>nd</sup> week</b>	<b>3<sup>rd</sup> week</b>	<b>4<sup>th</sup> week</b>
<b>1<sup>st</sup> week</b>	1	0.48*	0.45*	0.41*
<b>2<sup>nd</sup> week</b>		1	0.50*	0.46*
<b>3<sup>rd</sup> week</b>			1	0.49*
<b>4<sup>th</sup> week</b>				1
<b>Sulfate</b>	<b>1<sup>st</sup> week</b>	<b>2<sup>nd</sup> week</b>	<b>3<sup>rd</sup> week</b>	<b>4<sup>th</sup> week</b>
<b>1<sup>st</sup> week</b>	1	0.42*	0.39*	0.26*
<b>2<sup>nd</sup> week</b>		1	0.42*	0.40*
<b>3<sup>rd</sup> week</b>			1	0.44*
<b>4<sup>th</sup> week</b>				1
<b>Ozone</b>	<b>1<sup>st</sup> week</b>	<b>2<sup>nd</sup> week</b>	<b>3<sup>rd</sup> week</b>	<b>4<sup>th</sup> week</b>
<b>1<sup>st</sup> week</b>	1	0.76*	0.69*	0.66*
<b>2<sup>nd</sup> week</b>		1	0.77*	0.69*
<b>3<sup>rd</sup> week</b>			1	0.75*
<b>4<sup>th</sup> week</b>				1

\*  $P < 0.05$

**Web Table 4: Gene-specific methylation (%5mC) across visits [5<sup>th</sup>, 50<sup>th</sup>, and 95<sup>th</sup> percentiles]**

	<b>F3 mean</b>	<b>ICAM-1 mean</b>	<b>IFN-<math>\gamma</math> mean</b>	<b>TLR-2 mean</b>	<b>IL-6 mean</b>
<b>n<sub>observations</sub></b>	1,533	1,424	1,736	1,424	1,749
<b>n<sub>missing</sub></b>	265	374	62	374	49
<b>Baseline (n=777)</b>	[1.0, 2.0, 4.5]	[2.2, 4.1, 8.2]	[75.4, 85.2, 91.1]	[1.5, 2.8, 5.3]	[25.4, 43.7, 62.1]
Never smokers (n=223)	[0.9, 2.0, 4.7]	[2.1, 4.1, 8.1]	[72.4, 84.5, 91.0]	[1.7, 2.9, 5.7]	[23.7, 43.5, 60.3]
Former smokers (n=522)	[1.0, 2.0, 4.2]	[2.3, 4.1, 8.2]	[75.6, 85.3, 91.1]	[1.4, 2.8, 5.3]	[27.0, 43.8, 63.2]
Current smokers (n=32)	[1.1, 2.2, 4.6]	[2.1, 4.5, 10.1]	[79.7, 87.5, 91.6]	[1.6, 2.8, 3.8]	[19.7, 43.5, 62.1]
<b>Participants having one visit (n=221)</b>					
<b>Visit 1</b>	[1.1, 1.9, 3.5]	[2.6, 4.3, 7.7]	[72.4, 85.2, 91.8]	[1.4, 2.8, 5.0]	[23.7, 43.8, 61.6]
<b>Participants having two visits (n=217)</b>					
<b>Visit 1</b>	[1.0, 2.0, 4.2]	[2.2, 4.1, 8.4]	[75.4, 85.5, 90.9]	[1.5, 2.6, 5.1]	[23.7, 43.1, 65.3]
<b>Visit 2</b>	[0.8, 2.3, 4.4]	[2.2, 3.9, 8.2]	[75.8, 86.2, 91.4]	[1.0, 2.6, 5.7]	[24.7, 42.8, 59.8]
<b>Participants having three visits (n=216)</b>					
<b>Visit 1</b>	[1.0, 2.0, 4.5]	[2.1, 3.8, 7.6]	[75.8, 84.7, 91.1]	[1.3, 2.8, 5.2]	[28.9, 43.7, 59.8]
<b>Visit 2</b>	[0.9, 2.5, 4.5]	[2.1, 3.6, 7.8]	[76.4, 86.8, 90.7]	[1.5, 2.6, 5.3]	[28.4, 43.0, 57.5]
<b>Visit 3</b>	[0.9, 1.8, 4.3]	[2.9, 4.2, 6.7]	[76.3, 86.2, 91.1]	[0.9, 2.1, 4.9]	[24.9, 42.9, 59.7]
<b>Participants having four visits (n=120)</b>					
<b>Visit 1</b>	[0.4, 2.3, 5.2]	[2.1, 4.0, 9.8]	[76.9, 84.4, 90.7]	[1.9, 3.3, 5.9]	[28.9, 43.8, 61.8]
<b>Visit 2</b>	[1.0, 2.4, 4.8]	[2.0, 3.3, 9.9]	[76.9, 85.6, 91.4]	[1.7, 3.1, 6.0]	[25.3, 43.4, 58.4]
<b>Visit 3</b>	[1.8, 2.9, 4.5]	[2.5, 4.4, 6.1]	[75.0, 86.4, 89.3]	[1.5, 3.0, 6.3]	[28.7, 44.4, 62.9]
<b>Visit 4</b>	[0.7, 1.3, 3.1]	[2.8, 4.0, 8.3]	[77.5, 86.2, 92.7]	[0.9, 1.6, 4.0]	[26.3, 44.9, 60.5]
<b>Participants having five visits (n=3)</b>					
<b>Visit 1</b>	[NA*, 3.0, 3.2]	[3.0, 3.3, 4.5]	[82.0, 85.6, 93.9]	[2.3, 3.1, 3.9]	[NA*, 44.2, 51.8]
<b>Visit 2</b>	[2.6, 2.9, 3.3]	[NA*, 2.6, 2.7]	[84.2, 86.2, 89.9]	[NA*, 1.9, 2.8]	[36.8, 44.8, 50.1]
<b>Visit 3</b>	[2.4, 3.6, 8.5]	[NA*, 3.5, 3.7]	[83.9, 85.0, 86.2]	[NA*, NA*, 4.9]	[39.0, 42.8, 50.1]
<b>Visit 4</b>	[NA*, NA*, 2.2]	[2.5, 4.2, 7.1]	[87.7, 89.2, 89.7]	[NA*, NA*, 2.9]	[13.8, 30.4, 47.9]
<b>Visit 5</b>	[0.7, 1.6, 34.6]	[3.2, 5.2, 6.0]	[80.1, 86.8, 92.1]	[1.4, 2.1, 3.5]	[17.0, 28.6, 44.3]

\*NA=missing data

**Web Table 5: Association between Participants' Characteristics and Gene-Specific DNA Methylation**

Methylation mean ratio for a $\Delta$ increase in exposure								
	Age ( $\Delta=1$ year)		BMI ( $\Delta=1$ kg/m <sup>2</sup> )		Former smokers versus never smokers		Current smokers versus never smokers	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
F3	0.998	0.991, 1.004	0.990	0.980, 1.000	1.018	0.940, 1.103	1.094	0.870, 1.376
ICAM-1	0.998	0.994, 1.002	0.998	0.991, 1.004	1.018	0.963, 1.075	1.057	0.907, 1.232
TLR-2	<b>1.008</b>	<b>1.002, 1.014</b>	1.000	0.991, 1.009	<b>0.900</b>	<b>0.838, 0.967</b>	1.043	0.845, 1.287
Change in methylation (% 5mC) for for a $\Delta$ increase in exposure								
	Age ( $\Delta=1$ year)		BMI ( $\Delta=1$ kg/m <sup>2</sup> )		Former smokers vs never smokers		Current smokers versus never smokers	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
IFN- $\gamma$	-0.036	-0.092, 0.019	-0.023	-0.112, 0.065	<b>0.838</b>	<b>0.109, 1.567</b>	1.855	-0.180, 3.891
IL-6	0.017	-0.147, 0.114	-0.053	-0.258, 0.153	<b>1.842</b>	<b>0.095, 3.589</b>	-1.433	-5.831, 2.965

a) Variables included in the models:  $f_1$ (particle number)<sup>b</sup>,  $f_2$ (temperature)<sup>b</sup>,  $f_3$ (relative humidity)<sup>b</sup>, age, body mass index, smoking status, diabetes status, statin use, % neutrophils in blood count, % lymphocytes in blood count, seasonal sine and cosine, season, and methylation batch  
b)  $f_1$ (particle number),  $f_2$ (temperature), and  $f_3$ (relative humidity) represent the distributed-lag functions with sets of coefficients constrained by a natural spline (with 3 degrees of freedom) that correspond to the particle number, temperature, and relative humidity associations at lags 0 and 27 days.



**Web Table 6: Association between Air Pollution Exposure over the 4-week Period Preceding Medical Examination and Gene-Specific DNA Methylation according to the Obesity Status**

<b>Methylation mean ratio for an interquartile range increase in air pollution</b>									
	<b>Particle number</b>		<b>Black carbon</b>		<b>Sulfate</b>		<b>Ozone (March to August)</b>		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
<b>F3</b>									
Non obese	<b>0.731</b>	<b>0.658, 0.812</b>	<b>0.877</b>	<b>0.824, 0.933</b>	0.995	0.916, 1.081	1.076	0.878, 1.319	
Obese	<b>0.714</b>	<b>0.638, 0.799</b>	<b>0.877</b>	<b>0.821, 0.936</b>	1.037	0.945, 1.138	1.097	0.893, 1.348	
<b>ICAM-1</b>									
Non obese	<b>0.898</b>	<b>0.830, 0.973</b>	1.012	0.967, 1.059	0.948	0.896, 1.003	<b>0.757</b>	<b>0.661, 0.866</b>	
Obese	<b>0.873</b>	<b>0.802, 0.951</b>	0.996	0.949, 1.044	<b>0.927</b>	<b>0.870, 0.989</b>	<b>0.758</b>	<b>0.660, 0.871</b>	
<b>TLR-2</b>									
Non obese	0.941	0.847, 1.046	1.036	0.981, 1.093	0.992	0.923, 1.066	0.932	0.787, 1.103	
Obese	0.944	0.843, 1.056	1.022	0.965, 1.081	0.970	0.896, 1.051	0.904	0.762, 1.073	
<b>Change in methylation (% 5mC) for an interquartile range increase in air pollution</b>									
	<b>Particle number</b>		<b>Black carbon</b>		<b>Sulfate</b>		<b>Ozone (March to August)</b>		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
<b>IFN-<math>\gamma</math></b>									
Non obese	<b>-0.975</b>	<b>-1.834, -0.117</b>	-0.380	-0.888, 0.128	0.606	-0.181, 1.393	<b>1.831</b>	<b>0.177, 3.485</b>	
Obese	-0.452	-1.310, 0.407	-0.280	-0.789, 0.228	0.657	-0.130, 1.444	<b>2.170</b>	<b>0.515, 3.824</b>	
<b>IL-6</b>									
Non obese	1.525	-0.131, 3.182	0.781	-0.101, 1.664	0.500	-0.871, 1.872	-2.277	-5.215, 0.660	
Obese	0.980	-0.677, 2.636	0.820	-0.063, 1.702	-0.041	-1.412, 1.331	<b>-3.007</b>	<b>-5.944, -0.069</b>	

a) Variables included in the models:  $f_1$ (air pollutant)<sup>b</sup>,  $f_2$ (temperature)<sup>b</sup>,  $f_3$ (relative humidity)<sup>b</sup>, obesity status\* $f_1$ (air pollutant)<sup>b</sup>, age, body mass index, smoking status, diabetes status, statin use, % neutrophils in blood count, % lymphocytes in blood count, seasonal sine and cosine, season, and methylation batch

b)  $f_1$ (air pollutant),  $f_2$ (temperature), and  $f_3$ (relative humidity) represent the distributed-lag functions with sets of coefficients constrained by a natural spline (with 3 degrees of freedom) that correspond to the air pollution, temperature, and relative humidity associations at lags 0 and 27 days.

**Web Table 7: Association between Air Pollution Exposure over the 4-week Period Preceding Medical Examination and Gene-Specific DNA Methylation according to the Age category**

<b>Methylation mean ratio for an interquartile range increase in air pollution</b>									
	<b>Particle number</b>		<b>Black carbon</b>		<b>Sulfate</b>		<b>Ozone (March to August)</b>		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
<b>F3</b>									
≤72 years	<b>0.709</b>	<b>0.638, 0.788</b>	<b>0.872</b>	<b>0.819, 0.928</b>	0.986	0.903, 1.077	1.073	0.877, 1.313	
>72 years	<b>0.740</b>	<b>0.664, 0.826</b>	<b>0.886</b>	<b>0.832, 0.943</b>	1.025	0.942, 1.116	1.131	0.921, 1.390	
<b>ICAM-1</b>									
≤72 years	<b>0.885</b>	<b>0.816, 0.959</b>	0.995	0.951, 1.041	<b>0.936</b>	<b>0.879, 0.997</b>	<b>0.752</b>	<b>0.657, 0.860</b>	
>72 years	<b>0.893</b>	<b>0.823, 0.968</b>	1.025	0.980, 1.073	0.951	0.898, 1.008	<b>0.782</b>	<b>0.682, 0.897</b>	
<b>TLR-2</b>									
≤72 years	0.955	0.859, 1.063	1.038	0.983, 1.096	1.017	0.944, 1.097	0.916	0.775, 1.082	
>72 years	0.926	0.830, 1.033	1.025	0.971, 1.082	0.965	0.898, 1.036	0.884	0.745, 1.050	
<b>Change in methylation (% 5mC) for an interquartile range increase in air pollution</b>									
	<b>Particle number</b>		<b>Black carbon</b>		<b>Sulfate</b>		<b>Ozone (March to August)</b>		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
<b>IFN-γ</b>									
≤72 years	-0.892	-1.750, -0.033	-0.234	-0.742, 0.274	0.703	-0.084, 1.489	<b>2.003</b>	<b>0.349, 3.657</b>	
>72 years	-0.830	-1.688, 0.029	<b>-0.520</b>	<b>-1.028, -0.011</b>	0.514	-0.273, 1.300	<b>1.737</b>	<b>0.083, 3.391</b>	
<b>IL-6</b>									
≤72 years	1.530	-0.127, 3.186	0.766	-0.117, 1.648	0.597	-0.775, 1.969	-2.464	-5.402, 0.474	
>72 years	1.392	-0.265, 3.048	0.851	-0.032, 1.733	0.114	-1.258, 1.486	-2.641	-5.579, 0.297	

a) Variables included in the models:  $f_1$ (air pollutant)<sup>b</sup>,  $f_2$ (temperature)<sup>b</sup>,  $f_3$ (relative humidity)<sup>b</sup>, age category\* $f_1$ (air pollutant)<sup>b</sup>, age, body mass index, smoking status, diabetes status, statin use, % neutrophils in blood count, % lymphocytes in blood count, seasonal sine and cosine, season, and methylation batch

b)  $f_1$ (air pollutant),  $f_2$ (temperature), and  $f_3$ (relative humidity) represent the distributed-lag functions with sets of coefficients constrained by a natural spline (with 3 degrees of freedom) that correspond to the air pollution, temperature, and relative humidity associations at lags 0 and 27 days.

**Web Table 8: Association between Air Pollution Exposure over the 4-week Period Preceding Medical Examination on Gene-Specific DNA Methylation according to the levels of LINE-1 and ALU Methylation at Baseline**

Methylation mean ratio for an interquartile range increase in air pollution									
	Particle number		Black carbon		Sulfate		Ozone (March to August)		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
<b>F3</b>									
Low LINE-1	<b>0.765</b>	<b>0.678, 0.863</b>	<b>0.866</b>	<b>0.805, 0.931</b>	1.000	0.906, 1.103	0.972	0.743, 1.272	
High LINE-1	<b>0.718</b>	<b>0.640, 0.807</b>	<b>0.898</b>	<b>0.834, 0.967</b>	1.001	0.899, 1.115	1.155	0.900, 1.483	
Low ALU	<b>0.747</b>	<b>0.664, 0.840</b>	<b>0.898</b>	<b>0.835, 0.965</b>	1.046	0.946, 1.157	1.146	0.882, 1.490	
High ALU	<b>0.701</b>	<b>0.624, 0.788</b>	<b>0.851</b>	<b>0.791, 0.917</b>	0.979	0.888, 1.080	1.038	0.816, 1.320	
<b>ICAM-1</b>									
Low LINE-1	0.925	0.847, 1.010	0.993	0.941, 1.047	0.934	0.872, 1.001	<b>0.675</b>	<b>0.568, 0.803</b>	
High LINE-1	<b>0.862</b>	<b>0.788, 0.942</b>	1.029	0.976, 1.086	0.959	0.890, 1.033	0.879	0.746, 1.037	
Low ALU	<b>0.911</b>	<b>0.832, 0.998</b>	1.018	0.966, 1.074	0.967	0.903, 1.036	<b>0.734</b>	<b>0.618, 0.872</b>	
High ALU	<b>0.879</b>	<b>0.808, 0.957</b>	1.007	0.956, 1.061	<b>0.930</b>	<b>0.869, 0.995</b>	<b>0.812</b>	<b>0.692, 0.954</b>	
<b>TLR-2</b>									
Low LINE-1	0.930	0.827, 1.046	1.040	0.975, 1.103	0.945	0.869, 1.027	0.880	0.709, 1.091	
High LINE-1	0.920	0.817, 1.037	1.009	0.947, 1.076	1.000	0.913, 1.096	0.946	0.768, 1.164	
Low ALU	0.948	0.841, 1.069	1.016	0.953, 1.082	0.976	0.896, 1.062	0.953	0.767, 1.186	
High ALU	0.956	0.853, 1.071	1.046	0.981, 1.115	1.005	0.925, 1.091	0.908	0.743, 1.109	
Change in methylation (% 5mC) for an interquartile range increase in air pollution									
	Particle number		Black carbon		Sulfate		Ozone (March to August)		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
<b>IFN-<math>\gamma</math></b>									
Low LINE-1	<b>-1.114</b>	<b>-1.973, -0.256</b>	<b>-0.733</b>	<b>-1.241, -0.225</b>	0.992	-0.205, 1.779	<b>2.656</b>	<b>1.002, 4.310</b>	
High LINE-1	-0.594	-1.453, 0.264	0.005	-0.504, 0.513	0.593	-0.193, 1.380	1.586	-0.068, 3.240	
Low ALU	<b>-1.023</b>	<b>-1.882, -0.165</b>	-0.462	-0.971, 0.046	0.750	-0.037, 1.536	<b>3.529</b>	<b>1.875, 5.183</b>	
High ALU	-0.855	-1.713, 0.004	-0.175	-0.683, 0.333	0.426	-0.361, 1.212	1.029	-0.625, 2.683	
<b>IL-6</b>									
Low LINE-1	1.268	-0.388, 2.925	0.514	-0.369, 1.396	0.517	-0.855, 1.889	-0.042	-2.980, 2.895	
High LINE-1	<b>1.794</b>	<b>0.138, 3.451</b>	<b>0.987</b>	<b>0.105, 1.870</b>	0.504	-0.868, 1.876	<b>-4.482</b>	<b>-7.420, -1.544</b>	
Low ALU	1.185	-0.472, 2.842	<b>1.274</b>	<b>0.392, 2.157</b>	0.756	-0.616, 2.127	<b>-4.556</b>	<b>-7.494, -1.618</b>	
High ALU	<b>1.811</b>	<b>0.154, 3.468</b>	0.166	-0.716, 1.049	-0.175	-1.547, 1.197	-0.893	-3.831, 2.045	

a) Variables included in the models:  $f_1$ (air pollutant)<sup>b</sup>,  $f_2$ (temperature)<sup>b</sup>,  $f_3$ (relative humidity)<sup>b</sup>, baseline methylation status\* $f_1$ (air pollutant)<sup>b</sup>, baseline methylation status, age, body mass index, smoking status, diabetes status, statin use, % neutrophils in blood count, % lymphocytes in blood count, seasonal sine and cosine, season, and methylation batch

b)  $f_1$ (air pollutant),  $f_2$ (temperature), and  $f_3$ (relative humidity) represent the distributed-lag functions with sets of coefficients constrained by a natural spline (with 3 degrees of freedom) that correspond to the air pollution, temperature, and relative humidity associations at lags 0 and 27 days.

**Web Table 9: Associations between air pollution exposure over a 4-week period and gene-specific methylation across positions**

<b>Methylation mean ratio for an interquartile range increase in air pollution [95% CI]</b>				
<b>F3</b>	Particle number	Black carbon	Sulfate	O <sub>3</sub> (March to August)
Mean	<b>0.725 [0.655 to 0.803]</b>	<b>0.877 [0.825 to 0.932]</b>	1.008 [0.930 to 1.093]	1.082 [0.885 to 1.322]
Position 1	<b>0.677 [0.538 to 0.852]</b>	0.898 [0.778 to 1.038]	1.071 [0.863 to 1.328]	1.126 [0.741 to 1.711]
Position 2	0.892 [0.721 to 1.103]	0.948 [0.841 to 1.068]	0.874 [0.707 to 1.081]	<b>0.633 [0.439 to 0.912]</b>
Position 3	<b>0.686 [0.584 to 0.806]</b>	<b>0.824 [0.753 to 0.901]</b>	1.074 [0.949 to 1.215]	1.301 [0.969 to 1.746]
Position 4	<b>0.620 [0.496 to 0.774]</b>	<b>0.813 [0.712 to 0.929]</b>	<b>0.815 [0.686 to 0.969]</b>	0.843 [0.522 to 1.362]
Position 5	<b>0.770 [0.683 to 0.868]</b>	<b>0.895 [0.834 to 0.961]</b>	0.981 [0.889 to 1.082]	1.170 [0.933 to 1.466]
<b>ICAM-1</b>	Particle number	Black carbon	Sulfate	O <sub>3</sub> (March to August)
Mean	<b>0.889 [0.824 to 0.961]</b>	1.009 [0.965 to 1.055]	0.948 [0.896 to 1.003]	<b>0.759 [0.664 to 0.868]</b>
Position 1	<b>0.919 [0.852 to 0.992]</b>	1.020 [0.977 to 1.066]	<b>0.944 [0.894 to 0.995]</b>	<b>0.758 [0.665 to 0.865]</b>
Position 2	0.926 [0.824 to 1.042]	1.028 [0.970 to 1.089]	<b>0.898 [0.825 to 0.978]</b>	<b>0.664 [0.559 to 0.788]</b>
Position 3	<b>0.811 [0.729 to 0.902]</b>	0.969 [0.909 to 1.032]	1.012 [0.936 to 1.096]	0.886 [0.717 to 1.096]
<b>TLR-2</b>	Particle number	Black carbon	Sulfate	O <sub>3</sub> (March to August)
Mean	0.943 [0.851 to 1.044]	1.032 [0.979 to 1.088]	0.987 [0.920 to 1.058]	0.917 [0.775 to 1.086]
Position 1	0.894 [0.765 to 1.044]	1.049 [0.966 to 1.140]	0.927 [0.824 to 1.043]	<b>0.660 [0.505 to 0.863]</b>
Position 2	1.099 [0.967 to 1.249]	1.010 [0.940 to 1.085]	0.999 [0.904 to 1.105]	1.113 [0.877 to 1.412]
Position 3	0.845 [0.713 to 1.002]	1.030 [0.944 to 1.123]	1.028 [0.901 to 1.173]	0.809 [0.607 to 1.077]
Position 4	0.937 [0.830 to 1.058]	1.014 [0.947 to 1.087]	0.979 [0.893 to 1.074]	0.964 [0.772 to 1.202]
Position 5	0.895 [0.711 to 1.127]	1.006 [0.893 to 1.132]	0.931 [0.788 to 1.101]	1.116 [0.763 to 1.632]
<b>Change in methylation (% 5mC) for an interquartile range increase in air pollution [95% CI]</b>				
<b>IFN-<math>\gamma</math></b>	Particle number	Black carbon	Sulfate	O <sub>3</sub> (March to August)
Mean	-0.845 [-1.704 to 0.013]	-0.363 [-0.872 to 0.145]	0.589 [-0.198 to 1.376]	<b>1.898 [0.244 to 3.552]</b>
Position 1	<b>-1.258 [-2.271 to -0.266]</b>	<b>-0.951 [-1.548 to -0.355]</b>	0.339 [-0.557 to 1.235]	<b>2.453 [0.516 to 4.390]</b>
Position 2	-0.430 [-1.227 to 0.367]	0.225 [-0.251 to 0.702]	<b>0.835 [0.094 to 1.576]</b>	1.326 [-0.243 to 2.894]
<b>IL-6</b>	Particle number	Black carbon	Sulfate	O <sub>3</sub> (March to August)
Mean	1.412 [-0.245 to 3.068]	0.806 [-0.077 to 1.688]	0.317 [-1.055 to 1.688]	-2.486 [-5.424 to 0.452]
Position 1	<b>2.229 [0.397 to 4.062]</b>	<b>1.301 [0.293 to 2.309]</b>	0.378 [-1.137 to 1.893]	-3.035 [-6.490 to 0.420]
Position 2	0.624 [-1.065 to 2.314]	0.366 [-0.564 to 1.296]	0.273 [-1.182 to 1.727]	-2.362 [-5.468 to 0.743]

a) Variables included in the models:  $f_1$ (air pollutant)<sup>b</sup>,  $f_2$ (temperature)<sup>b</sup>,  $f_3$ (relative humidity)<sup>b</sup>, age, body mass index, smoking status, diabetes status, statin use, percentage of neutrophils in blood count, percentage of lymphocytes in blood count, seasonal sine and cosine, season, and batch

b)  $f_1$ (air pollutant),  $f_2$ (temperature), and  $f_3$ (relative humidity) represent the distributed-lag functions with sets of coefficients constrained by a natural spline (with 3 degrees of freedom) that correspond to the air pollution, temperature, and relative humidity associations at lags 0 and 27 days.

**Web Table 10: Associations between air pollution exposure over a 4-week period and gene-specific methylation using different models**

<b>Methylation mean ratio for an interquartile range increase in air pollution [95% CI]</b>				
<b>F3</b>	Particle number	Black carbon	Sulfate	Ozone (March to August)
Main model	<b>0.725 [0.655 to 0.803]</b>	<b>0.877 [0.825 to 0.932]</b>	1.008 [0.930 to 1.093]	1.082 [0.885 to 1.322]
Co-pollutant model	<b>0.715 [0.644 to 0.793]</b>	<b>0.883 [0.830 to 0.940]</b>	0.955 [0.871 to 1.046]	<b>0.713 [0.522 to 0.974]</b>
Model with further adjustments	<b>0.725 [0.655 to 0.803]</b>	<b>0.876 [0.824 to 0.931]</b>	1.009 [0.930 to 1.094]	1.075 [0.880 to 1.313]
GEE model (robust variance)	<b>0.715 [0.649 to 0.788]</b>	<b>0.882 [0.836 to 0.930]</b>	<b>0.920 [0.889 to 0.953]</b>	1.071 [0.887 to 1.293]
GEE model (robust variance and IPCW)	<b>0.758 [0.658 to 0.872]</b>	<b>0.878 [0.825 to 0.934]</b>	0.977 [0.875 to 1.092]	1.117 [0.915 to 1.365]
<b>ICAM-1</b>	Particle number	Black carbon	Sulfate	Ozone (March to August)
Main model	<b>0.889 [0.824 to 0.961]</b>	1.009 [0.965 to 1.055]	0.948 [0.896 to 1.003]	<b>0.759 [0.664 to 0.868]</b>
Co-pollutant model	<b>0.890 [0.824 to 0.962]</b>	1.004 [0.960 to 1.050]	0.968 [0.912 to 1.027]	0.953 [0.767 to 1.186]
Model with further adjustments	<b>0.892 [0.826 to 0.963]</b>	1.010 [0.966 to 1.056]	0.951 [0.899 to 1.006]	<b>0.762 [0.666 to 0.872]</b>
GEE model (robust variance)	<b>0.889 [0.831 to 0.951]</b>	1.028 [0.981 to 1.078]	0.948 [0.897 to 1.003]	<b>0.743 [0.623 to 0.887]</b>
GEE model (robust variance and IPCW)	<b>0.924 [0.856 to 0.999]</b>	<b>1.070 [1.010 to 1.130]</b>	0.946 [0.886 to 1.011]	<b>0.747 [0.630 to 0.885]</b>
<b>TLR-2</b>	Particle number	Black carbon	Sulfate	Ozone (March to August)
Main model	0.943 [0.851 to 1.044]	1.032 [0.979 to 1.088]	0.987 [0.920 to 1.058]	0.917 [0.775 to 1.086]
Co-pollutant model	0.924 [0.832 to 1.026]	1.029 [0.976 to 1.086]	0.964 [0.886 to 1.049]	0.881 [0.638 to 1.215]
Model with further adjustments	0.938 [0.847 to 1.040]	1.031 [0.977 to 1.087]	0.988 [0.921 to 1.060]	0.916 [0.773 to 1.084]
GEE model (robust variance)	0.943 [0.856 to 1.039]	1.031 [0.979 to 1.086]	0.988 [0.915 to 1.067]	0.917 [0.788 to 1.068]
GEE model (robust variance and IPCW)	0.899 [0.783 to 1.033]	1.048 [0.988 to 1.112]	0.955 [0.854 to 1.068]	0.935 [0.795 to 1.099]
<b>Change in methylation (% 5mC) for an interquartile range increase in air pollution [95% CI]</b>				
<b>IFN-<math>\gamma</math></b>	Particle number	Black carbon	Sulfate	Ozone (March to August)
Main model	-0.845 [-1.704 to 0.013]	-0.363 [-0.872 to 0.145]	0.589 [-0.198 to 1.376]	<b>1.898 [0.244 to 3.552]</b>
Co-pollutant model	-0.829 [-1.694 to 0.036]	-0.317 [-0.831 to 0.197]	0.535 [-0.335 to 1.406]	1.151 [-1.650 to 3.952]
Model with further adjustments	-0.803 [-1.662 to 0.057]	-0.328 [-0.837 to 0.180]	0.654 [-0.133 to 1.441]	<b>1.925 [0.271 to 3.579]</b>
GEE model (robust variance)	-0.753 [-1.740 to 0.238]	-0.358 [-0.877 to 0.162]	0.587 [-0.251 to 1.420]	<b>1.880 [0.286 to 3.470]</b>
GEE model (robust variance and IPCW)	-0.618 [-2.320 to 1.080]	-0.656 [-1.420 to 0.109]	0.935 [-0.314 to 2.180]	<b>2.290 [0.590 to 4.000]</b>
<b>IL-6</b>	Particle number	Black carbon	Sulfate	Ozone (March to August)
Main model	1.412 [-0.245 to 3.068]	0.806 [-0.077 to 1.688]	0.317 [-1.055 to 1.688]	-2.486 [-5.424 to 0.452]
Co-pollutant model	1.180 [-0.496 to 2.855]	0.827 [-0.065 to 1.719]	0.724 [-1.104 to 2.552]	-3.316 [-8.655 to 2.024]
Model with further adjustments	1.403 [-0.257 to 3.064]	0.800 [-0.086 to 1.686]	0.310 [-1.065 to 1.686]	-2.466 [-5.415 to 0.483]
GEE model (robust variance)	<b>2.560 [0.541 to 4.590]</b>	<b>1.380 [0.194 to 2.570]</b>	0.827 [-0.648 to 2.300]	<b>-4.520 [-8.620 to -0.425]</b>
GEE model (robust variance and IPCW)	0.588 [-2.580 to 3.750]	1.060 [-0.127 to 2.240]	-0.209 [-2.200 to 1.780]	<b>-4.820 [-8.190 to -1.460]</b>

Abbreviations: Generalized estimating equations (GEE), Inverse probability censoring weights (IPCW)

a) Variables included in the main model:  $f_1$ (air pollutant)<sup>f</sup>,  $f_2$ (temperature)<sup>f</sup>,  $f_3$ (relative humidity)<sup>f</sup>, age, body mass index, smoking status, diabetes status, statin use, % neutrophils in blood count, % lymphocytes in blood count, seasonal sine and cosine, season, and batch.

b) Air pollution variables included in the co-pollutant model:  $f_{11}$ (air pollutant<sub>1</sub>)<sup>f</sup>,  $f_{12}$ (air pollutant<sub>2</sub>)<sup>f</sup>, where air pollutant<sub>2</sub> is ozone when air pollutant<sub>1</sub> is particle number or black carbon and air pollutant<sub>2</sub> is particle number when air pollutant<sub>1</sub> is sulfate or ozone

c) Additional variables included in the model with further adjustments: cigarette pack-years, more than two drinks per day, and maximal education

d) Variables included in the GEE model with robust variance: same as in main model

e) Variables included in the GEE model with robust variance and IPCW (inverse probability censoring weights): same as in main model

f)  $f_1$ (air pollutant),  $f_2$ (temperature), and  $f_3$ (relative humidity) represent the distributed-lag functions with sets of coefficients constrained by a natural spline (with 3 degrees of freedom) that correspond to the air pollution, temperature, and relative humidity associations at lags 0 and 27 days.-