SUPPLEMENTAL MATERIAL

Supplemental Material, Table 1. Names and category of investigated metabolites, number of values below the detection limit and measurement accuracy.

	Full metabolite name (named in Shah et al., 2010)	Category	# LOD	R^2
Alanine	Alanine	Amino acid	0*	0.97
Arginine	Arginine	Amino acid	0*	0.98
Aspartic acid/asparagine	Aspartic acid/asparagine	Amino acid	0*	0.86
C10	Decanoyl carnitine	Acylcarnitine	92*	0.90
C10:1	Decenoyl carnitine	Acylcarnitine	5*	0.99
C10:2		Acylcarnitine	240	NA
C10:3	Decatrienoyl carnitine	Acylcarnitine	42*	0.74
C10-OH/C8-DC	3-Hydroxy-decanoyl carnitine or Suberoyl carnitine	Acylcarnitine	44*	0.91
C12	Lauroyl carnitine	Acylcarnitine	6*	0.48
C12:1	Dodecenoyl carnitine	Acylcarnitine	4*	0.91
C12-OH/C10-DC	3-Hydroxy-dodecanoyl carnitine or Sebacoyl carnitine	Acylcarnitine	531	0.94
C14		Acylcarnitine	152	0.26
C14:1	Tetradecenoyl carnitine	Acylcarnitine	25*	0.74
C14:1-OH/C12:1-DC	3-Hydroxy-tetradecenoyl carnitine	Acylcarnitine	72*	0.74
C14:2	Tetradecadienoyl carnitine	Acylcarnitine	54*	0.89
C14-OH/C12-DC	3-Hydroxy-tetradecanoyl carnitine or Dodecanedioyl carnitine	Acylcarnitine	70*	0.68
C16	Palmitoyl carnitine	Acylcarnitine	0*	0.36
C16:1	Palmitoleoyl carnitine	Acylcarnitine	13*	0.95
C16:1-OH/C14:1-DC	3-Hydroxy-palmitoleoyl carnitine or cis-5-Tetradecenedioyl carnitine	Acylcarnitine	63*	0.95
C16:2	Hexadecadienoyl carnitine	Acylcarnitine	142	NA
C16-OH/C14-DC	3-Hydroxy-hexadecanoyl carnitine or Tetradecanedioyl carnitine	Acylcarnitine	73*	0.95
C18	Stearoyl carnitine	Acylcarnitine	117	0.53
C18:1	Oleyl carnitine	Acylcarnitine	3*	0.90
C18:1-OH/C16-DC	3-Hydroxy-octadecenoyl carnitine	Acylcarnitine	209	0.78
C18:2	Linoleyl carnitine	Acylcarnitine	0*	0.81
C18:2-OH	3-Hydroxy-linoleyl carnitine	Acylcarnitine	477	NA
C18-OH/C16-DC	3-Hydroxy-octadecanoyl carnitine or Hexadecanedioyl carnitine, thapsoyl carnitine	Acylcarnitine	551	0.70
C2	Acetyl carnitine	Acylcarnitine	0*	0.84
C20	Arachidoyl carnitine, eicosanoyl carnitine	Acylcarnitine	240	0.65
C20:1-OH/C18:1-DC	Octadecenedioyl carnitine	Acylcarnitine	176	NA
C20:4	Arachidonoyl carnitine	Acylcarnitine	313	0.80
C20-OH/C18-DC	3-Hydroxy-eicosanoyl carnitine or Octadecanedioyl carnitine	Acylcarnitine	183	0.39
C22	Behenoyl carnitine, docosanoyl carnitine	Acylcarnitine	449	0.84
C3	Propionyl carnitine	Acylcarnitine	5*	0.75
C4:Ci4	Butyryl carnitine or Isobutyryl carnitine	Acylcarnitine	3*	0.75
C4-OH	β-Hydroxy-butyryl carnitine	Acylcarnitine	33*	0.40
C5	Isovaleryl carnitine, 3-methylbutyryl carnitine or 2-Methylbutyryl carnitine	Acylcarnitine	12*	0.51
C5:1	Tiglyl carnitine	Acylcarnitine	4*	0.46
C5-DC	Glutaryl carnitine	Acylcarnitine	29*	0.60
C5-OH/C3-DC		Acylcarnitine	385	NA
C6:1-DC/C8:1-OH	3-Hydroxy-cis-5-octenoyl carnitine or Hexenedioyl carnitine	Acylcarnitine	68*	NA
C6-DC	Adipoyl carnitine	Acylcarnitine	27*	0.54

C8	Octanoyl carnitine	Acylcarnitine	6*	0.96
C8:1	Octenoyl carnitine	Acylcarnitine	0*	0.86
C8:1-DC	Octenedioyl carnitine	Acylcarnitine	26*	NA
Ci4-DC/C4-DC	Methylmalonyl carnitine or Succinyl carnitine	Acylcarnitine	93*	NA
Citrulline	Citrulline	Amino acid	0*	0.57
Glutamine/glutamate	Glutamine/glutamate	Amino acid	0*	0.55
Glycine	Glycine	Amino acid	0*	0.85
Histidine	Histidine	Amino acid	0*	0.33
Leucine/Isoleucine	Leucine/Isoleucine	Amino acid	0*	0.95
Methionine	Methionine	Amino acid	0*	0.95
Ornithine	Ornithine	Amino acid	0*	0.86
Phenylalanine	Phenylalanine	Amino acid	0*	0.95
Proline	Proline	Amino acid	0*	0.68
Serine	Serine	Amino acid	0*	0.79
Tyrosine	Tyrosine	Amino acid	0*	0.94
Valine	Valine	Amino acid	0*	0.84
β-hydroxybutyrate	β-hydroxybutyrate	Basic metabolite	1*	0.90
Ketones	Ketones	Basic metabolite	1*	0.91
Non-esterified fatty acids	non-esterified fatty acids	Basic metabolite	0*	NA

* Metabolites with less than 10% of values below the limit of detection

Supplemental Material, Table 2. Spearman correlation coefficients between 22 metabolites. Main metabolite within a cluster is marked in green. Additionally selected (uncorrelated) metabolites are marked in blue. Correlation coefficients within the cluster >0.4 are marked in red.

		Cluster 1				Cluster 2					Cluster 3							Cluster 4		Cluster 5			
		ALA	LEUILE	PHE	TYR	ASX	ORN	GLY	MET	ARG	C8	C10	C8:1	C10-OH/ C8-DC	C10:1	C12:1	C16-OH/ C14-DC	KET	HBUT	C14:2	C16:1	C16:1-OH/ C14:1-DC	C18:1
	Zeros	0	0	0	0	0	0	0	0	0	6	92	0	44	5	4	73	1	1	54	13	63	3
	R^2	0.97	0.95	0.95	0.94	0.86	0.86	0.85	0.95	0.98	0.96	0.90	0.86	0.91	0.99	0.91	0.95	0.91	0.90	0.89	0.95	0.95	0.90
Cluster 1	ALA	1	0.25	0.29	0.38	0.13	0.2	0.08	0.34	0.15	-0.03	-0.06	0.03	-0.08	0.01	-0.07	0.00	-0.51	-0.48	-0.15	-0.11	-0.06	-0.08
	LEUILE		1	0.47	0.37	0.19	0.26	0.07	0.37	0.19	-0.03	-0.05	-0.01	-0.01	-0.02	-0.04	0.04	0.03	0.00	-0.05	-0.09	0.01	-0.04
	PHE			1	0.65	0.12	0.19	-0.22	0.11	0.07	-0.01	-0.02	-0.05	-0.1	0.03	0.01	-0.12	-0.11	-0.11	0.02	0.00	-0.06	0.05
	TYR				1	0.10	0.24	-0.16	0.23	0.13	-0.07	-0.08	-0.08	-0.16	-0.05	-0.06	-0.10	-0.21	-0.20	-0.05	-0.02	-0.07	0.01
Cluster 2	ASX					1	0.09	0.1	0.22	0.08	-0.03	0.02	-0.06	-0.03	0.07	-0.07	0.09	-0.03	-0.03	-0.05	-0.02	0.03	0.05
	ORN						1	0.32	0.32	0.09	0.12	0.12	0.14	0.14	0.16	0.16	0.08	-0.11	-0.11	0.10	0.09	0.07	0.26
	GLY							1	0.51	0.20	0.12	0.08	0.11	0.27	0.11	0.11	0.16	-0.02	-0.03	0.04	0.01	0.08	0.08
	MET								1	0.39	0.07	0.04	0.04	0.22	0.12	0.10	0.27	-0.10	-0.10	-0.01	0.01	0.11	0.02
	ARG									1	-0.06	-0.07	-0.10	-0.06	-0.03	-0.07	-0.02	-0.12	-0.12	-0.10	-0.11	-0.03	-0.16
Cluster 3	C8										1	0.81	0.43	0.57	0.74	0.7	0.29	0.23	0.24	0.59	0.46	0.33	0.37
	C10											1	0.33	0.46	0.75	0.67	0.26	0.23	0.24	0.59	0.46	0.38	0.40
	C8:1												1	0.42	0.51	0.47	0.18	0.11	0.10	0.37	0.15	0.10	0.15
	C10-OH/C8-DC													1	0.42	0.67	0.41	0.31	0.31	0.53	0.38	0.35	0.33
	C10:1														1	0.73	0.34	0.21	0.21	0.63	0.46	0.36	0.39
	C12:1															1	0.43	0.39	0.39	0.75	0.66	0.47	0.50
	C16-OH/C14-DC																1	0.27	0.27	0.37	0.42	0.47	0.33
Cluster 4	KET																	1	0.99	0.53	0.53	0.39	0.39
	HBUT																		1	0.54	0.55	0.40	0.41
Cluster 5	C14:2																			1	0.75	0.52	0.61
	C16:1																				1	0.61	0.73
	C16:1-OH/C14:1-DC																					1	0.54
	C18:1																						1

ALA: Alanine, LEUILE: Leucine/Isoleucine, PHE: Phenylalanind, TYR: Tyrosine, ASX: Aspartic acid/asparagine, ORN: Ornithine, GLY: Glycine, MET: Methionine, ARG: Arginine, KET: Ketones, HBUT: β-hydroxybutyrate

Supplemental Material, Table 3. Spearman correlation matrix of air pollutants and meteorological variables.

	$PM_{2.5}$ (BDFM)	Ozone (BDFM)	Temp	RH	$PM_{2.5}$ (AOD+GM)
$PM_{2.5}$ (BDFM)	1.000	0.437	0.339	-0.158	0.857
Ozone (BDFM)		1.000	0.499	-0.394	0.419
Temp			1.000	0.178	0.410
RH				1.000	-0.097
$PM_{2.5}$ (AOD+GM)					1.000

Temp: Air temperature; RH: Relative humidity; BDFM: Bayesian space-time "downscaler" fusion modeling approach; AOD + GM: combination of satellite-based aerosol optical depth retrievals and ground monitoring data.

Supplemental Material, Table 4. Percent change (95% confidence intervals) of the geometric mean of metabolites per interquartile range increase in $PM_{2.5}$ and ozone.

Cluster	Metabolite		$PM_{2.5}$		Ozone	
		Lag	% change	(95% CI)	% change	(95% CI)
1	Alanine	0	0.93	(-0.65;2.53)	1.54	(-0.80;3.94)
		1	-0.88	(-2.49;0.75)	-0.76	(-3.24;1.79)
		2	-1.09	(-2.70;0.53)	-1.42	(-3.89;1.11)
		3	-0.12	(-1.72;1.51)	0.18	(-2.32;2.75)
		4	1.03	(-0.56;2.64)	2.10	(-0.36;4.63)
		5-day	-0.01	(-1.63;1.64)	1.08	(-2.78;5.10)
1	Leucine/Isoleucine	0	-0.26	(-1.40;0.89)	0.30	(-1.40;2.02)
		1	-0.24	(-1.43;0.96)	1.07	(-0.79;2.96)
		2	0.77	(-0.42;1.98)	0.94	(-0.91;2.83)
		3	0.58	(-0.60;1.77)	1.08	(-0.77;2.96)
		4	-0.01	(-1.16;1.15)	-0.61	(-2.37;1.18)
		5-day	0.26	(-0.93;1.47)	1.46	(-1.39;4.39)
2	Arginine	0	-1.05	(-2.76;0.68)	-0.42	(-2.95;2.18)
		1	-2.61	(-4.35;-0.84)**	-2.83	(-5.51;-0.07)*
		2	-1.71	(-3.46;0.08)	-1.04	(-3.78;1.77)
		3	-0.14	(-1.90;1.65)	0.09	(-2.66;2.91)
		4	0.41	(-1.31;2.17)	1.58	(-1.11;4.33)
		5-day	-1.65	(-3.41;0.14)	-1.34	(-5.48;2.97)
2	Aspartic acid/asparagine	0	0.50	(-0.77;1.78)	2.15	(0.25;4.09)*
		1	-0.83	(-2.13;0.49)	0.66	(-1.38;2.74)
		2	-0.93	(-2.22;0.38)	-0.83	(-2.84;1.21)
		3	-0.54	(-1.83;0.76)	-0.01	(-2.03;2.04)
		4	0.19	(-1.08;1.47)	0.84	(-1.13;2.84)
		5-day	-0.51	(-1.81;0.81)	1.70	(-1.44;4.94)
2	Ornithine	0	0.92	(-0.52;2.39)	2.20	(0.04;4.41)*
		1	0.96	(-0.54;2.49)	2.13	(-0.22;4.53)
		2	0.93	(-0.57;2.46)	2.88	(0.52;5.30)*
		3	1.84	(0.35;3.36)*	2.44	(0.10;4.83)*
		4	2.23	(0.77;3.72)**	2.59	(0.33;4.90)*
		5-day	2.31	(0.79;3.85)**	6.84	(3.11;10.70) †
2	Glycine	0	-0.44	(-1.70;0.84)	0.72	(-1.17;2.65)
		1	-2.46	(-3.75;-1.16)†	-1.87	(-3.88;0.18)
		2	-1.31	(-2.61;0.01)	-1.00	(-3.03;1.06)
		3	0.90	(-0.41;2.23)	1.21	(-0.84;3.31)
		4	0.92	(-0.36;2.22)	2.56	(0.56;4.61)*
		5-day	-0.75	(-2.07;0.58)	1.01	(-2.13;4.26)
3	C10:1	0	-0.59	(-2.95;1.82)	1.61	(-1.94;5.30)
		1	0.21	(-2.26;2.74)	5.04	(1.05;9.18)*

		2	0.67	(-1.80;3.21)	1.34	(-2.50;5.34)
		3	0.65	(-1.80;3.15)	-1.31	(-5.03;2.56)
		4	-0.79	(-3.14;1.63)	1.71	(-1.99;5.54)
		5-day	0.02	(-2.45;2.54)	4.59	(-1.42;10.96)
3	C16-OH/C14-DC	0	-0.41	(-3.88;3.19)	1.82	(-3.39;7.32)
		1	0.56	(-3.09;4.35)	3.06	(-2.67;9.13)
		2	-1.01	(-4.59;2.72)	-2.85	(-8.26;2.87)
		3	-1.55	(-5.06;2.08)	-2.53	(-7.89;3.14)
		4	-0.13	(-3.62;3.48)	0.03	(-5.29;5.66)
		5-day	-0.85	(-4.45;2.89)	-0.17	(-8.50;8.92)
4	Ketones	0	-3.14	(-7.84;1.79)	-0.58	(-7.64;7.03)
		1	1.76	(-3.37;7.16)	9.77	(1.32;18.93)*
		2	3.36	(-1.83;8.83)	-0.54	(-8.20;7.75)
		3	2.76	(-2.34;8.13)	-0.98	(-8.56;7.22)
		4	1.36	(-3.56;6.52)	-0.46	(-7.80;7.47)
		5-day	1.89	(-3.24;7.29)	3.46	(-8.48;16.96)
5	C16:1	0	-1.69	(-4.06;0.74)	0.23	(-3.34;3.93)
		1	1.66	(-0.88;4.27)	4.43	(0.41;8.63)
		2	2.41	(-0.15;5.04)	0.18	(-3.69;4.20)
		3	2.79	(0.25;5.39)*	2.34	(-1.59;6.42)*
		4	1.27	(-1.18;3.77)	0.52	(-3.20;4.38)
		5-day	2.06	(-0.50;4.68)	4.07	(-2.01;10.53)

% change: Percent change of geometric mean 95% CI: 95% confidence interval; 5-day: 5-day average concentration;

Interquartile ranges for $PM_{2.5}$: Lags 0-4 8.1 $\mu g/m^3$, 5-day average 5.1 $\mu g/m^3$;

Interquartile ranges for ozone: Lags 0-4 22.7 ppb, 5-day average 20.5 ppb

* p-value < 0.05

** p-value < 0.01

† p-value < 0.001

Supplemental Material, Table 5. Sensitivity analyses for the effects of $PM_{2.5}$ and ozone on metabolite levels.

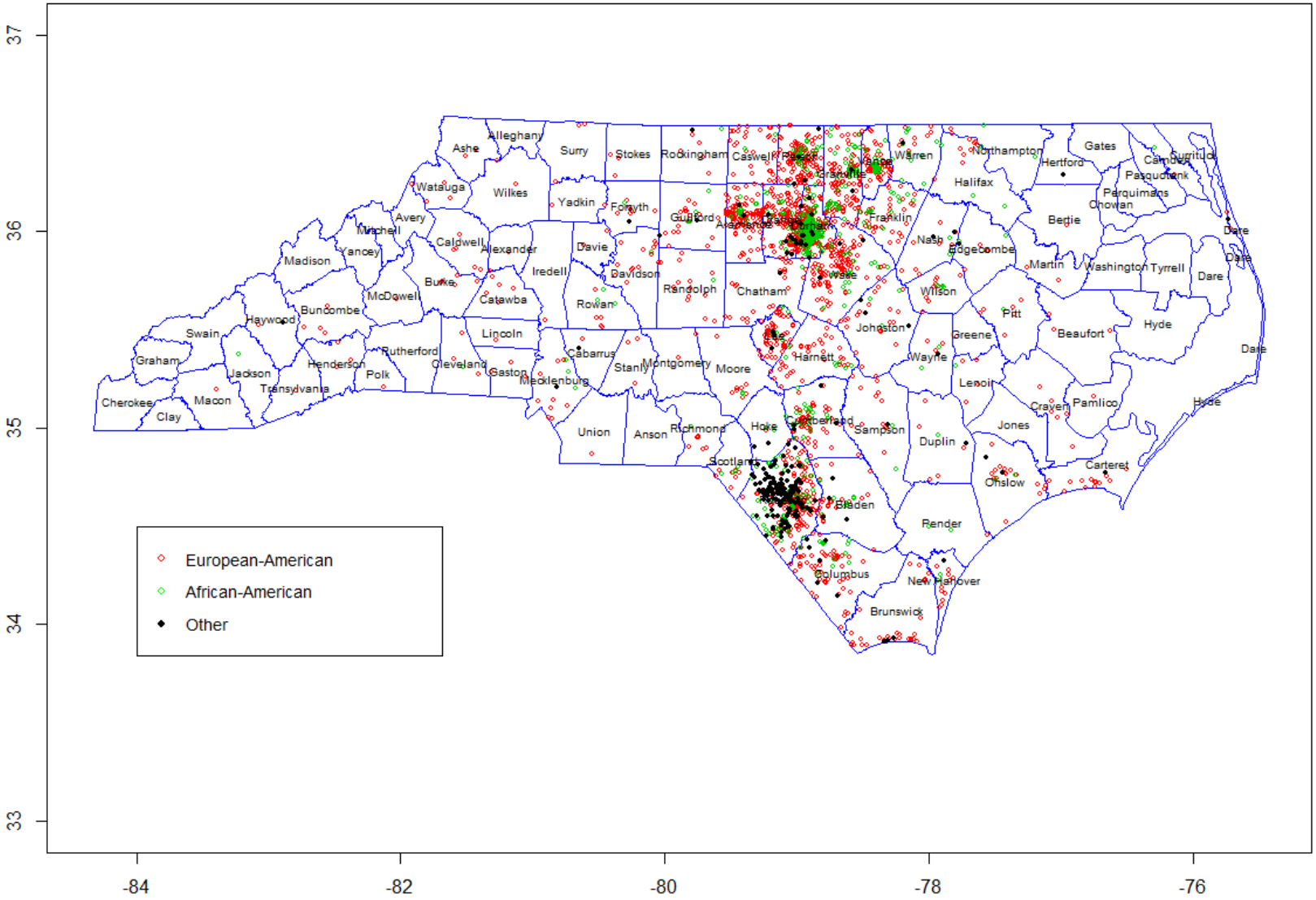
	Lag	Amino acids	$PM_{2.5}$		Ozone	
			% change	95% CI	% change	95% CI
Main model	1	Arginine	-2.61	(-4.35;-0.84)	-2.83	(-5.51;-0.07)
	1	Glycine	-2.46	(-3.75;-1.16)	-1.87	(-3.88;0.18)
	5-day	Ornithine	2.31	(0.79;3.85)	6.84	(3.11;10.70)
With adjustment	1	Arginine	-2.76	(-4.35;-1.14)	-2.43	(-4.65;-0.17)
only for counties	1	Glycine	-2.16	(-3.34;-0.96)	-0.64	(-2.3;1.06)
and time trend	5-day	Ornithine	2.18	(0.78;3.60)	5.44	(2.78;8.18)
Trend with 6 df	1	Arginine	-2.80	(-4.53;-1.02)	-2.92	(-5.66;-0.11)
per year	1	Glycine	-2.34	(-3.63;-1.03)	-1.56	(-3.62;0.53)
	5-day	Ornithine	2.26	(0.73;3.82)	6.44	(2.48;10.56)
Without season as	1	Arginine	-2.61	(-4.34;-0.85)	-2.86	(-5.49;-0.16)
categorical	1	Glycine	-2.36	(-3.64;-1.06)	-1.46	(-3.43;0.55)
variable	5-day	Ornithine	2.35	(0.83;3.89)	7.15	(3.49;10.95)
Without adjustment	1	Arginine	-2.34	(-4.03;-0.61)	-2.81	(-5.42;-0.12)
for counties	1	Glycine	-2.19	(-3.44;-0.92)	-1.74	(-3.69;0.25)
	5-day	Ornithine	2.11	(0.63;3.60)	6.82	(3.23;10.54)
Without adj. for	1	Arginine	-2.63	(-4.34;-0.90)	-2.92	(-5.56;-0.21)
time-invariant	1	Glycine	-2.13	(-3.39;-0.85)	-1.80	(-3.76;0.21)
variables[a]	5-day	Ornithine	1.79	(0.27;3.34)	7.20	(3.46;11.08)
Adj. for T and RH	1	Arginine	-2.93	(-4.68;-1.14)	-3.51	(-6.30;-0.64)
with same lag as	1	Glycine	-2.53	(-3.83;-1.21)	-1.56	(-3.66;0.59)
for air pollutant	5-day	Ornithine	2.36	(0.85;3.89)	6.86	(3.19;10.65)
Adj. for T and RH	1	Arginine	-2.60	(-4.35;-0.83)	-3.06	(-5.76;-0.28)
with 5 df	1	Glycine	-2.48	(-3.77;-1.17)	-1.97	(-3.99;0.10)
	5-day	Ornithine	2.28	(0.75;3.83)	7.03	(3.26;10.93)

% change: Percent change of geometric mean 95% CI: 95% confidence interval; 5-day: 5-day average concentration; T: Temperature; RH: relative humidity;
Interquartile ranges for $PM_{2.5}$: Lag 1 8.1 µg/m^3, 5-day average 5.1 µg/m^3;
Interquartile ranges for ozone: Lag 1 22.7 ppb, 5-day average 20.5 ppb
[a] Time-invariant variables: Counties, age, body mass index, gender, race, smoking

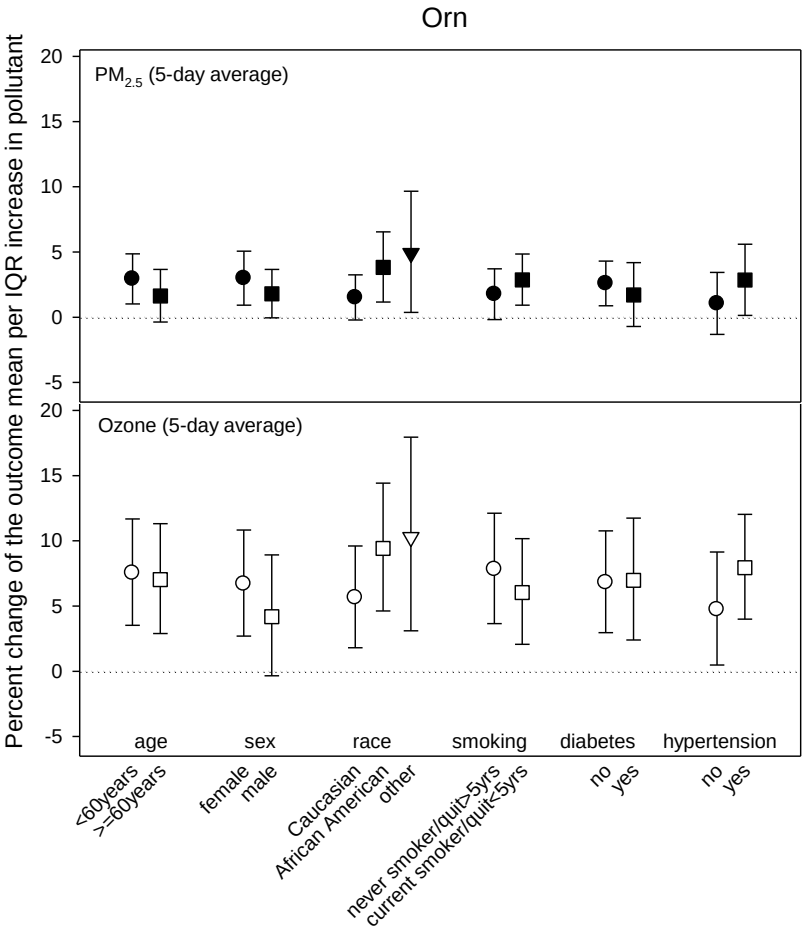
Supplemental Material, Table 6. Effects of $PM_{2.5}$ and ozone on metabolites – results of single- and two-pollutant models.

		Single-pollutant model				Two-pollutant model			
Metabolites		$PM_{2.5}$		Ozone		$PM_{2.5}$		Ozone	
	Lag	% change	(95% CI)	% change	(95% CI)	% change	(95% CI)	% change	(95% CI)
Alanine	4	1.03	(-0.56;2.64)	2.10	(-0.36;4.63)	0.45	(-1.37;2.31)	1.74	(-1.11;4.66)
Leucine/Isoleucine	2	0.77	(-0.42;1.98)	0.94	(-0.91;2.83)	0.62	(-0.73;1.99)	0.48	(-1.62;2.62)
Arginine	1	-2.61	(-4.35;-0.84)	-2.83	(-5.51;-0.07)	-2.24	(-4.18;-0.25)	-1.28	(-4.32;1.86)
Aspartic acid/asparagine	0	0.50	(-0.77;1.78)	2.15	(0.25;4.09)	-0.21	(-1.62;1.21)	2.31	(0.16;4.50)
Glycine	1	-2.46	(-3.75;-1.16)	-1.87	(-3.88;0.18)	-2.40	(-3.83;-0.94)	-0.19	(-2.47;2.14)
Ornithine	5-day	2.31	(0.79;3.85)	6.84	(3.11;10.70)	1.21	(-0.51;2.96)	5.35	(1.14;9.73)
C10:1	1	0.21	(-2.26;2.74)	5.04	(1.05;9.18)	-1.51	(-4.21;1.26)	6.17	(1.67;10.87)
C16-OH/C14-DC	1	0.56	(-3.09;4.35)	3.06	(-2.67;9.13)	-0.39	(-4.40;3.79)	3.34	(-3.07;10.16)
Ketones	1	1.76	(-3.37;7.16)	9.77	(1.32;18.93)	-1.18	(-6.71;4.67)	10.68	(1.19;21.07)
C16:1	3	2.79	(0.25;5.39)	2.34	(-1.59;6.42)	2.82	(0.30;5.41)	4.51	(0.48;8.70)

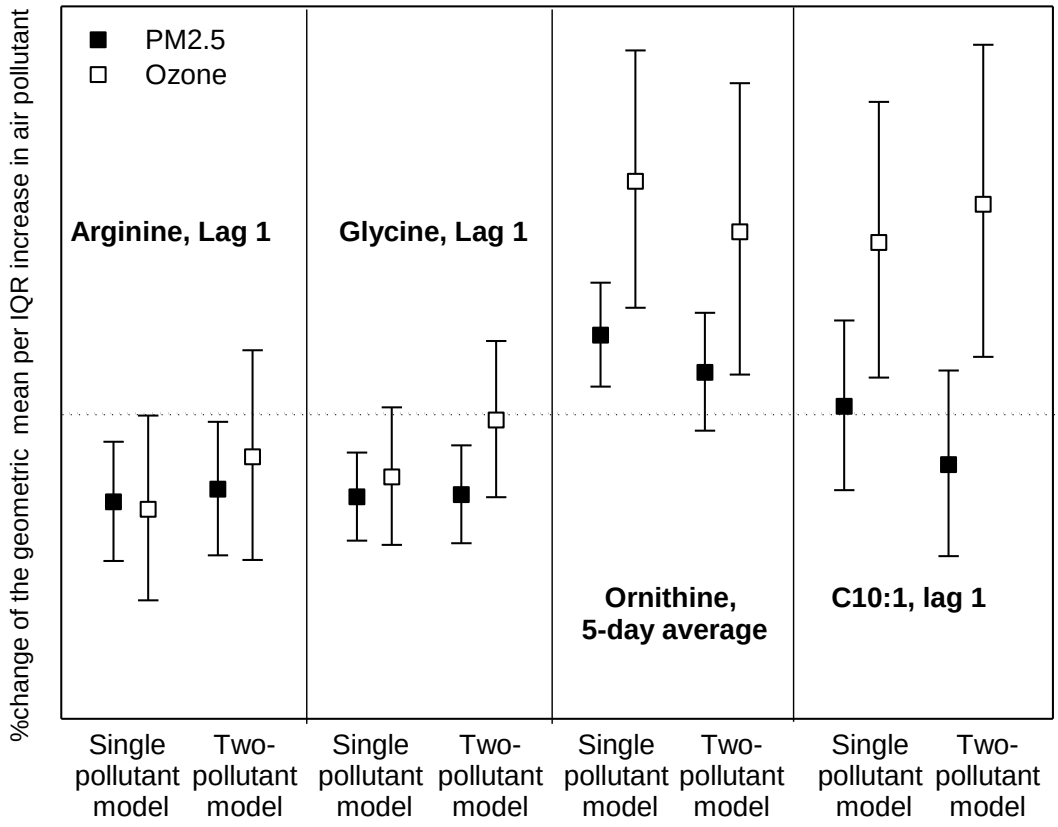
Supplemental Material, Figure 1. Residences of the study population between 2001 and 2007.



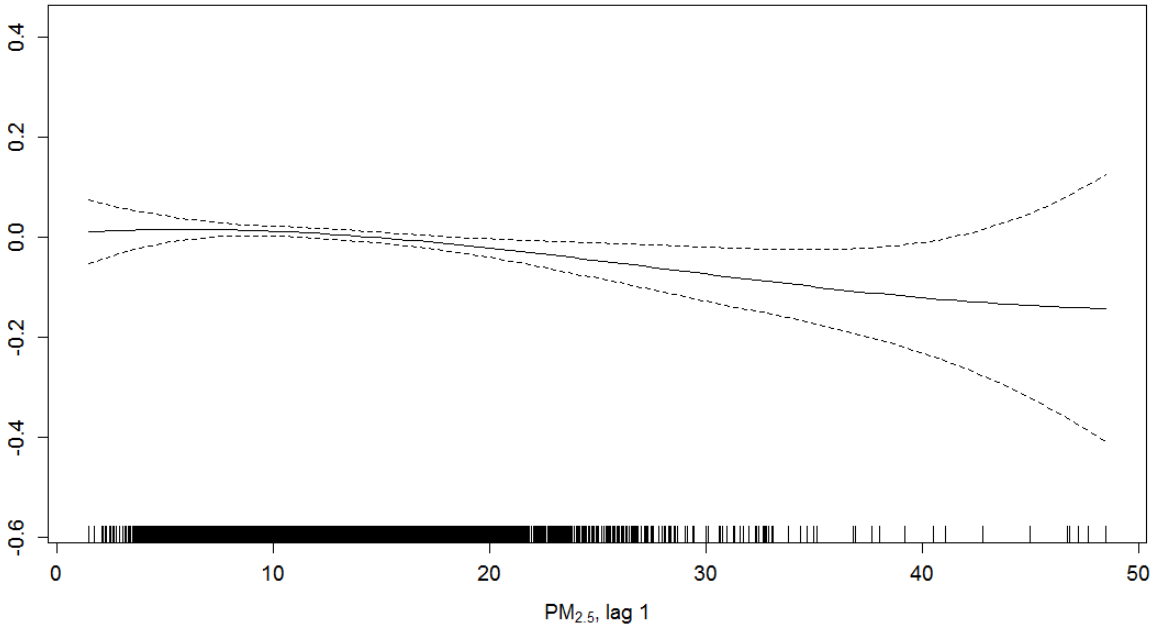
Supplemental Material, Figure 2. Air pollution and ornithine - effect modification.

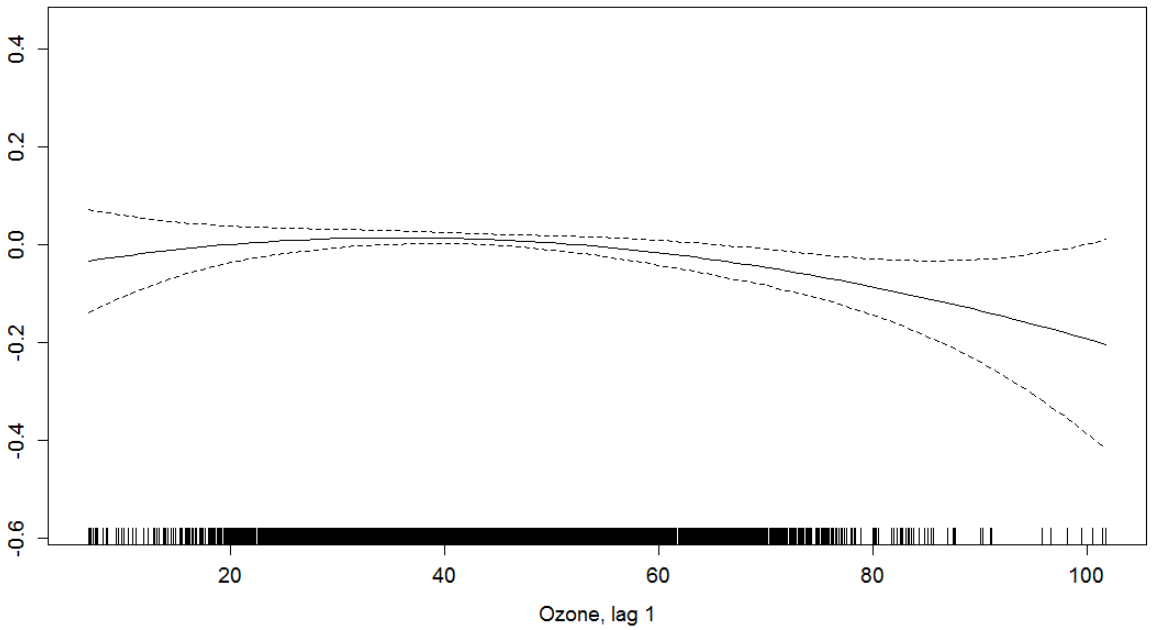


Supplemental Material, Figure 3. Effects of $PM_{2.5}$ and ozone on selected metabolites - two-pollutant models.

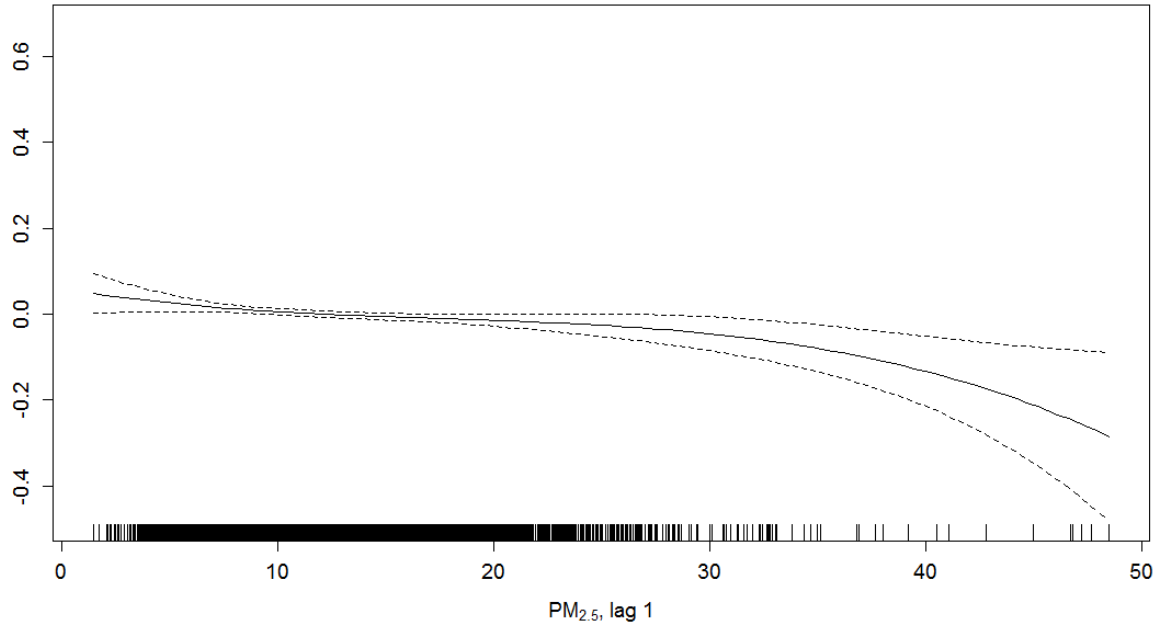


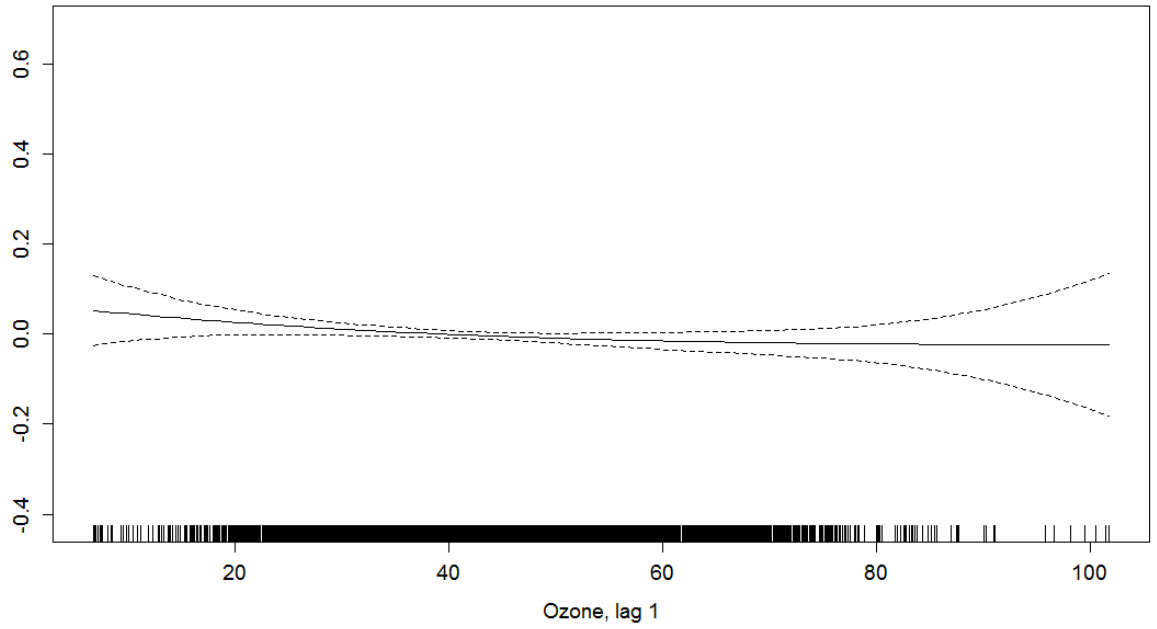
Supplemental Material, Figure 4. Exposure-response relationships between arginine, $PM_{2.5}$ and ozone for selected lags.





Supplemental Material, Figure 5. Exposure-response relationships between glycine, $PM_{2.5}$ and ozone for selected lags.





Supplemental Material, Figure 6. Exposure-response relationships between ornithine, $PM_{2.5}$ and ozone for selected lags.