Short-Term Effects of Airport-Associated Ultrafine Particle Exposure on Lung Function and Inflammation in Asthmatics

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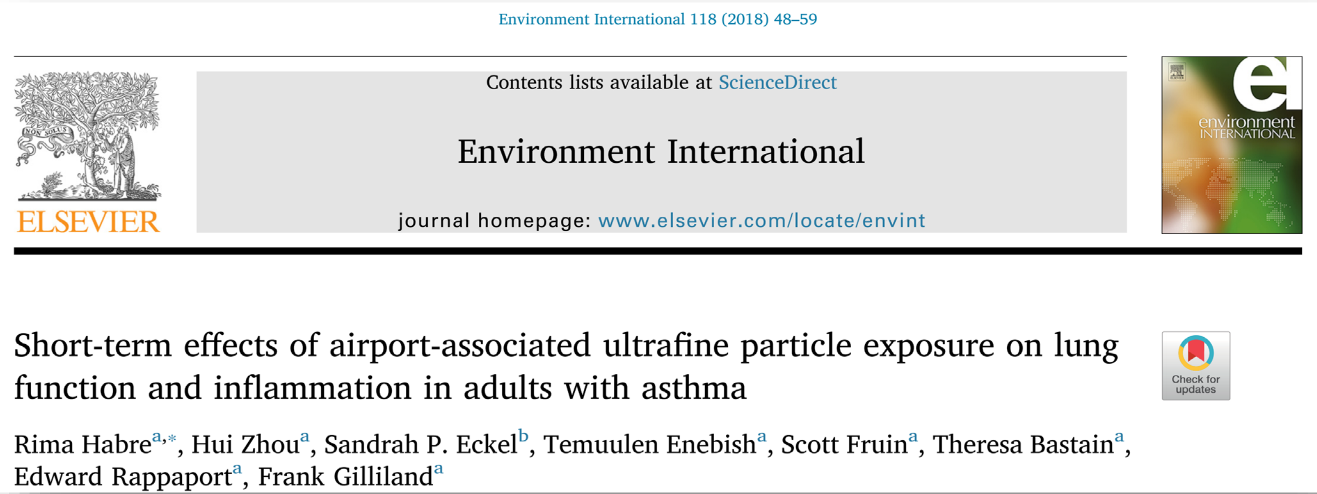
Study Motivation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Short-term effects of airport-associated ultrafine particle exposure on lung function and inflammation in adults with asthma

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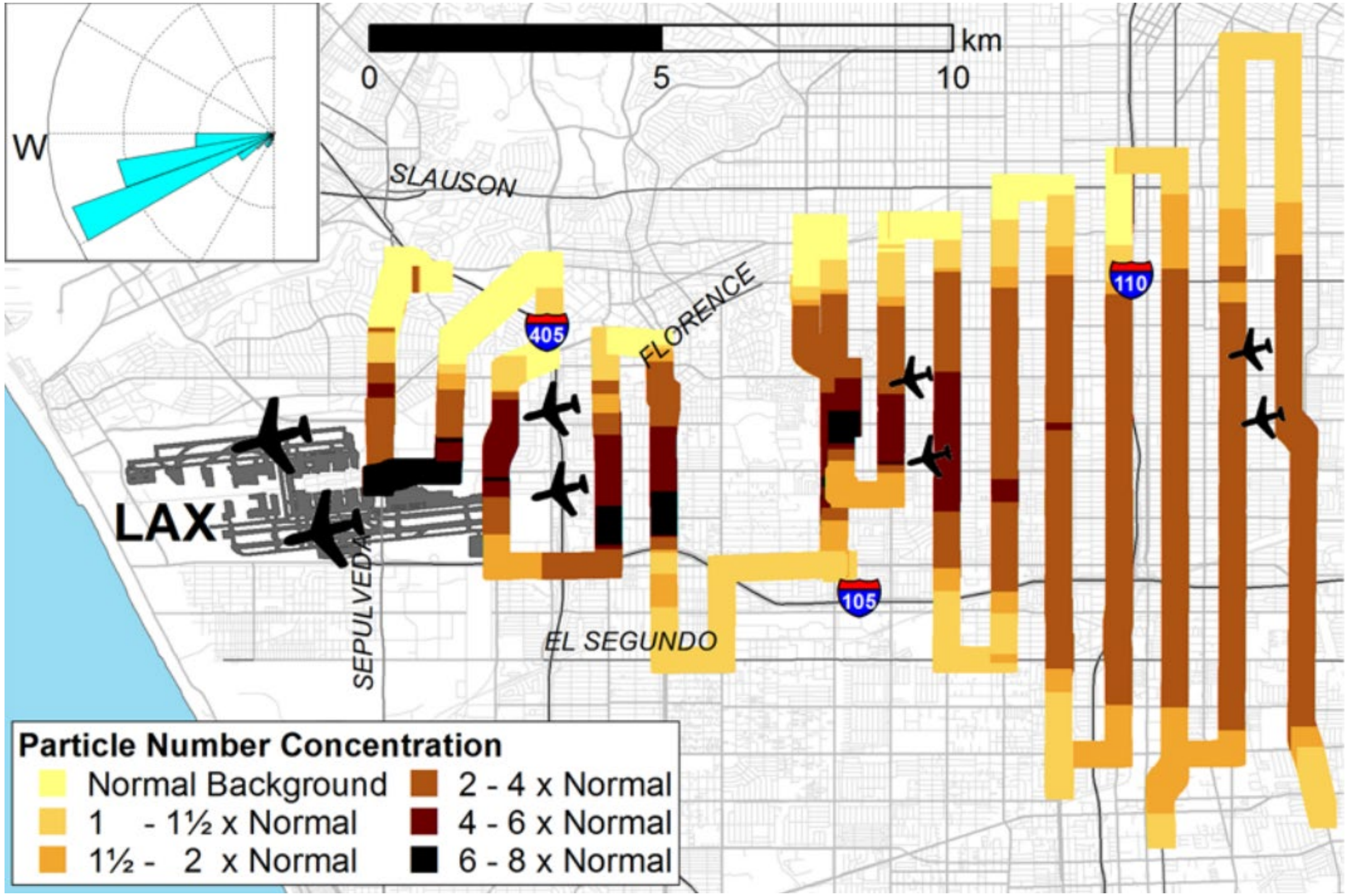
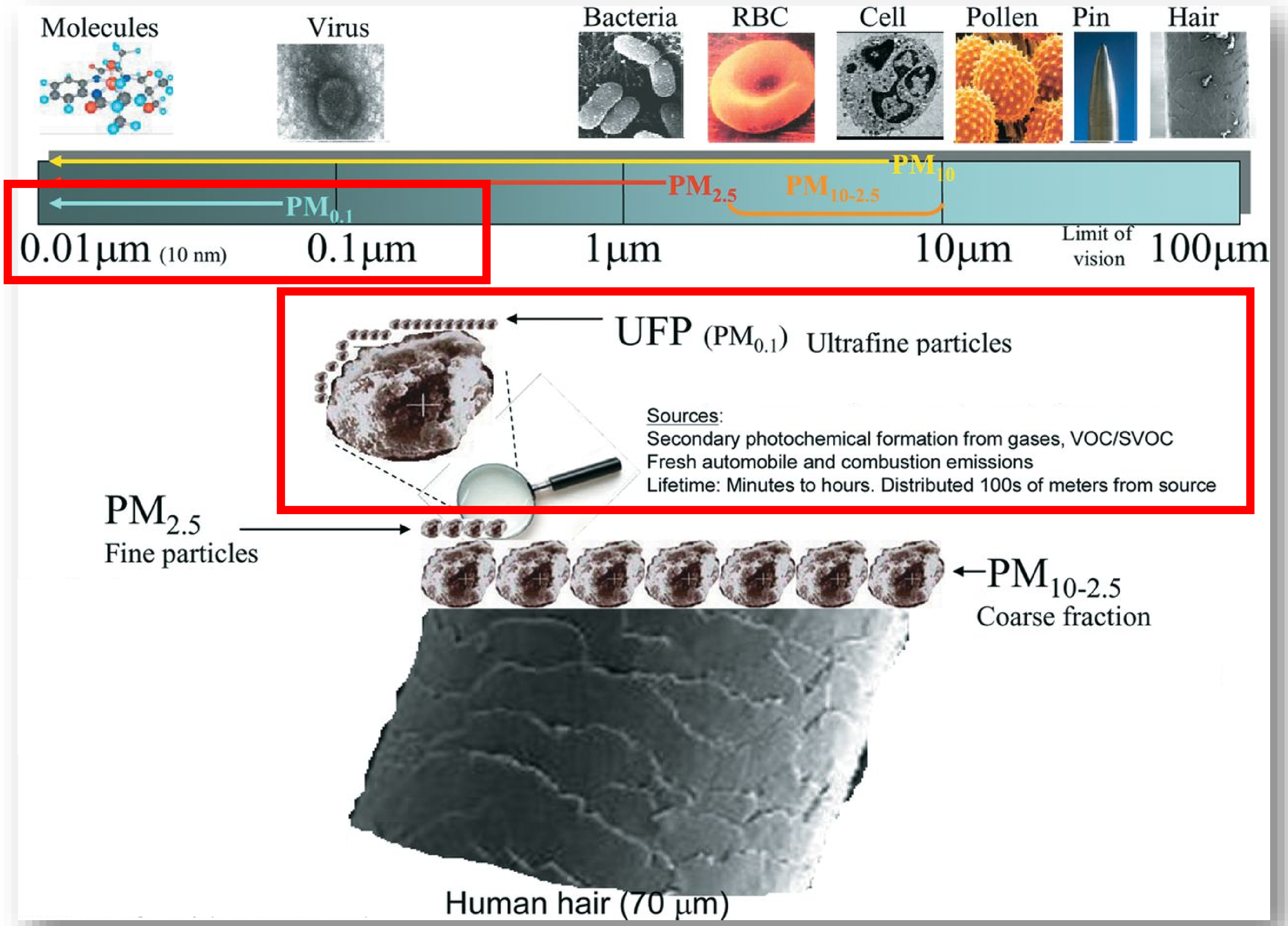
- UFPs (particles <100nm in aerodynamic diameter) unregulated, potentially higher toxicity than larger particles
- Preliminary evidence on UFP health effects from traffic exposure studies, very limited from airport sources
- Significant plume of ultrafine particles (UFPs) downwind of Los Angeles International Airport (Hudda et al 2014)

UFPs Downwind of LAX



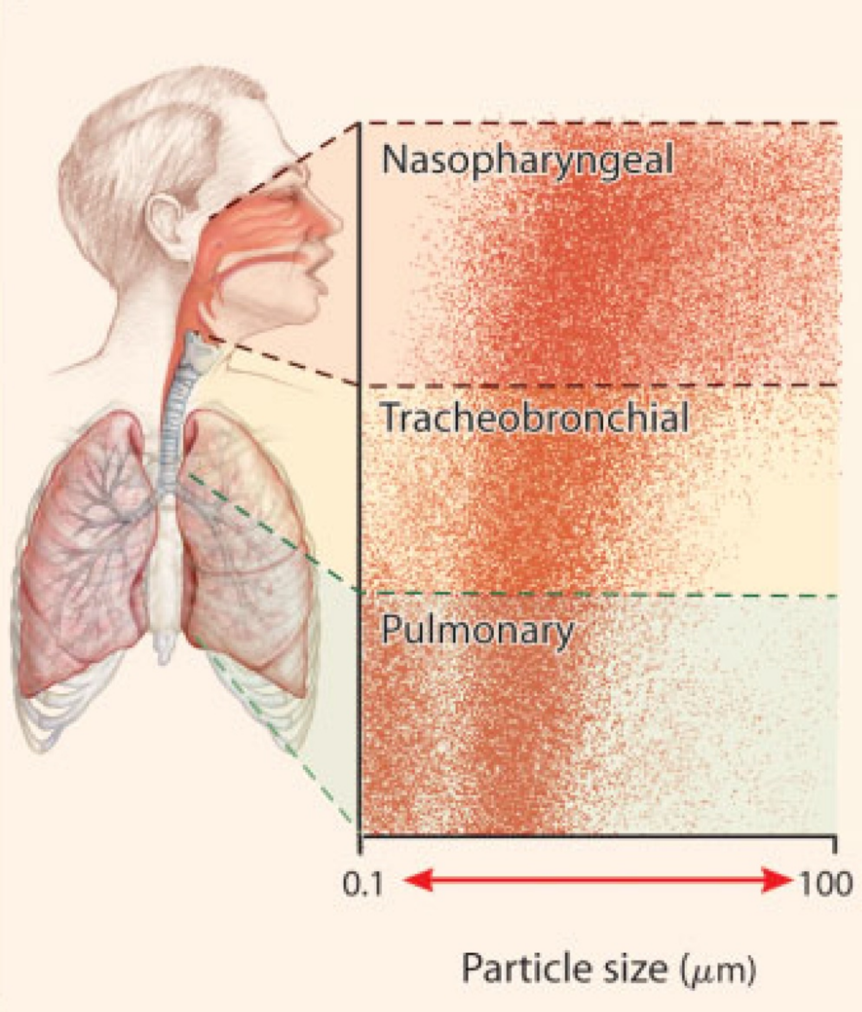
Hudda, N., Gould, T., Hartin, K., Larson, T. V., & Fruin, S. A. (2014). Emissions from an International Airport Increase Particle Number Concentrations 4-fold at 10 km Downwind. *Environmental Science & Technology*, *48*(12), 6628–6635. http://doi.org/10.1021/es5001566



http://doku6rqv4sqv7.cloudfront.net/content/ppclinsci/115/6/175/F1.large.jpg

UFPs Lung Deposition

- Diffusion driven behavior (<100 nm)
- Very efficient deposition in pulmonary alveolar region
- High surface area to mass ratio, efficient transport of adsorbed toxicants
- Evade mucociliary and macrophage clearance in the lungs, penetrate into cells and cross the epithelial barrier into systemic circulation
- Generally longer residence time in the lungs than $PM_{2.5}$



Roy and Milton, 2004

Epidemiological Evidence: Airport-related Air Pollution

- Children living in 17 MA communities < 5-miles from Boston Logan Int'l Airport 3-4 times more likely to have respiratory symptoms indicative of undiagnosed asthma (Massachusetts Department of Public Health 2014)
- Daily air pollution attributable to runway congestion at 12 largest CA airports leads to $1M in cardiorespiratory hospitalization costs for 6M individuals living within 10km (Schlenker and Walker, 2011)
- Mainly coarse spatial estimates of exposures due to challenging and highly dynamic nature in space and time, not UFP specific

Study Design

- Randomized crossover modeled after Mc Creanor et al 2007 quasi-experimental design
- Recruited 22 non-smoking adults with mild to moderately controlled asthma (ACT)
- Conducted scripted, mild walking activity midday on 2 occasions separated by at least a week, at 2 public parks during Nov - Dec 2014 and May – Jul 2015
- Extensive health phenotyping before and after, detailed personal and stationary multipollutant exposure assessment during

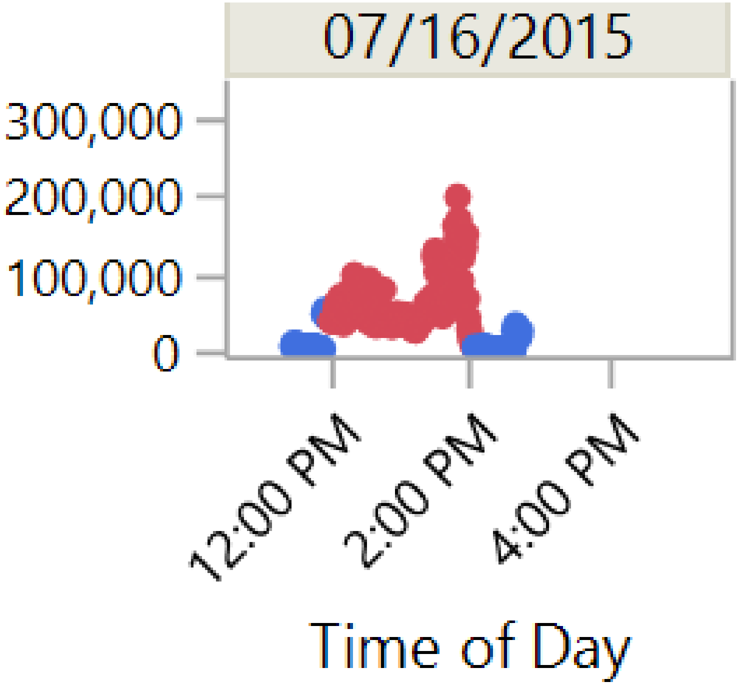
Study Sites

Kenneth Hahn State Recreational Park (Control)

Jesse Owens Park (Exposure)

Multipollutant Exposure Assessment

- Personal monitoring
  - DiscMini (PN, LDSA, Size), CPC 3007 (PN), Onset Hobo (RH, temp)
  - During transport in-vehicle and walking exposure
- Mobile monitoring platform
  - PN, BC, particle-bound PAHs, O_3, CO_2, PM_1, $PM_{2.5}$, PM_4, PM_{10}
  - Along transport route and stationary at parks



Example: PN Concentrations in-vehicle during transport (**blue**) and at the park during walking (**red**)

Health Assessments

- Baseline health
  - Detailed questionnaire
  - IgE specific upper respiratory allergens panel (16 allergens)
  - Complete blood count
  - Height, weight, resting heart rate, body composition (Tanita scale)
- Pre- and post-exposure, both visits (4 time points)
  - Lung function (FVC, FEV_1)
  - Multiple flow exhaled nitric oxide (FeNO, at 30, 50, 100 and 300 ml/s)
    - Derive *airway wall* ($J'_{aw}NO$, $D_{aw}NO$) and *alveolar* (C_ANO) sources of NO and predicted $FeNO_{50}$ (Eckel et al 2014)
  - Circulating inflammatory cytokines (hsIL-6, sTNFrII, vWF, fibrinogen)

Eckel, S.P., Linn, W.S., Berhane, K., Rappaport, E.B., Salam, M.T., Zhang, Y. and Gilliland, F.D., 2014. Estimation of parameters in the two-compartment model for exhaled nitric oxide. *PloS one*, *9*(1), p.e85471

Statistical Analysis: Exposure

- Principal components analysis (with oblique rotation)
  - Personal UFP particle numbers (PN), stationary UFP PN, particle size, black carbon (BC), particle-bound PAHs (PB-PAH), ozone (O_3), carbon dioxide (CO_2) and particulate matter ($PM_{1,}$ $PM_{2.5\,,}$ PM_{10}) mass
- Identify and resolve distinct ‘source factors’ that contributed to observed concentrations to disentangle the mixture

Statistical Analysis: Health Effect Models

- Single and multiple pollutant ANCOVA models examining *within-subject* changes in outcome per *walking period average exposure* to measured pollutants and modeled source factors

$$Y_{ij,T1} = \beta_0 + \beta_1 {*} Y_{ij,T0} + \boldsymbol{\beta_2} {*} \mathrm{Exposure(s)}_{ij} + U_i + \varepsilon_{ij}$$

i= subject, j=day, T1=Post-exposure, T0=Pre-Exposure

Results: Participant Characteristics (n=22)

		N (%)
Gender	Female	16 (73%)
Race	White	11 (50%)
	African-American	3 (14%)
	Asian	3 (14%)
	American Indian	1 (5%)
	Other	4 (18%)
Ethnicity	Hispanic	9 (43%)

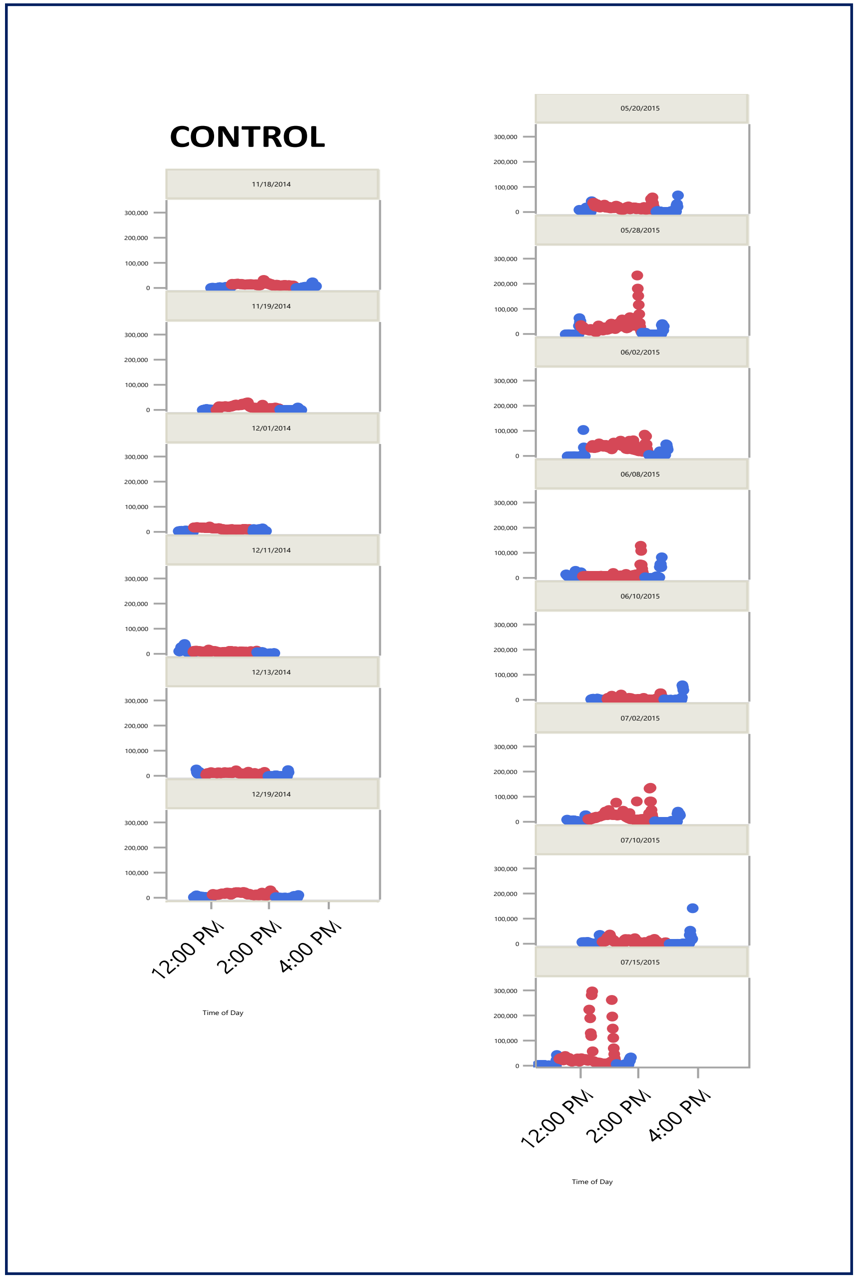
	Mean	Std Dev	Min	Max
Age	27	9.5	18	60
ACT* Score (Recruitment)	18.7	3.2	11	22
ACT* Score (Day of Visit)	20.6	3.8	11	25
Body Mass Index (kg/m²)	24.8	6.1	17.4	46.7

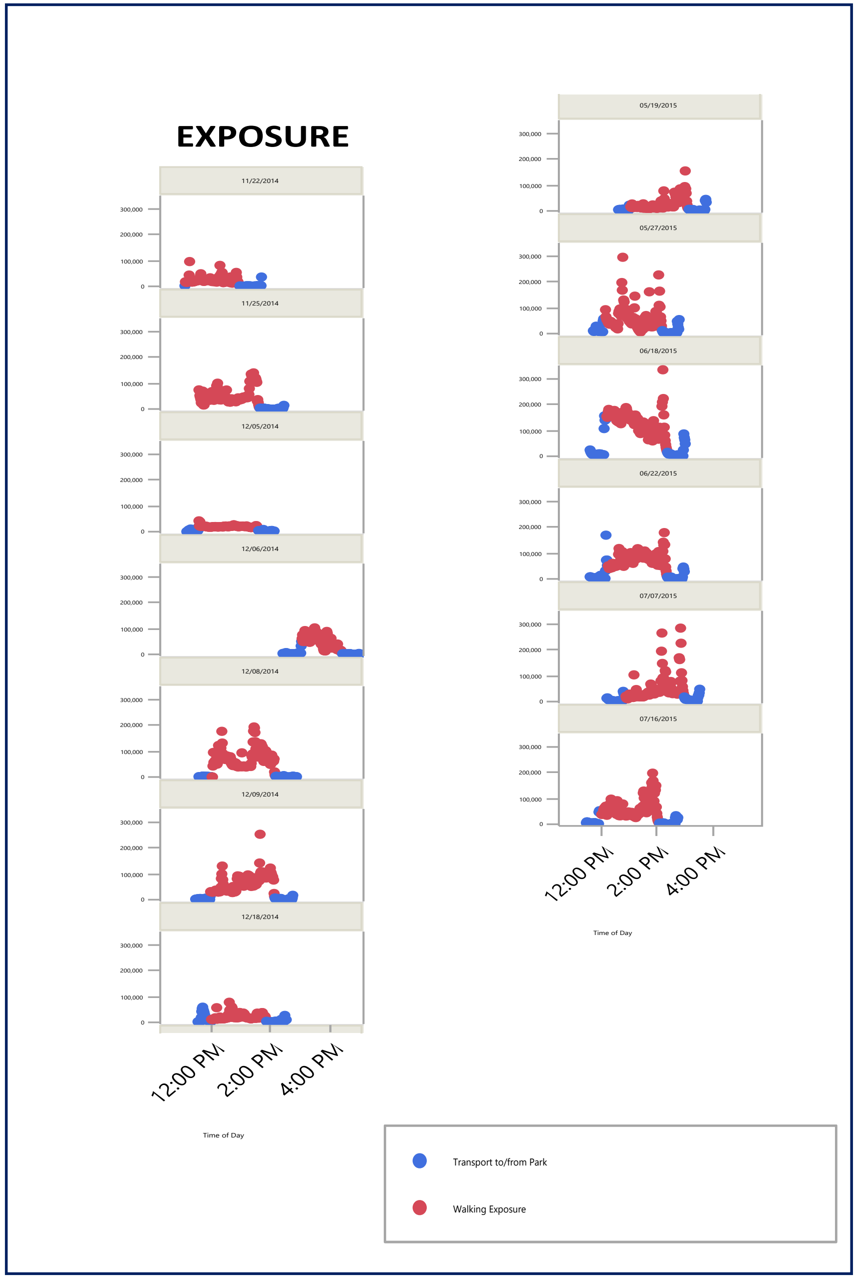
Specific IgE Response to Upper Airway Allergens (Top 5), N (%)

Class	0	1	2	3	4	5
D. pteronyssinus, d1	10 (45%)	1 (5%)	2 (9%)	5 (23%)	3 (14%)	1 (5%)
D. farinae, d2	11 (50%)	2 (9%)	5 (23%)	3 (14%)	1 (5%)	
Dog dander, e5	12 (55%)	1 (5%)	7 (32%)	1 (5%)	1 (5%)	
Cat dander, e1	13 (59%)	1 (5%)	2 (9%)	2 (9%)	4 (18%)	
Bermuda grass, g2	15 (68%)	2 (9%)	2 (9%)	2 (9%)	1 (5%)	

*ACT = Asthma Control Test

Results: UFP Particle Number Exposure (#/cm^3)





Results: Source apportionment

Resolved four factors: PM mass (PM_1, $PM_{2.5}$, PM_{10}), Traffic (BC, PB-PAH), Airport-Related UFP (PN, smaller size), and Secondary Photochemistry (O_3, $PM_{2.5}$)

	SOURCE FACTORS			
Pollutant	**Airport UFPs**	**PM Mass**	**Traffic**	**Secondary Photochemistry**
PN (personal DiscMini)	**0.72**	0.00	0.16	0.20
PN (stationary CPC)	**0.71**	-0.02	0.35	0.19
Particle Size	**-0.81**	0.01	0.23	0.15
PM_1	-0.04	**0.93**	0.07	0.06
$PM_{2.5}$	-0.10	**0.63**	0.09	**0.47**
PM_{10}	0.07	**0.98**	-0.07	-0.08
BC	0.05	0.17	**0.76**	-0.14
CO_2	-0.03	-0.10	**0.83**	-0.10
PB-PAH	0.19	0.07	**0.59**	-0.21
O_3	0.19	0.06	-0.63	**0.68**

Results: Exposures by Scenario

	Control (n=21)		Exposure (n=22)		Pearson t-test
Pollutants	Mean	Std Dev	Mean	Std Dev	p-value
PN (#/cm^3, stationary CPC)	13,036.0	4,491.7	32,537.6	13,480.1	**0.000**
PN (#/cm^3, personal CPC)	19,066.1	6,879.7	43,769.4	18,271.3	**0.000**
PN (#/cm^3, personal DiscMini)	19,556.6	11,131.0	53,342.1	25,528.5	**0.000**
Particle Size (nm)	33.2	11.5	28.7	9.5	0.167
LDSA (cm^2)	28.8	13.0	64.8	25.4	**0.000**
PM_1 (µg/m^3)	3.9	2.7	5.5	4.2	0.156
$PM_{2.5}$ (µg/m^3)	10.1	5.8	13.7	8.8	0.117
PM_4 (µg/m^3)	12.7	6.7	16.9	10.2	0.124
PM_{10} (µg/m^3)	27.4	12.3	32.6	28.7	0.442
BC (ng/m^3)	410.0	207.3	631.9	322.9	**0.011**
CO_2 (ppb)	401.4	9.3	413.9	13.8	**0.001**
PB-PAH (µg/m^3)	2.6	0.6	3.8	1.9	**0.008**
O_3 (ppb)	44.9	12.0	46.7	16.7	0.689
Source Factors					
Airport UFPs	-0.32	0.49	0.42	0.77	**0.001**
PM Mass	-0.14	0.33	0.04	0.55	0.185
Traffic	-0.53	0.58	0.23	0.92	**0.002**
Secondary Photochemistry	-0.31	0.62	0.21	0.88	**0.031**
Meteorology					
Temperature (°C)	26.3	2.5	27.7	2.8	0.096
Relative Humidity (%)	46.5	8.1	43.6	10.3	0.321
Dew Point	14.0	3.3	13.8	4.7	0.895

Results: Measured Pollutants

A) Pollutants

	Univariate			Multivariate												
	PN			$PM_{2.5}$			BC			PN			O_3			
Outcome	**Est**	**Std Err**	**P-value**	**Est**	**Std Err**	**P-value**	**Est**	**Std Err**	**P-value**	**Est**	**Std Err**	**P-value**	**Est**	**Std Err**	**P-value**	**N**
hsIL-6	0.05	0.03	0.100	-0.37	0.14	0.023	0.05	0.06	0.438	0.05	0.03	0.087	0.03	0.07	0.659	36
sTNFrII	4.06	6.24	0.525	-11.97	36.19	0.747	15.10	14.56	0.320	-1.19	6.19	0.850	-23.03	16.24	0.181	36
vWF	0.00	0.01	0.612	-0.03	0.06	0.659	0.01	0.03	0.646	-0.01	0.01	0.529	0.01	0.04	0.702	34
$FeNO_{50}$	0.19	0.23	0.406	-1.27	1.65	0.452	0.60	0.66	0.382	-0.06	0.37	0.868	0.62	0.80	0.454	41
C_ANO	-0.02	0.01	0.124	-0.10	0.10	0.322	0.02	0.04	0.664	-0.03	0.02	0.241	-0.01	0.05	0.792	41
$\log(J_{aw}NO)$	0.00	0.01	0.713	-0.07	0.06	0.270	0.00	0.02	0.879	0.00	0.01	0.783	0.04	0.04	0.261	41
$\log(D_{aw}NO)$	0.03	0.02	0.136	-0.03	0.11	0.812	-0.02	0.04	0.712	0.03	0.02	0.194	0.04	0.05	0.457	41
FEV_1	-0.20	0.18	0.293	-2.51	0.74	0.005	0.38	0.29	0.209	-0.29	0.14	0.065	1.04	0.40	0.021	40
FVC	0.05	0.16	0.746	0.99	1.18	0.418	-0.14	0.45	0.767	0.09	0.21	0.661	0.26	0.61	0.679	39
MMEF	0.10	0.54	0.851	-6.96	3.04	0.041	1.46	1.18	0.242	-0.33	0.59	0.581	0.98	1.68	0.569	39
PEFR	0.55	0.71	0.447	4.92	5.99	0.425	-1.12	2.32	0.637	0.50	0.97	0.612	1.03	2.58	0.694	41

Cytokines: hsIL6 = High-sensitivity Interleukin-6; sTNFrII = Soluble TNF receptor II; vWF = Von Willebrand Factor

Exhaled Nitric Oxide: $FeNO_{50}$ = Predicted exhaled nitric oxide at 50ml/s flow rate; C_ANO = Distal Alveolar Nitric Oxide; $J_{aw}NO$ = Proximal Bronchial Wall Flux; $D_{aw}NO$ = Diffusivity

Lung Function (% predicted): FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; MMEF = Maximum Midexpiratory Flow; PEFR = Peak Expiratory Flow Rate

Pollutants (scale of effect estimate): $PM_{2.5}$ = Particulate matter with aerodynamic diameter less than 2.5μm (10 μg/m³); BC = Black Carbon (100 ng/m³); PN = Ultrafine Particle Number (10,000 #/m³); O_3 = Ozone (10 ppb)

Results: Modeled Sources

B) Source Factors

Outcome	Univariate			Multivariate													
	Airport UFP			PM Mass			Traffic			Airport UFP			Sec. Photochem.			
	Est	Std Err	P-value	Est	Std Err	P-value	Est	Std Err	P-value	Est	Std Err	P-value	Est	Std Err	P-value	N
hsIL-6	0.28	0.08	0.003	0.12	0.25	0.652	0.10	0.12	0.423	0.24	0.09	0.017	-0.36	0.20	0.103	36
sTNFrII	-7.02	22.18	0.756	-72.74	63.01	0.271	75.22	31.15	0.033	-22.63	21.55	0.314	-8.05	51.24	0.878	36
vWF	-0.01	0.03	0.768	0.00	0.11	0.981	0.02	0.06	0.785	-0.01	0.04	0.707	-0.03	0.08	0.709	34
$FeNO_{50}$	0.51	0.74	0.506	-0.36	2.44	0.884	0.71	1.37	0.613	0.44	0.99	0.666	-0.14	1.70	0.936	41
C_ANO	-0.03	0.05	0.568	0.03	0.15	0.843	0.05	0.09	0.572	-0.05	0.06	0.412	-0.18	0.11	0.118	41
$\log(J_{aw}NO)$	0.05	0.04	0.195	0.06	0.12	0.615	-0.03	0.07	0.639	0.05	0.04	0.258	-0.06	0.10	0.532	41
$\log(D_{aw}NO)$	0.10	0.06	0.098	0.15	0.19	0.448	-0.06	0.10	0.542	0.13	0.07	0.109	-0.04	0.14	0.793	41
FEV_1	0.50	0.63	0.438	-1.36	1.41	0.353	-1.58	0.79	0.066	0.18	0.56	0.746	0.47	1.13	0.686	40
FVC	-0.06	0.55	0.920	1.79	1.94	0.376	-0.54	1.08	0.626	0.44	0.74	0.564	0.34	1.47	0.821	39
MMEF	2.01	1.69	0.252	-7.51	5.27	0.180	2.11	2.95	0.489	-0.57	2.15	0.795	-2.07	4.17	0.628	39
PEFR	1.69	2.71	0.540	14.18	6.93	0.060	-4.32	4.08	0.307	5.12	3.02	0.112	-0.74	5.86	0.901	41

Cytokines: hsIL6 = High-sensitivity Interleukin-6; sTNFrII = Soluble TNF receptor II; vWF = Von Willebrand Factor

Exhaled Nitric Oxide: $FeNO_{50}$ = Predicted exhaled nitric oxide at 50ml/s flow rate; C_ANO = Distal Alveolar Nitric Oxide; $J_{aw}NO$ = Proximal Bronchial Wall Flux; $D_{aw}NO$ = Diffusivity

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Pollutants (scale of effect estimate): $PM_{2.5}$ = Particulate matter with aerodynamic diameter less than 2.5μm (10 μg/m³); BC = Black Carbon (100 ng/m³); PN = Ultrafine Particle Number (10,000 #/m³); O_3 = Ozone (10 ppb)

Discussion

- The effect of the 'Airport UFP' source factor on IL-6 was higher and more significant than PN (measured)
- Inflammatory effects of 'Airport UFP' *different* than 'Traffic'
- Significant associations between $PM_{2.5}$ and 'PM Mass' source with decreased FEV_1
    - McCreanor et al 2007 walking for 2 hours on Oxford Street in London, UK, with high $PM_{2.5}$, UFPs, EC and NO_2 resulted in decreased FEV_1 and FVC in asthmatics

Discussion

- Significant associations between BC and ‘Traffic’ source with sTNFrII (similar for PB-PAHs)
  - Delfino et al 2008, 2009, and 2010, 61 elderly residents of a retirement home, outdoor $PM_{0.25}$ mass association with IL-6 and sTNFrII completely confounded by PAHs, vehicular emissions signal
- No FeNO effects
  - Buonanno et al 2013 *total daily* UFPs and FeNO, Strak et al 2012 RAPTES study after 5 hours walking exposure in healthy volunteers
- No vWF or fibrinogen effects
  - Hildebrandt et al 2009 males with COPD, UFPs and fibrinogen, vWF and several air pollutants

Conclusions

- First study to demonstrate acute inflammation following real-life airport-related UFPs exposure
- Shows importance of considering composition of real-life mixtures, and using dimension reduction to disentangle the impacts multiple UFP sources in a dense urban area
- Airport-related UFPs very different in size distribution and composition at the runway vs further downwind at impacted communities (primary vs secondary signals, see Habre et al 2018)
- Ongoing analyses
  - Metabolomics (Habre PI, KSOM Dean's pilot grant) and DNA methylation (Carrie Breton)

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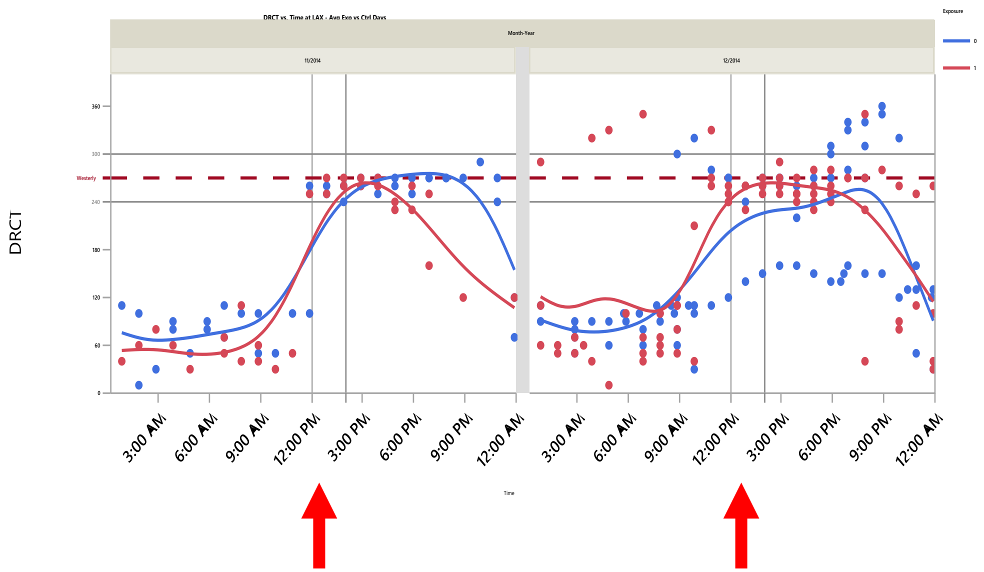
- Study participants for their time and effort

Thank You

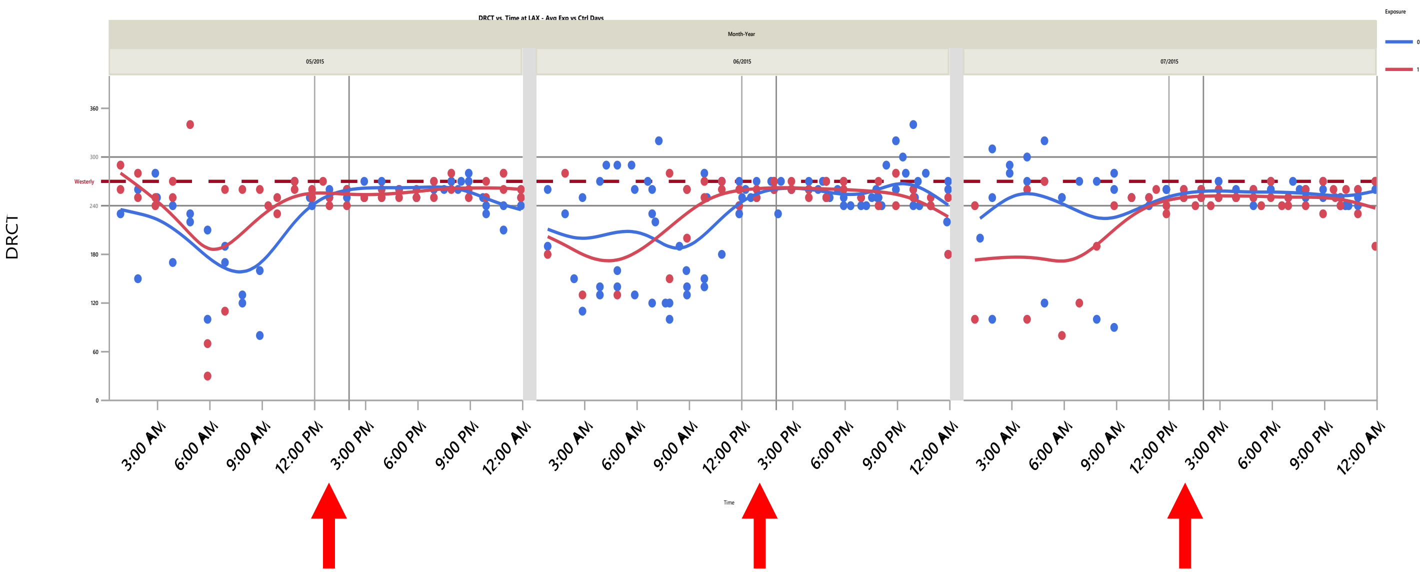
Variable	POLLUTANTS													SOURCE FACTORS				METEOROLOGY		
	PN (stationary CPC)	PN (personal CPC)	PN (personal DiscMini)	Particle Size	LDSA	PM_1	$PM_{2.5}$	PM_4	PM_{10}	BC	CO_2	PB-PAH	O_3	PM Mass	Traffic	Airport UFPs	Secondary Photochemistry	Temperature	Relative Humidity	Dew Point
PN (stationary CPC)		0.98	0.96	-0.45	0.93	0.29	0.35	0.38	0.51	0.42	0.40	0.52	0.25	0.33	0.45	0.83	0.49	0.47	-0.23	0.08
PN (personal CPC)	0.98		0.96	-0.45	0.93	0.34	0.39	0.42	0.53	0.40	0.39	0.53	0.22	0.38	0.46	0.81	0.52	0.45	-0.13	0.15
PN (personal DiscMini)	0.96	0.96		-0.52	0.92	0.32	0.37	0.39	0.52	0.30	0.29	0.42	0.32	0.36	0.36	0.85	0.52	0.59	-0.19	0.18
Particle Size	-0.45	-0.45	-0.52		-0.19	0.37	0.39	0.38	0.13	0.43	0.39	0.14	-0.32	0.33	0.44	-0.86	0.19	-0.40	0.37	0.08
LDSA	0.93	0.93	0.92	-0.19		0.53	0.59	0.61	0.64	0.60	0.58	0.61	0.17	0.56	0.66	0.62	0.66	0.50	-0.14	0.20
PM_1	0.29	0.34	0.32	0.37	0.53		0.91	0.87	0.73	0.62	0.48	0.40	0.05	0.99	0.67	-0.12	0.76	0.15	0.27	0.37
$PM_{2.5}$	0.35	0.39	0.37	0.39	0.59	0.91		0.99	0.81	0.57	0.45	0.36	0.19	0.92	0.65	-0.09	0.94	0.16	0.33	0.45
PM_4	0.38	0.42	0.39	0.38	0.61	0.87	0.99		0.85	0.57	0.43	0.35	0.23	0.90	0.64	-0.06	0.96	0.17	0.32	0.45
PM_{10}	0.51	0.53	0.52	0.13	0.64	0.73	0.81	0.85		0.46	0.24	0.30	0.34	0.80	0.46	0.21	0.82	0.21	0.13	0.30
BC	0.42	0.40	0.30	0.43	0.60	0.62	0.57	0.57	0.46		0.89	0.85	-0.41	0.58	0.95	-0.09	0.41	-0.04	-0.16	-0.20
CO_2	0.40	0.39	0.29	0.39	0.58	0.48	0.45	0.43	0.24	0.89		0.79	-0.49	0.42	0.93	-0.08	0.30	-0.06	-0.06	-0.11
PB-PAH	0.52	0.53	0.42	0.14	0.61	0.40	0.36	0.35	0.30	0.85	0.79		-0.49	0.37	0.84	0.15	0.25	-0.02	-0.09	-0.14
O_3	0.25	0.22	0.32	-0.32	0.17	0.05	0.19	0.23	0.34	-0.41	-0.49	-0.49		0.14	-0.45	0.40	0.42	0.45	-0.04	0.37
PM Mass	0.33	0.38	0.36	0.33	0.56	0.99	0.92	0.90	0.80	0.58	0.42	0.37	0.14		0.63	-0.06	0.80	0.18	0.26	0.39
Traffic	0.45	0.46	0.36	0.44	0.66	0.67	0.65	0.64	0.46	0.95	0.93	0.84	-0.45	0.63		-0.08	0.50	-0.03	0.05	-0.01
Airport UFPs	0.83	0.81	0.85	-0.86	0.62	-0.12	-0.09	-0.06	0.21	-0.09	-0.08	0.15	0.40	-0.06	-0.08		0.13	0.54	-0.37	0.01
Secondary Photochemistry	0.49	0.52	0.52	0.19	0.66	0.76	0.94	0.96	0.82	0.41	0.30	0.25	0.42	0.80	0.50	0.13		0.29	0.28	0.50
Temperature	0.47	0.45	0.59	-0.40	0.50	0.15	0.16	0.17	0.21	-0.04	-0.06	-0.02	0.45	0.18	-0.03	0.54	0.29		-0.44	0.24
Relative Humidity	-0.23	-0.13	-0.19	0.37	-0.14	0.27	0.33	0.32	0.13	-0.16	-0.06	-0.09	-0.04	0.26	0.05	-0.37	0.28	-0.44		0.72
Dew Point	0.08	0.15	0.18	0.08	0.20	0.37	0.45	0.45	0.30	-0.20	-0.11	-0.14	0.37	0.39	-0.01	0.01	0.50	0.24	0.72	

Results: Wind Direction Patterns

Phase 1 (Nov – Dec 2014)



Phase 2 (May – Jul 2015)



Predominant westerly winds during ~ 12-2 PM exposure times

Results: Health Outcomes

	Baseline Level						Change (Post-Pre)					
							Control			Exposure		
Outcome	N	Mean	Std Dev	Min	Median	Max	N	Mean	Std Dev	N	Mean	Std Dev
Cytokines												
IL-6	18	1.7	2.8	0.4	0.8	12.3	20	0.3	1.7	18	0.4	0.4
sTNFrII	18	1083.1	922.9	146.2	940.6	2384.0	20	-79.0	131.7	18	-85.6	87.8
vWF	17	0.5	0.2	0.3	0.5	0.8	18	0.0	0.2	18	0.0	0.1
Fibrinogen												
% Predicted Spirometry	17	78.4	29.6	45.4	67.4	127.6	18	0.6	19.7	18	-0.5	19.9
FEV_1	22	105.0	14.5	72.3	105.7	132.8	21	0.0	4.2	22	-1.2	3.4
FVC	22	108.9	11.3	80.5	108.4	129.0	20	-0.8	2.8	22	-0.7	3.1
MMEF	22	99.9	30.4	34.2	96.9	153.5	20	-0.3	9.5	22	-0.7	9.2
PEFR	22	107.4	24.1	59.6	105.6	152.6	21	3.0	8.4	22	2.1	10.3
Exhaled Nitric Oxide												
$\log(FeNO_{50,pred})$	22	37.9	32.5	8.9	19.6	102.2	21	-1.2	5.2	22	-1.4	6.4
C_ANO	22	1.1	0.9	-0.7	1.2	2.5	21	0.0	0.2	22	-0.2	0.3
$\log(D_{AW}NO)$	22	3.7	0.6	2.5	3.7	4.8	21	0.0	0.2	22	0.1	0.3
$\log(J_{AW}NO)$	22	7.6	0.8	6.4	7.5	8.8	21	0.0	0.1	22	0.0	0.1

Epidemiological Evidence: UFPs

- Daily alveolar-deposited UFP surface area dose and *exhaled nitric oxide* (Buonanno et al, 2013)
- Quasi-ultrafine $PM_{0.25}$ and *inflammation cytokines IL-6 and TNF-α* (Delfino et al 2009)
- Fresh combustion products in traffic exhaust with *asthma attacks and chronic bronchitis* (Brauer at al 2002, Kunzli et al 2000), *lung function decrease* in asthmatics (McCreanor et al 2007) and *asthma* (Gauderman et al 2005)
- Four-day lag central site PN and *cardiorespiratory mortality* (Stolzel et al 2007), *thrombogenic effects and platelet activation* in coronary heart disease patients (Ruckerl et al 2006)
- Immediate changes in *heart rate variability* in diabetics and people with impaired glucose metabolism (Peters et al 2015)