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

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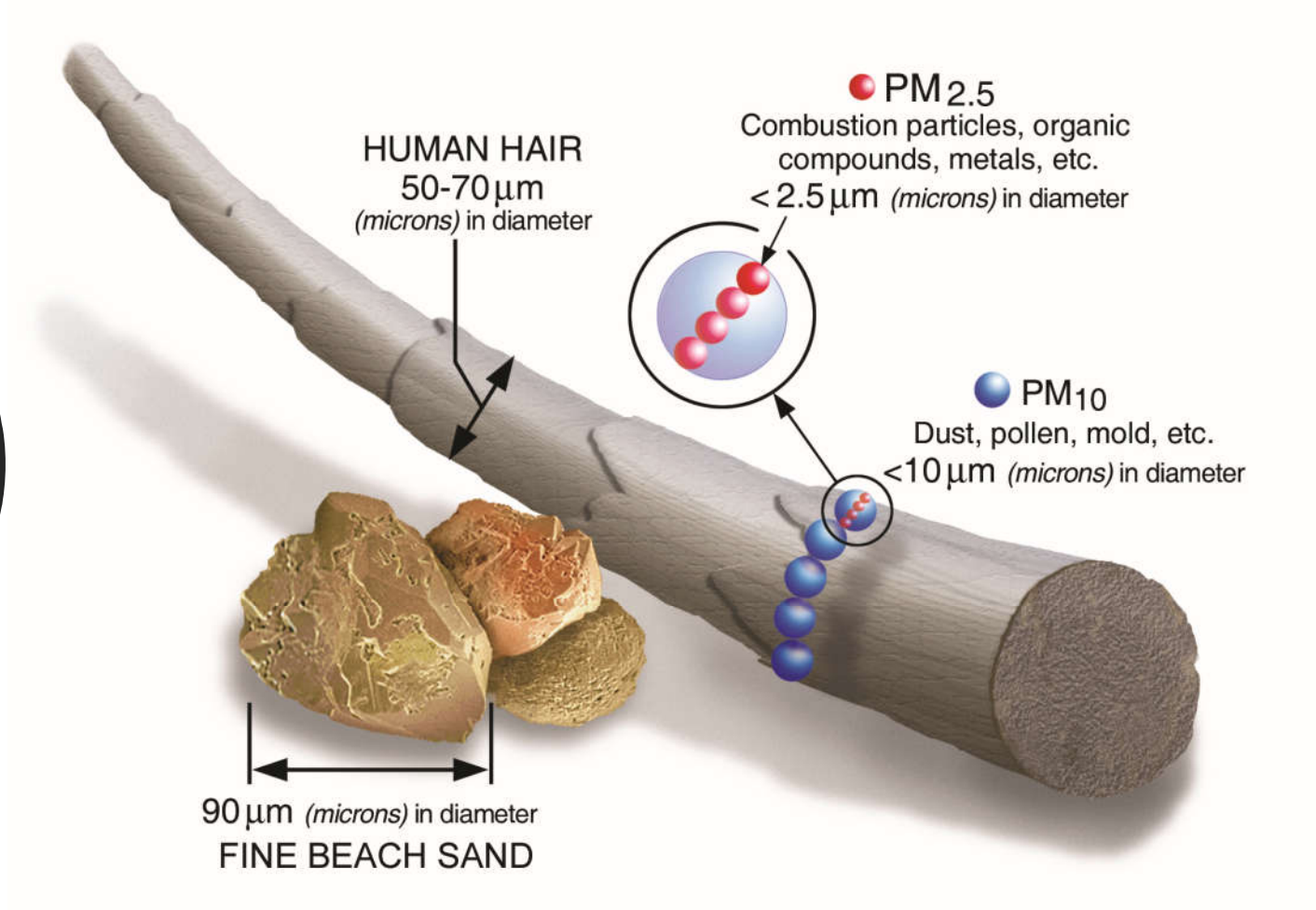
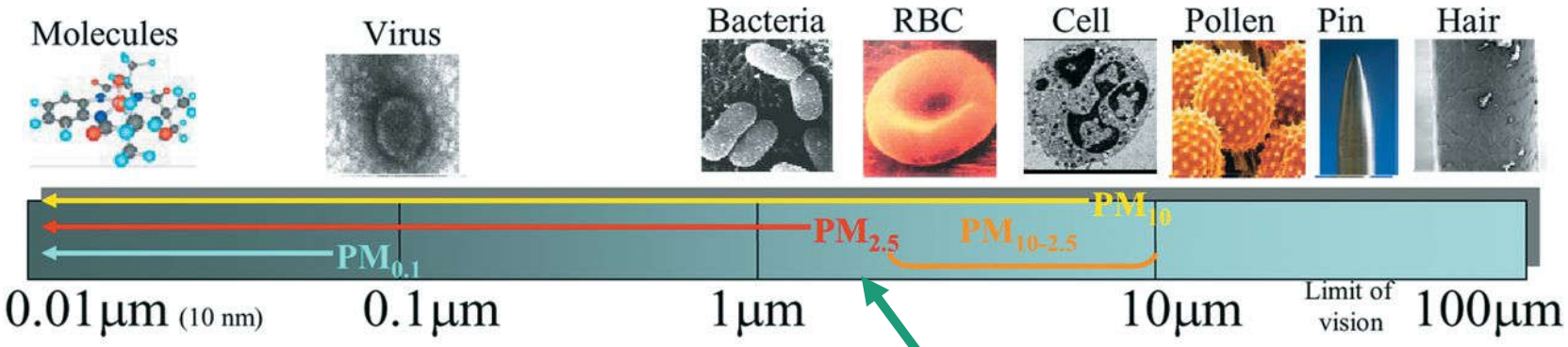
Particulate Matter Air Pollution

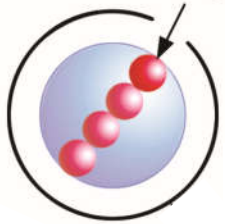




UFPs (particles <100 nm in aerodynamic diameter)

Ultrafine Particulate Matter $PM_{0.1}$

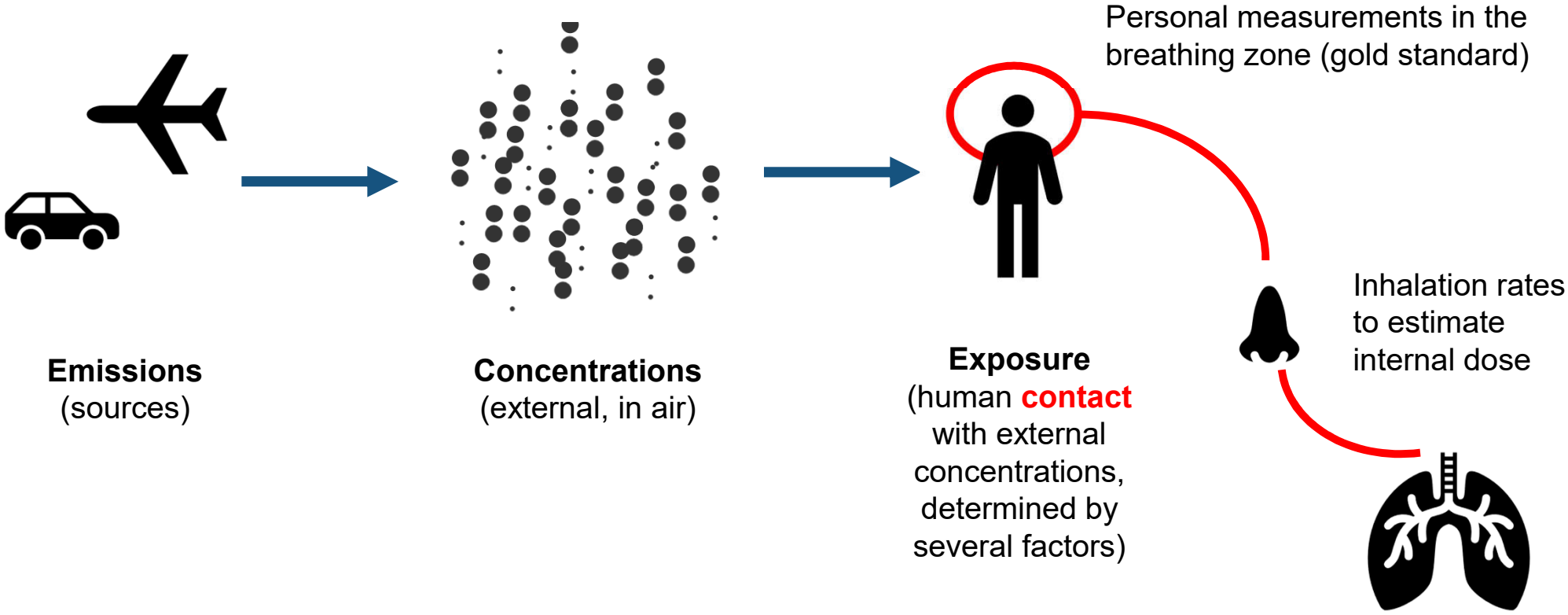
$PM_{2.5}$
Combustion particles, organic compounds, metals, etc.
< 2.5 µm *(microns)* in diameter



Motivation for investigating UFPs

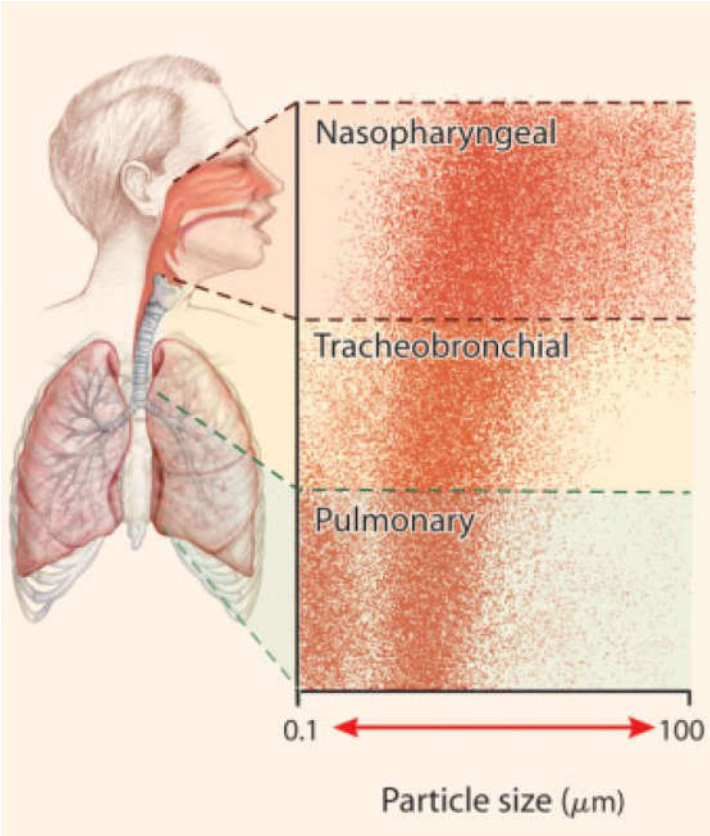
- UFPs (particles <100 nm in aerodynamic diameter) unregulated, potentially higher toxicity than larger particles ($PM_{2.5}$ and PM_{10})
- Negligible mass, particle number (# / cm^3)
  - Lung deposited surface area (LDSA), particle size
- UFP sources can be primary (combustion) and secondary (formation from precursor gases)
- Preliminary evidence on UFP health effects more focused on traffic sources, very limited from airport sources
- UFPs are highly dynamic in space and time → challenges in human exposure assessment

Assessing human exposure to UFPs



UFPs behavior in lungs

- 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 on 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)

Epidemiological evidence on airport-related air pollution in general

- 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

Motivation for Habre et al. 2018 study

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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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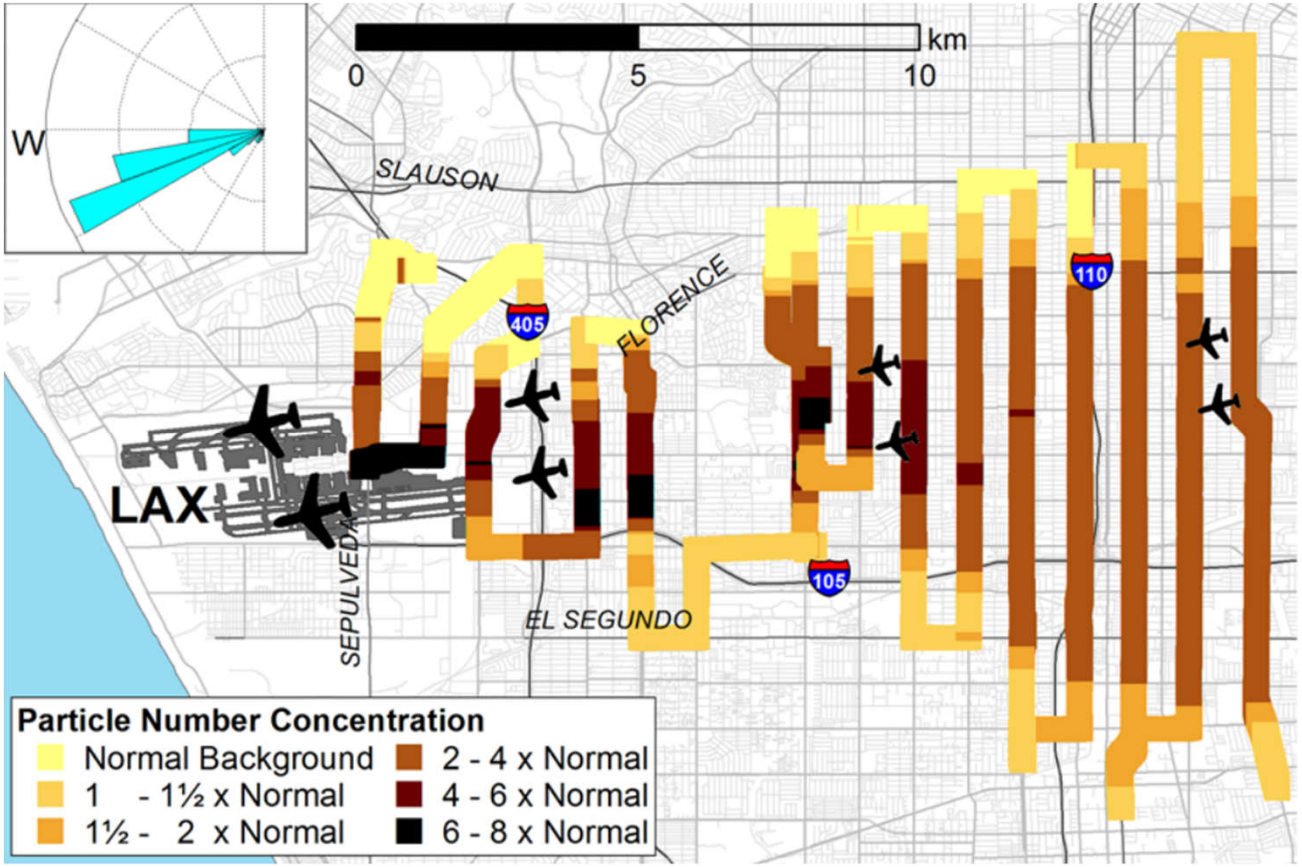
- Preliminary evidence on UFP health effects from traffic exposure studies, very limited from airport sources
- Significant plume of ultrafine particles (UFPs) downwind of Los Angeles International Airport (Hudda et al 2014)

Hudda et al. 2014 show elevated 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

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

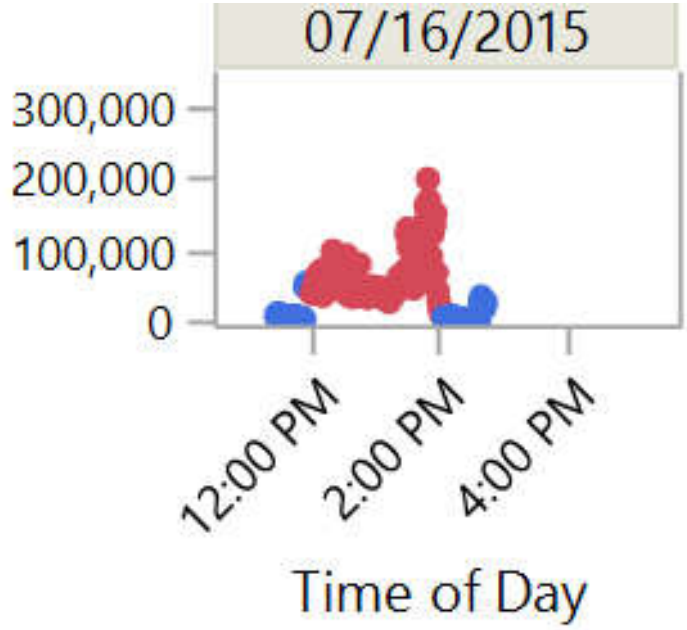
Kenneth Hahn State Recreational Park (Control site)

Hudda et al., 2014

Jesse Owens Park (Exposure site)

Multipollutant measurements

- Personal monitoring in breathing zone while walking
  - 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 measurements pre- and post-walking on both visits

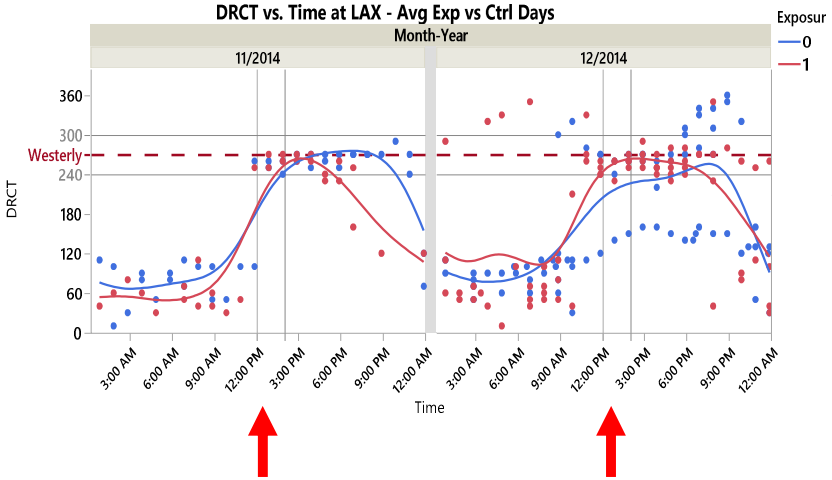
- Lung function (FVC, FEV_1)
- Multiple flow exhaled nitric oxide (FeNO, at 30, 50, 100 and 300 ml/s) as marker of airway inflammation
- Circulating inflammatory and thrombotic cytokines in blood (hsIL-6, sTNFrII, vWF, fibrinogen)

Statistical modeling to separate sources of air pollution at study sites and relate them to health outcomes

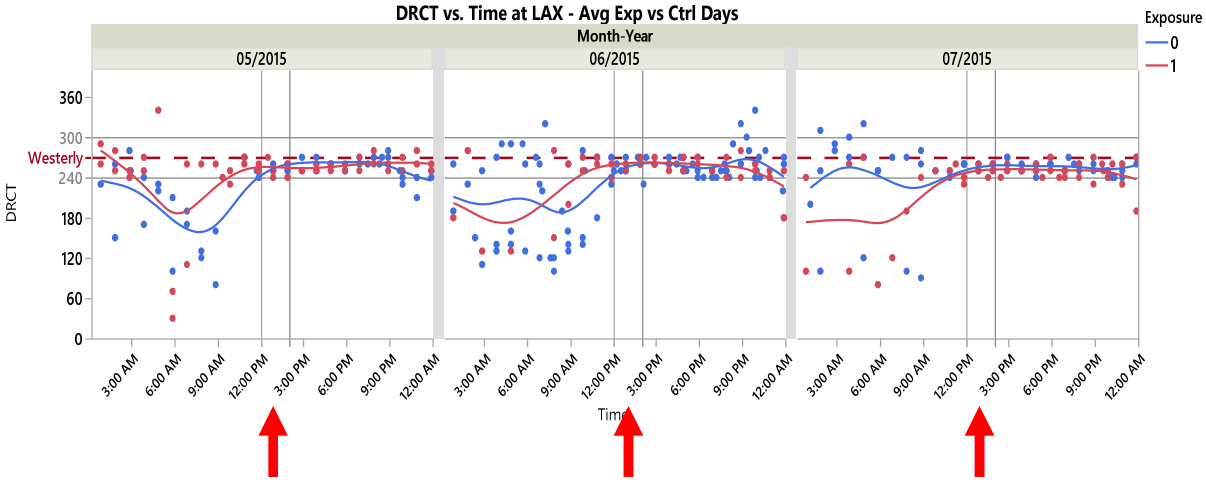
- Principal components analysis (with oblique rotation) to identify and resolve distinct 'source factors' that contributed to observed concentrations
- Health models to investigate within-person changes in health response based on walking period *measured* pollutants and *modeled* source factors
  - General question: Is the health response within a person significantly different following a 2-hour walk at the LAX exposure site versus the control site?

Results: wind direction patterns

Phase 1 (Nov – Dec 2014)

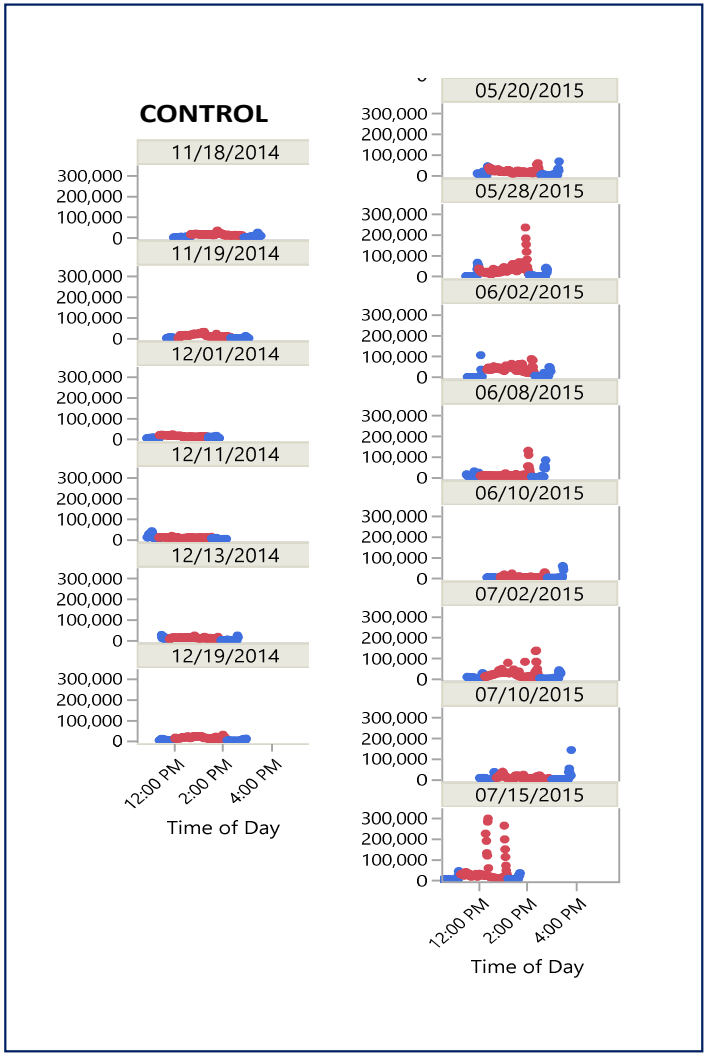


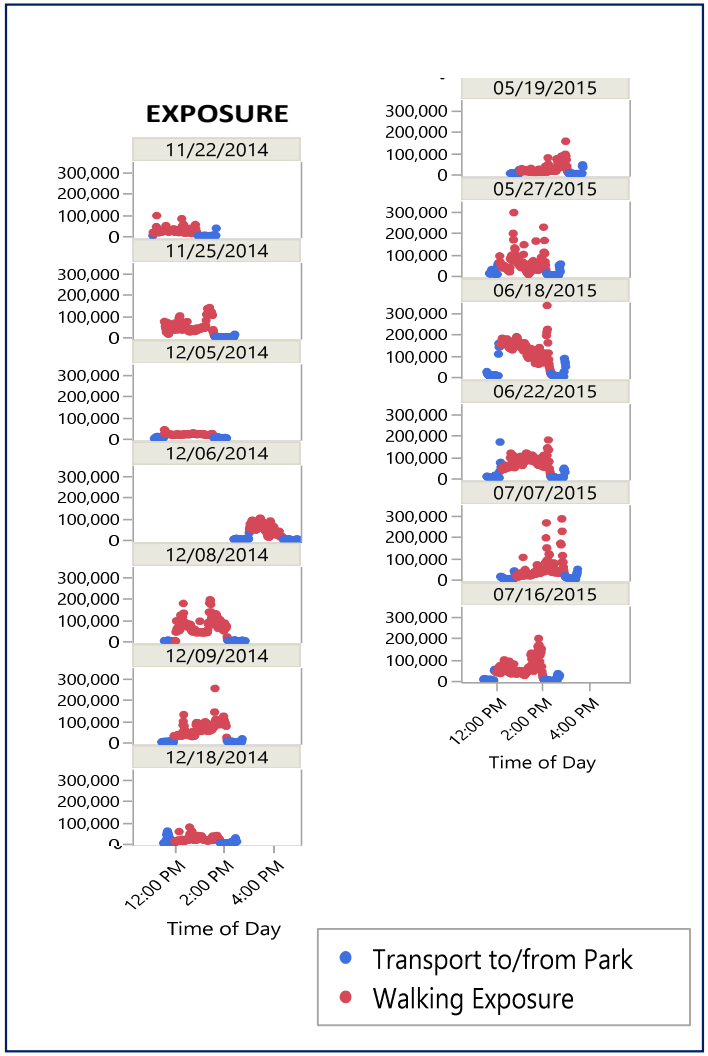
Phase 2 (May – Jul 2015)



Predominant westerly winds during ~ 12-2 PM exposure times

Results:
UFP Particle Number (#/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 site

	Control (n=21)		Exposure (n=22)		Pearson t-test
Pollutants	**Mean**	**Std Dev**	**Mean**	**Std Dev**	**p-value**
PN (#/cm³, stationary CPC)	13,036.0	4,491.7	32,537.6	13,480.1	**0.000**
PN (#/cm³, personal CPC)	19,066.1	6,879.7	43,769.4	18,271.3	**0.000**
PN (#/cm³, 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 (cm²)	28.8	13.0	64.8	25.4	**0.000**
PM_1 (µg/m³)	3.9	2.7	5.5	4.2	0.156
$PM_{2.5}$ (µg/m³)	10.1	5.8	13.7	8.8	0.117
PM_4 (µg/m³)	12.7	6.7	16.9	10.2	0.124
PM_{10} (µg/m³)	27.4	12.3	32.6	28.7	0.442
BC (ng/m³)	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/m³)	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

Health 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)

Health results: modeled sources

B) Source Factors

	Univariate			Multivariate											
	Airport UFP			PM Mass			Traffic			Airport UFP			Sec. Photochem.			
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	0.28	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

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Conclusions

- First study to demonstrate acute inflammation following real-life airport-related UFPs exposure
- The effect of the ‘Airport UFP’ source factor on IL-6 was higher and more significant than UFP PN (not as specific to aviation activity)
- Inflammatory effects of ‘Airport UFP’ *not identical to* ‘Traffic’

Conclusions

- 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
- Advantages: Within-subject quasi-experimental design, extensive phenotyping, Los Angeles setting with real-world UFP exposure assessment, personal monitoring and multipollutant modeling
- Limitations: Short follow-up time, small pilot sample size, convenient sample of asthmatics

Considerations for future health studies

- Disentangle aviation-related UFPs from other sources of UFPs
  - Measure PM chemical composition and multiple pollutants
  - Indoor sources of UFPs (cooking, smoking, candle burning, etc.)
  - Need better source profiles or chemical signatures of fresh *and* aged aviation-related UFPs
  - Impacts on downwind communities often from aged UFPs, **not captured during emissions testing or at the runway**!
- Adjust for confounding factors that might explain (or hide) associations in observational health studies
  - Socioeconomic status, co-pollutant exposures, noise exposure, etc..
- Acute vs chronic effects? Effect modification (are the effects of aviation-related UFPs greater in certain groups or people with certain characteristics or vulnerabilities)? Occupational exposures?

Ongoing work, meetings and studies

- Ongoing analyses in the LAX UFP study
  - Metabolomics (Habre and Walker) and DNA methylation (Habre and Breton)
- Health and source characterization sessions at May 2019 FAA Aviation Emissions Characterization meeting
  - University of Washington (Seto and Austin), Boston University (Levy and Lane), and more.. https://www.faa.gov/about/office_org/headquarters_offices/apl/research/aecr/media/2019_aec_agenda.pdf
  - Lots of interest and work in EU
- Zurich ETH Combustion Generated Nanoparticles June 2019 meeting
  - http://www.nanoparticles.ch/2019_ETH-NPC-23.html
- Mobile ObserVations of Ultrafine Particles Study
  - https://deohs.washington.edu/mov-mobile-observations-ultrafine-particles-study
- Copenhagen Airport Cohort Study (occupational focus)
  - https://bmjopen.bmj.com/content/7/5/e012651

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