Comparisons of ultrafine and fine particles in their associations with biomarkers reflecting physiological pathways

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Summary of the supporting information:

Number of pages: 11

Number of appendix: 2

Number of figures: 2

Number of tables: 4

Appendix 1: Air pollution measurement:

In brief, a Quad-Channel ambient particulate sampler (TH-16A) was used in the field to collect a set of four Teflon and quartz filters at size cut of $PM_{2.5}$, every 24 h between 10 and 9 a.m. Sulfate concentrations were analyzed from the quartz filters by ion chromatography. EC and OC were collected on heat-treated quartz fiber filters and measured using the NIOSH Method 5040 in a commercial laboratory. We also measured gaseous pollutants (sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone) using monitors that were calibrated and maintained following the manufacturer's protocols (Ecotech Ltd). We measured ambient temperature and relative humidity at the same site. Detailed information of the air pollution measurement technologies can be found in an HEI report.[1]

Appendix 2: Rationale and Measurement Methods for the Biomarkers:

Summary of physiological endpoints and biomarkers measured in the Study

Physiological function	**Specimen type**	**Biomarkers**
Autonomic function	N/A	Heart rate
		Systolic blood pressure (SBP)
		Diastolic blood pressure (DBP)
Hemostasis	Blood	von Willebrand factor (VWF)
		Soluble CD40 ligand (sCD40L)
		sP-Selectin (sCD62P)
Pulmonary inflammation and oxidative stress	EBC	pH
		Malondialdehyde (MDA)
		Nitrite
	Exhaled air	Nitric oxide (FeNO)
Systemic Inflammation and oxidative stress	Blood	Cell counts (white/red blood cells)
		Fibrinogen
	Urine	8-Hydroxy-2'-deoxyguanosine (8-OHdG)
		Malondialdehyde (MDA)

Autonomic function was assess by systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate. Decreased heart rate, a general measure of cardiac autonomic tone, has been associated with premature mortality in subjects with a prior myocardial infarction (MI).[2] Several studies have reported associations between heart rate decreases and 24-hr mean particulate matter (PM) concentrations in both elderly and younger subjects,[3, 4] making this one of the more consistent PM/biomarker associations observed in epidemiologic studies.

Heart rate was measured through 12-lead 3-channel MGY-S2 Electrocardiogram (ECG) Analysis Systems (ECG Lab 3.0, Meigaoyi Corp, Beijing) and the software program of the ECG systems (ECG lab 3.0, DM software Incorporation, Stateline, NV, US). Blood pressure [systolic (SBP) and diastolic (DBP)] was measured using a manual sphygmomanometer after 5 mins of rest.

Pulmonary inflammation and oxidative stress were assessed using exhaled breath condensate markers (EBC: pH, nitrite and malondialdehyde (MDA)), and fractional exhaled nitric oxide (FeNO). Biomarkers measured from EBC have been found to be associated with human's short-term (within a week) exposure to air pollution,[5-7] including particles. Increased hydrogen ions (lower pH) have been measured in EBC during respiratory infection and asthma exacerbation;[8] decreased levels of MDA and nitrite were found in healthy adults associated with decreased levels of exposure to the mixtures of air pollution;[5] and FeNO is typically used as a marker of disease activity in asthma. The magnitude of FeNO is increased in proportion to bronchial wall inflammation or induced-sputum eosinophila as well as airway hyperresponsiveness. Adamkiewicz and colleagues found an association between $PM_{2.5}$ and FeNO in 29 elderly subjects, at least half of whom did not have a diagnosis of chronic lung disease nor had ever smoked.[9] Jansen et al. measured FeNO in older adults with asthma and COPD and found significant associations between PM_{10}, $PM_{2.5}$ and black carbon and FeNO.[10]

Exhaled breath condensates from tidal breathing were collected using a commercial breath-condensate collector (EcoScreen, Erich Jaeger, Germany). EBC pH was measured using an electronic pH meter (OakTon, pH 500, US); EBC nitrite was analyzed through an HPLC system (Waters Model 2695, USA) with a UV detector (Waters Model 2996, USA). The method for analyzing MDA in EBC and urine samples used an HPLC system with fluorescent detection. Exhaled air from functional residual capacity was collected into a NO-impermeable aluminum foil bag (Huayuan Gas Center, China). The NO was analyzed by a NOx chemiluminescence analyzer (Model 42C NO-NO2-NOX Analyzer, Thermo).

Hemostasis was assessed by sP-selectin (sCD62P), CD40 Ligand (sCD40L), and von Willebrand Factor (VWF) in plasma. VWF is an adhesive glycoprotein that is produced by endothelial cells and allows platelets to attach to the subendothelial vessel wall despite the high shear stress of the vascular lumen.[11, 12] VWF levels in the circulation were reported to increase 11.8% per 10 $\mu g/m^3$ $PM_{2.5}$ 24 hours after exposure onset in an occupational study of police officers.[4] Platelet activation leading to thrombosis is now widely recognized to underlie acute complications of atherosclerosis such as unstable angina and MI,[13] and platelet may be directly activated by particles.[14] In this study, we measured two soluble plasma markers, i.e. sCD62P and sCD40L, to assess the platelet functional status.

VWF was measured using a commercially available ELISA kit (Hushang Biotech). Concentrations of sCD62P and sCD40L in the plasma were measured using an enzyme-linked immunosorbent assay ([ELISA] Rapidbio).

Systemic inflammation and oxidative stress was evaluated by plasma: Fibrinogen and white blood cell counts (WBC) from plasma, and MDA and 8-Hydroxy-2′-deoxyguanosine (8-OHdG) from urine. Elevation of white blood cell (WBC) count even within the normal range is a marker for increased cardiovascular disease risk.[15]

WBC increases have been shown to occur acutely following exposure to diesel exhaust.[16] Exposure to inhaled PM results in lung injury and induces a local inflammatory response with release of proinflammatory mediators,[17] some of which can leave the lung and enter the circulation inducing systemic effects.[18, 19] In the liver, these cytokines initiate production of acute phase proteins, including fibrinogen, a potential mediator of the effects of inhaled PM on the cardiovascular system.[16, 20, 21] Field studies suggest an association between PM exposures and fibrinogen levels.[22, 23] Measurement of 8-OHdG in urine has been used to assess "whole-body" oxidative DNA damage and has been suggested by the NIEHS Biomarkers of Oxidative Stress Study (BOSS) as a useful biomarker of systemic oxidative stress.[24]

We measured urinary 8-OHdG using an HPLC equipped with an electrochemical detector (Waters, Milford, MA). Urinary MDA was analyzed using the same method as used for the measurement of EBC MDA. White blood cell counts were measured using standard automated clinical methods in the hospital. Plasma fibrinogen concentrations were analyzed using an automated ACL9000 analyzer.

Table S1. Percent changes in each outcome reflecting autonomic function associated with each IQR increase in UFP and $PM_{2.5}$ by lag day when outcome measurement was made

	UFP[a]	$PM_{2.5}$[b]
Outcomes and lag day (hr)	Percent changes in outcomes (95% CI)	Percent changes in outcomes (95% CI)
SBP		
0 (0-23)	-0.43 (-1.50, 0.64)	0.67 (-0.31, 1.64)
1 (24-47)	0.93 (-0.35, 2.20)	-0.39 (-1.24, 0.45)
2 (48-71)	0.32 (-0.48, 1.13)	0.47 (-0.28, 1.22)
3 (72-95)	0.01 (-0.73, 0.74)	1.03 (0.36, 1.71)**
4 (96-119)	1.38 (0.67, 2.09) ***	-0.55 (-1.19, 0.10)
5 (120-143)	0.52 (-0.28, 1.32)	-0.96 (-1.71, -0.21)
6 (144-167)	-0.33 (-1.35, 0.68)	0.44 (-0.34, 1.22)
DBP		
0 (0-23)	0.17 (-1.45, 1.78)	-0.45 (-1.45, 0.55)
1 (24-47)	-0.63 (-2.23, 0.97)	-0.39 (-1.37, 0.58)
2 (48-71)	0.21 (-0.88, 1.31)	-0.54 (-1.59, 0.50)
3 (72-95)	-0.51 (-1.75, 0.72)	0.44 (-0.34, 1.23)
4 (96-119)	0.77 (-0.65, 2.19)	-0.16 (-0.82, 0.50)
5 (120-143)	0.47 (-1.00, 1.94)	-0.06 (-0.89, 0.77)
6 (144-167)	1.17 (-0.59, 2.93)	-0.42 (-1.24, 0.41)
Heart rate		
0 (0-23)	1.12 (-0.01, 2.26)	0.21 (-1.06, 1.49)
1 (24-47)	-0.003 (-1.17, 1.17)	1.49 (0.24, 2.75)*
2 (48-71)	-0.57 (-1.68, 0.55)	0.91 (-0.14, 1.98)
3 (72-95)	0.98 (-0.11, 2.09)	0.72 (-0.19, 1.64)
4 (96-119)	-0.35 (-1.44, 0.75)	0.59 (-0.35, 1.55)
5 (120-143)	0.28 (-0.85, 1.43)	0.01 (-0.94, 0.97)
6 (144-167)	0.91 (-0.38, 2.21)	-0.06 (-1.03, 0.92)

[a]IQR increases of 5,340 particles/cm-3 (24-hr mean). [b]IQR increase of 76.8 $\mu g/m^3$ (24-hr mean).
*p<0.05, **p<0.01, ***p<0.001.

Table S2. Percent changes in each biomarker, reflecting hemostasis, associated with each IQR increase in UFP and $PM_{2.5}$ by lag day when outcome measurement was made

	UFP[a]	$PM_{2.5}$[b]
Outcomes and lag day (hr)	Percent changes in outcomes (95% CI)	Percent changes in outcomes (95% CI)
sCD62P		
0 (0-23)	7.71 (3.05, 12.57)***	8.26 (4.39, 12.27)***
1 (24-47)	9.05 (4.55, 13.74)***	8.31 (4.89, 11.85)***
2 (48-71)	0.13 (-2.98, 3.35)	11.44 (8.28, 14.70)***
3 (72-95)	3.09 (-0.27, 6.56)	8.69 (6.02, 11.42)***
4 (96-119)	2.88 (-0.11, 5.96)	5.68 (3.04, 8.39)***
5 (120-143)	5.78 (2.43, 9.24)***	-1.10 (-4.05, 1.93)
6 (144-167)	2.91 (-0.75, 6.71)	-1.36 (-4.85, 2.25)
sCD40L		
0 (0-23)	5.87 (1.83, 10.08)**	-1.30 (-4.92, 2.45)
1 (24-47)	-2.45 (-6.78, 2.08)	-0.09 (-3.46, 3.40)
2 (48-71)	-0.30 (-3.83, 3.36)	-0.30 (-3.17, 2.66)
3 (72-95)	-2.77 (-5.90, 0.47)	2.93 (0.37, 5.54)*
4 (96-119)	-4.05 (-7.06, -0.94)	3.53 (0.99, 6.14)**
5 (120-143)	-2.39 (-5.62, 0.95)	1.89 (-0.83, 4.68)
6 (144-167)	-0.57 (-4.42, 3.44)	0.54 (-2.30, 3.46)
VWF		
0 (0-23)	2.48 (-0.75, 5.71)	4.96 (1.16, 8.76)*
1 (24-47)	3.51 (-0.05, 7.06)	3.72 (1.02, 6.41)**
2 (48-71)	2.37 (-0.03, 4.78)	2.42 (-0.04, 4.88)
3 (72-95)	1.13 (-1.17, 3.42)	5.26 (3.04, 7.47)***
4 (96-119)	-3.15 (-5.76, -0.55)	2.28 (0.26, 4.30)*
5 (120-143)	5.25 (1.70, 8.80)**	-1.43 (-3.81, 0.95)
6 (144-167)	2.16 (-1.17, 5.50)	0.30 (-2.22, 2.83)

[a]IQR increases of 5,340 particles/cm-3 (24-hr mean). [b]IQR increase of 76.8 $\mu g/m^3$ (24-hr mean).
*p<0.05, **p<0.01, ***p<0.001.

Table S3. Percent changes in each outcome, reflecting pulmonary inflammation and oxidative stress, associated with each IQR increase in UFP and $PM_{2.5}$ by lag day when outcome measurement was made

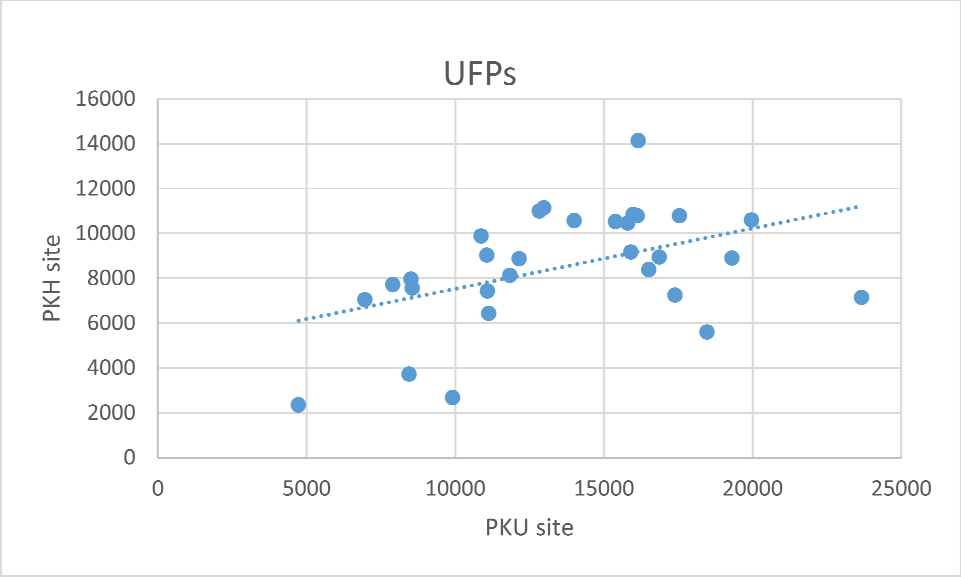
	UFP[a]	$PM_{2.5}$[b]
Outcomes and lag day (hr)	Percent changes in outcomes (95% CI)	Percent changes in outcomes (95% CI)
FeNO		
0 (0-23)	25.34 (12.96, 39.01)***	40.71 (26.10, 57.02)***
1 (24-47)	-3.30 (-14.09, 8.84)	19.95 (9.89, 30.94)***
2 (48-71)	-13.77 (-20.81, -6.10)	19.48 (10.34, 29.38)***
3 (72-95)	-12.87 (-19.73, -5.43)	25.84 (17.29, 35.02)***
4 (96-119)	-7.16 (-14.50, 0.81)	19.91 (12.68, 27.60)***
5 (120-143)	9.72 (-1.00, 21.61)	11.11 (3.01, 19.86)**
6 (144-167)	-9.57 (-18.89, 0.82)	30.84 (20.40, 42.19)***
EBC pH		
0 (0-23)	0.67 (-0.09, 1.44)	1.18 (0.22, 2.14)*
1 (24-47)	1.54 (0.79, 2.28)***	1.21 (0.39, 2.03)**
2 (48-71)	-0.43 (-1.10, 0.25)	0.86 (0.13, 1.60)*
3 (72-95)	0.07 (-0.51, 0.66)	0.66 (0.05, 1.27)*
4 (96-119)	0.08 (-0.50, 0.66)	0.92 (0.32, 1.52)**
5 (120-143)	-0.37 (-0.98, 0.23)	1.11 (0.49, 1.72)***
6 (144-167)	-0.29 (-1.03, 0.46)	-0.01 (-0.74, 0.72)
EBC nitrite		
0 (0-23)	8.80 (0.15, 18.20)*	21.90 (12.04, 32.63)***
1 (24-47)	14.81 (6.38, 23.92)***	6.14 (-1.30, 14.13)
2 (48-71)	16.62 (7.11, 26.98)***	2.04 (-4.63, 9.20)
3 (72-95)	3.41 (-3.19, 10.45)	8.76 (2.38, 15.54)**
4 (96-119)	4.93 (-0.74, 10.93)	0.40 (-6.12, 7.37)
5 (120-143)	8.90 (2.25, 15.97)**	-2.38 (-8.00, 3.59)
6 (144-167)	25.64 (16.12, 35.94)***	-1.00 (-7.71, 6.19)
EBC MDA		
0 (0-23)	6.12 (-3.68, 15.92)	2.46 (-6.92, 11.84)
1 (24-47)	7.58 (-1.63, 16.79)	-4.40 (-12.41, 3.60)
2 (48-71)	1.73 (-8.22, 11.68)	2.65 (-4.63, 9.93)
3 (72-95)	-14.93 (-22.47, -7.39)	6.89 (0.90, 12.88)*
4 (96-119)	-1.24 (-8.51, 6.03)	11.26 (4.83, 17.69)***
5 (120-143)	-4.17 (-12.84, 4.50)	9.90 (3.93, 15.88)**
6 (144-167)	3.32 (-7.84, 14.49)	1.55 (-6.05, 9.16)

[a]IQR increases of 5,340 particles/cm-3 (24-hr mean). [b]IQR increase of 76.8 μg/m^3 (24-hr mean).
*p<0.05, **p<0.01, ***p<0.001.

Table S4. Percent changes in each outcome reflecting, systemic inflammation and oxidative stress, associated with each IQR increase in UFP and PM2.5 by lag day when outcome measurement was made

	UFP[a]	$PM_{2.5}$[b]
Outcomes and lag day (hr)	Percent changes in outcomes (95% CI)	Percent changes in outcomes (95% CI)
Urinary MDA		
0 (0-23)	-2.34 (-13.40, 10.13)	15.27 (3.44, 28.44)*
1 (24-47)	-5.47 (-16.25, 6.69)	13.21 (2.09, 25.55)*
2 (48-71)	8.40 (-2.06, 19.98)	11.63 (2.13, 22.01)*
3 (72-95)	10.89 (0.56, 22.28)*	7.12 (-0.81, 15.70)
4 (96-119)	9.44 (0.04, 19.73)*	2.68 (-4.95, 10.91)
5 (120-143)	9.54 (-0.33, 20.38)	3.13 (-4.86, 11.80)
6 (144-167)	-0.24 (-11.09, 11.95)	2.52 (-5.64, 11.38)
Urinary 8-OHdG		
0 (0-23)	-0.68 (-22.85, 27.85)	38.22 (7.79, 77.22)*
1 (24-47)	-9.26 (-34.38, 25.47)	57.58 (26.06, 96.99)***
2 (48-71)	5.08 (-16.11, 31.63)	52.46 (26.14, 84.27)***
3 (72-95)	28.86 (4.08, 59.53)*	31.84 (12.18, 54.95)***
4 (96-119)	37.88 (13.66, 67.27)**	5.61 (-10.90, 25.19)
5 (120-143)	42.81 (18.18, 72.57)***	0.43 (-16.87, 21.33)
6 (144-167)	26.40 (0.84, 58.44)*	-5.76 (-23.71, 16.41)
FIB		
0 (0-23)	0.78 (-1.15, 2.71)	1.19 (-0.55, 2.93)
1 (24-47)	0.71 (-1.23, 2.65)	1.00 (-0.53, 2.53)
2 (48-71)	-0.37 (-1.85, 1.11)	1.37 (0.13, 2.61)*
3 (72-95)	-1.27 (-2.80, 0.26)	1.31 (0.20, 2.41)*
4 (96-119)	-0.11 (-1.63, 1.40)	-0.38 (-1.51, 0.75)
5 (120-143)	0.63 (-1.01, 2.27)	-1.04 (-2.15, 0.07)
6 (144-167)	0.62 (-1.44, 2.68)	0.66 (-0.50, 1.82)
WBC		
0 (0-23)	4.13 (1.23, 7.04)*	-1.16 (-6.80, 4.47)
1 (24-47)	1.96 (-1.17, 5.09)	-2.53 (-7.12, 2.07)
2 (48-71)	-0.98 (-3.38, 1.42)	-2.41 (-6.24, 1.42)
3 (72-95)	-1.09 (-3.29, 1.10)	-1.41 (-4.80, 1.99)
4 (96-119)	-4.00 (-6.06, -1.94)	-0.61 (-4.22, 3.01)
5 (120-143)	-0.81 (-2.98, 1.36)	-2.76 (-7.14, 1.61)
6 (144-167)	-2.80 (-5.30, -0.28)	0.20 (-4.93, 5.34)

[a]IQR increases of 5,340 particles/cm-3 (24-hr mean). [b]IQR increase of 76.8 μg/m^3 (24-hr mean).
*p<0.05, **p<0.01, ***p<0.001.



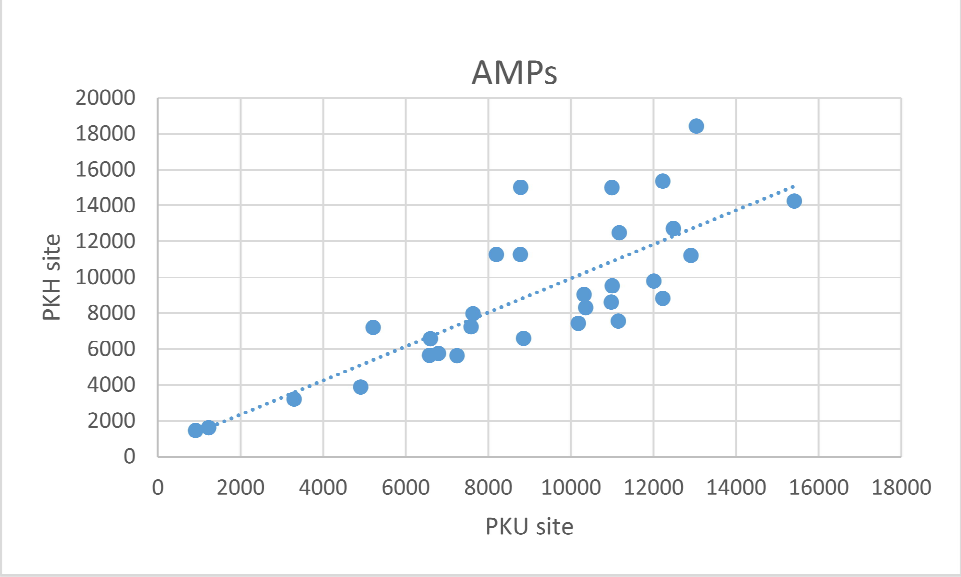


Figure S1. Linear regression plots of UFPs and AMPs between PKU and PKH sites.

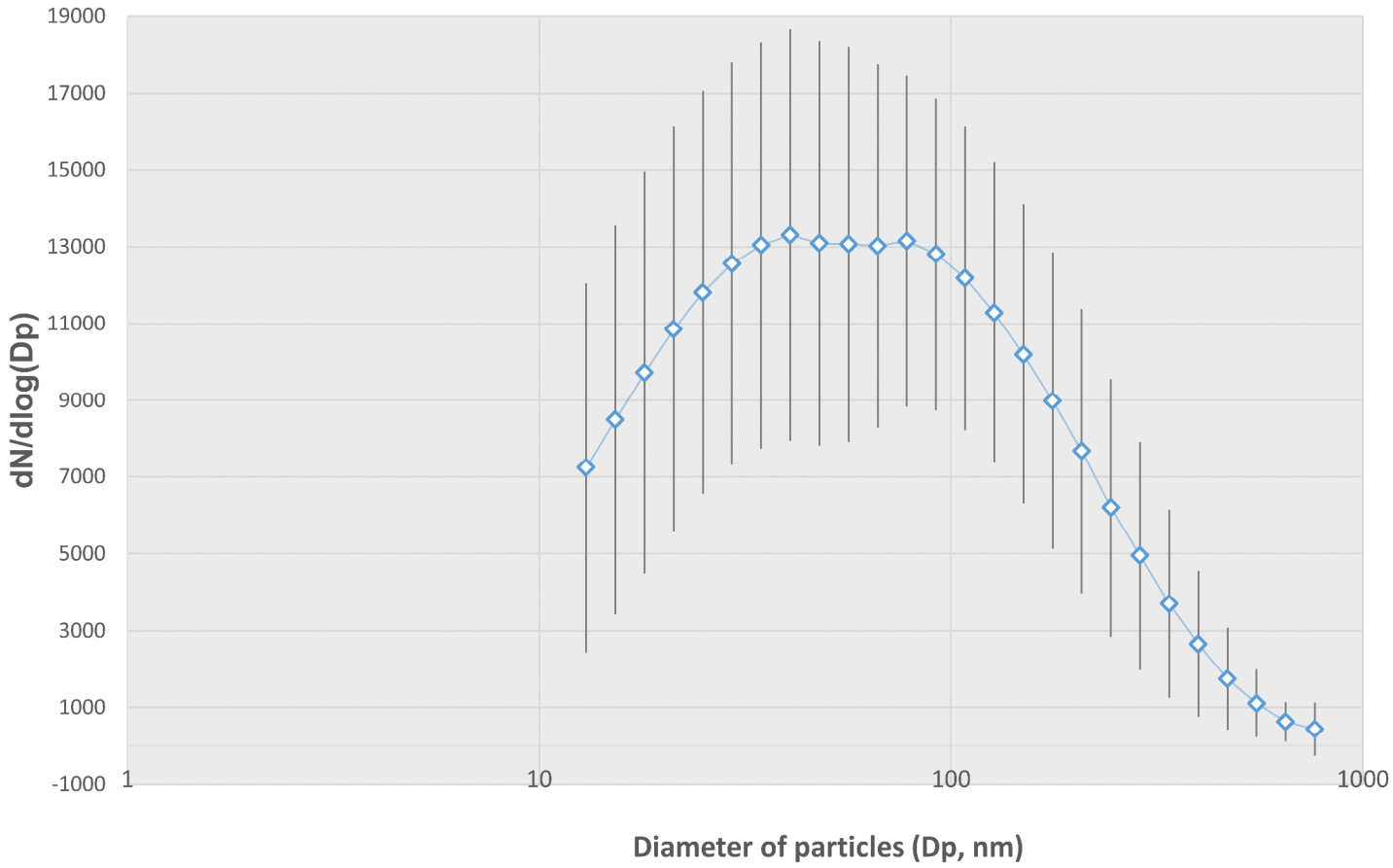


Figure S2. Particle distribution for the entire sampling period. The square dots mean number concentrations of the particles and the vertical lines mean the standard deviations of the means.

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