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Acute Effects of Air Pollution and Noise from Road Traffic in A Panel of Young Healthy Subjects †

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Abstract: Twenty-four healthy students walked at least 4 times for one hour under each of the 4 settings: By a busy road, by a busy road wearing ear plugs, in a park, in a park but exposed to traffic noise (65 dB) through speakers. Particles (PM2.5, particle number) and noise levels were measured throughout each walk. Lung function and exhaled NO were measured before, immediately, one hour, and approximately 24 hours after each walk. Blood pressure and heart rate variability were measured every 15 minutes during each walk. Air pollution levels reduced lung function levels. Noise levels reduced systolic blood pressure and heart-rate variability.

Keywords: road traffic; air pollution; noise; physiological effects; panel study; healthy young adults

1. Introduction

Acute effects of air pollutants have been demonstrated repeatedly in respiratory [1-15] and cardiovascular patients [16-21]. Such panel studies have been performed in the elderly [22-25] and in areas with high air pollution [1,14, 26-30], but less so in young and healthy people in settings with moderate to low air pollution levels [31-39]. We recruited healthy students from Vienna to study physiological reactions of the cardiovascular and respiratory system on everyday urban air pollution exposure.

2. Materials and Methods

Twenty-four healthy students walked at least 4 times for one hour under each of the 4 settings: By a busy road, by a busy road wearing ear plugs, in a park, in a park but exposed to traffic noise (65 dB) through speakers. Particles (PM2.5, particle number) and noise levels were measured throughout each walk. PM2.5 was measured using a Grimm Portable Laser Aerosol Spectrometer Model 1.108. For measureing particle numbers (PN) a miniature diffusion size classifier (miniDiSC, http://www.fierz.ch/minidisc/) was used. Concentrations were stored for every 6 second intervals. Noise was measured with a Brühl&Kjaer sound level meter, type 2236. Every 15 minutes the equivalent continuous sound level was noted and then the instrument was reset.

Spirometric lung function and exhaled NO were measured before, immediately, one hour, and approximately 24 hours after each walk. Spirometry was performed using an EasyOne spirometer (ndd Medizintechnik AG) in upright standing position and applying a nose clip following standard procedures [40,41]. NO in exhaled air [42] was measured using the portable instrument NObreath (Bedfont Technical Instruments Ltd.).

Blood pressure and heart rate variability were measured every 15 minutes during each walk. For heart-rate variability the mobile ECG device eMotion Faros was used. ECG-files were analyzed over windows of 15 minutes each with the Kubios software version 2.2.

Temperature was obtained from a nearby stationary meteorological station. Data on fine particle (PM10) background concentration were also obtained from a nearby fixed monitor operated by the City of Vienna (Station near the General Hospital: AKH).

Data of respiratory and of cardiovascular markers were entered in two separate files for further statistical analysis. In this study setting each participant serves as his own control. Respiratory parameters (immediately, 1 hour and approximately 24 hours after the exposure) were assessed per participant with single air pollution markers as independent variables applying random-effects GLS regression. Fixed effect models mostly gave very similar results and the Hausman test was mostly not significant. In two adjusted models either the same respiratory marker or NO in exhaled air before the exposure were included in the model to characterize unmeasured influences.

Cardiovascular markers were assessed every 15 minutes separately and again using random-effects GLS regression. Exposures in the preceding 15 minutes (noise and dust) served as independent variables. Temperature was included in the models as a confounder.

All calculations were done with STATA SE Vers. 13.1 [43].

3. Results

3.1. Participants and Exposure

In a first run from December 2016 until May 2017 20 students (11 male, 9 female) with an average age of 24 years (range 21-33) had on average 20 one-hour walks (range 13-38). They were all non-smokers and reported to be healthy. In a second run 4 more students were recruited. They underwent the same procedures in May and June 2018.

Air pollution and ambient noise were higher near the street but were not correlated with each other due to different time trends. Individual noise exposure was further de-coupled from ambient conditions by design. Particle measures correlated well with each other and with PM10 levels at a nearby fixed monitoring station (R-values for all particle mass measures > 0.9). Either personal exposure concentrations were actually higher than concentrations at the fixed monitoring station or the Aerosol Spectrometer overestimated particle mass concentrations systematically. As an example hourly values of PM2.5 measured with the spectrometer and PM10 measured at the fixed station displayed a correlation coefficient of 0.96. A linear regression model with PM10 at the fixed station and setting (road versus park) explained 92.5% of the variation of PM2.5. In this model the difference between road and park was significant ($p=0.016$) but not very large (4.2 µg/m³). The slope (ß of PM10) at the fixed station was 1.57 ($p<0.001$). Table 1 describes the range of exposure for PM10 at the fixed station and the personal exposure measured as PM2.5 and PN. Because of the high correlation between the particle mass values only PM1 from the personal monitoring and PM10 from the fixed site (controlling for setting – road versus park –) were further analyzed for health effects. In addition personal particle number concentrations (R with mass concentrations between 0.72 and 0.77) were investigated.

Table 1. Exposure to particles during walks.

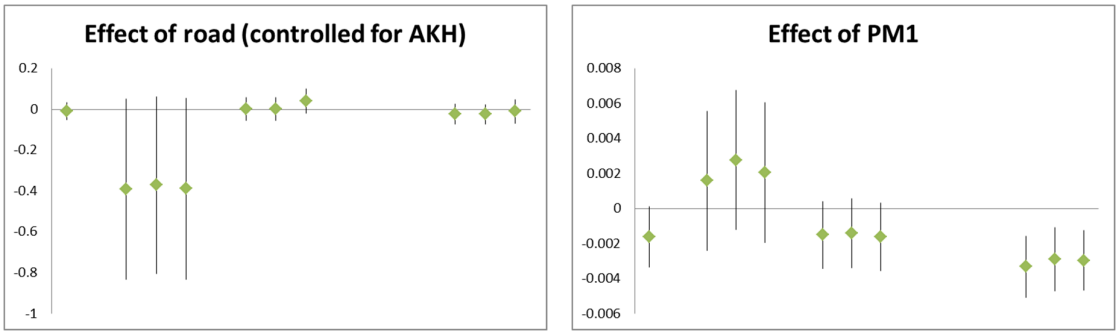
Metric	Arithmetic Mean	+/- Std.Dev.	Range
PM10 fixed station	28.0 µg/m³	26.5	5–95
PM2.5 personal	38.7 µg/m³	43.5	2–146
PN personal	21,347.8/cm³	18,826.5	4,198.9–80,059.6

After controlling for seasonal and daily trends ambient noise levels at the road were approximately 10 dB louder than in the park. These ambient noise levels were partly overruled by ear plugs and/or speakers. Average sound pressure level $L_{A,eq}$ was about 56 dB at the road. At the

road wearing ear plugs noise was assumed to be 30 dB lower. In the park it was measured as about 46 dB and the speakers were set to 65 dB.

3.2. Air Pollution and Respiratory Health

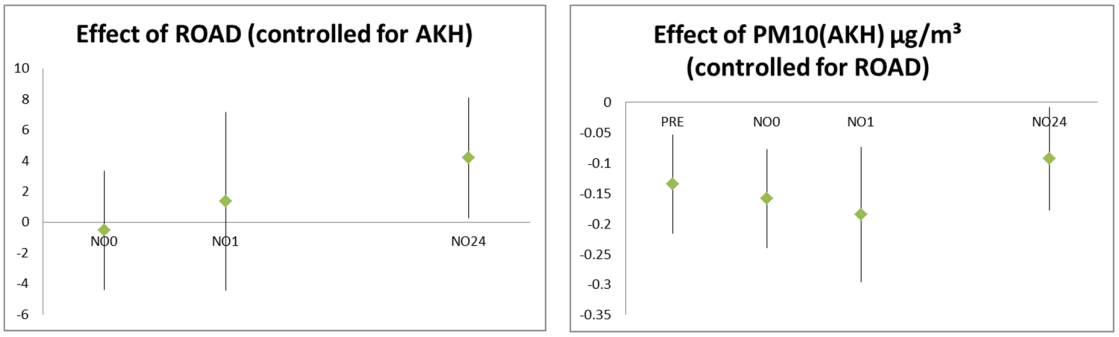
Air pollution levels reduced lung function levels. Measures of large airways resistance like FEV1 were reduced immediately after the walk while measures indicative of the small airways like MEF25 remained low even 24 hours later (Figure 1).



(**a**) (**b**)

Figure 1. Examples for air pollution effects on lung function: (**a**) Effect of the setting "road" on FEV1 (in liter), controlled for background pollution; (**b**) Effect of PM1 (µg/m³) on MEF25 (in l/s). Each triplet stands for: unadjusted, adjusted for lung function before exposure, adjusted for exhaled NO before exposure. The time points are (left to right): Before exposure (one value only), immediately after the walk, 1 hour, and 24 hours after the walk.

Exhaled NO was significantly reduced immediately after and 1 hour after the walk with increasing dust levels. After controlling for background dust levels walking besides the road increased NO 24 hours later (Figure 2).



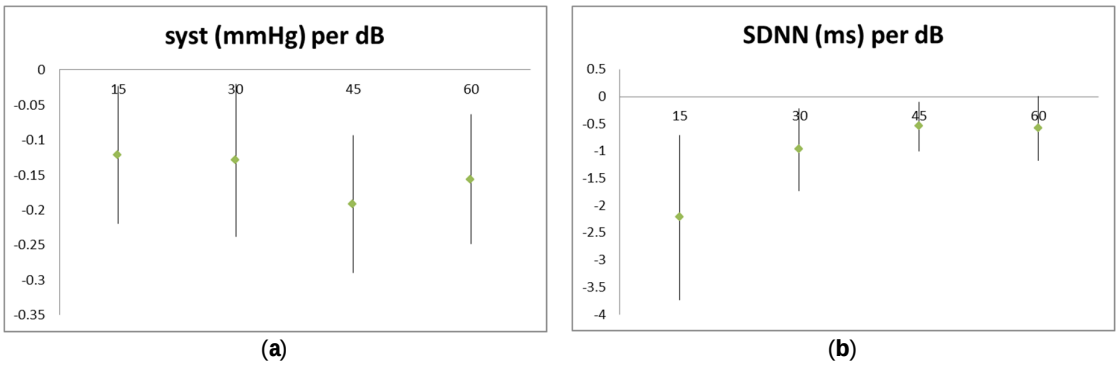
(**a**) (**b**)

Figure 2. Effect of exposure on exhaled NO values (in ppb) at different time points: (**a**) Exposure near the road compared to a park, controlled for background concentration; (**b**) Effect of background concentration (PM10 in µg/m³) controlled for setting. The background reflects the average exposure at that time for a longer period (and thus also affects NO before the setting) while the setting is added to the background exposure for a short and defined period of 1 hour.

3.2. Air Pollution and Noise Effects on Cardiovascular System

Noise levels reduced systolic blood pressure and heart-rate variability (Figure 3). Temperature also had clear effects on cardiovascular parameters but did not confound noise effects. Air pollution effects were less pronounced and not very consistent (data not shown).

As in the previous sub-chapter only examples can be presented that are typical and representative for effects on other parameters as well.



(**a**) (**b**)

Figure 3. Effect of noise on cardiovascular parameters: (**a**) systolic blood pressure; (**b**) Standard deviation of the NN intervals. Noise levels are averaged over 15 minutes (4 periods per 1 hour walk) each. Blood pressure was measured at the end of each period; ECG readings were taken over the whole period.

4. Discussion

Exposures near a busy road cause statistically significant respiratory and cardiovascular reactions even in healthy young adults. The effects were reversible and generally not very severe, but nevertheless clear and consistent.

Exhaled NO originates from different sources [44-46]. It is secreted by epithelial cells inducing relaxation of the smooth muscle cells of the bronchial walls. This secretion is inducible and is a reaction after a reflective muscular narrowing of the air-ways: An irritant stimulus will at first lead to increased muscle tone and thus after a very short interval to an increased airway resistance. This resistance will be released by NO and therefore increased NO will predict a lower airway resistance in the near future. NO also serves as messenger molecule in inflammatory processes. Here it is mostly involved in eosinophilic inflammation and will signify allergic asthma (and thus increased bronchial reactivity and likely also increased airway resistance). Epithelial cells capable of producing NO can be compromised during (neutrophil) inflammation and by some toxic substances e.g. in cigarette smoke. Therefore smokers generally have lower NO levels and after the smoking of cigarettes NO is further reduced.

NO might relax smooth muscles and thus reduce airway resistance. But on the other hand NO in the tissue acts as an oxidative stressor and thus contributes to an inflammatory response secondary to a reflective muscular response to an irritant. Therefore after a certain delay higher NO levels might predict increased airway resistance again.

These different complex pathways make the interpretation of NO in a panel study a challenge. Timing is essential and maybe even with our repeated measures (before, immediately after, 1 hour and 24 hours after a defined exposure of one hour) we were not fully able to fully capture the complete time course. Considering both background pollution levels that likely better represent the longer term average exposure and the effects per setting which by design lasted only for one hour, we could further disentangle the temporal variation. In that endeavor we were hindered by the finding that between setting differences were small compared to differences in background exposure over time.

Nevertheless we were able to demonstrate reduced NO levels due to higher background exposures indicative of toxic damage to epithelial cells and also increased levels of NO with 24 hour latency after a one hour acute exposure indicative of inflammatory response. A reduced lung function led to an increase in NO levels and higher NO levels were indicative of increased lung function levels at the next measurement point.

Effects on the larger airways signified by e.g. FEV1 were seen immediately after exposure likely indicative of a muscular reflex response. Effects on the small airways signified e.g. by MEF25 persisted for 24 hours likely representing inflammatory responses that might be clinically more relevant.

Lung function values mostly remained in the physiologically normal range. This is not surprising considering the comparatively low exposures and the generally healthy state of the participants. We observed effects during everyday activities in everyday settings. Massive detrimental health effects therefore were not expected. But it seems noteworthy that even under these conditions even in young and healthy subjects and even with a comparatively small number of subjects and a moderate number of repeated observations most effects reached or at least approached significance. While acute effects shortly after the exposure are likely physiological protective reactions under nervous control, the longer term changes most clearly seen in the end-expiratory flows and thus indicative of an increase in resistance in the small air-ways are likely caused by inflammatory tissue responses and thus are cause of concern. Even small effects, when cumulated over the years, will in the long run hasten the functional decline of the respiratory system.

Cardiovascular effects were mostly observed in relation to noise levels. These effects remained even after controlling for temperature which was the most important predictor of heart rate, heart rate variability, and blood pressure. Also these effects remained in the physiological range which again was to be expected. Again even subtle effects to everyday exposures during everyday activities still can be of concern in the long turn.

Other acute effects of air pollution have also been demonstrated in some panel studies, notably on glucose metabolism [47,48] and inflammation [49]. But we are confident that we have covered the most important endpoints including respiratory [50] and cardiovascular [51-54] effects.

Author Contributions: HM designed the study and wrote the paper. The other authors carried out the field work and collected the data.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Li, H.; Wu, S.; Pan, L.; Xu, J.; Shan, J.; Yang, X.; Dong, W.; Deng, F.; Chen, Y.; Shima, M.; Guo, X. Short-term effects of various ozone metrics on cardiopulmonary function in chronic obstructive pulmonary disease patients: Results from a panel study in Beijing, China. *Environ Pollut* **2018**, *232*, 358-366.
2. Magzamen, S.; Oron, A. P.; Locke, E. R.; Fan, V. S. Association of ambient pollution with inhaler use among patients with COPD: a panel study. *Occup Environ Med* **2018**, *75 (5)*, 382-388.
3. Chen, S.; Gu, Y.; Qiao, L.; Wang, C.; Song, Y.; Bai, C.; Sun, Y.; Ji, H.; Zhou, M.; Wang, H.; Chen, R.; Kan, H. Fine Particulate Constituents and Lung Dysfunction: A Time-Series Panel Study. *Environ Sci Technol* **2017**, *51(3)*, 1687-1694.
4. Prieto-Parra, L.; Yohannessen, K.; Brea, C.; Vidal, D.; Ubilla, C. A.; Ruiz-Rudolph, P. Air pollution, PM2.5 composition, source factors, and respiratory symptoms in asthmatic and nonasthmatic children in Santiago, Chile. *Environ Int* **2017**, *101*, 190-200.
5. Bloemsma, L. D.; Hoek, G.; Smit, L. A. Panel studies of air pollution in patients with COPD: Systematic review and meta-analysis. *Environ Res* **2016**, *151*, 458-468.
6. Maikawa, C.L.; Weichenthal, S.; Wheeler, A. J.; Dobbin, N. A.; Smargiassi, A.; Evans, G.; Liu, L.; Goldberg, M. S.; Pollitt, K. J. Particulate Oxidative Burden as a Predictor of Exhaled Nitric Oxide in Children with Asthma. *Environ Health Perspect* **2016**, *124(10)*, 1616-1622.
7. Ni, Y.; Wu, S.; Ji, W.; Chen, Y.; Zhao, B.; Shi, S.; Tu, X.; Li, H.; Pan, L.; Deng, F.; Guo, X. The exposure metric choices have significant impact on the association between short-term exposure to outdoor particulate matter and changes in lung function: Findings from a panel study in chronic obstructive pulmonary disease patients. *Sci Total Environ* **2016**, *542 (Pt A)*, 264-270.
8. Schachter, E.N.; Moshier, E.; Habre, R.; Rohr, A.; Godbold, J.; Nath, A.; Grunin, A.; Coull, B.; Koutrakis, P.; Kattan, M. Outdoor air pollution and health effects in urban children with moderate to severe asthma. *Air Qual Atmos Health* **2016**, *9*, 251-263.
9. Wu, S.; Ni, Y.; Li, H.; Pan, L.; Yang, D.; Baccarelli, A. A.; Deng, F.; Chen, Y.; Shima, M.; Guo, X. Short-term exposure to high ambient air pollution increases airway inflammation and respiratory symptoms in chronic obstructive pulmonary disease patients in Beijing, China. *Environ Int* **2016**, *94*, 76-82.

10. Moshammer, H.; Hutter, H.-P.; Hauck, H.; Neuberger, M. Low levels of air pollution induce changes of lung function in a panel of schoolchildren *Eur Respir J* **2006**, *27*, 1138-1143
11. Cortez-Lugo, M.; Ramírez-Aguilar, M.; Pérez-Padilla, R.; Sansores-Martínez, R.; Ramírez-Venegas, A.; Barraza-Villarreal, A. Effect of Personal Exposure to PM2.5 on Respiratory Health in a Mexican Panel of Patients with COPD. *Int J Environ Res Public Health* **2015**, *12(9)*, 10635-10647.
12. Loftus, C.; Yost, M.; Sampson, P.; Arias, G.; Torres, E.; Vasquez, V. B.; Bhatti, P.; Karr, C. Regional PM2.5 and asthma morbidity in an agricultural community: A panel study. *Environ Res* **2015**, *136*, 505-512.
13. Mirabelli, M. C.; Golan, R.; Greenwald, R.; Raysoni, A. U.; Holguin, F.; Kewada, P.; Winquist, A.; Flanders, W. D.; Sarnat, J. A. Modification of Traffic-related Respiratory Response by Asthma Control in a Population of Car Commuters. *Epidemiology* **2015**, *26(4)*, 546-555.
14. Romieu, I.; Meneses, F.; Ruiz, S.; Huerta, J.; Sienra, J. J.; White, M.; Etzel, R.; Hernandez, M. Effects of intermittent ozone exposure on peak expiratory flow and respiratory symptoms among asthmatic children in Mexico City. *Arch Environ Health* **1997**, *52/5*, 368-375.
15. Hiltermann, T. J. N.; de Bruijne, C. R.; Stolk, J.; Zwinderman, A. H.; Spieksma, F. T. M.; Roemer W.; Steerenberg, P. A.; Fischer, P. H.; van Bree, L.; Hiemstra, P. S. Effects of photochemical air pollution and allergen exposure on upper respiratory tract inflammation in asthmatics *Am J Respir Crit Care Med* **1997**, *156*, 1765-1772
16. Link, M. S.; Luttmann-Gibson, H.; Schwartz, J.; Mittleman, M. A.; Wessler, B.; Gold, D. R.; Dockery, D. W.; Laden, F. Acute Exposure to Air Pollution Triggers Atrial Fibrillation. *Journal of the American College of Cardiology* **2013**, *62(9)*, 816-825. doi:10.1016/j.jacc.2013.05.043.
17. Lee, M. W.; Choi, B. G.; Kim, S. W.; Rha, S. W.; Shim, M. S.; Kim, D. J.; Seo, H. S.; Oh, D. J.; Jeong, M.H.; Other Korea Acute Myocardial Infarction Registry (KAMIR) investigators. Air pollution and short-term clinical outcomes of patients with acute myocardial infarction. *Clin Exp Pharmacol Physiol* **2017**, *44(6)*, 631-638.
18. Rückerl, R.; Schneider, A.; Hampel, R.; Breitner, S.; Cyrys, J.; Kraus, U.; Gu, J.; Soentgen, J.; Koenig, W.; Peters, A. Association of novel metrics of particulate matter with vascular markers of inflammation and coagulation in susceptible populations -results from a panel study. *Environ Res* **2016**, *150*, 337-347.
19. Wang, M.; Utell, M. J.; Schneider, A.; Zareba, W.; Frampton, M. W.; Oakes, D.; Hopke, P. K.; Wiltshire, J.; Kane, C.; Peters, A.; Breitner, S.; Chalupa, D.; Rich, D. Q. Does total antioxidant capacity modify adverse cardiac responses associated with ambient ultrafine, accumulation mode, and fine particles in patients undergoing cardiac rehabilitation? *Environ Res* **2016**, *149*, 15-22.
20. Goldberg, M. S.; Wheeler, A. J.; Burnett, R. T.; Mayo, N. E.; Valois, M. F.; Brophy, J. M.; Giannetti, N. Physiological and perceived health effects from daily changes in air pollution and weather among persons with heart failure: A panel study. *J Expo Sci Environ Epidemiol* **2015**, *25(2)*, 187-199.
21. Imaizumi, Y.; Eguchi, K.; Kario, K. Coexistence of PM2.5 and low temperature is associated with morning hypertension in hypertensives. *Clin Exp Hypertens* **2015**, *37(6)*, 468-472.
22. Stieb, D. M.; Shutt, R.; Kauri, L.; Mason, S.; Chen, L.; Szyszkowicz, M. et al. Cardio-Respiratory Effects of Air Pollution in a Panel Study of Outdoor Physical Activity and Health in Rural Older Adults. *Journal of Occupational and Environmental Medicine* **2017**, *59(4)*, 356-364. doi:10.1097/JOM.0000000000000954.
23. Hassanvand, M.;, Naddafi, K.; Kashani, H.; Faridi, S.; Kunzli, N.; Nabizadeh, R.; Momeniha, F.; Gholampour, A.; Arhami, M; Zare, A.; Pourpak, Z.; Hoseini, M.; Yunesian, M. Short-term effects of particle size fractions on circulating biomarkers of inflammation in a panel of elderly subjects and healthy young adults. *Environ Pollut* **2017**, *223*, 695-704.
24. Karottki, D. G.; Spilak, M.; Frederiksen, M.; Jovanovic Andersen, Z.; Madsen, A. M.; Ketzel, M.; Massling, A.; Gunnarsen, L.; Møller, P.; Loft, S. Indoor and outdoor exposure to ultrafine, fine and microbiologically derived particulate matter related to cardiovascular and respiratory effects in a panel of elderly urban citizens. *Int J Environ Res Public Health* **2015**, *12(2)*, 1667-1686.
25. Zhang, X.; Staimer, N.; Tjoa, T.; Gillen, D. L.; Schauer, J. J.; Shafer, M. M.; Hasheminassab, S.; Pakbin, P.; Longhurst, J.; Sioutas, C.; Delfino, R. J. Associations between microvascular function and short-term exposure to traffic-related air pollution and particulate matter oxidative potential. *Environmental Health* **2016**, *15*, 81. doi:10.1186/s12940-016-0157-5.
26. Huang, W.; Wang, L.; Li, J.; Liu, M.; Xu, H.; Liu, S.; Chen, J.; Zhang, Y.; Morishita, M.; Bard, R. L.; Harkema, J. R.; Rajagopalan, S.; Brook, R. D. Short-Term Blood Pressure Responses to Ambient Fine Particulate Matter Exposures at the Extremes of Global Air Pollution Concentrations. *Am J Hypertens* **2018**, *31(5)*, 590-599.

27. Shutt, R. H.; Kauri, L. M.; Weichenthal, S.; Kumarathasan, P.; Vincent, R.; Thomson, E. M.; Liu, L.; Mahmud, M.; Cakmak, S.; Dales, R. Exposure to air pollution near a steel plant is associated with reduced heart rate variability: a randomised crossover study. *Environmental Health* **2017**, *16*, 4. doi:10.1186/s12940-016-0206-0.
28. Hu, L.-W.; Qian, Z.; Bloom, M. S.; Nelson, E.J.; Liu, E.; Han, B.; Zhang, N.; Liu, Y.; Ma, H.; Chen, D.-H.; Yang, B.-Y.; Zeng, X.-W.; Chen, W.; Komppula, M.; Leskinen, A.; Hirvonen, M.-R.; Roponen, M.; Jalava, P.; Bai, Z.; Dong, G.-H. A panel study of airborne particulate matter concentration and impaired cardiopulmonary function in young adults by two different exposure measurement. *Atmospheric Environment* **2018**, *180*, 103-109.
29. Chen, R.; Zhao, Z.; Sun, Q.; Lin, Z.; Zhao, A.; Wang, C.; Xia, Y.; Xu, X.; Kan, H. Size-fractionated Particulate Air Pollution and Circulating Biomarkers of Inflammation, Coagulation, and Vasoconstriction in a Panel of Young Adults. *Epidemiology* **2015**, 26/3, 328-336.
30. Chen, R.; Qiao, L.; Li, H.; Zhao, Y.; Zhang, Y.; Xu, W.; Wang, C.; Wang, H.; Zhao, Z.; Xu, X.; Hu, H.; Kan, H. Fine Particulate Matter Constituents, Nitric Oxide Synthase DNA Methylation and Exhaled Nitric Oxide. *Environ Sci Technol* **2015**, *49(19)*, 11859-11865.
31. Cole-Hunter, T.; de Nazelle, A.; Donaire-Gonzalez, D.; Kubesch, N.; Carrasco-Turigas, G.; Matt, F.; Foraster, M.; Martínez, T.; Ambros, A.; Cirach, M.; Martinez, D.; Belmonte, J.; Nieuwenhuijsen, M. Estimated effects of air pollution and space-time-activity on cardiopulmonary outcomes in healthy adults: A repeated measures study. *Environ Int* **2018**, *111*, 247-259.
32. Day, D. B.; Xiang, J.; Mo, J.; Li, F.; Chung, M.; Gong, J.; Weschler, C. J.; Ohman-Strickland, P. A.; Sundell, J.; Weng, W.; Zhang, Y.; Zhang, J. J. Association of Ozone Exposure with Cardiorespiratory Pathophysiologic Mechanisms in Healthy Adults. *JAMA Intern Med* **2017**, *177(9)*, 1344-1353.
33. Brook, R. D.; Sun, Z.; Brook, J. R.; Zhao, X.; Ruan, Y.; Yan, J.; Mukherjee, B.; Rao, X.; Duan, F.; Sun, L.; Liang, R.; Lian, H.; Zhang, S.; Fang, Q.; Gu, D.; Sun, Q.; Fan, Z.; Rajagopalan, S. Extreme Air Pollution Conditions Adversely Affect Blood Pressure and Insulin Resistance: The Air Pollution and Cardiometabolic Disease Study. *Hypertension* **2016**, *67(1)*, 77-85.
34. Cole-Hunter, T.; Weichenthal, S.; Kubesch, N.; Foraster, M.; Carrasco-Turigas, G.; Bouso, L.; Martínez, D.; Westerdahl, D.; de Nazelle, A.; Nieuwenhuijsen, M. Impact of traffic-related air pollution on acute changes in cardiac autonomic modulation during rest and physical activity: a cross-over study. *J Expo Sci Environ Epidemiol* **2016**, *26(2)*, 133-140.
35. Lee, M. S.; Eum, K. D.; Rodrigues, E. G.; Magari, S. R.; Fang, S. C.; Modest, G. A.; Christiani, D. C. Effects of Personal Exposure to Ambient Fine Particulate Matter on Acute Change in Nocturnal Heart Rate Variability in Subjects Without Overt Heart Disease. *Am J Cardiol* **2016**, *117(1)*, 151-156.
36. Provost, E. B.; Louwies, T.; Cox, B.; Op 't Roodt, J.; Solmi, F.; Dons, E.; Int Panis, L.; De Boever, P.; Nawrot, T. S. Short-term fluctuations in personal black carbon exposure are associated with rapid changes in carotid arterial stiffening. *Environ Int* **2016**, *88*, 228-234.
37. Wu, C. F.; Shen, F. H.; Li, Y. R.; Tsao, T. M.; Tsai, M. J.; Chen, C. C.; Hwang, J. S.; Hsu, S. H.; Chao, H.; Chuang, K. J.; Chou, C. C. K.; Wang, Y. N.; Ho, C. C.; Su, T. C. Association of short-term exposure to fine particulate matter and nitrogen dioxide with acute cardiovascular effects. *Sci Total Environ* **2016**, 569-570, 300-305.
38. Jarjour, S.; Jerrett, M.; Westerdahl, D.; de Nazelle, A.; Hanning, C.; Daly, L.; Lipsitt J.; Balmes, J. Cyclist route choice, traffic-related air pollution, and lung function: a scripted exposure study. *Environmental Health* **2013**, *12*, 14.
39. Strak, M.; Boogaard, H.; Meliefste, K.; Oldenwening, M.; Zuurbier, M.; Brunekreef, B.; Hoek, G. Respiratory health effects of ultrafine and fine particle exposure in cyclists. *Occup Environ Med* **2010**, *67(2)*, 118-124.
40. Miller, M. R.; Crapo, R.; Hankinson, J.; Brusasco, V.; Burgos, F.; Casaburi, R.; Coates, A.; Enright, P.; van der Grinten, C. P.; Gustafsson, P.; Jensen, R.; Johnson, D.C.; MacIntyre, N.; McKay, R.; Navajas, D.; Pedersen, O. F.; Pellegrino, R.; Viegi, G.; Wanger, J.; ATS/ERS Task Force. General considerations for lung function testing. *Eur Respir J* **2005**, *26(1)*, 153-161.
41. Miller, M. R.; Hankinson, J.; Brusasco, V.; Burgos, F.; Casaburi, R.; Coates, A.; Crapo, R.; Enright, P.; van der Grinten, C. P.; Gustafsson, P.; Jensen, R.; Johnson, D. C.; MacIntyre, N.; McKay, R.; Navajas, D.; Pedersen, O. F.; Pellegrino, R.; Viegi, G.; Wanger, J.; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* **2005**, *26(2)*, 319-338.

42. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* **2005**, *171(8)*, 912-930.
43. STATA SE Vers. 13.1, StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA
44. Gemicioglu, B.; Musellim, B.; Dogan, I.; Guven, K. Fractional exhaled nitric oxide (FeNo) in different asthma phenotypes. *Allergy & Rhinology* **2014**, *5(3)*, e157-e161. doi:10.2500/ar.2014.5.0099.
45. Price, D.; Ryan, D.; Burden, A.; Von Ziegenweidt, J.; Gould, S.; Freeman, D.; Gruffydd-Jones, K.; Copland, A.; Godley, C.; Chisholm A.; Thomas, M. Using fractional exhaled nitric oxide (FeNO) to diagnose steroid-responsive disease and guide asthma management in routine care. *Clinical and Translational Allergy* **2013**, *3*, 37.
46. Dweik, R. A.; Boggs, P. B., Erzurum, S. C.; Irvin, C. G.; Leigh, M. W.; Lundberg, J. O.; Olin, A. C.; Plummer, A. L.; Taylor, D. R.; American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* **2011**, *184(5)*, 602-615. doi: 10.1164/rccm.9120-11ST.
47. Wang, C.; Chen, R.; Zhao, Z.; Cai, J.; Lu, J.; Ha, S.; Xu, X.; Chen, X.; Kan, H. Particulate air pollution and circulating biomarkers among type 2 diabetic mellitus patients: the roles of particle size and time windows of exposure. *Environ Res* **2015**, *140*, 112-118.
48. Peters, A.; Hampel, R.; Cyrys, J.; Breitner, S: Geruschkat, U.; Kraus, U.; Zareba, W.; Schneider, A. Elevated particle number concentrations induce immediate changes in heart rate variability: a panel study in individuals with impaired glucose metabolism or diabetes. *Part Fibre Toxicol* **2015**, *12*, 7.
49. Fernandes, E. C.; Silva, C. A.; Braga, A. L.; Sallum, A. M.; Campos, L. M.; Farhat, S. C. Exposure to air pollutants increased disease activity in childhood-onset systemic lupus erythematosus patients. *Arthritis Care Res (Hoboken)* **2015**, *67(11)*, 1609-1614.
50. Peters, A.; Wichmann, H. E.; Tuch, T.; Heinrich, J.; Heyder, J. Respiratory effects are associated with the number of ultrafine particles *Am J Respir Crit Care Med* **1997**, *155*, 1376-1383.
51. Weichenthal, S.; Hatzopoulou, M.; Goldberg, M. S. Exposure to traffic-related air pollution during physical activity and acute changes in blood pressure, autonomic and micro-vascular function in women: a cross-over study. *Part Fibre Toxicol* **2014**, *11*, 70. doi:10.1186/s12989-014-0070-4.
52. Buteau, S.; Goldberg, M. S. A structured review of panel studies used to investigate associations between ambient air pollution and heart rate variability. *Environ Res* **2016**, *148*, 207-247.
53. Chang, L. T.; Chuang, K. J.; Yang, W. T.; Wang, V. S.; Chuang, H. C.; Bao, B. Y.; Liu, C. S.; Chang, T. Y. Short-term exposure to noise, fine particulate matter and nitrogen oxides on ambulatory blood pressure: A repeated-measure study. *Environ Res* **2015**, *140*, 634-640.
54. Morishita, M.; Bard, R. L.; Kaciroti, N.; Fitzner, C. A.; Dvonch, T.; Harkema, J. R.; Rajagopalan, S.; Brook, R. D. Exploration of the composition and sources of urban fine particulate matter associated with same-day cardiovascular health effects in Dearborn, Michigan. *J Expo Sci Environ Epidemiol* **2015**, *25(2)*, 145-152.