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2

Effect of Short-Term Exposure to Near Highway Pollutants in Motor Vehicle Exhaust on Inflammation Sensitive Biomarkers

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1. Introduction

Urban atmospheric air pollution is considered a significant challenge for environmental Health (Brunekreef & Holgate, 2002; World Health Organization [WHO], 2003). Growing epidemiological evidence has supported the association between air pollution and cardiovascular morbidity and mortality (Brook et al., 2010). The biological mechanisms underlying these associations remain obscure (Kaufman 2010). One possible explanation to this association is that air pollution has been shown to cause pulmonary inflammation which is further associated with the production of local inflammatory mediators (Nurkiewicz et al., 2008; Nurkiewicz et al., 2009; Kido et al., 2011). These mediators in turn enter the systemic circulation and could contribute to the acceleration of atherothrombotic disease (Seaton et al., 1999; Ghio et al., 2000; Peters et al., 2001b; van Eeden & Hogg, 2002; Pope et al., 2004). Animal models of accelerated atherosclerosis following exposure to air pollution, strongly support this potential mechanism (Sun et al., 2005; Niwa et al., 2008). Low grade systemic inflammation has repeatedly been shown to be a contributing factor in the etiopathogenesis of atherothrombotic disease (Libby 2002; Danesh et al., 2005; Libby, 2006). A hint to the link between air pollution and systemic inflammation arises from studies demonstrating some type of correlation between inflammatory biomarkers, and the amount of outdoor atmospheric particles and volatile gases (Schwartz, 2001; Ghio et al., 2003; Liao et al., 2005; Diez Roux et al., 2006; Steinvil et al., 2008).

Exposure to combustion-derived air pollution is associated as well to an early (1-2 h) and sustained (24 h) rise in cardiovascular morbidity and mortality (Peters et al., 2001a; Peters et al., 2004). Toxicological diesel exposure studies have demonstrated a selective and persistent impairment of endothelium-dependent vasodilatation that occurs in the presence of mild systemic inflammation (Mills et al., 2007; Tornqvist et al., 2007), coronary vasoconstriction (Cherng et al., 2009), as well as an increase in ex-vivo thrombus formation and in- vivo platelet activation (Lucking et al., 2008). Less attention has however been given to measuring pollutants and exposures near heavily-trafficked highways. The most widely reported pollutants in vehicular exhaust include carbon monoxide, nitrogen and sulfur oxides, unburned hydrocarbons (from fuel and crankcase oil), particulate matter, polycyclic aromatic hydrocarbons, and other organic compounds that derive from combustion (Brugge

et al., 2007). While several recent studies have shown that sharp pollutant gradients exist near highways, most reports did not however examine this effect on the inflammatory response in over 400 meters (Brugge et al., 2007).

2. Methods

In the present analysis we have investigated the relationship between commonly measured combustion derived air pollutants and inflammatory biomarkers in apparently healthy individuals residing at a 1000 meter radius from a traffic air pollution monitoring station.

2.1 Population

In the present study we analyzed the data collected as part of the Tel-Aviv Medical Center Inflammation Survey (TAMCIS), a registered data bank of the Israeli Ministry of Justice (Rogowski et al., 2006). This is a relatively large survey comprising of apparently healthy individuals attending a center for periodic health examinations. In our study, patients attending the Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel for a routine health examination between September 2002 and August 2010 were invited to participate in the TAMCIS. All individuals enrolled were recruited during their routine annual health check-up and gave their written consent in accordance with the guidelines of the Institutional Ethics Committee. A total of 15,605 subjects gave their informed consent (9,881 males, 5,724 females). 2,773 subjects were later excluded from the analysis due to known inflammatory disease (arthritis, inflammatory bowel disease, psoriasis, etc.), pregnancy, steroidal or nonsteroidal treatment (except for aspirin at a dose of ≤ 325 mg/dl), acute infection or invasive procedures (surgery, catheterization, etc.) during the last 6 months. An additional 12,387 subjects were further excluded for living more than 1000 meter away from the nearest traffic-related air pollution monitoring station. Following these exclusions the study group comprised of 445 individuals (262 males and 183 females). All distance calculations between the traffic-related air pollution monitoring stations and the specific household addresses of all TAMCIS participants were performed by the Survey of Israel, a national authority for mapping, cadastre, geodesy and geoinformation.

2.2 Laboratory methods

As part of the survey, we employed a set of analyzes to assess the levels of the inflammation sensitive biomarkers of the acute phase: Fibrinogen was quantified by the method of Clauss (Clauss, 1957) and a Sysmex 6000 (Sysmex Corporation, Hyaga, Japan) autoanalyzer while the high sensitivity C-reactive protein (hs-CRP) was measured using a Behring BN II Nephelometer (DADE Behring, Marburg, Germany) (Rifai et al., 1999). The erythrocyte sedimentation rate (ESR) was determined by using the method of Westergren(International Council for Standardization in Haematology [ICSH], 1993).

2.3 Definition of atherothrombotic risk factors

Results of the routine health check-up were assessed employing certain definitions in order to recognize atherothrombotic risk factors in individuals. These included diabetes mellitus which was defined as a fasting blood glucose concentration of ≥ 126 mg/dl (7.0 mmol/L) or the intake of insulin or oral hypoglycemic medications. Hypertension was defined as a

blood pressure of >140/90 mm Hg on two separate measurements or the use of antihypertensive medications. Dyslipidemia was defined as the low density lipoprotein cholesterol (LDL-C) or non-high density lipoprotein cholesterol (non-HDL-C) concentrations, for individuals displaying elevated triglyceride concentrations of > 200 mg/dl (2.26 mmol/L), above the recommended levels according to the risk profile defined by the updated adult treatment panel III (ATP III) recommendations or the use of lipid lowering medications(National Cholesterol Education Program/Adult Treatment Panel III [NCEP/ATPIII], 2001). The diagnosis of the metabolic syndrome was based on the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (Alberti et al., 2009). In short, Elevated waist circumference was defined as ≥94 cm (37 inches) in men and ≥80 (31.5 inches) in women as recommended for europid and middle east; Elevated triglycerides (TG) were defined as ≥150 mg/dl (1.7 mmol/l) or on drug treatment for elevated triglycerides; Reduced HDL-C was defined as <40 mg/dL (1.0 mmol/l) in men and <50 mg/dl (1.3 mmol/l) in women or on drug treatment for reduced HDL-C; Elevated blood pressure was defined as ≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension; Elevated fasting glucose was defined as ≥100 mg/dl (5.55 mmol/l). Smokers were defined as individuals who smoked at least 5 cigarettes per day while past smokers had quit smoking for at least 30 days prior to examination.

2.4 Air pollution and weather data

Air pollution and weather data were downloaded online from the Israeli Ministry of Environmental Protection web page. Major air pollutants and the weather data are routinely measured every half hour by the same traffic-related air pollution monitoring stations, which are adjacent to specific heavy traffic sites. The Israeli Ministry of Environmental Protection has deployed seven of such stations thorough out Israel. These stations routinely measure several major pollutants including nitrogen oxides (NO, NO_2, NOx) and carbon monoxide (CO). Since only one traffic-related air monitoring station measured PM_{10} (particles less than 10 microns in aerodynamic diameter) and sulfur dioxide (SO_2) the number of individuals included in a 1 km radius was too small for statistical power. Thus we have only analyzed the effect of the former pollutants on the inflammatory variables. The analytical monitors in each station are fully automated and U.S. Environmental Protection Agency (EPA) approved. They also include a daily automated calibration system. Once a year, the stations conduct quality control and quality assurance tests. Nitrogen dioxide was measured by Chemiluminescence NO-NO_2-NO_x analyzer (*Thermo Environmental Instruments Inc. USA*, Model 42C) and Carbon monoxide by Gas Filter Correlation (GFC) CO Analyzer (*Thermo Environmental Instruments Inc. USA*, *Model 48C).*

2.5 Statistical analysis

All data was summarized and displayed as mean, standard deviation (SD), and quartiles for the continuous variables and as number of patients plus the percentage in each group for categorical variables. Since High Sensitivity C-Reactive Protein (hs-CRP), ESR and the

triglyceride concentrations displayed irregular distributions, we used a logarithmic transformation which converted the distributions to normal ones for all statistical procedures. Therefore all results of hs-CRP, ESR or triglyceride concentrations are expressed as back transformed geometrical mean and standard deviation. The One-Way Kolmogorov-Smirnov test was used to assess the distributions.

In contrast to many other studies that evaluated air pollution, we did not divide the different air pollutants into tiles or commonly used cut-off points, rather we treated them as continuous variables. In order to quantify the contribution of each air pollutant to the variability of the different inflammation sensitive biomarkers we performed linear regression models using the forward stepwise method, where the inflammatory biomarkers were regarded as the dependent variable and many possible and known confounding parameters in addition to the air pollution as the independent variables. These confounders include parameters with known or suspected influences on inflammatory sensitive biomarkers and in addition to each air pollution, included gender, age, waist circumference, BMI, complete lipid profile including low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, diastolic and systolic blood pressure measurements, glucose concentration, alcohol consumption, sport intensity, medications including aspirin, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, statins, fibrates and oral contraceptives or hormonal replacement therapy for women, cardiovascular risk factors including diabetes mellitus, current and past smoking status and family history of coronary heart disease or personal history of proven atherothrombotic event (myocardial infarction, cerebrovascular event or peripheral artery disease).

In addition, in order to control for seasonal variation and for the differences in climate between the years the models included the same day's climate parameters (temperature and relative humidity), the season and the year of measurement. Single pollutant linear regression models were fitted for the inflammatory variables and air pollution parameters with the appropriate meteorological parameters with various lag days ranging from the day of blood withdrawal to as much as three days lag. In all linear regression models we tested the distribution of the residuals for normality. The results of the linear regression models are presented as the mean change plus the 95% confidence interval for one standard deviation (SD) increase in the air pollutant. According to the logarithmic transformation of hs-CRP and ESR, the expected change in the linear model for hs-CRP and ESR reflects relative change and is presented as percent of change, rather than absolute change. All above analyses were considered significant at $p<0.05$ (two tailed). The SPSS statistical package was used to perform all statistical evaluation (SSPS Inc., Chicago, IL, USA).

3. Results

We have presently analyzed a total of 445 individuals (262 males and 183 females) at the respective mean (SD) age of 44 (13). The characteristic age, BMI, blood pressure, lipid profile as well as alcohol consumption and sport intensity are presented in Table 1, while the respective percentage of individuals with different cardiovascular risk factors and relevant medications in Table 2. Table 3 presents the distribution of the different air pollutants and weather parameters collected.

	Mean	S.D	25th percentile	Median	75th percentile
Age (years)	45	13	34	45	55
Waist (cm)	88	13	79	89	97
BMI (kg/m^2)	26	4	23	25	28
Systolic BP (mmHg)	121	17	110	120	130
Diastolic BP (mmHg)	76	9	70	75	80
Glucose (mg/dL)	93	17	84	90	97
HDL Cholesterol (mg/dL)	58	17	46	55	68
LDL Cholesterol (mg/dL)	119	32	95	117	139
Triglycerides (mg/dL)	103	2	70	105	143
Alcohol consumption (glass/week)	1.4	2.9	0	0	2
Sport intensity (hours/week)	2.3	3.1	0	2	3.5
hsCRP (mg/L)	1.4	3.0	0.7	1.3	2.9
Fibrinogen (mg/dL)	292	59	246	289	330
ESR (mm/hr)	10	2	6	12	19

BMI – Body Mass Index; HDL – High Density Lipoprotein; LDL – Low Density Lipoprotein; hsCRP – High-Sensitivity C-Reactive Protein.

Table 1. Baseline topometric and laboratory data of the study population.

	N	%
Current smoker	98	22.0
Past Smoker	96	21.6
Diabetes Mellitus	21	4.7
Hypertension	97	21.8
Dyslipidemia	124	27.9
Family History of CHD	68	15.3
Aspirin	35	7.9
Beta blockers	29	6.5
Calcium channel blockers	12	2.7
ACE Inhibitors / ARB's	17	3.8
Statins	48	10.8
Fibrates	5	1.1
Oral hypoglycemics	11	2.5
Insulin	2	0.4

ACE – Angiotensin Converting Enzyme; ARB – Angiotensin II Receptor Blocker; CHD – Coronary Heart Disease.

Table 2. Baseline characteristics and medications use of the study population.

	Mean	S.D.	25th percentile	Median	75th percentile
Temperature (˚C)	21.1	5.3	16.6	20.9	26.6
Relative Humidity (%)	65.4	10.0	59.9	67.1	72.5
NO_2 (PPB)	29.9	9.3	23.0	27.7	35.4
NO (PPB)	50.6	41.6	21.3	38.6	64.8
NO_X (PPB)	63.2	47.4	32.2	46.8	81.9
CO (PPM)	0.8	0.4	0.6	0.8	1.0

PPB – Parts Per Billion; PPM – Parts Per Million.

Table 3. Air pollution and meteorology parameters

We systematically evaluated the contribution of each air pollution parameter to the variability of the inflammatory biomarker following adjustment for weather conditions at the same day, seasonal influence and many known and possible contributors. The results are displayed in Table 4 through 6 for hs-CRP, fibrinogen and ESR. It is evident that, in our study group, a statistically significant increase was noted in hs-CRP following exposure to NO_2 and NO at the day of measurement alone. This affect was only marginally significant with regard to CO and NOx. Fibrinogen however, showed a statistically significant decrease following same day exposure to NO and CO as well as following exposure of a 3 day lag. The ESR however, was not significantly affected by any air pollutant in our study.

		Partial correlation	Relative (95% CI) change (%) for 1 SD increase	P Value
NO_2	*Same day*	*0.280*	*38% (19% – 59%)§*	*<0.001*
	Previous day	0.119	13% (-1% – 30%)	0.080
	2 days ago	0.073	8% (-6% – 23%)	0.283
	3 days ago	0.052	5% (-7% – 18%)	0.441
NO	*Same day*	*0.193*	*22% (7% – 39%)§*	*0.004*
	Previous day	0.077	9% (-6% – 26%)	0.261
	2 days ago	0.086	8% (-4% – 23%)	0.205
	3 days ago	0.080	7% (-4% – 18%)	0.232
NO_X	Same day	0.113	13% (-2% – 31%)	0.097
	Previous day	-0.022	-3% (-18% – 15%)	0.743
	2 days ago	-0.016	-2% (-14% – 13%)	0.814
	3 days ago	0.030	3% (-9% – 16%)	0.655
CO	Same day	0.120	12% (-1% – 28%)	0.077
	Previous day	0.114	12% (-2% – 29%)	0.095
	2 days ago	0.051	4% (-7% – 17%)	0.449
	3 days ago	0.074	6% (-5% – 18%)	0.269

Table 4. Partial correlation and mean (95% CI) change in hs-CRP for one SD increase in each air pollutant

		Partial correlation	Mean (95% CI) change (%) for 1 SD increase	P Value
NO_2	Same day	0.047	3.1 (-5.8 – 12.0)	0.494
	Previous day	0.092	5.6 (-2.6 – 13.9)	0.182
	2 days ago	0.054	3.2 (-4.7 – 11.1)	0.054
	3 days ago	-0.087	-4.8 (-12.1 – 2.5)	0.197
NO	Same day	-0.141	-8.3 (-16.1 – -0.4)	0.040
	Previous day	-0.105	-6.6 (-15.1 – 1.8)	0.127
	2 days ago	-0.074	-4.1 (-11.4 – 3.3)	0.279
	3 days ago	-0.160	-7.6 (-13.8 – -1.4)	0.018
NO_X	Same day	-0.006	-0.4 (-8.9 – 8.1)	0.925
	Previous day	0.020	1.5 (-8.6 – 11.6)	0.768
	2 days ago	0.010	0.6 (-7.4 – 8.7)	0.882
	3 days ago	-0.038	-2.1 (-9.4 – 5.3)	0.577
CO	Same day	-0.151	-8.4 (-15.8 – -0.9)	0.028
	Previous day	-0.123	-7.4 (-15.4 – 0.7)	0.075
	2 days ago	-0.116	-5.8 (-12.5 – 0.9)	0.090
	3 days ago	-0.166	-8.0 (-14.4 – -1.7)	0.014

Table 5. Partial correlation and mean (95% CI) change in fibrinogen for one SD increase in each air pollutant

		Partial correlation	Relative (95% CI) change (%) for 1 SD increase	P Value
NO_2	Same day	0.085	7% (-4% - 20%)	0.231
	Previous day	0.015	1% (-9% - 12%)	0.838
	2 days ago	-0.088	-6% (-15% - 4%)	0.215
	3 days ago	-0.032	-2% (-11% - 7%)	0.641
NO	Same day	-0.049	-4% (-13% - 7%)	0.484
	Previous day	-0.091	-7% (-17% - 4%)	0.200
	2 days ago	-0.085	-6% (-14% - 4%)	0.228
	3 days ago	-0.039	-2% (-10% - 6%)	0.572
NO_X	Same day	0.016	1% (-9% - 13%)	0.820
	Previous day	-0.011	-1% (-13% - 13%)	0.873
	2 days ago	-0.001	0% (-10% - 11%)	0.993
	3 days ago	0.049	3% (-6% - 14%)	0.480
CO	Same day	-0.084	-6% (-14% - 4%)	0.236
	Previous day	-0.035	-3% (-12% - 8%)	0.624
	2 days ago	-0.085	-5% (-13% - 3%)	0.230
	3 days ago	0.008	0% (-7% - 9%)	0.911

Table 6. Partial correlation and mean (95% CI) change in ESR for one SD increase in each air pollutant

4. Discussion

In the present analysis we present statistically significant associations between the short term exposure to traffic-related air pollutants and several inflammatory biomarkers including hs-CRP, and quantitative fibrinogen. The effect was documented in individuals residing within a 1000 meter radius of a traffic-related air pollution monitoring station, intentionally positioned in proximity to specific heavy traffic sites. We believe our results support the hypothesis of a direct influence of this short term exposure to traffic-related air pollutants and an eventual heightened inflammatory response that might trigger clinical events (Brook et al., 2010).

Notably, we found CRP to be increased by ~40% following a one SD increase in NO_2, and by ~20% following a one SD increase in NO. Similar, albeit smaller and marginally significant increments, were noted for both NO_x and CO, implying that an analysis in a larger sample size might have shown more consistent results. This rise in CRP was noted for the same day exposure alone, supporting the notion of its role as an acute phase reactant (Steel & Whitehead, 1994). In their toxicological studies in men with and without prior myocardial infarction, who were exposed to dilute diesel exhaust (300 μg per cubic meter) or filtered air for 1 hour during periods of rest and moderate exercise in a controlled-exposure facility, both Mills and Tornqvist did not show increments in serum C-reactive protein concentrations 6 or 24 hours by exposure to diesel exhaust or filtered air (Mills et al., 2007; Tornqvist et al., 2007). Lucking et al (Lucking et al., 2008) has shown similar results when reporting his toxicological study in which no changes in plasma TNF-a, IL-6, C-reactive protein, and soluble ICAM-1 concentrations were observed. These measurements were obtained however, only 6 hours following both diesel exhaust and filtered air exposures. Tornqvist et al, did in fact show a 24 hour significant rise in IL-6 following diesel exhaust exposure (Tornqvist et al., 2007). IL-6 is widely known as a direct inducer of CRP production in the liver hepatocytes (Steel & Whitehead 1994). Thus, our environmental real-life 1000 meter radius traffic-related exposure findings can be supported by his toxicological findings. Interestingly, following exposure to CO and NO, fibrinogen concentrations decreased both in same day as well in 3 days following exposure. Previous environmental air pollution epidemiological studies have shown conflicting trends. Although some have demonstrated increased levels of fibrinogen, other studies measuring the same factors have failed to show any association with particulate exposure. Schwartz et al (Schwartz, 2001) found a significant negative association between the previous day fibrinogen concentration and NO_2, as did Seaton et al (Seaton et al., 1999) for the previous three days average of PM_{10}. In contrast, Pekkanen et al. (Pekkanen et al., 2000) reported a positive significant correlation between fibrinogen concentration and NO_2 or CO in London, with three days lag. In a large epidemiological study we have previously reported that mainly NO_2, SO_2 and CO affected fibrinogen in several lag days, with maximal effect for a lag of four days (Steinvil et al., 2008). Finally, Baccarelli et al (Baccarelli et al., 2007) reported no consistent relations between air pollution and fibrinogen in 1218 normal subjects from the Lombardia Region, Italy. Thus, Even though both fibrinogen (Danesh et al., 2005) and air pollution (Maitre et al., 2006) have been independently shown to be positively correlated with cardiovascular morbidity and mortality, most epidemiological studies report mainly negative correlations between the air pollutants measured and fibrinogen concentrations. Unfortunately enough, the direct affect of diesel exhaust exposure on fibrinogen concentration was not reported in most of the recent human toxicological studies (Carlsten et al., 2007; Mills et al., 2007;

Tornqvist et al., 2007; Lucking et al., 2008). As far as we know the only toxicological report was by Bloomberg et al (Blomberg et al., 2005) were no effect was found on fibrinogen concentrations. Due to the scarcity of data fibrinogen role as an acute phase reactant following diesel exhaust exposure cannot be evaluated. Fibrinogen however, can be viewed both as an inflammatory acute phase reactant, as well as a marker for thrombus formation. Its consumption, and therefore decrease in concentration following thrombus formation has been proposed to increase the diagnostic accuracy of venous thromboembolism (Kucher et al., 2003). Lucking et al (Lucking et al., 2008) has established that diesel exhaust inhalation increased thrombus formation under low and high shear conditions. The concept of fibrinogen consumption due to increased thrombus formation, subsequently leading to a decrease in its concentration following exposure to air pollutants, is therefore a subject for future toxicological studies.

Among the possible reasons for the previous conflicting results, in similar studies are: the lack of consistent air pollution measurement methodology, the lack of systematic examination of the time relationship between air pollution variables and markers of inflammation, and the fact that not all studies were controlled for multiple possible confounders. These confounders include parameters with known influences on the inflammatory response such as age (Larbi et al., 2004), gender (Zeltser et al., 2004), body mass index (BMI) and waist circumference (Santos et al., 2005), exercise (Petersen & Pedersen, 2005), the presence of hyperlipidemia (Pirro et al., 2004), hypertension (Tsioufis et al., 2006), alcohol consumption (Imhof et al., 2001), smoking habits (Yasue et al., 2006), glucose concentrations (Kerner et al., 2005), as well as the intake of medications with a potential pro- and anti-inflammatory effect (Kushner et al., 2006). In addition there are many possible confounders regarding air pollution, mainly meteorological parameters (temperature, humidity and precipitants) which may also be related to cardiovascular events (Danet et al., 1999) as well as wind speed (Brugge et al., 2007). Finally there are seasonal confounders that are closely associated with both cardiovascular morbidity and mortality, and air pollution (Nawrot et al., 2006). In order to attain more accurate results we accordingly controlled for all these possible confounders. Other than the effect possible confounders could have, there were some reports about enhanced sensitivity to the effect of air pollution in specific subgroups including asthmatic (Barck et al., 2002), elderly persons (Le Tertre et al., 2002), individuals with history of heart failure or arrhythmia (Mann et al., 2002), females (Chen et al., 2005), naturally higher fibrinogen concentrations (Prescott et al., 2000), history of cardiorespiratory hospitalization (Zanobetti & Schwartz, 2005) or myocardial infarction (von Klot et al., 2005). This enhanced sensitivity was also suggested in diabetic, obese and hypertensive individuals who display an association to systemic inflammation as evident by CRP, IL-6 and WBC levels (Dubowsky et al., 2006).

We acknowledge several limitations of the present study. First, we did not account for the effect indoor pollutants could have on our study population and their possible influence on the results. Second, we did not account for time spent outdoors, which depends on the work status and occupation type of each individual in the study. Third, as gender has been known to have a significant role in inflammation (Zeltser et al., 2004) and air pollution research (Chen et al., 2005) this might have stumped our results. Finally, we note that most previous studies have shown a significant decrease in combustion derived air pollutants in distances of above 400 meters (Brugge et al., 2007). Thus, and in spite of our multiple adjustments, the possibility exist the associations we present are of chance. We therefore encourage repeating this analysis in future studies.

5. Conclusion

We have found significant associations between inflammation sensitive biomarkers and between combustion derived air pollutants, in individuals residing in a 1000 meter radius from a traffic-related air pollution monitoring station, positioned in proximity to heavy traffic sites. While our significant results suggest a positive correlation with CRP and a negative correlation with fibrinogen and several air pollutants, our results showed be cautiously interpreted due to the study limitations.

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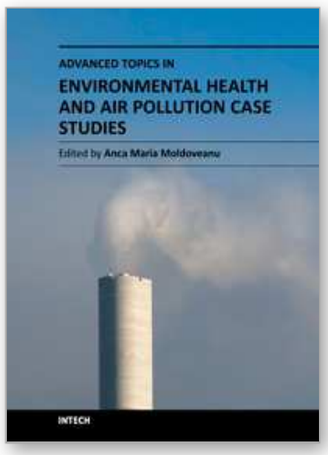

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The book describes the effects of air pollutants, from the indoor and outdoor spaces, on the human physiology. Air pollutants can influence inflammation biomarkers, can influence the pathogenesis of chronic cough, can influence reactive oxygen species (ROS) and can induce autonomic nervous system interactions that modulate cardiac oxidative stress and cardiac electrophysiological changes, can participate in the onset and exacerbation of upper respiratory and cardio-vascular diseases, can lead to the exacerbation of asthma and allergic diseases. The book also presents how the urban environment can influence and modify the impact of various pollutants on human health.

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