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Association of novel metrics of particulate matter with vascular markers of inflammation and coagulation in susceptible populations –results from a panel study

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ABSTRACT

Background and aims: Epidemiological studies have shown adverse effects of ambient air pollutants on health with inflammation and oxidative stress playing an important role. We examine the association between blood biomarkers of inflammation and coagulation and physical attributes of particulate matter which are not routinely measured such as particle length or surface area concentration and apparent density of PM.

Methods: Between 3/2007 and 12/2008 187 non-smoking individuals with type 2 diabetes mellitus (T2D) or impaired glucose tolerance (IGT) were examined within the framework of the KORA Study in Augsburg, Germany. In addition, we selected 87 participants with a potential genetic predisposition on detoxifying and inflammatory pathways. This was defined by the null polymorphism for *glutathione S-transferase M1* in combination with a certain single nucleotide polymorphism on the *C-reactive protein (CRP)* gene (rs1205) or the *fibrinogen* gene (rs1800790). Participants had blood drawn up to seven different times, resulting in 1765 blood samples. Air pollutants were collected at a central measurement station and individual 24-h averages calculated. Associations between air pollutants and high sensitivity CRP, myeloperoxidase (MPO), interleukin (IL)−6 and fibrinogen were analysed using additive mixed models.

Results: For the panel with genetic susceptibility, increases were seen for CRP and MPO with most attributes, specifically particle length and active surface concentration. The %change of geometric mean and 95% confidence intervals for the 5-day average exposure for CRP and MPO were 34.6% [21.8;48.8] and 8.3% [3.2;13.6] per interquartile range increase of particle length concentration and 29.8% [15.9;45.3] and 10.4 [4.4;16.7] for active surface area. Results for the panel of T2D and IGT and the other blood biomarkers were less conclusive.

Abbreviations: AIC, Akaike's information criterion; APS, Aerodynamic Particle Sizer; BET, Brunauer, Emmet and Teller Method; CPC, Condensation Particle Counter; CRP, C-reactive protein; DCPS, Diffusion Charging Particle Sensor; DMA, differential mobility analyser; Dp,, mobility equivalent diameter; EAD, Electric Aersol Detector; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; FDMS, Filter Dynamics Measurement Systems; GSTM1, glutathione S-transferase M1; IL-6, interleukin-6; IGT, impaired glucose tolerance; IQR, interquartile range; KORA studies, Cooperative Health Research in the Region Augsburg; LC, particle length concentration; LC (EAD), particle length concentration measured by EAD; MPO, myeloperoxidase; MI, myocardial infarction; NC, number concentration; NO, nitric oxide; $PM_{2.5}$, particulate matter (mass) with a size range of <2.5 μm in aerodynamic diameter; PM_{10}, particulate matter (mass) with a size range of <10 μm in aerodynamic diameter; PSD, particle size distribution; SC, particle surface concentration; SC (DCPS), particle surface concentration measured by DCPS; TDMPS, Twin Differential Mobility Particle Sizer; TEOM, Tapered Element Oscillating Microbalances; T2D, type 2 diabetes; UCPC, ultrafine Condensation Particle Counter; UDMA, ultrafine Differential Mobility Analyser; UFP, ultrafine particles, particle number concentration, with a size range of <0.1 μm in diameter; $\rho 2.5$, Apparent density for $PM_{2.5}$; $\rho 10$, Apparent density for PM_{10}

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Conclusions: Particle length concentration and active surface concentration showed strong positive associations with blood biomarkers reflecting inflammation. These air pollution metrics might reflect harmful aerosol properties better than particulate mass or number concentration. They might therefore be important for epidemiological studies.

1. Introduction

Epidemiological studies have shown that ambient air pollutants can negatively affect human cardiovascular health (Ruckerl et al., 2011; Brook et al., 2010). It has been reported that some subpopulations may be more at risk from the harmful effects of particulate air pollution than the general population. These subpopulations include e.g. patients with chronic obstructive pulmonary disease, previous myocardial infarction (MI) or diabetes (Brook et al., 2010).

Traditionally, particles are classified by size, such as PM_{10}, $PM_{2.5}$ (particulate matter of particles with less than 10 μm and 2.5 μm in aerodynamic diameter, respectively) and ultrafine particles (UFP), which have a diameter below 100 nm. The size classification of PM mass concentration into $PM_{2.5}$ and PM_{10} has been mostly driven by the different behaviour of the two particle fractions in human respiratory system: $PM_{2.5}$ reaches terminal bronchioles and the alveoli region, whereas the coarse particles (in the size range 2.5–10 μm) tend to deposit in the upper (thoracic) regions of the human respiratory system.

Particulate matter is a complex mixture of solid and liquid particles from various sources. Their physical and chemical properties change depending on the relative contributions from sources such as vehicle exhaust, household and industry emissions, road dust, forest fires or wind-blown soil. For example, combustion particles consist of an elemental carbon core surrounded by a layer of chemicals that include organic hydrocarbons, metals, nitrates and sulphates. The carbon core as well as the enclosing chemicals determine the toxicity of the particle (Donaldson and Tran, 2002). Combustion particles also have characteristic size distributions in ambient settings as suggested by source apportion approaches (Gu et al., 2012). Depending on size, surface area and chemical composition particles might vary in their ability to illicit pathophysiological responses as well as where they are deposited in the respiratory tract.

However, the roles of specific physical and chemical properties of particles remain still rather unclear and are not reflected by studying $PM_{2.5}$ and PM_{10} alone (Schlesinger et al., 2006). Long-term continuous measurements of particle properties such as particle number concentration (PNC), particle size distribution (PSD), chemical composition of particles, surface area concentration, particle length concentration and other particulate variables are needed to assess their relevance for health effects (Gu et al., 2012).

In order to collect an enhanced PM measurement data set and to study the effects of different attributes of particulate pollution on human health, we established a fixed monitoring station in an urban background area of Augsburg, Germany (Pitz et al., 2008a). This monitoring station has been designed for the collection of a number of physical and chemical particulate variables. Empirically, this data can be used to derive number concentrations, surface area concentrations and mass concentrations in various size ranges and relate it to health outcomes (Peters et al., 1997). To validate these calculations done under rather strong assumptions, we also measured active (Fuchs) surface by a Diffusion Charging Particle Sensor ('SC(DCPS)') and particle length concentration by an Electric Aersol Detector ('LC(EAD)'). In addition, we used the data in combination with $PM_{2.5}$ and PM_{10} to calculate apparent density of $PM_{2.5}$ and PM_{10} (ρ2.5 and ρ10, respectively) providing indirect measures of chemical composition of the particles.

In earlier analyses, we assessed the association between a range of blood biomarkers of coagulation/fibrinolysis and inflammation and UFP, $PM_{2.5}$, PM_{10}, coarse particles ($PM_{2.5-10}$), black carbon (BC), nitric oxide (NO), nitrogen dioxide (NO_2) and carbon monoxide (CO) in susceptible populations (Ruckerl et al., 2014). We found clear positive associations for the inflammatory markers myeloperoxidase (MPO) and high sensitivity (hs) C-reactive protein (CRP) for a five-day average exposure to $PM_{2.5}$ and BC, especially in a population that contained the null polymorphism for *glutathione S-transferase M1* (GSTM1) in combination with a specific single nucleotide polymorphism on the *CRP* or the *fibrinogen* gene.

In this publication, we explore the role of novel attributes of particulate matter such as SC(DCPS), LC(EAD), ρ2.5 and ρ10 as specified above. We concentrated on the four blood markers which we have previously shown to have significant associations with $PM_{2.5}$ and PM_{10}, namely hsCRP, MPO, interleukin (IL)−6 and fibrinogen, to facilitate comparison between traditional measurers of PM and novel physical attributes. We hypothesised that the associations for the analysed blood biomarkers would generally show positive associations, as we previously reported for $PM_{2.5}$ or PM_{10} mass (Ruckerl et al., 2014), but that specifically, measures of the surface area of particles would display stronger associations as suggested previously (Stoeger et al., 2006).

2. Methods

2.1. Study population

The details of the study have been described in detail elsewhere (Ruckerl et al., 2014). Briefly, our study comprised individuals with type 2 diabetes (T2D) or impaired glucose tolerance (IGT, n=187) and patients with potential genetic susceptibility in a detoxifying pathway (n=87). These latter patients did not have known IGT or diabetes but had to have the null-polymorphism for GSTM1 and either two major alleles of the single nucleotide polymorphism (SNP) rs1205 located in the *CRP* gene (Kolz et al., 2008; Sunyer et al., 2008) or at least one minor allele of the SNP rs1800790 located in the *fibrinogen* gene *FGB* (Peters et al., 2009; Jacquemin et al., 2008), or both.

Exclusion criteria for the study were (1) current smoking, (2) intake of platelet aggregation inhibitors except for acetylsalicylic acid, (3) a myocardial infarction and/or interventional procedures (percutaneous coronary intervention, PCI; coronary artery bypass grafting), less than six months before the recruitment for the study, and (4) chronic inflammatory diseases such as Crohn's disease, rheumatoid arthritis or ulcerative colitis. Information on life-style, additional diseases and medication intake were collected at baseline and throughout the study. All individuals participated in up to seven repeat visits scheduled every four to six weeks on the same weekday and the same time of the day resulting in a total of 1766 blood samples (1197 and 569 for T2D or IGT and participants with potential genetic susceptibility, respectively).

Written informed consent was obtained from all participants.