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Recent versus chronic fine particulate air pollution exposure as determinant of the retinal microvasculature in school children

Eline B. Provost[a,b], Luc Int Panis[b,c], Nelly D. Saenen[a], Michal Kicinski[a], Tijs Louwies[a,b], Karen Vrijens[a], Patrick De Boever[a,b], Tim S. Nawrot[a,d,*]

[a] Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium
[b] Environmental Risk and Health, Flemish Institute for Technological Research (VITO), Mol, Belgium
[c] School for Mobility, Hasselt University, Hasselt, Belgium
[d] Department of Public Health & Primary Care, Leuven University, Leuven, Belgium

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ABSTRACT

Background: Microvascular changes may represent an underlying mechanism through which exposure to fine particulate matter with a diameter ≤ 2.5 µm ($PM_{2.5}$) contributes to age-related disease development. We investigated the effect of recent and chronic exposure to $PM_{2.5}$ on the microcirculation, exemplified by retinal vessel diameters, using repeated measurements in 8- to 12-year-old children.

Methods: 221 children (49.1% girls; mean age 9.9 years) were examined repeatedly (25 one, 124 two, and 72 three times) adding up to 489 retinal vessel examinations. Same-day exposure to $PM_{2.5}$ was measured at school. In addition, recent (same and previous day) and chronic (yearly mean) exposure was modelled at the child's residence using a high-resolution interpolation model. Residential proximity to major roads was also assessed. Changes in retinal vessel diameters associated with recent and chronic exposures were estimated using mixed models, while adjusting for other known covariates such as sex, age, BMI, blood pressure and birth weight.

Results: Each 10 µg/m^3 increment in same-day exposure to $PM_{2.5}$ measured at school was associated with 0.35 µm (95% CI: 0.09–0.61 µm) narrower retinal arterioles and 0.35 µm (−0.03 to 0.73 µm) wider venules. Children living 100 m closer to a major road had 0.30 µm (0.05–0.54 µm) narrower arterioles.

Conclusions: Blood vessel diameters of the retinal microcirculation of healthy school-aged children respond to same-day $PM_{2.5}$ exposure. Furthermore, children living closer to major roads had smaller arteriolar diameters. Our results suggest that the microcirculation, with retinal microvasculature as a proxy in this study, is a pathophysiological target for air pollution in children.

1. Introduction

The microcirculation constitutes the majority of the circulatory system. Its role in age-related disease development is however less explored than that of the macrocirculation. The microvasculature plays a unifying role in diverse pathological conditions such as hypertension, (Ding et al., 2014) chronic kidney disease (Yau et al., 2011), left ventricular dysfunction (Cheung et al., 2007), obesity (Wang et al., 2006), diabetes mellitus (Wong et al., 2002), and cognitive impairment (Shalev et al., 2013). The state of the microvasculature and its physiological response are important factors on the trajectory from healthy to unhealthy ageing.

Numerous epidemiological studies have shown that exposure to particulate air pollution affects the vascular system, reporting associations between particulate matter exposure and increases in both cardio- and cerebrovascular mortality and morbidity (Brook et al., 2010; Franklin et al., 2015; Scheers et al., 2015). However, few studies have addressed the role of the microcirculation in these associations (Ljungman et al. (2014; Zhang et al., 2016). The retinal microvasculature is considered a proxy for the systemic microcirculation and can be characterized non-invasively by means of fundus photography. Adar and colleagues were the first to associate retinal arteriolar narrowing with air pollution (Adar et al., 2010). Among 4607 participants of the Multi-Ethnic Study of Atherosclerosis (MESA), the retinal arteriolar narrowing associated with chronic ambient exposure to particulate matter with a diameter less than 2.5 µm ($PM_{2.5}$) was equivalent to a 7-year increase in age (Adar et al., 2010). A repeated measurements study of the retinal microvessels in healthy volunteers found that increases in recent ambient particulate matter with a diameter less than 10 µm (PM_{10}) exposure were associated with decreases in both

* Correspondence to: Centre for Environmental Sciences, Agoralaan Gebouw D, 3590 Diepenbeek, Belgium.
E-mail address: tim.nawrot@uhasselt.be (T.S. Nawrot).

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arteriolar and venular diameters (Louwies et al., 2013). Results from these studies show that the retinal microcirculation is influenced by both recent and chronic exposure to particulate air pollution in adults.

The effect of early life exposures on children's health is a growing research field because lasting effects may have major public health implications (Merlo et al., 2009; Gluckman et al., 2008). Children are potentially more susceptible than adults when exposed to comparable levels of air pollutants (Sacks et al., 2011). Not only are they exposed during a critical developmental period, children also differ from adults in physiological characteristics and exposure patterns (Sacks et al., 2011).

However, to date, no research has evaluated children's retinal blood vessel characteristics in relation to recent versus chronic particulate air pollution exposure. Since the microvasculature plays a pivotal role in age-related disease development, we set up a panel study with repeated retinal microvascular measurements in 8- to 12-year-old children.

2. Methods

2.1. Study population

This research was part of the COGNAC (COGNition and Air pollution in Children) study (Saenen et al., 2016). Children aged 8–12 years from two primary schools in Flanders (Belgium) were invited for repeated clinical examinations. The two schools were 3.7 km apart and located in the agglomeration of Hasselt (~70 km east from Brussels). Of the 482 invited children, 221 (45.9%) agreed to participate of which 72 (33%) underwent three clinical examinations, 124 (56%) completed two examinations and 25 (11%) had only one examination, amounting to a total of 489 retinal microvascular examinations. The examinations took place in school years 2012–2013 for one school and 2013–2014 for the other, from November to February on Monday, Tuesday, Thursday, and Friday between 8:30a.m. and 3:30p.m. Participating children were examined at their school during school time. The average (SD) time between two consecutive examinations was 49 (19) days. The clinical examinations of each child were scheduled on the same time of day and day of the week to minimize circadian variation.

We conducted the study according to the principles outlined in the Helsinki declaration for research on human participants. The ethics committees of Hasselt University and Ziekenhuis Oost-Limburg approved the study. Written informed consent was obtained from the parents as well as oral assent from the children. The parents filled out a questionnaire addressing aspects related to sociodemographics and medical characteristics of the child and its family. Additional information on the indoor and outdoor environment of the residence, including current smoking status of the parents and time spent in traffic, was collected.

2.2. Clinical examination

Clinical examinations were performed by a trained examiner and included imaging of the retinal microvasculature, and measuring of blood pressure and heart rate.

The fundus of the left and right eye of each participant was photographed with a Canon 45° 6.3 megapixel digital nonmydriatic retinal camera (Hospithera, Brussels, Belgium), as described by De Boever and colleagues (De Boever et al., 2014). The diameters of the retinal blood vessels were measured using IVAN fundus image analysis software according to previously reported protocols (Knudtson et al., 2003). Vessel diameters were summarized per image as the Central Retinal Arteriolar Equivalent (CRAE) and Central Retinal Venular Equivalent (CRVE). The equivalents represent a summary of the vessel diameters within an area equal to 0.5–1 times the disc diameter from the optic disc margin. The respective vessel diameters were averaged over both eyes.

Blood pressure and heart rate were measured according to the guidelines of the European Society of Hypertension (Parati et al., 2008). The participating children rested for five minutes, after which heart rate, systolic (SBP) and diastolic (DBP) blood pressure were measured five times consecutively using an automated upper-arm blood-pressure monitor (Stabil-O-Graph®, I.E.M., Stolberg, Germany) with a special sized cuff for children. The last three measurements were averaged and used in the analyses.

2.3. Particulate air pollution exposure assessment

2.3.1. Measured exposure to $PM_{2.5}$ at school

Concentrations of $PM_{2.5}$ on the day of the examination were measured with the portable Aerocet 531 (Met One Instruments Inc. Grants Pass, OR, USA) both inside the classroom and outside at the school playground. The measurements were performed according to the manufacturer's instructions. Recent outdoor exposure was defined as 10-min average outside concentrations of $PM_{2.5}$ preceding the clinical examination, during the school breaks when children were playing outside. Recent indoor exposure was defined as the classroom concentrations during the clinical examination averaged over 30 min between entering the room until the retinal images were captured.

2.3.2. Modelled residential air pollution

We used a spatial temporal interpolation method to model the daily residential exposure levels (μg/m^3) of $PM_{2.5}$ at each child's home address. This method takes into account land cover data obtained from satellite images (CORINE land cover data set) (Janssen et al., 2008) and pollution data from fixed monitoring stations in combination with a dispersion model (Lefebvre et al., 2013; Maiheu et al., 2012). The model calculates the daily interpolated exposure concentrations in a high resolution receptor grid (25 × 25 m) based on information from the Belgian telemetric air quality networks, point sources, and line sources. Overall model performance was evaluated by leave-one-out cross-validation. Validation statistics of the interpolation tool gave a temporal explained variance of more than 0.80 and spatial explained variance of 0.60–0.80 for $PM_{2.5}$ (Maiheu et al., 2012; Lefebvre et al., 2011). We used the model to assess the residential same-day to 48 h of exposure up to the clinical examination as well as long-term exposure as reflected by the annual mean concentration in the year prior to the examination. When a child had more than one residential address at the moment of the study, we calculated a weighted average using the proportion of time spent at each location. In addition we used a Geographical Information System (ArcGIS version 10.0) to assess the residential proximity to major roads, defined as highways and national roads (Appendix, Fig. A.1).

Daily mean ambient temperature and relative humidity were obtained from the Belgian Royal Meteorological Institute in order to calculate apparent temperature on the day of the clinical examination based on a standard formula (Steadman, 1979; Kalkstein and Valimont, 1986). The region of Flanders is homogenous regarding temperature since both altitudinal and latitudinal gradients are extremely small. Furthermore, elevations range from 0 to 200 m above sea level and the distance between the most northern and southern part is only 100 km. Meteorological parameters were therefore used from the measuring station in Uccle (Brussels, Belgium), which is central and representative for Flanders (Scheers et al., 2011).