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Traffic-related air pollution and eczema in the elderly: Findings from the SALIA cohort

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ABSTRACT

Childhood eczema results from an interplay of genetic and environmental factors including Traffic-Related Air Pollution (TRAP). In contrast, little is known about eczema in the elderly in general and its association with TRAP in particular. Animal experiments indicate that the arylhydrocarbon receptor (AHR) might link TRAP and eczema.

We investigated (i) incidence and prevalence of eczema in elderly women, (ii) its association with long-term TRAP exposure and (iii) the effect modification by *AHR* polymorphism rs2066853.

The study is based on the SALIA cohort. The women's average age was 55 years at baseline (1985–1994) and 74 years at follow-up (2008–2009) examination. Incidence and prevalence of eczema were assessed by an adapted version of the International Study of Asthma and Allergies in Childhood (ISAAC) symptom questionnaire. TRAP was determined using land-use regression models. Adjusted logistic regression models were used.

After age 55, the incidence and prevalence of eczema symptoms were 7.9% and 8.8%, respectively. Significant associations ($p < 0.05$) were found between all parameters of TRAP at the baseline visit and eczema incidence. The risk was higher for minor allele carriers of rs2066853 e.g. NOx: OR = 3.75, p = 0.030 vs. OR = 1.34, p = 0.317 in non-carriers (p(interaction) = 0.122).

These results indicate a high incidence for eczema in elderly women, which is associated with chronic exposure to TRAP and possibly mediated by AHR.

1. Introduction

According to the World Allergy Organization nomenclature, eczema is "an aggregation of several skin diseases with certain clinical characteristics in common involving a genetically determined skin barrier defect" and categorized into atopic eczema, eczema in a person of the atopic constitution, and non-atopic eczema (Johansson et al., 2004). In this manuscript, we will use the term eczema according to this definition.

Although in the past atopic eczema was traditionally considered a disease primarily occurring in childhood, more recent epidemiologic evidence supports the stratification of different eczema phenotypes based on age of onset (Bieber et al., 2017). In fact, recent reports indicate a high point prevalence and one-year prevalence of atopic eczema in adults (Rönmark et al., 2012; Vinding et al., 2014), and an increased prevalence of eczema even in the elderly (Tanei and Hasegawa, 2016). However, studies on the association between TRAP and eczema in adults are rare and the findings are inconsistent (Li et al., 2016; Pujades-Rodríguez et al., 2009; Tang et al., 2017). Surprisingly, such studies have never been conducted in the elderly, who might have been exposed to TRAP for even longer time periods.

Little is known about the biological mechanisms that may cause TRAP-induced eczema. In this regard a recent animal study has shown that topical application of air pollutants to mouse skin induced a signaling response, which was mediated by the Aryl Hydrocarbon Receptor (AHR) and thereby caused the production of neurotrophic factors in mouse skin which contributed to the development of pruritic, atopic eczema-like skin symptoms (Hidaka et al., 2016). The authors proposed that AHR signaling might link TRAP to atopic eczema. If these observations are relevant for the association between TRAP and eczema in humans is currently not known.

In the human *AHR* gene, SNPs occur predominantly in a region that

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encodes a major part of the transcriptional activation domain (TAD) (Harper et al., 2002). As a non-synonymous SNP rs2066853 causes an arginine to lysine exchange within the acidic sub-domain of *AHR*-TAD at position 554 (R554K). This transition is the first discovered SNP of human *AHR* gene and the most widely studied mutation of it. Up to now, rs2066853 has been studied in more than 50 peer-reviewed articles (compare PubMed or http://www.ensembl.org) and has been linked to a large variety of phenotypes (Aftabi et al., 2016).

In the present study, we therefore investigated (i) incidence and prevalence of eczema in elderly women, (ii) its association with long-term exposure to TRAP and (iii) the interaction between the *AHR* polymorphism rs2066853 and TRAP on eczema.

2. Methods

2.1. Study design and study population

The Study on the influence of Air pollution on Lung function, Inflammation and Ageing (SALIA) began in 1985 and focused on women aged 55 years old from the urban Ruhr area (Dortmund, Duisburg, Essen, Gelsenkirchen and Herne) and two rural northern counties (Sothern Münsterland) in West Germany. The Ruhr area was historically exposed to a range of airborne PM due to the traffic pollution and the highly industrial nature of the district. Men were not recruited because of the high occupational exposure of many men in this area, where coal mining and steel industry constituted the predominant sources of income in the time period before the baseline examination (Vossoughi et al., 2014). This cohort study explores the health effects of TRAP on different organs (Krämer et al., 2010; Ranft et al., 2009; Schikowski et al., 2005; Vossoughi et al., 2014) including skin (Hüls et al., 2016; Vierkötter et al., 2010).

The current study is based on the clinical follow-up examination (2008–2009) in which 834 women aged 69–79 years participated. It consisted of an interview, lung function measurement, cognition and cardio-vascular system tests, a detailed questionnaire to assess eczema, and determination of single-nucleotide polymorphisms (SNPs).

All participants gave written consent. The Medical Ethics Committee of the University of Bochum approved the follow-up examination.

2.2. SALIA-Questionnaire: assessment of eczema

The 2008–2009 dermatological questionnaire was developed in collaboration with dermatologists and was adapted from a questionnaire developed for adolescents within the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al., 1995), where symptom questions are used to define eczema. Specifically, we asked: 'Have you ever had an itchy rash which was coming and going for at least 6 months?'. In the following text, this information has been abbreviated to 'symptoms of eczema ever'. We also used the question 'How old were you when it occurred for the first time?' to define incidence of eczema symptoms after age 55. The prevalence of eczema symptoms at the follow-up examination was defined by the question 'Have you had this itchy rash at any time in the last 12 months?'. The definition of 'atopic eczema disease' used a combination of the questions: 'Did you ever have neurodermatitis (atopic/endogenous eczema)? and 'Was atopic eczema/neurodermatitis ever diagnosed by a physician and at what age it occurred for the first time?'. Neurodermatitis is a specific German name for atopic eczema (Krämer et al., 1998) and has been successfully used in ISAAC questionnaires before (Krämer et al., 2009).

2.3. Exposures

Both, the baseline and follow-up investigations measured TRAP. The follow-up TRAP exposure of the participants was estimated by land-use regressions from the ESCAPE study (European Study of Cohorts for TRAP Effects) (Beelen et al., 2013; Eeftens et al., 2012). Three two weeks' measurements made at 40 sites from the Ruhr and Southern Muensterland area's estimated the exposure to nitrogen dioxide (NO_2) and nitrogen oxides (NO_X) in a one-year TRAP monitoring campaign. Simultaneously, exposure to PM was estimated from measurements performed at 20 sites for $PM_{2.5}$ (PM of an aerodynamic diameter of 2.5 µm or less), absorbance of $PM_{2.5}$ ($PM_{2.5abs}$) defined as the $PM_{2.5}$ filter's reflectance, PM_{10} (aerodynamic diameter of 10 µm or less) and PMcoarse ($PM_{2.5\text{-}10}$). Because the ESCAPE TRAP monitoring campaign only operated in 2008–2009, TRAP exposure at baseline was estimated using a back-extrapolation algorithm. Values of the baseline investigation (1985–1994) were calculated using the measurements of the campaign and adjustments gained from measurements of monitoring sites in the area which operated between 1984 and 2009 (Schikowski et al., 2015b). The mean concentration of the respective pollutant at baseline measured by the routine monitoring station was divided by the respective annual concentration of the pollutant of the year, when measurements for the land use regression (LUR) model were performed. With this ratio, we multiplied the corresponding modeled LUR concentration to obtain the back extrapolated value (Fuks et al., 2014). The implicit assumption of proportional spatial contrasts over time was tested with data from six routine monitoring stations situated in the investigation area and covering the investigation period. The trend concordance between baseline (1985–1994) and follow-up investigation (2008–2009) was good (e.g. for PM_{10} r^2 between 0.42 in Duisburg and 0.84 in Gelsenkirchen).

2.4. Determination of genetic markers

DNA was extracted from blood samples of 484 individuals using a standard procedure (QIAamp DNA Mini Kit, QIAGEN, Hilden, Germany). LCG/KBioscience (Hoddesdon, UK) performed the DNA amplification and genotyping using the competitive allele-specific polymerase chain reaction SNP genotyping system (KASPar) with an error rate < 0.3%.

2.5. Confounders

We started with crude (unadjusted) regression models and then included based on the literature the following potential confounders in our main models: Age, educational status (the highest school level reached by the participant or her husband was used as indicator, < 10years as low social status, medium status for 10 years, > 10 years as high status), measured body mass index (BMI), smoking behavior (classified as following: current/ex-smokers/never), as well as second hand smoking (SHS) at home and/or at work), indoor TRAP by heating with fossil fuels and information about moving within the study period.

2.6. Statistical analysis

For the descriptive analysis, counts and percentage were calculated for each categorical variable. The arithmetic means were reported with their corresponding standard deviations for the continuous variables, which were all approximately normally distributed.

Logistic regression models were used to analyze the association between TRAP and eczema. Effect estimates (odds ratios, ORs) and 95% confidence intervals (CIs) were estimated per increase of one interquartile range (IQR) in TRAP concentration.

We used exposure estimates for the time before or at outcome assessment. For the association analysis with eczema ever and incidence of eczema symptoms, we made use of the TRAP exposure at baseline investigation, when all women were 55 years old. For the association analysis with the prevalence of eczema symptoms, we made use of the follow-up TRAP exposure (2008–2009). In a sensitivity analysis we excluded the participants who moved within the study period to reduce