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The association between Traffic-Related Air Pollution and eczema in elderly women: findings from the SALIA cohort.

Dissertation

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A ma famille.

« Sans la curiosité de l'esprit, que serions-nous ? Telle est bien la beauté et la noblesse de la science : désir sans fin de repousser les frontières du savoir, de traquer les secrets de la matière et de la vie sans idée préconçue des conséquences éventuelles. »

Marie Skłodowska-Curie

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Die Assoziation zwischen Luftverschmutzung und Ekzem in älteren Frauen aus der SALIA-Kohorte.

Autor: Winnie Schnass

Zusammenfassung

Ekzem wird allgemein als pädiatrische Krankheit angesehen, die sich in der Regel in den zwei ersten Lebensjahren entwickelt. Bei den meisten betroffenen Kindern kommt es vor dem Schulalter zu einer Remission (1). Laut World Allergy Organization (WAO) Nomenklatur wird es als „Aggregation zwischen mehreren Hauterkrankungen mit gemeinsamen spezifischen klinischen Charakteristiken einbeziehend eines genetische n Defekts der Hautbarriere“ definiert (2), (3). Die Prävalenz beträgt 15 bis 30% der Kinder (1) und 0,3 bis 11,5% der Erwachsenen weltweit und ist in den letzten Jahrzehnte n angestiegen (4). Die Pathogenese von Ekzem ist sehr komplex und umfasst allergisc h-inflammatorische Reaktionen und genetisch und umwelt-bedingte Hautbarrieredefekte (5), (6). Mehrere Studien zeigten bisher nur den Einfluss von Luftverschmutzung auf Ekzem bei Kindern (7–9). Aber der Einfluss von Luftverschmutzung auf Ekzem bei Erwachsenen oder älteren Menschen ist bis jetzt kaum beschrieben worden. Tiermodelle zeigten, dass der Arylhydrocarbon Rezeptor (AHR) eine Verbindung zwischen Luftverschmutzung und Ekzem herstellt (10). AHR ist ein ligand-aktivierter Transkriptionsfaktor, der die Expression von Genen, für die Zellproliferation, -differentiation (11) und Organentwicklung (12), (13) induziert.

Ziel dieser Studie war es, die Inzidenz und Prävalenz von Ekzem bei älteren Frauen darzustellen, den Zusammenhang zwischen Langzeitexposition mit Luftverschmutzung und Ekzem zu untersuchen und die Effektmodifikation durch den AHR Polymorphis m rs2066853 auf Luftverschmutzungs-induziertes Ekzem zu prüfen.

Diese Studie basiert auf Daten der SALIA-Kohorte (Study on the Influence of Air pollution on Lung function, Inflammation and Ageing). An der Basisuntersuchung haben 834 55-jährige Frauen teilgenommen (1985-1994). Die Inzidenz und die Prävalenz von Ekzem und Symptomen wurden mithilfe eines adaptierten Fragebogens aus der *International Study of Asthma and Allergies in Childhood* (ISAAC) abgefragt. Die Luftverschmutzung wurde mittels *Landnutzungsmodellen* (LUR) abgeschätzt. Die statistische Analyse wurde mit logistischen Regressionsmodellen kalkuliert, die Alter, Schulstatus, gemessenen *body mass*

index (BMI), Raucherstatus inklusive Passivrauchen, ungünstige Heizungsart sowie Umzug während der Studie mit einbezieht.

Nach 55 Jahren betrugen die Inzidenz von Ekzem 7,9% und die Prävalenz 8,8%. Es konnte ein Zusammenhang zwischen Luftverschmutzung aus der Basisuntersuchung und der Inzidenz von Ekzem in einem Alter über 55 Jahre gezeigt werden (zum Beispiel bei NOx mit einem Odds Ratio von 1.54 und einem p-Wert von 0.021). Weitere Assoziationen waren stärker für Träger von minor Allele vom rs2066853SNP (zum Beispiel bei NOx: OR=3.75, p=0.030 bei OR=1.34, p=0.317 in Nichtträger (p(Interaktion)=0.122).

Die Ergebnisse aus dieser Studie zeigen eine hohe Inzidenz von Ekzem bei älteren Frauen, welches mit einer chronischen Luftschadstoffbelastung verbunden ist und wahrscheinlich durch AHR vermittelt wird. Weitere Erforschung der Ätiologie von Ekzem ist notwendig, um bessere Verlaufskontrollen, bessere Therapieoptionen und Prävention zu ermöglichen.

The association between Traffic-Related Air Pollution and eczema in the elderly: findings from the SALIA cohort.

Author: Winnie Schnass

Summary

The general opinion is that eczema is primarily a childhood disease, developing during the first two years of life and remitting before school age in the majority of the affected children (1). Referring to the World Allergy Organization (WAO) nomenclature, eczema is defined as an "aggregation of several skin diseases with certain clinical characteristics in common involving a genetically determined skin barrier defect" (2), (3). Its prevalence is 15-30% in children (1) and 0.3 to 11.5% in adults worldwide and is increasing in the last decades (4). The pathogenesis of eczema is very complex and involves allergic inflammation and skin barrier defect probably due to genetic and environmental factors (5), (6). Several studies have shown the environmental impacts on eczema in children, and particularly of Traffic-Related Air Pollution (TRAP) exposure (7–9). In contrast, little is known about eczema in the elderly in general and its association with air pollution in particular. Animal experiments indicate that the aryl hydrocarbon receptor (AHR) might link air pollution and eczema (10). AHR is a ligand-activated transcription factor which induces the expression of genes for cell proliferation, differentiation (11) and organ development (12), (13) among others.

The aim of the study was to investigate the incidence and prevalence of eczema in elderly women, its association with long-term air pollution exposure and the effect modification by AHR polymorphism rs2066853 on TRAP-induced eczema.

The study is based on the SALIA (Study on the Influence of Air pollution on Lung function, Inflammation and Ageing) cohort, in which 834 55 years old women took part at baseline investigation (1985-1994) and at the follow-up investigation (2008-2009), in which 834 69 to 79 years old took part. Incidence and prevalence of eczema were assessed by an adapted version of the International Study of Asthma and Allergies in Childhood (ISAAC) symptom questionnaire. Air pollution was determined using land-use regression (LUR) models. The statistical analysis was calculated using logistic regression models which were adjusted for age, educational status, measured body mass index (BMI), smok ing behaviour, as well as second-hand smoking (SHS), indoor air pollution exposure by heating with fossil fuels, and information about moving within the study period.

After the age of 55 years, the incidence and prevalence of eczema symptoms were 7.9% and 8.8%, respectively. Associations were found between baseline TRAP (e.g. NOx: OR=1.54, p=0.021) and the incidence of eczema after an age of 55 years. Further associations were stronger 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).

The results of the current study indicate a high incidence of eczema in elderly women, which is associated with chronic exposure to air pollutants and possibly mediated by AHR. Further research on the etiology of eczema is needed for a better follow-up of the patients, better-targeted therapy options, and better prevention.

LIST OF ABBREVIATIONS

AHR	Aryl hydrocarbon receptor
APC	Antigene presenting cell
BMI	Body mass index
EPA	Environmental Protection Agency
FLG	Filaggrin
IgE	Immunoglobuline E
IL-x	Interleukines
IUF	Leibniz Research Institute for Environmental Medicine
LUR	Land-use regression
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
PAHs	Polycyclic aromatic hydrocarbons
PM_x	Particulate Matter (x = number indicating the size of the particle)
PM_{abs}	Particulate Matter (absorbance)
SALIA	Study on the influence of Air pollution on Lung function, Inflammation and Ageing
SHS	Second-hand smoke
SNPs	Single-nucleotide polymorphisms
TH	T helper cell
TNFα	Tumor necrosis factor alpha
TRAP	Traffic-Related Air Pollution
TSLP	Thymic and stromal lymphopoietin
UFP	Ultrafine particles
WAO	World Allergy Organisation
WHO	World Health Organisation

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1. INTRODUCTION

1.1 Definition of eczema

Primarily known as a disease of childhood, which occurs during the first two years of life and generally remits before school age, eczema can also affect other age categories (1). It is classified into the group of dermatitis skin conditions. Dermatitis is a general term used to describe an inflammatory reaction of the skin and is divided in several sub-groups (see figure 1) (2).

The current study focuses on eczema and its sub-groups, defined by Johansson et al. as atopic eczema and non-atopic eczema (2).

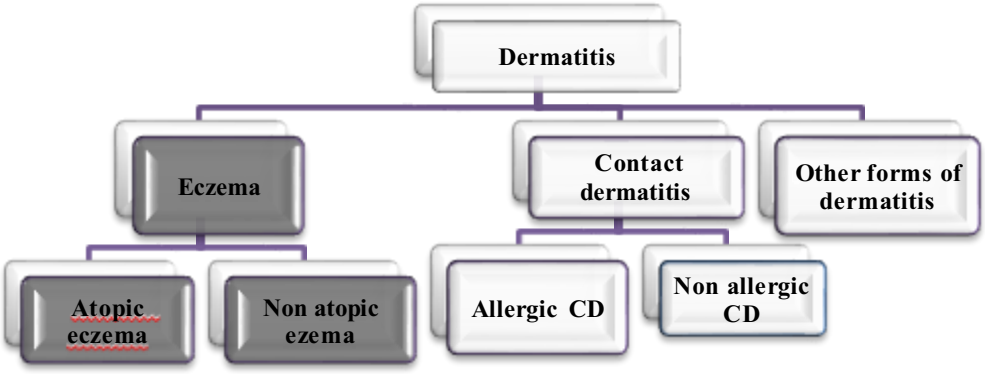

Figure 1 Dermatitis Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113(5):832–6.

CD: contact dermatitis

Referring to the World Allergy Organization (WAO) nomenclature, eczema is defined as an "aggregation of several skin diseases with certain clinical characteristics in common involving a genetically determined skin barrier defect" (2), (3). Atopic eczema is a chronic relapsing inflammatory skin condition characterized by dry skin, pruritus and multiple forms of eczematous dermatitis with a predilection for the skin flexural areas (1). Its pathogenes is involves allergic inflammation and defect of the skin barrier (5), (6).

At least four types of eczema were found, depending on the age when the symptoms occurred for the first time: infantile, childhood, adolescent/adults and elderly eczema (14). Each category shows specific symptoms for every age category. For example, acute lesions are more often in the infantile type, chronic lesions appear in later types.

The infantile type typically appears between the age of three months and two years. It principally affects the cheeks of the patient with edematous papules and papulovesicles. But the scalp, neck, extensor parts and trunk can also be affected. Further development of crusts of the lesions is possible.

The children type of eczema affects children aged between two and twelve years. Acute and chronic phases with lichenification are possible and it typically affects flexural regions of the body and the perioral region on the head.

The adolescent and adult type affects patients aged between twelve and 60 years. The classical symptomatic areas are the head, neck, flexural areas and hands for the adult type (15).

Elderly eczema appears at an age over 60 and is characterized as extensive eczematous lesions of the skin up to erythrodermic aspects and with strong pruritus. This type was recently added to the classification so that more research is needed. There are several differential diagnoses of elderly eczema, for example allergic contact dermatitis and cutaneous t-cell lymphoma. Those make elderly eczema difficult to differentiate from other disease and thus complicate to diagnose it (6), (3).

Both types, IgE-allergic and non-IgE-allergic, are observed in elderly and a predomina nce in male was observed (5), (14).

One way of stratifying eczema is by differentiating its severity, starting from very mild to very severe. Another possibility is the stratification by the age of (very early, early onset, childhood onset, adolescent type, adult-onset between 20 and 60, very late onset) as show in the classification above (6).

Another classification of eczema is the differentiation between into extrinsic and intrins ic eczema with respectively 80 and 20% of adult patients. Extrinsic eczema is defined by high serum IgE levels, atopy in the family history and specific IgE to food or aeroallerge ns. Higher eosinophilia is present in patients with extrinsic eczema (16).

Johansson et al. defined atopic eczema as an IgE –antibody-associated inflammation reaction of the skin in children and young adults showing signs of the atopic constitution. The disease can be defined as atopic eczema in the presence of IgE-antibodies in the serum or with a positive skin prick test of the patients. It was shown that chronic cases of atopic eczema are less influenced by IgE-antibodies and that the dominating cells are lymphocytes in that

particular case. In cases where the immunological status of the patient is not clear, the skin reaction should be referred as eczema (2), (3). Furthermore, an evolution into atopic eczema is possible in preschool children without atopic constitution (2).
Several criteria were established to diagnose atopic eczema in children: pruritus, dry skin in the past year, involvement of the skin creases, asthma or hay fever in the medical histo ry, visible flexural dermatitis (17), (18). However, eczema in the elderly is not defined as the pediatric type and further research is needed to assess the diagnosis in that group of patients.

Little is known about atopic eczema of the elderly. Evidence was found for a male predominance. A differentiation between an IgE-allergic and a non IgE-allergic type was made. The first type is characterised by an environmental sensitisation to allergens and high serum levels of IgE (more than 200-400 U/l) or a positive skin prick test (14).
Patients with IgE-allergic type of atopic eczema showed a T-helper 2 cytokine response which uses interleukin IL-4, IL-5 and IL-13. The non IgE type shows a predominance of a T-helper (Th)1 response with IL-2 and interferon-γ (14).
The manifestation of atopic eczema in elderly is similar to the skin manifestation in elderly, however the lichenification is more common in unaffected areas of elbows and knees. The affected chronic areas are typically the face and the neck and lichenified lesions can be found on the trunk and extremities. The presence of pruriginous papules and nodules is found in some cases (14).
Subtypes of eczema of the elderly were classifed: a geriatric onset, a geriatric recurrence after childhood atopic eczema or recurrence of adult atopic eczema.
As in the children type of atopic eczema associations with IgE allergic status and asthma bronchialeas as well as a lower malignancy were observed in the IgE-allergic atopic eczema type (14).
Concerning the therapy a good prognosis is found in case of a consequent treatment and follow-up. However it was shown that atopic eczema of the elderly rarely comes to a full remission (14).

1.2 Epidemiology

Eczema is the most common pediatric chronic inflammatory skin disorder. Its prevalence is increasing with 15 to 30% of children affected worldwide in the past five decades (1), (6), (19), (20). A stabilization of its prevalence could be observed in developed countries,

whereas an increasing prevalence is observed in emerging countries (4), (21–23). The ISAAC Study, showed differences of the prevalence of eczema between different countries : 2% in Iran, 20% in Scandinavian countries for example (24), (25).

In 70% of the cases the symptoms start in children under five years, with a fluctuation of the symptoms and 50% of the patients have recurrences in adulthood after an onset during childhood (1), (15), (21), (26). A start of the symptomatic at an adult age was found in 10% of the cases reported in hospitals (1).

The prevalence of eczema in adults is decreasing with the increasing age and its one-year prevalence was found in 0,3 to 11,5% worldwide (4), (27–29). However a rise of the prevalence in older patients was found in the last years (27). In Germany, 3% of the adults are affected by eczema (23), (30). Concerning the persistence of atopic eczema, it comes to a remittance of the symptoms in most of the cases after childhood. When a persistency was already observed during childhood, a later onset occurs more often. The symptoms are more severe and a higher persistency is found in the adult age (31).

Tanei and Hasegawa also found an increasing prevalence of eczema in elderly with an estimated prevalence of 1-3% affected patients in industrialised countries. They showed a male predominance, particular patterns and clinic of eczema in elderly (5), (14).

1.3 Pathogenesis

The skin barrier function could be enhanced by the regular use of emollients and, in consequence, prevent the symptoms of eczema (32–34). Thus, it shows the important role of the skin barrier, but what are the pathomechanisms leading to this skin reaction?

1.3.1 The barrier function of the skin

The skin is the biggest organ of the body. It protects the organism as a barrier against external factors and from intrinsic loss of molecules and water through it (35), (36), (37). The skin undergoes a turnover every 28 days (38). The skin is divided in the epidermis, the dermis and the subcutaneous fatty tissue. The epidermis is itself divided in the stratum basale, stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum. The skin contains different types of cells: the keratinocytes, the melanocytes, the Langerhans cells and the Merkel cells (37).

The stratum corneum of the epidermis plays the role of barrier with its anucleated keratinocytes and its intercellular lipid layers (39), (40). The keratinocytes differentiate at

the basal layer and then migrate to the upper layer (39), (41). They are also producing lipids which are extruded in the extracellular space of the stratum corneum. There, omega-hydroxy-ceramides bind covalently to proteins to form the basis for the addition of further three lipid classes: free ceramides, free fatty acids and cholesterol (39), (40), (41). Those lipids are essential to the barrier role against water and water loss. The keratinocytes also produce antimicrobial peptides (AMPs), which are essential for the defence against microbiological attack, form the chemical barrier of the skin and have a role in inflamma t ion reactions of the epidermis (42–47). Each differentiation phase occurs in different layers of the stratum corneum and is dominated by the expression of specific proteins such as filaggr in (FLG) (39), (41), (48), (49). Cell adhesion and permeability barrier are warranted by tight junctions, desmosomes, and adherent junctions (50–53). Further, it was recently shown that the microbiome of the skin also plays a major role in the barrier function as it defends the organism against the intrusion of bacteria through the skin as *Staphylococcus epidermidis* for example (54–60).

FLG is produced by the keratinocytes of the stratum corneum. It provokes the aggregation of keratin filaments, which are processed to amino acids in the upper layers of the stratum corneum. There they play a role in the hydration of the stratum corneum and keeping the skin pH (59).

The interplay of all the factors listed above guarantees a functional skin barrier.

1.3.2 The abnormal skin barrier

Several factors can cause an abnormal skin barrier, for example an immune disbalance, defects of the cell differentiation of the epidermis such as a lack of filaggrin, deficiency of AMPs, altered composition of the lipids of the stratum corneum or altered skin microbio me (35), (37), (66). The pathogenesis of eczema is very complex and not fully understood yet. It probably results of an interaction between environmental and genetical factors, which lead to a skin barrier dysfunction and dysfunction of the immune system on a genetic basis (23). The skin barrier dysfunction may be caused by physiological, biochemical, and immunological defects. There are two theories about the pathomechanism of eczema: eczema occurs first of all because of the barrier dysfunction, or the immune disbalance occurs before the skin barrier defect and both factors lead to the development of the symptoms (60), (62). The barrier dysfunction facilitates the entry of irritants, pathogens, allergens in the skin thus inducing the production of pro-inflammatory cytokines and

chemokines, the increase of TH2-cell response and the decrease of FLG in the skin thus leading to the atopic inflammatory reaction (23). Psychological stress also induces oxidative stress and has repercussions on the skin barrier function (63), (64).

Eczema is differentiated in two phases: the acute and the chronical phase. Both have differe nt immunological responses.

The acute phase of eczema is dominated by an immunological TH-2 response. It is enabled by the presence of non-functional regulatory T-cells, apoptosis of TH-1 cells and the production of the specific cytokine thymic and stromal lymphopoietin (TSLP) by the keratinocytes (23). TSLP is a cytokine produced in the epithelium in response to pro-inflammatory stimuli. It activates the lymphocytes maturation via dendritic cells and activates the TH-2 type inflammation (65). This cytokine is also known for playing a role in the development and exacerbation of asthma. Monoclonal anti-cytokines are already used as a therapy option (66).

Thus, it comes to an increased IgE level in the serum with specific IgE-antibodies against environmental allergens and to an eosinophilia, which are typical for atopic eczema (23).

Allergens are caught by the antigen presenting cells, which then present them to TH-2 cells thus causing a complex cascade of reactions with among others cytokines Interleukin-3 and -4, generating the IgE-production into the skin by B lymphocytes. A further reaction is the entry of eosinophil granulocytes in the skin, provoked by the production of Interleukin-5.

The following chronic eczema reaction is caused by a TH1 cells reaction through an Interferon gamma production, which induces the apoptosis of keratinocytes mediated by the first apoptosis signal receptor (Fas) (23).

The change from acute to chronic eczema is mediated by Interleukin-12 and -4 and the production of TSLP. IL-18 induces with IL-2 the dominance of the TH-2 response, and IL-2 is responsible for the TH1 production of cytokines (23), (67), (68).

Figure 2 represents a simplified schema of the pathomechanism of acute eczema.

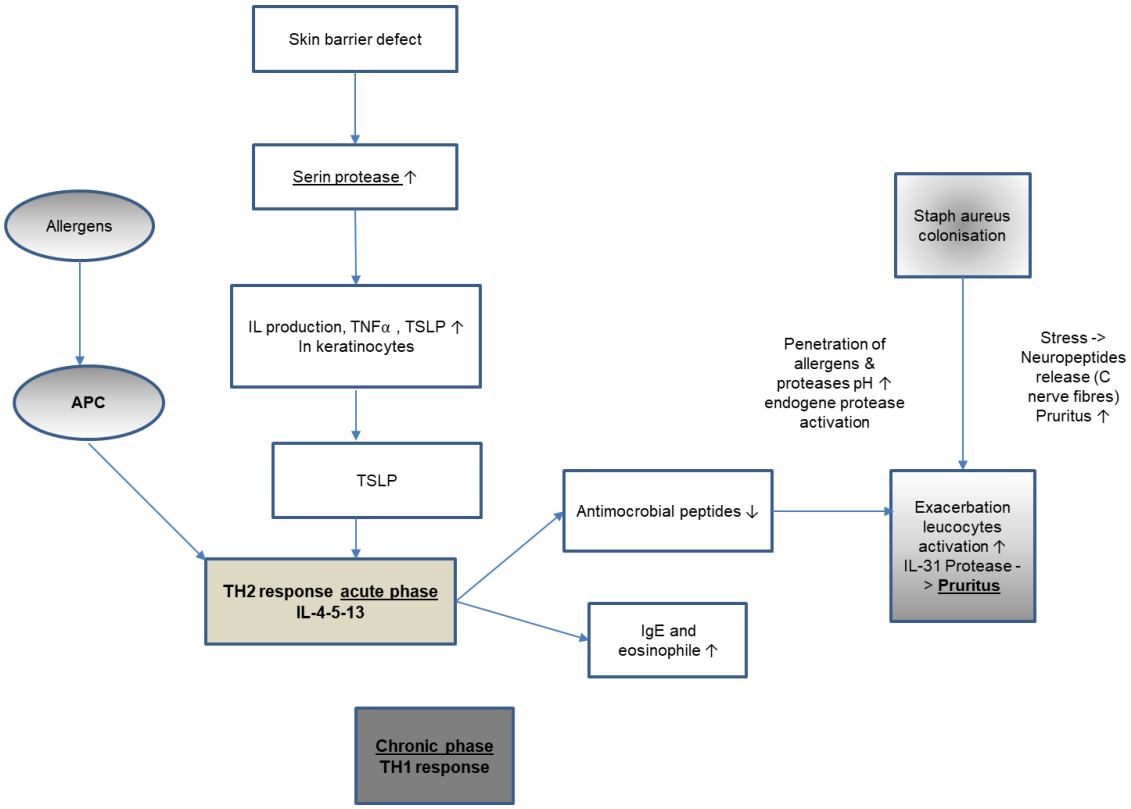

Figure 2 Simplified pathomechanism of eczema. Atopisches Ekzem – Grundlagen und Updates. Fölster-Holst, Schwarz. 2011 UNI-MED Verlag AG, D-28323 Bremen. (APC: Antigene presenting cell, IL: Interleukine, TNFα: Tumor necrosis factor alpha, TSLP: Thymic stromal lymphopoetin , TH: T helper cell, IgE: Immunoglobuline E).

In summary, atopic eczema is caused by an impaired barrier function of the skin due to an interplay of different factors. The loss of terminal skin differentiation products, by mutation of the FLG gen for example, leads to a decrease of the water content of the skin, to enhanced allergen and microbial penetration of the skin and to an increase of the pH and the epidermis (44), (55), (69–71). Increased transepidermal water loss, higher penetration of allergens and microbes through the skin and a decreased skin cohesion are caused by a loss of function of the tight junctions also due to genetic mutation (79), (71). Decreased microbial barrier induces higher skin inflammation, skin infections, death of keratinocytes and the exacerbation of atopic eczema by cutaneus dysbiosis (42), (72–74). A modified epidermal lipid composition and decreased levels of ceramides of the skin increase the rate of staphylococcal infection, the transepidermal water loss and make the skin dryer (35), (75), (76). Alteration of the immune barrier of the skin enable recurrent microbial infection, skin dysbiosis as well as exacerbation of atopic eczema (35), (37), (42), (47), (77).

Another theory is that eczema is caused by an IgE-associated autoimmune response or an intrinsic defect in epithelial cells, which causes the skin barrier dysfunction. Still, the importance of this reaction and its role in the etiology of atopic eczema is unclear (3).

The pathomechanism of eczema of the elderly is not well understood yet. Factors such as immunescence, changes to sex hormone milieu, defects of the barrier function of the skin and digestive system, defects of sweat production and environmental influence were found to be probable causes of eczema of the elederly (14).

1.4 Treatment of eczema

A better understanding of the pathogenesis and pathomechanism of eczema is fundame ntal to provide better treatment options and thus a better quality of life for the patients. Its treatment is based on a step therapy depending on the severity of the symptoms.
The basic therapy options to avoid the development and exacerbation of symptoms is the systematic use of emollients (32–34), a training of the patients, and, if possible, the avoidance of trigger factors (3). For mild eczema, the use of antiseptics, antipruritic drugs and the topical application of corticosteroids (class I and II) and/or calcineurin inhibitors are sufficient. Phototherapy also showed good results as therapy option for eczema in adults (3). Moderate symptoms should be treated with corticosteroids (class II and III) and with calcineurin inhibitors or with both. Severe eczema implicates a systemic treatment with cyclosporine as guideline therapy, or azathioprine, methotrexate, mycophenolatmofetil or newly Biologicals to reduce the immune pathways and the general inflammation (1), (3), (23).

Adult eczema is more therapy refractory to topical treatment and the use of calcineur in inhibitors than the childhood type, so that a more frequent long-term use of systemic oral immunosuppressive drugs is needed (78). Systemic treatment of eczema is not free of side effects. For example, corticosteroids have the following adverse effects: risk of diabetes, arterial hypertension, gastric ulcer, osteoporosis, glaucoma and Cushing syndrome. The side effects of cyclosporine are nephrotoxicity, arterial hypertension, tremors, cephalalgia, paresthesia, nausea, diarrhea, myalgias, hyperkalemia and hypomagnese mia, hyperlipidemia, hypertrichosis and gingival hyperplasia. Methotrexate has side effects such as gastrointestinal disturbance, hematological abnormalities, pulmonary and liver toxicity,

fatigue, cephalalgia. Newly applied Biologicals such as Dupilumab also have adverse effects such as an increased risk of infection, headaches, gastrointestinal disturbances, and injectio n site reactions. Biologicals have specific posologies and are expensive (78).

As listed before, those drugs may have strong side effects and thus have a negative impact on the quality of life of the patients (78). Because of the lack of long-term data on the therapeutic approach of adult eczema worldwide, there are no specific guidelines for the treatment and follow-up of eczema (78). In addition, the safety of systemic therapy is not guaranteed. Therefore, it is of first importance to have a better understanding of the etiology of eczema. Thus it will be possible to provide a more targeted therapy, a better follow- up and avoidance of side effects and so ensure a better quality of life of the patients (23), (78).

1.5 Risk and protective factors

A plethora of studies on children has been conducted on the risk and protective factors of eczema as it is a high psychological and economic burden for the patients, their families, and the health system. Williams et al. showed that families with a child affected by moderate to severe eczema presented higher stress levels than families with children suffering from diabetes mellitus type 1 (79), mainly because of economic costs, care time of eczema, loss of employment and sleep deprivation (25). In consequence, better knowledge of the risk factor and protective factors is needed to enable a better prevention and guarantee a better quality of life for the patients and their families.

Several factors of risk were found for eczema: the possession of pets at home such as cats showed a higher risk of developing symptoms (80). Several triggers were found such as dust mites (81). An exposition to second hand smoke (SHS) during the pregnancy and early childhood might be lead to the development of symptoms and could also be the cause of a late-onset eczema in adults (82). Traffic-related air pollution (TRAP) exposition as well as climatic factors might have an impact on the development of eczema in children and adults (83–85). Atopic eczema is linked with the presence of other atopic diseases such as asthma or atopic rhinitis and atopy in the medical family history might also have an influence on the development of symptoms (1). Genetic factors such as mutations of the FLG gene or mutations of AHR could also be associated with eczema (86), (10). Rönmark et al. found

associations between eczema and childhood daycare, female sex and exposure to gas, dust or fumes (87).
There are also protective factors against eczema for children, such as breast feeding, for example as breast feeding during the four first months of life (88), an equilibrated diet during pregnancy and the breastfeeding time (89). Exposition to sunlight was also found as protective factor (1) and growing up in rural areas (90). A higher socioeconomic status is related to a decreasing prevalence (91).

Only a few studies were conducted on eczema of adults and the elderly, so risk and protective factors have not been researched sufficiently. For example, Tanei and Hasegawa found that males have a higher risk of developing symptoms of atopic eczema (14).
Further associated risk factors might be the food intake, lifestyle, socio and economic status, environment, interior environmental conditions, degree of humidity and temperature and daily biological and chemical materials (92).
In a study conducted in adults, obesity and cardiovascular risk was linked with atopic eczema in North America and Asia but not in Europe (93).
Further studies focusing on the factors of risk and the protective factor of eczema of adults and the elderly are needed.

1.6 Air pollution

Research on the environmental impact on the human skin was already proceeded in several studies, for example the effects of ultraviolet radiation on the skin condition (94–97). Moreover, only a few studies established the impact of outdoor air pollution on the skin (94). The consequences of air pollution on the human organism have been already exposed in a plethora of studies and are one of the most urgent topics for global warming. However, its dermatological issues have been less explored until now (94).

For a better understanding of the subject of the current study, a definition of air pollution is needed.

Organic and non-organic molecules rejected in the atmosphere compose outdoor air pollution. According to the Environmental Protection Agency (EPA) nomenclature, outdoor

air pollution can be classified in different categories of pollutants as follows: gaseous pollutants, persistent organic pollutants, PM, heavy metals and TRAP (94).

This study focuses on the effects of PM and nitrogen oxides on the human skin condition and particularly on eczema.

Nitrogen dioxides, together with ozone, CO and SO2 for example, are classified in the group of gaseous pollutants which are mainly produced by fossil fuel combustion such as combustion of coal, natural gas or fuel (94).

PM is produced by industrial processes and is composed of dust, soil and dusty emission. It is a suspension of solid and liquid drops contained in gas. PM is divided in function of the sizes of the particles, $PM_{2.5}$ with an aerodynamic diameter of 2.5 $\mu m/m^3$ or less, PM_{10} with an aerodynamic diameter of 10 $\mu m/m^3$ or less and PM_{coarse} with a diameter from 2.5 to 10 $\mu m/m^3$ (94). PM is known to play a "Trojan horse" role by carrying other noxious molecules on their surface (such as bacteria, metals, carcinogen particles) (94,98).

Persistent organic pollutants are derived from pesticides, dioxins and dioxin- like polychlorinated biphenyls and are emitted during industrial processes. They are known for their long-lasting bioaccumulation in the organism. However, their concentration is lower in the air than in the soil (94).

Another type of pollutants responsible of the outdoor air pollution are the heavy metals, which are produced by waste incineration, cement, iron and steel production or volcanic eruptions.

The last category which is the one explored in this particular study is the TRAP which is released by vehicle emissions of diesel and gasoline. The main pollutants included in this group are CO2, NOx, CO, VOCs, PM (94).

1.7 Eczema & Traffic-Related Air Pollution

As already explained above, worldwide the prevalence of eczema in children and adults has undergone radical changes in the last decades, making its environmental etiology probable as genetics cannot be influenced that quickly. Additionally, investigations, which were conducted on the prevalence of atopic eczema in migrant population in comparison to its prevalence in their origin countries have shown great differences between the groups. Chinese immigrant's children who moved to Hawaii had a higher prevalence than the Chinese prevalence (99), and black Caribbean children born in London also had a higher prevalence than those living in their home country (100), (101) .

Effects of Traffic-Related Air Pollution (TRAP) are well known on the human organism, such as cardio-respiratory morbidity and mortality, are probably due to acute pulmonar y inflammation and oxidative stress (64), (102), (103). In vivo and in vitro studies have shown that PM can deteriorate the skin and only a few studies explored the impact of TRAP on the skin condition. Valacchi et al. demonstrated rising oxidative reaction of the stratum corneum and stress responses due to activation of particular pathways in the epidermis after an exposition to ozone on mouse skin (104–106). Larrieu et al. investigated the short- time effects of TRAP on the human organism. In their study, they explored the probability of a visit to a physician after an increase of TRAP levels. The risk of visit was higher for a skin rash during the three first days after an increase of PM_{10} and ozone levels in Bordeaux (103). Mancebo et al. investigated how the ambient air pollution might influence the skin condition via the generation of free radicals, the induction of inflammatory reaction cascade causing the skin barrier dysfunction, the activation of the Aryl hydrocarbon Receptor (AHR) and by the alteration of the skin microbiome (94).

1.7.1 In children

Most of the investigations on the etiology of eczema have been assessed in studies focusing on children. These studies found that environmental (7), (107) as well as genetic (108), (109) factors are involved in the pathogenesis of eczema. An increase of eczema has been seen in developing countries while a plateau or even a decrease was reached in industrialised countries, thus sustaining the environmental etiology of eczema in children (25).

Specifically, TRAP has been linked to eczema in children in some studies (7–9). The strongest associations were found for Nitrogen Dioxide (NO_2), particulate matter (PM) of an aerodynamic diameter of 2.5 µm/m3 or less ($PM_{2.5}$) and ultrafine particles (9). In fact, an analysis on American children showed that higher levels of NO_2, SO_2 and SO_3 had a relationship with higher atopic eczema prevalence. Additionally, moderate-severe atopic eczema was associated with higher levels of NO_3 and OC in warm and cold months and with $PM_{2.5}$ only in cold months (9). A seasonal impact on atopic eczema (higher in winter and spring) was also found with a higher prevalence of the disease among boys (110). Another study leads to the conclusion, that long-term exposure to $PM_{2.5}$ and NO_2 may conduct to the development of atopic eczema, high levels of $PM_{2.5}$, PM_{10} and ultrafine particles are associated with exacerbation of the symptomatic in children (111). The impact of indoor air pollution exposure could be observed by toluene on the exacerbation of atopic eczema (112)

and a reduction of the symptomatic in children was shown after reducing the indoor levels of PM_{10} (113). Analysis of air pollution exposure of women in the preconceptional phase and during pregnancy and exposure to air pollutants in early childhood was also conducted. An impact on children's development of atopic eczema and allergies in relationship with the trimesters of pregnancy when the exposure occurred could be established (114), (115). However, several studies did not show any effect of TRAP on eczema in children (91,116,117).

1.7.2 In adults & elderly

Silverberg et al. conducted a study on the impact of environmental factors on allergies and eczema. There they showed that the birthplace of the patients plays a role in the developme nt of eczema. In fact, the foreigners born in the United-States of America had a higher risk of developing eczema than those born abroad (91). This makes the environmental etiology of eczema probable.

Most of the studies about the association between air pollution and eczema were conducted on children as shown above (7–9). A few studies investigated the effects of air pollution on adult eczema. A research group in Turkey showed that occupational exposure as the use of wood for house heating augmented the risk of development of eczema (118). Rönmark et al. found a positive association between occupational exposure to gas, dust or fumes and symptoms of eczema (87).

Only rare studies were conducted on the impact of TRAP on eczema. One of them, conducted by Pujades-Rodriguez et al. found no association between exposure to TRAP and eczema (119). However, two Chinese studies have shown a relationship between exposure to TRAP and adult eczema, one of them demonstrating short-time effects of TRAP and eczema (92), and the second based on the impact of PM2.5 on eczema of the adult (120).

To our knowledge, there is no study investigating the impact of TRAP on newly developed eczema of the elderly till now.

1.8 Genetics & eczema

As explained above, eczema is the results of a complex interplay of environmental and genetic factors. An ethnic influence was already shown in the development of eczema (6). A study group explored the influence of ethnicity in the occurrence of eczema and it showed that the different cytokines and cells involved are dependent on the origin of the patients,

thus making the genetic origin of eczema plausible (121). But further research on its etiology is needed as it is not fully understood yet. Noda et al also found ethnic differences in adult atopic eczema in dependence on the origin of the patients. For this study, a group of 27 Asian patients aged from 18 to 74 years and including five females was compared to a group of 25 European American patients aged from 23 to 79 years and including nine females. Most of the atopic eczema patients suffered from extrinsic atopic eczema (24/27 and 14/25). The Asian group counted a higher percentage of extrinsic atopic eczema than the European American group. In the Asian group, a better demarcation of the lesions, more promine nt scaling and lichenification, an increased epidermal hyperplasia and a larger number of Ki67+ cells from the basal layer of the epidermis were found, as well as increased counts of dendritic cells. The Asian type was characterized by higher Th17-related cytokines inductio n and IL-17 induced markers, as well as a higher Th22 cytokine up-regulation, thus inducing different gen pathways than the European type (122).

1.8.1 Genetics and eczema and TRAP

AHR is ligand-activated transcription factor which binds to enhancer gene sequences (123), (124), so entering the cell nucleus and forming a complex with its nuclear translocator (125) to induce the expression of specific target genes for carcinogenesis, immunosuppression and tumour development (126–128) as well as cell proliferation, differentiation (11) and organ development (12), (13).

Single-nucleotide polymorphisms (SNPs) are the most common genetic variation in the human genome (128) and they occur in the region encoding the transactivation domain of the AHR gene (129). Aftabi et al. explored the AHR polymorphisms caused by the substitution of arginine to lysine at position 554 of the acidic subdomain of the transactivation domain and they showed that it might affect the interaction of AHR with its transactivation domain (108), (109). The role of those mutation was examined in several studies, some showing significant association with cancer for example (131–135). Though, other studies found no evidence for such associations (136–138).

As already defined in the parts above, eczema is an inflammatory skin disease. Totlandsdal et al. identified polycyclic aromatic hydrocarbons (PAHs) as a cause of PM-induced inflammation (138). The PAHs enter easily into the stratum corneum of the skin due to their lipophilic structure and they remain there on a long-term basis (10). PAHs bind to AHR, a

ligand-activated transcription factor. There it activates the expression of genes producing enzymes responsible for detoxification (139). It also increases the release of TH2 type cytokines, but the exact mechanism is still unclear (139). Recent studies showed that topical application of air pollutants, including PAHs, to mouse skin induced the development of atopic eczema like skin symptoms in mice. The described response was associated with an increased AHR-dependent production of the neurotrophic factor Artemin, which codes for epidermal hyper-innervation. Subsequently, an increase of nerve fibers of the skin, pruritus, and the further development of an atopic eczema-like skin phenotype followed the AHR activation. Hidaka et al. observed a correlation between AHR and the expression of AHR in the skin of patients suffering from atopic eczema (10).

As already described in the part about the pathogenesis of eczema, FLG is a fundame ntal protein for the epidermal barrier function. After being degraded into free amino acids, it functions like a barrier in the stratum corneum. Its role is to maintain the pH of the skin and to retain water in the body. Thus it maintains the osmolarity of the stratum corneum (59).
Decreased levels of FLG lead to altered shape of the corneocytes of the skin, increasing skin inflammation and reduction of the skin barrier function, and thus facilitating the entry of irritants and allergens in the skin. Decreased levels of FLG are observed in patients suffering from atopic eczema caused by an overexpression of inflammatory cytokines such as IL-4, IL-13,-IL25, IL-17 and IL-22 (140). Further proteins necessary for the skin barrier functio n (loricrin and involucrin) are also down-regulated due to the inflammatory cascade (57).
A plethora of studies has shown that mutations of the FLG gene conduct to a skin barrier defect and are a predisposing factor for the development of atopic eczema (108), (141). Early-onset atopic eczema and persisting atopic eczema are particularly influenced by mutations of FLG (86). An association between FLG mutation and atopic eczema was shown in 50% of the patients (108) . Additionally, 40% of patients with mutation of FLG do not have atopic eczema (86).
Decreased levels of FLG were also shown in patients suffering from atopic eczema who did not have a genetic mutation of FLG (140). The skin sensitization to allergens through the dysfunctional skin barrier is the start of the atopic march. FLG could be used as predictive marker for the atopic march (142).
Other studies also indicate that mutations of the FLG gene and other genes could influe nce the severity of the symptoms of the skin disease (86).

A new strategy for the therapy of atopic eczema was found via an upregulation of the FLG expression in mice (59).

The present study is the first, to our knowledge, to explore the AHR activation in TRAP-induced eczema in humans.

1.9 Objective

Due to demographic changes it is estimated that the percentage of people aged 60 years and over will have doubled or tripled by 2050 (143). In our ageing civilization the question of geriatric diseases will constantly gain more importance and become a dilemma for the healthcare system with major economic repercussions. The skin is the human organis m's largest organ and has a barrier role against external aggressions. Thus, geriatric dermatological diseases are particularly important in the modern world, because of their medical, psychological and social consequences. They have direct effects on the quality of life and self-esteem as the skin is the most visible organ. In consequence elderly persons with dermatological diseases have a higher risk of depression (144). Worldwide, skin diseases are the fourth burden caused by nonfatal diseases and so have a major impact on the quality of life of the population (145).

Living in industrialized areas exposes the organism in general and the skin in particular to all kind of pollutants. The SALIA Study (Study on the influence of Air pollution on Lung function, Inflammation and Ageing) started in 1985 and was conducted on women (aged 55 at that time) from the Ruhr district and two non-industrial small-towns from the Muensterland (northern from the Ruhr district). The Ruhr district in Germany represents a range of exposures to airborne particulate matter from traffic and steel and coal industr ies and was the area the most polluted with soot among European cities during the 70s and 80s (146). In the SALIA study, associations between air pollution, allergic diseases and the skin condition were studied.

They are only few publications about elderly eczema in spite of its increasing prevalence in the last years in developed countries (147). Eczema affects the quality of life and the symptoms may lead to a feeling of uneasiness, financial difficulties, occupational limitat io ns and social isolation of the patients (148), (149). Therefore, it is important to further explore

the etiology and the pathomechanism of the development of eczema in elderly populatio ns. The skin barrier defect hypothesis of the physiopathology of atopic eczema makes the environmental theory credible, in which air pollutants are seen as factors provoking atopic eczema or causing its exacerbation.

The objective of the study was to explore the incidence and prevalence of eczema symptoms in a cohort of elderly women. We further investigated the associations between long- term exposure to TRAP and eczema. Additionally, we examined the role of mediator of AHR polymorphisms in the development of TRAP-induced eczema in elderly women.

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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 aryllhydrocarbon 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. NO_2: 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 (Barber 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-Rodriguez 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 (Haftek 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 (Aftahi 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; Rauh 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 (Kramer 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 ($PM_{2.5-10}$). 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

Table 1
Characteristics of the study population.

	SALIA cohort
N	824
Age [years], mean ± SD	72.5 ± 3.0
Educational status (years of schooling), n (%)	
< 10 years	148 (17.7%)
10 years	404 (48.4%)
> 10 years	279 (33.5%)
BMI [kg/m²], mean ± SD	27.3 ± 4.5
Smoking behaviour, n (%)	
Current	23 (2.8%)
Ex-smokers	143 (17.1%)
Never	668 (80.1%)
Second hand smoke (SHS), n (%)	503 (60.3%)
Heating with fossil fuels, n (%)	137 (16.4%)
Participants that did not move within the study period, n (%)	718 (86.1%)

Abbreviation: SD: standard deviation.

exposure bias.

Since the AHR signaling pathway was proposed to be involved in the association between TRAP and eczema (Hidaka et al., 2016), we investigated the interaction between genotypes of the functional *AHR* polymorphism rs2066853 (dominant model: AA and AG vs. GG) (Afshari et al., 2016; Harper et al., 2002) and TRAP on eczema.

In a sensitivity analysis we explored the interaction between passive smoking, TRAP and the incidence of eczema and ever symptoms of eczema.

P-Values < 0.05 were interpreted as statistically significant for both main effects and interactions.

All statistical analyses were conducted using the computer software R x64 3.3.0.

3. Results

3.1. Description of the study population

The characteristics of the study participants are shown in Table 1. The mean age of the 824 women at follow-up was 73.5 years ± 3.0 (with a range from 66.7 to 79.8). Most of the participants left school after 10 years (medium educational status (48.4%)) and 17.7% had a lower educational status. The mean body mass index (BMI) was 27.3 ± 4.5. The majority (80.1%) had never smoked, 2.8% were current smokers, however, 60.3% had been exposed to second hand smoke (SHS) previously. 16.4% used fossil fuel heating.

As shown in Table 2, 15.9% of the participants reported ever

Table 2
Prevalence and incidence of eczema in the SALIA cohort.

	n/N (%)
Symptoms of eczema	
Ever	122/832 (15.9%)
Prevalence*	73/832 (8.8%)
Incidence after age 55	46/760 (7.9%)
Age at the first time (years, min-max)	46.8 (1.0-78.0)
Atopic eczema disease	
Self-reported	42/824 (5.1%)
Doctor-diagnosed	44/824 (5.3%)
Self-reported or doctor-diagnosed*	55/816 (6.7%)
Incidence after age 55	9/790 (1.1%)
Age at the first time (years, min-max)	35.0 (1.0-71.0)

* Itchy rash at any time in the last 12 months.

* 11/816 (1.3%) participants had only self-reported atopic eczema and 13/816 (1.6%) participants had only a doctor-diagnosed atopic eczema. 31/816 (3.8%) participants had self-reported and doctor-diagnosed atopic eczema.

Table 3
TRAP exposures.

	Baseline (1985–1994)		Follow-up (2008–2009)	
	Mean (IQR)	Min-max	Mean (IQR)	Min-max
NO_{2a} (µg/m³)	37.36 (14.69)	20.26–84.14	28.64 (9.71)	19.66–70.34
NO_x (µg/m³)	70.31 (43.18)	26.80–216.08	46.70 (22.58)	23.88–138.72
$PM_{2.5}$ (µg/m³)	32.11 (4.69)	21.97–41.31	17.88 (1.86)	15.59–21.98
PM_{10} (µg/m³)	48.37 (6.77)	32.24–65.06	26.92 (2.22)	23.88–33.83
PM_{coarse} (µg/m³)	17.27 (4.67)	5.33–27.75	9.58 (1.83)	2.05–14.80
$PM_{2.5\ absorbance}$ (10^{-5}/m)	2.68 (1.01)	1.33–6.39	1.49 (0.42)	0.97–4.00

Abbreviations: IQR: interquartile range, NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 µm/m³ or less; PM_{10}: PM of an aerodynamic diameter of 10 µm/m³ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 µm/m³; $PM_{2.5\ absorbance}$: absorbance of $PM_{2.5}$. Differences between the average exposure levels between baseline and follow-up investigation were all highly significant (Schikowski et al., 2015a,b).

symptoms of eczema. The prevalence of symptoms of eczema was 8.8% and its incidence after the age of 55 years was 7.9%. The mean age at which the women developed symptoms of eczema for the first time was 46.8 years with a large range from 1 to 78 years (SD = 21.7).

Reports of atopic eczema disease were less frequent (6.7% self-reported and/or doctor-diagnosed) and the mean age of symptom development was younger (35 years). Incidence of atopic eczema disease after age 55 was only 1.1%.

Table 3 shows the exposure to NO_2, NO_x, $PM_{2.5}$, PM_{10}, PM_{coarse} and $PM_{2.5\ absorbance}$ from the baseline (1985–1994) and the follow-up (2008–2009) investigation. A decrease of all pollutants between baseline and follow up examination can be observed.

3.2. Association between TRAP and symptoms of eczema

The association between TRAP exposure at baseline and ever symptoms of eczema was not significant, but consistently positive for all considered pollutants (Table 4, Fig. 1).

Incidence of eczema symptoms after the age of 55 was positively and significantly associated with nearly all pollutants at baseline (Table 4, Fig. 1). The incidence of eczema symptoms showed an OR of 1.49 per 14.69 µg/m³ (IQR) increase in NO_2 (p = 0.03), OR = 1.50 per 43.18 µg/m³ (IQR) increase in NOx (p = 0.021), OR = 1.45 per 4.69 µg/m³ (IQR) increase in $PM_{2.5}$ (p = 0.019), OR = 1.36 per 6.77 µg/m³ (IQR) increase in PM_{10} (p = 0.047) and OR = 1.45 per 1.03 10^{-5}/m (IQR) increase in $PM_{2.5\ absorbance}$ (p = 0.012) (Table 4, Fig. 1). These associations were even stronger after excluding participants that moved between baseline and follow-up investigation (Table E1) and remained robust in the crude models, which were only adjusted for age (Table E2). As shown in table E2, the association between TRAP and the incidence of eczema after the age of 55 were significant for almost all the air pollutants. The association between TRAP exposure at follow-up examination and the prevalence of eczema symptoms was not statistically significant, but consistently positive (Tables 4 and E1).

3.3. Association between TRAP and atopic eczema disease

A further analysis on the association between TRAP exposure at baseline and atopic eczema disease (self-reported and/or doctor-diagnosed) was conducted. The associations were consistently positive, but not statistically significant (Tables 4 and E1). Due to small numbers, an analysis of the association between TRAP and incidence of atopic eczema disease could not be conducted.

Table 4
Association between TRAP and eczema.

Exposures						
	NO_2	NO_x	$PM_{2.5}$	PM_{10}	PM_{coarse}	$PM_{2.5\ absorbance}$
Symptoms of eczema						
Ever	1.21 (0.92, 1.59) p = 0.173	1.18 (0.9, 1.54) p = 0.221	1.25 (0.97, 1.5) p = 0.093	1.16 (0.93, 1.45) p = 0.183	1.2 (0.91, 1.57) p = 0.191	1.21 (0.97, 1.51) p = 0.085
Incidence after age 55	**1.69 (1.04, 2.15)** **p = 0.036**	**1.5 (1.06, 2.13)** **p = 0.021**	**1.45 (1.06, 1.98)** **p = 0.019**	**1.36 (1.00, 1.83)** **p = 0.047**	1.20 (0.83, 1.9) p = 0.189	**1.45 (1.09, 1.94)** **p = 0.012**
Prevalence [a]	1.17 (0.86, 1.58) p = 0.319	1.14 (0.84, 1.55) p = 0.386	1.3 (0.93, 1.8) p = 0.124	1.14 (0.86, 1.47) p = 0.323	1.08 (0.81, 1.44) p = 0.587	1.16 (0.96, 1.44) p = 0.119
Atopic eczema disease						
Ever	1.15 (0.77, 1.71) p = 0.497	1.1 (0.76, 1.63) p = 0.586	1.33 (0.95, 1.81) p = 0.094	1.23 (0.93, 1.8) p = 0.069	1.4 (0.95, 2.05) p = 0.086	1.3 (0.96, 1.77) p = 0.088

Odds ratio with 95% confidence interval per interquartile range of baseline TRAP. Adjusted for: age, educational status, body mass index (BMI), smoking habits (smoking and SHS) and indoor air pollution by heating with fossil fuels. [a]: Itchy rash at any time in the last 12 months. The associations with the prevalence were estimated with TRAP exposures at follow-up investigation instead of baseline exposures because this phenotype describes the presence of current eczema symptoms. Abbreviations: NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 μm/m³ or less; PM_{10}: PM of an aerodynamic diameter of 10 μm/m³ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 μm/m³; $PM_{2.5\ absorbance}$: absorbance of $PM_{2.5}$.
Bold: Significant associations (p-value < 0.05).

3.4. Interaction between *AHR* and *TRAP* on incidence of eczema

We investigated the impact of a functional *AHR* polymorphism rs2066853 on the association between TRAP and incidence of eczema symptoms. In total, the SNP was genotyped in a subgroup of 484 women and 20% of these (95/484) were carriers of at least one minor allele (A). Minor allele carriers were more susceptible to TRAP-induced eczema symptoms than homozygote major allele carriers (Table 5). The highest ORs were found for minor allele carriers with an increase of 43.18 μg/m³ (IQR) in NO_x (OR = 3.75 (95%-CI: 1.14–12.41)), this can be contrasted with the much lower ORs in homozygote major allele carriers (OR = 1.34 (95%-CI: 0.76–2.36)). However, none of the gene-environment interactions was significant (e.g. p-value for interaction = 0.122 for NO_x).

3.5. Interaction between secondhand smoking and TRAP on eczema

In a further sensitivity analysis we explored the interaction between ETS and TRAP on the incidence of eczema symptoms after the age of 55 years (supplementary table E4) and on ever having symptoms of eczema (supplementary table E5). None of the ETS-TRAP interactions were significant.

4. Discussion

Based on a long-term follow-up of the SALIA study cohort, we here investigated eczema in elderly women. Our major findings are a high prevalence and incidence of eczema symptoms in women over 55 years of age, as well as significant associations between exposure to air pollutants and the incidence of eczema symptoms after an age of 55. Interestingly, we also observed that minor allele carriers of the *AHR* polymorphism rs2066853 were more susceptible to TRAP-induced incidence of eczema symptoms thus indicating that the AHR signaling pathway might be involved in this association.

In general, prevalence of eczema decreases by age (Rönmark et al., 2012; Williams, 2005). In our study population of elderly German women, we observed a prevalence of current eczema symptoms of 8.8% and 15.9% had ever symptoms of eczema. The observed prevalence is in

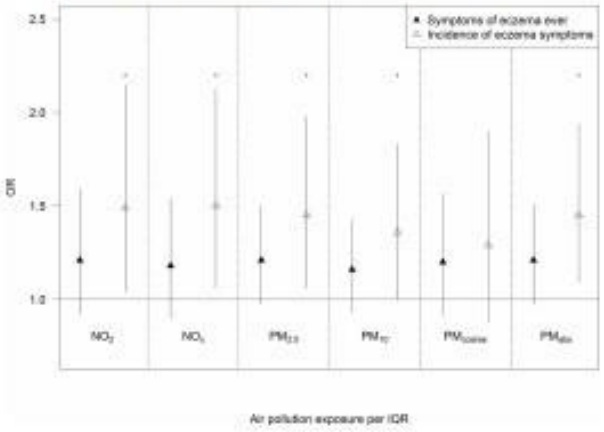

Fig. 1. Association between air pollution and eczema symptoms. Odds ratio with 95% confidence interval per interquartile range of air pollution at baseline investigation. Adjusted for: age, educational status, body mass index (BMI), smoking habits (smoking and SHS) and indoor air pollution by heating with fossil fuels.
Abbreviations: NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 μm/m³ or less; PM_{10}: PM of an aerodynamic diameter of 10 μm/m³ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 μm/m³; $PM_{2.5}$ absorbance: absorbance of $PM_{2.5}$; *P-value < 0.05; **P-value < 0.01; ***P-value < 0.001.

Table 5
Gene-environment interaction between the AHR polymorphism rs2066853 and TRAP on the incidence of eczema symptoms after the age of 55 years (n = 484).

TRAP exposure	Stratified by genotype	OR (95%-CI)	p-value	p-value for interaction
NO_2	no minor allele	1.36 (0.77, 2.39)	0.294	0.273
	one or two minor alleles	2.68 (0.88, 8.19)	0.084	
NO_x	no minor allele	1.34 (0.76, 2.36)	0.317	0.122
	one or two minor alleles	**3.75 (1.34, 12.48)**	**0.030**	
$PM_{2.5}$	no minor allele	1.41 (0.89, 2.25)	0.142	0.356
	one or two minor alleles	2.64 (0.84, 8.24)	0.095	
PM_{10}	no minor allele	1.25 (0.86, 1.83)	0.245	0.467
	one or two minor alleles	1.72 (0.77, 3.84)	0.184	
PM coarse	no minor allele	0.98 (0.55, 1.77)	0.954	0.146
	one or two minor alleles	2.54 (0.8, 8.03)	0.113	
$PM_{2.5}$ absorbance	no minor allele	1.36 (0.90, 2.05)	0.139	0.741
	one or two minor alleles	1.55 (0.81, 2.98)	0.187	

OR, 95%-confidence intervals (CIs) and p-values are given for the association between baseline TRAP exposure (per increase of IQR) and incidence of eczema stratified by the number of minor alleles in rs2066853. In addition, p-values are given for the interaction term.
NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 μm/m³ or less; PM_{10}: PM of an aerodynamic diameter of 10 μm/m³ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 μm/m³; $PM_{2.5\ absorbance}$: absorbance of $PM_{2.5}$.
All associations adjusted for: age, educational status, body mass index (BMI), smoking habits (smoking and SHS) and indoor air pollution by heating with fossil fuels.
Bold: Significant associations (p-value < 0.05).

line with Rönmark et al. (2012) who reported a prevalence of 9.3% in men and women aged 66–75 years from Sweden (Rönmark et al., 2012). The authors further showed that 10.5% of the study population had ever symptoms of eczema, which is much less than in our cohort (15.9%). However, that difference might be caused by differences between men and women, because some studies could show that women have a higher eczema risk than men (Rönmark et al., 2012).

The general opinion is that eczema is primarily a disease of childhood developing during the first two years of life (Williams, 2005). Virtually nothing is known about the incidence of newly developed eczema at an older age. Here, we report a high incidence of eczema with a very late onset after the age of 55 years of 7.9%.

Most of the publications related to eczema were focused on children, where associations between TRAP exposure and eczema could be established (Brunekreef et al., 2009; Deng et al., 2016; Kathuria and Silverberg, 2016; Krämer et al., 2009; Lee et al., 2008). There are only few studies on the association between TRAP and eczema in adults (Li et al., 2016; Pujades-Rodriguez et al., 2009; Tang et al., 2017). Pujades-Rodriguez et al. (2009) performed a population-based cross-sectional study of 2644 Nottingham adults aged 18–70 years, in which they did not find any evidence for an association between TRAP and eczema (Pujades-Rodriguez et al., 2009). However, they used a very rough definition of eczema ("Have you ever had eczema or any kind of skin rash?") and only used cross-sectional data. We here report strongest effects for the incidence of eczema symptoms in our elderly population. Therefore, our findings do not contradict those of Pujades-Rodriguez et al. (2009).

To the best of our knowledge, there are only two studies, both based on Chinese populations, showing an association between TRAP and eczema in adults. The first study was a time-series study using daily outpatient visits between 2007 and 2011 (1826 days) from Huashan Hospital in Shanghai, China (Li et al., 2016), demonstrating short-time effects of TRAP on eczema. A major limitation of that study was that they could not adjust for individual confounders (such as sex, age, smoking, socio-economic status). The second, very recent Chinese study was based on cross-sectional data from the National Health Insurance Research Database in Taiwan (1023 cases and 4092 age- and sex-matched controls) (Tang et al., 2017). The authors report an association between particulate matter < 2.5 μm in diameter or the Pollutant Standards Index (the highest sub-index of the concentrations of 5 main air pollutants after transformation) and adult atopic eczema. In that study, all associations were adjusted for potential confounders. Using the National Health Insurance Data Base, however, the authors used a very strict definition of eczema because only adult patients with atopic eczema who sought medical advice were defined as cases and they had no information regarding the age at first diagnosis. Therefore, our study is, to the best of our knowledge, the first population-based cohort study showing an association between TRAP and incidence of eczema in elderly women.

We further found that the well-known functional *AHR* polymorphism rs2066853 (Aftabi et al., 2016; Harper et al., 2002) might influence the susceptibility for the development of eczema symptoms after exposure to TRAP in our elderly population. However, possibly due to the small sample size, the gene-environment interaction was not significant (e.g. p-value for interaction = 0.122 for NO_x) and needs to be replicated in larger cohorts. Eczema is an inflammatory skin disease. Polycyclic aromatic hydrocarbons (PAHs) have been identified as one of the main causes of PM-induced inflammation (Totlandsdal et al., 2012). The lipophilic PAHs may easily penetrate into the stratum corneum and this results in their long-term retention in the skin (Hidaka et al., 2016). PAHs exert their biological effects via binding to the ligand-activated transcription factor AHR, which activates the expression of genes encoding detoxification enzymes (Fujii-Kuriyama and Mimura, 2005). Recently, topical application of air pollutants to mouse skin including PAHs was reported to induce the development of atopic eczema like skin symptoms. This response was associated with an AHR-dependent increase in the production of the neurotrophic factor Artemin, a subsequent increase in the number of nerve fibers, pruritus, and the development of an atopic-eczema like skin phenotype (Hidaka et al., 2016). The present study is first to provide evidence in humans that air-pollution and eczema might be linked via AHR activation.

We would like to mention, however, that the role of AHR signaling in the pathogenesis of atopic eczema might be janus-faced as proposed previously by Haarmann-Stemmann et al. (2015). Accordingly, AHR activation by pollutants might cause disease worsening through the mechanisms mentioned above, but AHR activation by coal tar treatment may be beneficial since it might help to improve skin barrier function by increasing filaggrin expression (van den Bogaard et al., 2013).

In the present study, we have chosen to use (a version modified for adults) of the ISAAC questionnaire because it previously was proven to be suitable to assess the incidence and prevalence of eczema in children and its association with TRAP (Krämer et al., 2009). Accordingly, the ISAAC study is the biggest and only allergy study that has taken a global approach and the ISAAC questionnaire is currently considered to be the method of choice to assess the incidence and prevalence of eczema at population level (Pearce et al., 2009).

The quality of the data obtained by this questionnaire relies on the

accuracy of the participants' declarations. Participants with a higher educational level are more familiar with medical terms. This may have led to an underreporting of atopic eczema disease in less educated people (Krämer et al., 1998). In addition, participants with a lower social status live in more exposed areas (Bravo et al., 2016; Pinault et al., 2016) which might have led to an underestimation of the associations with TRAP.

Further limitations of the study are associated with the LUR model. The quality of the LUR models depends on the number and the quality of the predictor variables, the number of monitoring stations and their geographical disposition. Another limitation of the method is that temporality is not taken into consideration in LUR modeling. (Choi et al., 2017; Beelen et al., 2013).

Another limitation of our study is that the main outcome, i.e. eczema in the elderly, was assessed by a questionnaire. The dermatological questionnaire was developed in collaboration with dermatologists, but it has not been validated in other elderly populations.

We are fully aware of the fact that this approach has a number of shortcomings. For example, eczema as assessed by questionnaire may include atopic eczema, non-atopic eczema, but also eczema due to exsiccation, or allergic/toxic contact eczema or even seborrhoic eczema. At this stage, we are not able to differentiate between these different forms of eczema. Further research is needed to clarify the characteristics of eczema in the elderly. Presence of specific IgE antibodies, allergic comorbidities (e.g. asthma, atopic rhinitis) and filaggrin mutations might be used to distinguish between atopic and non-atopic eczema (Johansson et al., 2015) and transepidermal water loss measurements might be used to clarify the role of a decreased skin barrier function in the elderly (Ramos-e-Silva et al., 2012).

Another limitation is that ultrafine particle (UFP) concentrations were not included in the pollutants concentrations assessments. Some studies indicated that UFP (< 100 nm) may have a bigger impact on health than particles with a bigger size (Franck et al., 2011) and an influence of UFP on the exacerbation of atopic eczema has been shown in children (Song et al., 2011). However, UFP are generated, as is NO_2, by the combustion process, and therefore UFP and NO_2 are likely to correlate closely (Seaton and Dennekamp, 2003). Therefore, assuming NO_2 and NO_x being a proxy for UFP, these findings are in line with our study in which we found the strongest associations with NO_2 and NO_x.

In conclusion, our results indicate a high incidence for eczema symptoms in elderly women, which is associated with chronic exposure to air pollutants, and is possibly mediated by AHR.

As the world population continues to age, particularly in developing countries, the consequences of TRAP on health in the elderly in general and skin diseases in this growing part of the population in particular will become a major medical, sociological and financial issue with consequences on the quality of life of the concerned persons. Thus, further studies on the pathogenesis of eczema in the elderly are warranted.

Conflict of interest

All authors declare they have no actual or potential competing financial interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijheh.2018.06.002.

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3 DISCUSSION

The SALIA cohort study was based on a long-term follow-up observation of 834 women aged 55 years at the baseline investigation (1985) and living in the high industrialized Ruhr area and two northern counties of the Münsterland. In this study, the effects of TRAP were explored on human health. This particular study is based on eczema in adults. The clinica l follow-up examination occurred in 2008-2009 and assessed the presence of eczema in the participants using a questionnaire based on the International Study of Asthma and Allergies in Childhood (ISAAC). Furthermore, a genetic analysis was conducted in 484 of the participants to explore SNPs of the AHR gene. The TRAP exposures were determined with Land-use Regression (LUR) models and were calculated for NO_2, NO_x, $PM_{2.5}$, PM_{10}, PM_{coarse} and $PM_{2.5\ absorbance}$. These associations were calculated with logistic regression models which were adjusted for age, educational status, body mass index (BMI), smoking behaviour, indoor air pollution by heating by fossil fuels and changing address during the study period. The SALIA population showed a high prevalence (8.8%) and incidence (7.9%) of eczema. A further objective was the investigation of the influence of TRAP on eczema. Significa nt associations were found between air pollutants such as NO_2, NO_x, $PM_{2.5}$, PM_{10} and $PM_{2.5\ absorbance}$ and the incidence of eczema after an age of 55 years in the participants. These associations were also high for the same air pollutants in the crude model, which was only adjusted for the age of the participants. In the sensitivity analysis, where we excluded the participants who moved during the study period, the associations were even higher for the incidence of eczema after an age of 55 years apart from PM_{10} which showed no significa nce. No positive associations were found between TRAP exposure and the prevalence of eczema. Furthermore, no evidence of the association between TRAP and atopic eczema was found in the cohort, probably due to the small size of the sample. In a second step we explored the interaction between AHR polymorphism rs2066853 and TRAP, which might lead to the development of eczema. In the study, carriers of minor allele of AHR might have a higher risk of developing eczema. With our results, the theory of the mediation of the AHR pathway for TRAP-induced eczema is plausible, but further research is necessary in this topic.

Eczema is a common relapsing inflammatory dermatological disease characterized by dry skin, pruritus and multiple forms of eczematous dermatitis with specific predilection areas

depending of the subtype (1). It mainly affects children, but recurrences into adulthood were observed in 50% of the cases, so that it might be a lifelong disease (150). Adult onsets of eczema are also possible (6). Its prevalence is increasing in the last decades, not only in children, but it was also observed in adults and in elderly (1), (6), (14)(151). The etiology of eczema is complex and is the result of an interaction between genetics and environme ntal factors causing defects of the skin barrier (37), (57). Quality of life is affected mainly by sleep disturbance, because of the chronification of the symptoms and the comorbidities of eczema. The symptoms also shave negative repercussions on the ability to work (29), (152), (153). Furthermore, a cohort study in the United States showed that most of the reported cases were not diagnosed by a physician, causing an undertreatment of the symptoms (29) .

Lately, associations of atopic eczema with systemic diseases were discussed. In fact, eczema may not only be a dermatological disease but a systemic disease as correlations with cardiovascular diseases were found (93), (154). Still, further research is needed to assess the etiology of eczema. The presence of immune activation, due to eczema, in the peripheral blood might enable systemic infections, links with neuropsychiatric diseases and cancer need to be further explored (93), (155). One of the pathomechanisms of eczema might be caused by mutation of the AHR gene (10). AHR is a ligand-activated transcription factor which codes for xenobiotic response inducing carcinogenesis, immunosuppression and tumour development (126), (127), (156) as well as cell proliferation and differentiation (11) and organ development (12), (13). It was also identified as an ozone sensor, inducing the expression of CYP1 enzymes, which metabolize toxic factors and activate procarcinoge ns (94), (157).

A special report of the World Health Organization (WHO) about air pollution assessed that one in nine deaths was due to TRAP exposure in 2018, thus making it the major environmental factor of risk for diseases. Next to the well-known complications of the cardio-respiratory system due to ambient TRAP exposure, milder effects of air pollutants are also present on the human organism. Over 80% of the persons living in cities are exposed to air pollution levels above the WHO limits; 4.2 million deaths every year are a result of exposure to air pollution. The latest results of the WHO investigations on air quality showed that nine out of ten persons breathe polluted air worldwide (158). Supposing an environmental origin of eczema and observing an increase of TRAP exposure worldwide and knowing the demographic changes in emerging countries, it is essential to explore the

etiology of eczema and its treatments to avoid an expansion of the symptomatic in the concerned countries.

As written above, a high incidence (7.9%) and prevalence (8.8%) were found in the current study. Eczema is a dermatological disease with a prevalence of 20% in children. It mostly occurs during the two first years of life and then remises in most of the cases. However, 50% of the patients have recurrences till adulthood (1). The prevalence decreases with the age of the patients. (6). Rönmark et al. conducted a study on the prevalence of eczema, its risk factors and its association with diseases of the respiratory tract in a population of subjects aged between 16 and 75 years in Sweden. There they found a prevalence of 9.3% of eczema in men and women of an age of 66 to 75 years. In the SALIA cohort, 15.9% of the participants had ever had symptoms of eczema, which is more than in Rönmarks study with a percentage of 10.5 % of the participants. However, the cohort was constituted of women and men, which could explain the difference between the respective findings in the two cohorts. In fact, Rönmark found out that women have a higher risk of developing eczema than men (27). Vinding et al. found a one-year prevalence of eczema of 0.3 to 11.5% of adults worldwide, which correlates with the results of our study with a prevalence of 8.8% of the participants, knowing that the Ruhr area is very polluted due to the high industrialization of the region (4). Tanei and Hasegawa found a prevalence of 1 to 3 % of elderly persons with atopic eczema in industrialized countries (14). In our study we did not calculate the prevalence of elderly with atopic eczema because of the low number of participants with atopic eczema at an age over 55 years, only 1.1% of the SALIA participants. In their study, they explored the factors of risk of elderly eczema and found that men had a higher risk of developing atopic eczema in a higher age, so that further research on a bigger study cohort with both male and female participants is needed (14).
The latest studies have shown that eczema might have ethnic differences in the pathomechanism and the patterns so that the different origins of the study cohort should be kept in mind while comparing groups with different ethnicities (122).

A new stratification of eczema was settled, according to the age of first appearance and based on the differences of the symptomatic. In the new classification four groups were distinguished: the infantile, childhood, adolescent/adult and the elderly type. Each category

is defined by different skin symptoms (14). In fact, each type is categorized by variant skin lesions, affected areas and probability to become chronic for example (6) . The impact of TRAP on the development and exacerbation of symptoms of eczema was already shown in children (7–9), (159). The influence of TRAP on eczema was also demonstrated during the pregnancy and the first months of life in children (114), (115). With the increasing prevalence of eczema also in adults and supposing the environmental repercussion on the symptomatic it is important to investigate the effects of TRAP in the adult and elderly type of eczema. Research on adult onset atopic eczema is rare. However indoor air pollut ion exposure, climatic situation and exposure to outdoor and indoor air pollutants seem to have an impact on adults‘ development of atopic dermatitis (27), (160). Till now only a few research groups investigated the association between TRAP and eczema in adults.

Pujades-Rodriguez et al. investigated the association between TRAP and eczema among allergic diseases. In a study cohort of 2644 18 to 70 years old adults (50% of them were men) in the United-Kingdom, they explored the impact of nitrogen dioxide (NO_2) and the distance between the home address and closest main road on the participants' health. Eczema was assessed in an interview- led questionnaire and was defined as 'ever eczema' 'Have you ever had eczema or any kind of skin rash?'. The statistical analysis was adjusted for age, sex, smoking status and the socio-economic status of the participants. No evidence of the impact of NO_2 and living close to a major road on eczema was found in this study cohort (119). In their study, Pujades-Rodriguez et al. used a rough definition of eczema in comparison with the questionnaire used in our study to assess eczema.

Tang et al. also investigated the repercussion of exposure to TRAP on the development of atopic eczema in adults. Therefore, they explored a group of 1023 Taiwanese patients aged from 20 to over 65 years with atopic eczema in a cross-sectional study. The study population presents a female predominance of 57%. The patients were chosen from a randomized population of 1 000 000 patients after being diagnosed of atopic eczema by a dermatologist, an allergologist or a pediatrician or after a hospital admission. The air pollutants which were explored in the study were SO_2, NO_2, O_3, CO, $PM_{2.5}$ and PM_{10}. The statistical analysis was adjusted for sex, age, levels of urbanization, income and exposure to air pollutants. This study group found significant positive associations between $PM_{2.5}$ and the development of atopic eczema in adults (120). In this study, the cohort was restricted to adults who required

medical advice, thus limiting the study population as it was found that most of the patients suffering from eczema do no visit physicians for the symptoms (29).

Another research group studied the effects of ambient air pollution and meteorologica l factors on eczema in outpatients in China. There they explored the short-term effects of PM_{10}, SO_2 and NO_2 and air temperature and humidity on daily outpatients visits between 2007 and 2011 (1826 days) in Huashan Hospital in Shanghai because of skin condition. There they demonstrated short-term effects of air pollutants on eczema. Increased levels of the measured air pollutants were positively associated with visits for eczema. However, the statistical analysis was not adjusted for confounders such as age, sex, socioeconomic status (92).

The current study is, to our knowledge, the first exploring the effects of TRAP on elderly eczema and therefore further investigations are needed for a better understanding of those reactions.

A further objective of the study was to explore the influence of the *AHR* polymorphis m rs2066853 on the susceptibility to develop symptoms of eczema after an exposure to TRAP in the SALIA cohort. Aftabi et al. performed investigations on the effects of the AHR gene polymorphism on an *in silico* analysis (130). AHR is a helix- loop-helix transcription factor which binds to enhancer gene sequences after being activated by ligands (123), (124). After activation, it enters the cell nucleus and forms a complex with its nuclear translocator (125) and then binds to specific target genes for xenobiotic response inducing carcinogenes is, immunosuppression and tumor development (126), (127),(156) as well as cell prolifera t ion and differentiation (11) and organ development (12), (13). SNPs are the most common genetic variation in the human genome (128) and they occur in the region encoding the transactivation domain of the AHR gene (129). The polymorphism that was explored in the current study causes an arginine to lysine substitution at position 554 of the acidic subdomain of the transactivation domain (129,130) and it might affect the interaction of AHR with its transactivation domain. The role of the SNPs mutation the AHR gene was investigated in a plethora of studies, some showing significant association with cancer for example (131–135) while other did not find any association between the SNPs mutation and abnormalities (136–138). The gene-environment interaction was not significant in the current study (e.g. p-value for interaction = 0.122 for NO_x), probably due to the small sample size and needs to be replicated in larger cohorts.

Hidaka et al. conducted research on the effects of AHR on the development of eczema in transgenic mice. Polycyclic aromatic hydrocarbons (PAHs) was identified as a cause of PM-induced inflammation (138), as it enters easily into the stratum corneum of the skin due to its lipophilic structure and remains in the skin on a long-term basis (10). There it binds to AHR, and so activates the expression of genes encoding detoxification enzymes (139). Topical application of air pollutants, including PAHs, to mouse skin induces the development of atopic eczema like skin symptoms in mice, so increasing an AHR-dependent production of the neurotrophic factor Artemin, the number of nerve fibers, pruritus, and the further development of an atopic eczema-like skin phenotype (10).

Mancebo et al. investigated the effects of air pollutants on the skin condition and the skin reactions to TRAP (94). They found out that exposure to TRAP induces the generation of free radicals, of the inflammatory cascade, activation of AHR and alterations of the microflora of the skin. In this part we will focus on the AHR activation which we also investigated in the current study. AHR is a ligand-activated transcription factor located in the cytosol of various skin cells. It regulates the cell proliferation, inflammation reactions and the melanogenesis. When ligands bind to AHR it provokes the translocation to the cell nucleus and binding to specific DNA. The genes activated by AHR include detoxifica t ion enzymes such as cytochrome P450. Those reactions might be an explanation of the TRAP-mediated reaction of the skin. Other studies investigated how AHR activation could influence the development of inflammatory cutaneous lesions. Eczema with pruritus and atopic eczema-like inflammation reactions were observed in transgenic mice with activated AHR without ligand stimulation. A gene profiling of the skin of those mice showed a significant increase of genes associated with inflammatory reactions (161).

However, AHR-activation might not only have negative impacts on the skin condition via TRAP but could also improve the skin barrier function. Van de Boogard et al. showed that AHR could also be activated by coal and thus increase the epidermal and protein expression, accelerate the epidermal differentiation. An increase of FLG expression in the skin and in lesional atopic eczema skin was also observed. After application of coal tar on skin equivalents stimulated by specific TH2 cytokines, a reduction of the spongiosis and the apoptosis of the cells could be reached. Coal tar induces a normalization of the

histopathological hallmarks in skin equivalents probably due to anti-oxidative response (162).

The exact mechanisms of AHR-mutations and activation via TRAP in the pathogenesis of eczema need to be further investigated to provide a better understanding of its etiology and give better therapy options for the symptoms.

It is fundamental to know the limitations of each study to permit further precise research of the topic. A limitation of this study is that the assessment of eczema is based on the ISAAC questionnaire, which was already used for the investigation of the prevalence and the incidence of eczema in children (7). The ISAAC study is the biggest study on allergy worldwide and the ISAAC questionnaire is the method of choice to assess allergies and atopic diseases, so that it should be used to asses eczema and its prevalence and incidence in populations of children and teenagers (163). The questionnaire for the SALIA study was developed with dermatologists but it was not validated in adult and elderly population before.

Furthermore, as the questionnaire is based on self-reported declarations, the results rely on the adequacy of the response of the participants. Krämer et al. have explored the cultural and educational impact on the accuracy of the given answers concerning atopic eczema. They have shown an underreporting of atopic eczema in relationship with the socio-economic status of the parents of the affected children (164). The questionnaire asked the follow ing questions: 'Have you ever had a skin rash which was lasting over six months?', 'Did the skin rash occur in the last 12 months?', 'How old were you when it occurred for the first time?', 'Did you ever have atopic or endogenous eczema or *Neurodermitis*?' and 'Was atopic eczema or *Neurodermitis* ever diagnosed by a physician?'. As listed above, eczema was described in different terms, which may influence the validity of the reported answers (164). Furthermore, a underreporting of the eczema was observed in German parents more frequently than in English families, suggesting that the German terms to describe the disease are related with a higher severity of the disease than the name in English (164).
The SALIA questionnaire was divided in subgroups about different topics. One part was focusing on skin diseases and diseases of the respiratory system, another part examined the medical history of the participants and more precisely illnesses which were diagnosed by a physician. Interestingly, only 3.8% of the participants reported an atopic eczema and a

physician-diagnosed atopic eczema. A small number of the women reported atopic eczema (6.7% of the cohort), but the reported answers are not completely correspondent between the different parts of the questionnaire.

Eczema is a skin disease complicated to diagnose, especially in adult and elderly population because of its various differential diagnosis such as allergic contact dermatitis and cutaneous t-cell lymphoma (6). The skin lesions present in eczema of adults and elderly persons show different patterns than those habitually present in eczema of children, also making the diagnosis more complex (152). Eczema is divided in subgroups including atopic eczema, non-atopic eczema, eczema due to exsiccation, allergic or toxic contact eczema, or seborrheic eczema but it is not clear which type was reported by the participants as the declaration are only based on self-reported answers with no verifications.

For a better distinction between the different types of eczema reported by the participants of the cohort, specific IgE-antibodies, allergic comorbidities (asthma, atopic rhinitis, food allergies) and the FLG status of the women should be researched (165). Thus, it will be possible to differentiate between atopic and non-atopic eczema, which was not fully possible in this current study. Eczema might be caused by a decrease of the barrier function of the skin, which can be measured by transepidermal water loss and it could be interesting to examine the loss of the barrier function of the skin in eczema of the elderly (166).

Tanei and Hasegawa found that eczema of the elderly is characterized by different patterns of the skin lesions than in other types of eczema (5), (14). A new stratification of eczema was assessed in dependence of the age of occurrence (6). It would be interesting to define the areas affected by the symptoms to be able to document the symptoms and rank them more precisely.

Also other skin disorders and systemic diseases might cause a pruritus and side-effects of the drugs taken by the participants might also cause a pruritic skin rash (14). This should also be kept in mind in regard of the differential diagnosis of eczema in an elderly study population.

The study population is composed exclusively of women of the Ruhr region. The men of the region had high occupational exposure to air pollutants because of the coal mining and the steel industry (167). However, Tanei and Hasegawa found a male predominance in atopic eczema of the elderly, so that examination of the impact of TRAP on eczema of the elderly in a mixed-gender study population is needed (14).

Some studies showed that persons with a lower socioeconomic status live in areas, which are more exposed to TRAP (168), (169). The TRAP exposure of some of the women of the SALIA cohort with a lower socioeconomic status might have been underestimated.

A further limitation of the study is that the TRAP exposure was only conducted on PM. The concentrations of ultrafine particle (UFP) were not included in the exposure measurements. In fact, some studies indicated that UFP, particles smaller than 100nm, may have bigger impacts on human health. Franck et al. have shown the repercussions of TRAP on health and compared those effects according to the size of the particles, UFP, $PM_{2.5}$, and PM_{10}. There they found significant increase of cardiovascular illnesses and particularly hypertens ive crises shortly after an increase of UFP concentrations in the air (170). The association between UFP and atopic eczema was examined in school children. In a study population of 41 children aged from 8 to 12 years, the short-time effects of TRAP including UFP were investigated on the exacerbation of atopic eczema for 67 consecutive days. An increase of UFP concentrations was associated with higher pruritus of atopic eczema in those children, thus showing that concentrations of UFP might be linked with an exacerbation of the symptoms in children (171).
However, Seaton and Dennekamp demonstrated that UFP and NO_2 are generated by combustion processes and therefore might closely correlate when their emissions result from a common source (172). In our study, the strongest associations between TRAP and eczema were found for NO_2 (odds ratio of 1.49 with a confidence interval between 1.04 and 2.15, p-value of 0.030) and NO_x (odds ratio of 1.5 with a confidence interval between 1.06 and 2.13, p-value of 0.021) and the incidence of eczema after an age of 55 years. Thus, those findings are in line with our findings if assuming NO_2 and NO_x as a proxy of UFP.

Another limitation of the study regarding the assessment of the exposure to air pollutants is that it did not include the distance to major roads. A Korean research group examined the effects of TRAP on atopic eczema in 14765 children living in Seoul with a sex distribut ion of 50% of girls in the study cohort. The study group counted a high prevalence of eczema with 36.2% of the children assessed with the ISAAC questionnaire. The exposure to TRAP was calculated by measuring the proximity of the address to major roads and the density of major roads in the area where the participants lived. This study indicated that children who lived in areas near to major roads might have a higher risk of developing atopic eczema (173). However, Pujades-Rodriguez et al. investigated the impacts of TRAP on allergic

diseases including eczema. In statistical analysis they examined the impact of living close to major roads (distance to the closest major road) and they found no association between exposure to TRAP and eczema (119).

Other limitations of the study are associated with the method of calculation of the exposure to TRAP, the LUR model. The quality of the measurements computed by LUR models depend on several factors. The number and the quality of the predictor variables used for the models influence the results, and the number and geographical situation such as traffic density and meteorological factors for example of the monitoring stations have an impact on the results. Besides, LUR models do not include temporality, so that only cross-sectional analyses are possible using this kind of models. It is not possible to evaluate the evolution of the exposure concentrations and consequently the association of variation of TRAP exposure on the development and exacerbation of the symptoms of eczema in the cohort (174), (175).

A strength of this study is that it is based on a long-term observation of TRAP effects on human health, on the same well-characterized study population in a time range of 24 years. The health state evolution of the participants could thus be well followed, allowing a consequent follow-up of the womens' condition. The study participants who moved during the study period where excluded from the logistic model in a sensitivity analysis, where even stronger effects of TRAP on the incidence of eczema after an age of 55 years could be observed. Most of the SALIA participants were housewives so that occupational bias such as exposures to air pollutants at workplace could be avoided.

Several research groups examined eczema and its risk factor and found higher eczema prevalence in women, so that the SALIA cohort represents a risk group, better to investigate the environmental impact in eczema (91), (27).

Another advantage is that we made use of the most state of the art air pollution estimates based on LUR regression models developed during the ESCAPE study (174), (175). Eczema was assessed using the ISAAC-study questionnaire which is well established and the method of choice in investigations of allergies and atopic diseases in children (163). Though, it was not used and validated in adult population yet so that further research and validation of the method are needed.

CONCLUSION

This study aimed to investigate the epidemiology of eczema in a cohort of elderly women, to examine the associations between TRAP exposure and eczema in elderly, and to study the role of AHR polymorphisms in the mechanisms of TRAP-induced eczema in humans.

Eczema is a chronic relapsing inflammatory skin condition with high pruritus which affects all age categories with a higher prevalence in children (1). The diagnostic of eczema of adults and elderly persons is difficult because of the difference in the patterns of the lesions in comparison with the pediatric type (15), (152). Its etiology is complex and genetic and environmental factors might play a role in the development of the symptoms, probably due to an impaired skin barrier function (35), (37), (57).

Eczema is associated with a high socio-economic burden as there is no possibility to control the disease on long-term (6). A better knowledge of the pathogenesis of atopic eczema and a division of its classification into subgroups will make a better patients care possible for the symptoms (6).

A follow-up of the patients with biomarkers will enable a better diagnosis of the subgroups and thus more specific therapy options as target therapy will be available. Developing screening methods will make possible to identify patients with a high risk of developing severe eczema. And thus, making possible to find an early diagnosis, in early stadiums, an early beginning of the therapy, a better follow-up of the patients and to control the individ ua l sensitization. It could also be a predictor of the therapeutic response and a prognosis marker (6). Thus a prevention of symptoms and exacerbation of eczema will be probable to a certain degree, making the quality of life of the patients better (25).

Associations between eczema and other comorbidities such as cardiovascular diseases and cancer have been newly hypothesized. Therefore a better knowledge of the differe nt subtypes of eczema and their different pathomechanisms is fundamental to prevent complications of eczema and to provide better treatment with less side-effects for the patients (93), (154), (155).

Exposure to ambient air pollution is rising worldwide since the beginning of the industrialization era. Historically, the first description of atopic rhinitis was made in England during the 19th century. But it is only at the end of the 20th century that associations were

hypothesized between exposure to ambient air pollution and the development of allergic diseases and particularly eczema (176).

The impact of TRAP on health is now well researched and higher morbidities and mortalit y due to an increase of TRAP exposure is well assessed, mainly affecting the cardiorespirator y system (64), (102), (103). According to the reports of WHO about air Pollution, 24% of the stroke deaths might be related to the exposure to ambient air pollution. But the role of TRAP on the development of skin disorders is not clear yet.

It was shown that PM can damage the skin barrier function via releasing free radicals through oxidative stress reaction and so inducing the inflammatory cascade, activation of AHR and alterations of the microflora of the skin (94). The increase of the inflammatory cascade plays a role in the development and exacerbation of skin disorders including inflammatory skin reactions, skin cancers and skin aging (111).

Knowing the impact of TRAP on human health, WHO assessed guidelines to limit the ambient TRAP concentration worldwide, for example, PM_{10} concentration should not exceed an annual mean of 20 $\mu g/m^3$ and a 24h- mean of 50 $\mu g/m^3$ (111).

This study supports first indications showing a high prevalence and incidence of eczema in elderly women, which was probably related to long-term exposure to TRAP. A mediation of AHR in the development of TRAP-induced eczema might be probable. In ageing populatio ns and regarding the modernization of the world (especially in developing countries), the consequences of increasing air pollution on health and geriatric dermatological questions will become a major medical, sociological and financial issue with consequences on the quality of life of the concerned persons. Thus, further examination of the pathogenesis and pathomechanisms of elderly eczema, including the environmental impacts and the role of genetics, are necessary.

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SUPPLEMENTARY MATERIAL

Table E1: Association between air pollution and eczema excluding participants that moved within the study period

	Exposures					
	NO_2	**NO_x**	**$PM_{2.5}$**	**PM_{10}**	**PM_{coarse}**	**$PM_{2.5\ absorbance}$**
Symptoms of eczema						
Ever	1.24 (0.93, 1.64) p=0.138	1.17 (0.90, 1.54) p=0.248	1.17 (0.93, 1.47) p=0.183	1.13 (0.88, 1.44) p=0.334	1.18 (0.88, 1.60) p=0.274	1.24 (0.97, 1.57) p=0.083
Incidence after age 55	**1.58 (1.08, 2.30) p=0.018**	**1.54 (1.08, 2.19) p=0. 0.017**	**1.48 (1.06, 2.07) p= 0.021**	1.41 (1.00, 2.00) p=0.051	1.37 (0.90, 2.11) p=0.145	**1.55 (1.12, 2.14) p=0.008**
Prevalence [a]	1.15 (0.85, 1.55) p=0.380	1.11 (0.81, 1.52) p=0.504	1.29 (0.91, 1.82) p=0.149	1.13 (0.87, 1.47) p=0.373	1.02 (0.76, 1.38) p=0.882	1.14 (0.92, 1.43) p=0.223
Atopic eczema disease						
Ever	1.22 (0.82, 1.82) p=0.317	1.18 (0.81, 1.71) p=0.387	1.37 (0.99, 1.91) p=0.056	1.39 (0.99, 1.94) p=0.059	1.41 (0.94, 2.12) p=0.099	1.36 (0.99, 1.87) p=0.059

Odds ratio with 95% confidence interval per interquartile range of baseline air pollution exposure. Adjusted for: age, educational status, body mass index (BMI), smoking habits (smoking and SHS) and indoor air pollution by heating with fossil fuels. [a]: Itchy rash at any time in the last 12 months. The associations with the prevalence were estimated with air pollution exposures at follow-up investigation instead of baseline exposures because this phenotype describes the presence of current eczema symptoms.

Abbreviations: NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 µm/m³ or less; PM_{10}: PM of an aerodynamic diameter of 10 µm/m³ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 µm/m³; $PM_{2.5\ absorbance}$: absorbance of $PM_{2.5}$;

Bold: Significant associations (p-value < 0.05)

Table E2: Association between air pollution and eczema crude effects

	Exposures					
	NO_2	**NO_x**	**$PM_{2.5}$**	**PM_{10}**	**PM_{coarse}**	**$PM_{2.5\ absorbance}$**
Symptoms of eczema						
Ever	1.22 (0.94, 1.60) p=0.139	1.21 (0.93, 1.56) p=0.153	1.23 (0.99, 1.53) p=0.058	1.17 (0.95, 1.44) p=0.143	1.20 (0.92, 1.57) p=0.168	1.20 (0.97, 1.49) p=0.090
Incidence after age 55	**1.47 (1.04, 2.08) p=0.030**	**1.51 (1.08, 2.11) p=0.016**	**1.46 (1.08, 1.97) p=0.015**	**1.34 (1.01, 1.80) p=0.045**	1.27 (0.87, 1.84) p=0.210	**1.38 (1.05, 1.82) p=0.022**
Prevalence	1.16 (0.86, 1.56) p=0.323	1.15 (0.86, 1.55) p=0.344	1.27 (0.92, 1.76) p=0.145	1.10 (0.86, 1.41) p=0.444	1.06 (0.80, 1.40) p=0.703	1.14 (0.94, 1.39) p=0.198
Atopic eczema disease						
Ever	1.18 (0.82, 1.72) p=0.370	1.17 (0.81, 1.68) p=0.400	1.31 (0.96, 1.80) p=0.087	1.31 (0.97, 1.76) p=0.077	1.36 (0.94, 1.97) p=0.101	1.27 (0.95, 1.69) p=0.112

Odds ratio with 95% confidence interval per interquartile range of baseline air pollution.

[a]: Itchy rash at any time in the last 12 months. The associations with the prevalence were estimated with air pollution exposures at follow-up investigation instead of baseline exposures because this phenotype describes the presence of current eczema symptoms.

Abbreviations: NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 $\mu m/m^3$ or less; PM_{10}: PM of an aerodynamic diameter of 10 $\mu m/m^3$ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 $\mu m/m^3$; $PM_{2.5\ absorbance}$: absorbance of $PM_{2.5}$;

All associations adjusted for age.

Bold: Significant associations (p-value < 0.05)

Table E3 Gene-environment interaction between the *AHR* polymorphism rs2066853 and air pollution on the incidence of eczema symptoms after the age of 55 years (n=484).

Air pollution exposure	Stratified by genotype	OR (95%-CI)	p-value	p-value for interaction
NO_2	no minor allele	1.29 (0.76-2.19)	0.352	0.286
	one or two minor alleles	2.4 (0.84-6.85)	0.101	0.286
NO_x	no minor allele	1.27 (0.75-2.16)	0.376	0.098
	one or two minor alleles	**3.63 (1.16-11.33)**	**0.026**	0.098
$PM_{2.5}$	no minor allele	1.39 (0.9-2.15)	0.142	0.357
	one or two minor alleles	2.32 (0.84-6.45)	0.106	0.357
PM_{10}	no minor allele	1.23 (0.86-1.75)	0.262	0.576
	one or two minor alleles	1.52 (0.75-3.09)	0.244	0.576
PM coarse	no minor allele	0.98 (0.56-1.7)	0.929	0.196
	one or two minor alleles	2.14 (0.73-6.3)	0.166	0.196
$PM_{2.5}$ absorbance	no minor allele	1.3 (0.89-1.89)	0.18	0.825
	one or two minor alleles	1.41 (0.75-2.65)	0.289	0.825

OR, 95%-confidence intervals (CIs) and p-values are given for the association between baseline air pollution exposure (per increase of IQR) and incidence of eczema stratified by the number of minor alleles in rs2066853. In addition, p-values are given for the interaction term.
NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 $\mu m/m^3$ or less; PM_{10}: PM of an aerodynamic diameter of 10 $\mu m/m^3$ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 $\mu m/m^3$; $PM_{2.5\ absorbance}$:absorbance of $PM_{2.5}$. All associations adjusted for age.
Bold: Significant associations (p-value < 0.05).

Table E4 Secondhand smoking-environment interaction between SHS and air pollution on the incidence of eczema symptoms after the age of 55 years (n=484).

TRAP exposure	SHS exposure	OR (95%-CI)	p-value	p-value for interaction
	no SHS	1.49 (0.77-2.91)	0.24	
NO_2	SHS	**1.49 (1.01-2.22)**	**0.046**	0.999
	no SHS	1.56 (0.82-2.97)	0.177	
NO_x	SHS	**1.49 (1.01-2.2)**	**0.045**	0.899
	no SHS	1.24 (0.76-2)	0.392	
$PM_{2.5}$	SHS	**1.55 (1.09-2.19)**	**0.014**	0.393
	no SHS	1.17 (0.73-1.86)	0.508	
PM_{10}	SHS	**1.43 (1.03-1.99)**	**0.033**	0.416
	no SHS	0.96 (0.49-1.91)	0.912	
PM coarse	SHS	1.42 (0.93-2.15)	0.101	0.298
	no SHS	1.4 (0.81-2.42)	0.227	
$PM_{2.5}$ absorbance	SHS	**1.47 (1.06-2.04)**	**0.02**	0.873

OR, 95%-confidence intervals (CIs) and p-values are given for the association between baseline air pollution exposure (per increase of IQR) and incidence of eczema stratified by the number of minor alleles in rs2066853. In addition, p-values are given for the interaction term. NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 µm/m³ or less; PM_{10}: PM of an aerodynamic diameter of 10 µm/m³ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 µm/m³; $PM_{2.5\ absorbance}$: absorbance of $PM_{2.5}$

All associations adjusted for: age, educational status, body mass index (BMI) and indoor air pollution by heating with fossil fuels.

Bold: Significant associations (p-value < 0.05)

Table E5 Secondhand smoking -environment interaction between SHS and air pollution on ever symptoms of eczema symptoms (n=484).

TRAP exposure	SHS exposure	OR (95%-CI)	p-value	p-value for interaction
	no SHS	1.19 (0.72-1.96)	0.501	
NO_2	SHS	1.22 (0.9-1.64)	0.2	0.932
	no SHS	1.21 (0.74-1.97)	0.445	
NO_x	SHS	1.17 (0.87-1.58)	0.303	0.911
	no SHS	1.22 (0.87-1.71)	0.253	
$PM_{2.5}$	SHS	1.2 (0.94-1.53)	0.139	0.94
	no SHS	1.13 (0.82-1.56)	0.466	
PM_{10}	SHS	1.17 (0.92-1.47)	0.197	0.849
	no SHS	1.04 (0.66-1.65)	0.859	
PM coarse	SHS	1.26 (0.93-1.7)	0.133	0.463
	no SHS	1.13 (0.74-1.73)	0.562	
$PM_{2.5}$ absorbance	SHS	1.24 (0.97-1.58)	0.087	0.714

OR, 95%-confidence intervals (CIs) and p-values are given for the association between baseline air pollution exposure (per increase of IQR) and incidence of eczema st ratified by the number of minor alleles in rs2066853. In addition, p-values are given for the interaction term.

NO_2: Nitrogen Dioxide; NO_x: Nitrogen Oxides; $PM_{2.5}$: particulate matter (PM) of an aerodynamic diameter of 2.5 µm/m³ or less; PM_{10}: PM of an aerodynamic diameter of 10 µm/m³ or less; PM_{coarse}: PM of a diameter from 2.5 to 10 µm/m³; $PM_{2.5\ absorbance}$: absorbance of $PM_{2.5}$

All associations adjusted for: age, educational status, body mass index (BMI) and indoor air pollution by heating with fossil fuels.

Bold: Significant associations (p-value < 0.05)

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Invictus

By William Ernest Henley

Out of the night that covers me,
Black as the pit from pole to pole,
I thank whatever gods may be
For my unconquerable soul.

In the fell clutch of circumstance
I have not winced nor cried aloud.
Under the bludgeonings of chance
My head is bloody, but unbowed.

Beyond this place of wrath and tears
Looms but the Horror of the shade,
And yet the menace of the years
Finds and shall find me unafraid.

It matters not how strait the gate,
How charged with punishments the scroll,
I am the master of my fate,
I am the captain of my soul.