

# Association between ambient air pollution and development and persistence of atopic and non-atopic eczema in a cohort of adults

Diego Lopez Peralta<sup>1</sup>, caroline lodge<sup>1</sup>, Dinh Bui<sup>2</sup>, Nilakshi Waidyatillake<sup>1</sup>, John Su<sup>3</sup>, Jennifer Perret<sup>1</sup>, Luke Knibbs<sup>4</sup>, Bircan Erbas<sup>5</sup>, Paul Thomas<sup>6</sup>, Garun Hamilton<sup>3</sup>, Bruce Thompson<sup>7</sup>, Michael Abramson<sup>3</sup>, Haydn Walters<sup>1</sup>, Shyamali Dharmage<sup>1</sup>, Gayan Bowatte<sup>1</sup>, and Adrian Lowe<sup>1</sup>

<sup>1</sup>The University of Melbourne School of Population and Global Health

<sup>2</sup>The University of Melbourne

<sup>3</sup>Monash University

<sup>4</sup>The University of Queensland School of Public Health

<sup>5</sup>La Trobe University

<sup>6</sup>University of New South Wales

<sup>7</sup>Swinburne University of Technology

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## Abstract

**Background:** There is limited information on risk factors for eczema in adults. Recent evidence suggests that air pollution may be associated with increased incidence of eczema in adults. We aimed to assess this possible association. **Methods:** Ambient air pollution exposures (distance from a major road, nitrogen dioxide [NO<sub>2</sub>], fine particulate matter with an aerodynamic diameter [?]2.5 µm [PM<sub>2.5</sub>]) were assessed for the residential address of Tasmanian Longitudinal Health Study participants at ages 43 and 53 years. Eczema incidence (onset after age 43 years), prevalence (at 53 years) and persistence were assessed from surveys, while sensitisation was assessed using skin prick tests. The presence or absence of eczema and sensitisation was classified into four groups: no atopy or eczema, atopy alone, non-atopic eczema, and atopic eczema. Adjusted logistic and multinomial regression models were fitted to estimate associations between ambient air pollution and eczema, and interaction by sex was assessed. **Results:** Of 3153 participants in both follow ups, 2369 had valid skin prick tests. For males, a 2.3 ppb increase in baseline NO<sub>2</sub> was associated with increased risk of prevalent eczema (OR=1.15 [95%CI 0.98-1.36]), both non-atopic (OR=1.39 [1.02-1.90]) and atopic eczema (OR=1.26 [1.00-1.59]). These associations were not seen in females (P for interaction=0.08, <0.01). For both sexes, a 1.6 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> exposure at follow-up was associated with increased odds of aeroallergen sensitisation (OR=1.15 [1.03-1.30]). **Conclusion:** Increased exposure to residential ambient air pollutants was associated with an increased risk of eczema, only in males, and aeroallergen sensitisation in both genders.

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Diego J. Lopez<sup>1</sup>, Caroline J. Lodge<sup>1</sup>, Dinh S. Bui<sup>1</sup>, Nilakshi T Waidyatillake<sup>1</sup>, John C. Su<sup>2,3</sup>, Jenny L Perret<sup>1</sup>, Luke D. Knibbs<sup>4</sup>, Bircan Erbas<sup>5</sup>, Paul S. Thomas<sup>6</sup>, Garun S. Hamilton<sup>7,8</sup>, Bruce R Thompson<sup>9</sup>, Michael J Abramson<sup>10</sup>, E. Haydn Walters<sup>1,11</sup>, Shyamali Dharmage<sup>1</sup>, Gayan Bowatte<sup>1</sup>, Adrian J. Lowe<sup>1</sup>

1 Allergy and Lung Health Unit, the University of Melbourne, Melbourne, VIC, Australia

- 2 Department of Dermatology, Monash University, Eastern Health and the Population allergy group,
- 3 Murdoch Children's Research Institute, University of Melbourne, Melbourne, VIC, Australia
- 4 Faculty of Medicine, School of Public Health, The University of Queensland, Herston, QLD, Australia
- 5 School of Psychology and Public Health, La Trobe University, Melbourne, VIC
- 6 Prince of Wales' Clinical School, and Mechanisms of Disease and Translational Research, Faculty of Medicine, UNSW and Prince of Wales' Hospital, Sydney, NSW.School of
- 7 Department of Lung and Sleep Medicine, Monash Health, Melbourne, VIC, Australia
- 8 School of Clinical Sciences, Monash University, Melbourne, VIC, Australia
- 9 School of Health Sciences, Swinburne University of Technology, Melbourne, VIC
- 10 School of Public Health & Preventive Medicine, Monash University, Melbourne, VIC
- 11 Medicine, University of Tasmania, Hobart, TAS

Adrian J. Lowe and Gayan Bowatte should be considered joint senior author

**Corresponding author;**

Professor Shyamali C. Dharmage:

Allergy and Lung Health Unit

Centre for Epidemiology and Biostatistics

Melbourne School of Population and Global Health, The University of Melbourne

207, Bouverie Street, Carlton, Vic 3052

Tel: +61 3 83440737 Fax: +61 3 9349 5815

E mail [s.dharmage@unimelb.edu.au](mailto:s.dharmage@unimelb.edu.au)

*Author Contributions:* Conception and design: D.J. Lopez, G. Bowatte, S. Dharmage, A.J. Lowe Acquisition of data: L.D. Knibbs, M.J. Abramson, P.S. Thomas, G.S. Hamilton, B.R. Thompson, B. Erbas, E.H. Walters, S. Dharmage, G. Bowatte. Analysis and interpretation of data: D.J. Lopez, A.J. Lowe, C.J. Lodge, D.S. Bui, N.T. Waidyatillake, J.C. Su. Drafting the article : D.J. Lopez, A.J. Lowe, C.J. Lodge, D.S. Bui, N.T. Waidyatillake, J.C. Su. Revision for important intellectual content and approval of final submission : all authors.

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Abstract

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*Methods:* Ambient air pollution exposures (distance from a major road, nitrogen dioxide [NO<sub>2</sub>], fine particulate matter with an aerodynamic diameter [?]2.5 µm [PM<sub>2.5</sub>]) were assessed for the residential address of Tasmanian Longitudinal Health Study participants at ages 43 and 53 years. Eczema incidence (onset after age 43 years), prevalence (at 53 years) and persistence were assessed from surveys, while sensitisation was assessed using skin prick tests. The presence or absence of eczema and sensitisation was classified into four groups: no atopy or eczema, atopy alone, non-atopic eczema, and atopic eczema. Adjusted logistic and multinomial regression models were fitted to estimate associations between ambient air pollution and eczema, and interaction by sex was assessed.

*Results:* Of 3153 participants in both follow ups, 2369 had valid skin prick tests. For males, a 2.3 ppb increase in baseline NO<sub>2</sub> was associated with increased risk of prevalent eczema (OR=1.15 [95%CI 0.98-1.36]), both non-atopic (OR=1.39 [1.02-1.90]) and atopic eczema (OR=1.26 [1.00-1.59]). These associations were not seen in females (P for interaction=0.08, <0.01). For both sexes, a 1.6 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> exposure at follow-up was associated with increased odds of aeroallergen sensitisation (OR=1.15 [1.03-1.30]).

*Conclusion:* Increased exposure to residential ambient air pollutants was associated with an increased risk of eczema, only in males, and aeroallergen sensitisation in both genders.

*Keywords:* adults, atopy, dermatitis, eczema, middle-age, ambient air pollution

Word count: 249

## Introduction

Eczema, also known as atopic dermatitis, is a chronic inflammatory skin condition, characterized by defective skin barrier function and it affects around 5% to 10% of adults and up to 20% of children.<sup>1</sup> Eczema has a heterogeneous presentation, which varies in terms of severity, age of onset, and response to treatment.<sup>2</sup> This variation in presentation is determined by an interplay of genetics, immunity and environmental factors, including skin microbiome and indoor and outdoor air pollution.<sup>2,3</sup>

The World Allergy Organization has recognized at least two types of eczema.<sup>4</sup> An atopic type (AE) with skin inflammation driven by T-cell responses and Th<sub>2</sub> cytokines in the initial phase, which is usually associated with IgE-mediated sensitisation to environmental allergens and high levels of both total and allergen-specific IgE. This form of eczema is strongly associated with increased tendency of developing other allergic conditions.<sup>5</sup> The second form, non-atopic eczema (NAE), is characterized by normal levels of total IgE and lack of sensitisation to environmental allergens.<sup>5</sup> The pathophysiology of NAE is poorly understood<sup>4</sup>, and, particularly in older patients and those with chronic eczema, other non-atopic inflammatory mechanisms might be involved.<sup>5</sup>

There have been relatively few studies of the risk factors for eczema in adults.<sup>6</sup> In paediatric studies, higher levels of ambient air pollutants have been associated with increased eczema prevalence.<sup>7</sup> It has been proposed that air pollutants may generate reactive oxygen species which damage the outer-most layer of the skin through oxidative stress.<sup>8</sup> This process may drive the inflammation and pruritus that are associated with eczema, and this may subsequently downregulate filaggrin expression, further compromising the structural integrity of the epidermal barrier.<sup>9</sup> The effect of ambient air pollution on the prevalence and incidence of eczema in adults has received less attention.

A recent longitudinal analysis of middle aged German women, which investigated the influence of traffic related air pollution on lung function, inflammation and Aging (SALIA) found that baseline concentrations of traffic-related air pollution (TRAP) markers (NO<sub>2</sub>, NO<sub>x</sub>, PM<sub>2.5</sub> and PM<sub>10</sub>) were significantly associated with increased odds of incident eczema over a 19-year follow-up period, these associations being stronger for NAE.<sup>6</sup> Therefore, environmental factors, including air pollution, might be important for development of eczema in middle age, particularly NAE. These findings need to be replicated using similar longitudinal data to draw firmer conclusions. Better understanding of the potential effects of ambient air pollution on

adult eczema may lead to targeted interventions to prevent eczema. Using data from a large established longitudinal health study, we investigated whether exposure to ambient air pollution was associated with the incidence and prevalence of AE or NAE in middle-aged adults of both sexes.

## Methods

### Study population

The Tasmanian Longitudinal Health study (TAHS) is a population-based prospective cohort study, that has followed participants since 1968 when 7-year-old children (98.7%, n=8583) attending schools in the Australian state of Tasmania were recruited.<sup>10</sup> Several follow-up surveys have subsequently been conducted and study methodology has been reported in detail elsewhere.<sup>10</sup> The data for this analysis came from participants of the 2002 and 2012 proband studies when participants were 43 and 53 years old respectively. Participants completed a self-administered postal survey that collected the following baseline (2002) and follow-up (2012) data: sociodemographic characteristics, occupation, residence, health service use, medical diagnoses, smoking, reproductive histories, and symptoms. Only participants who completed both assessments and had valid skin prick tests (performed at the 2012 follow-up) were included in the analysis. The study was approved by the Human Research Ethics Committee of the University of Melbourne; all participants provided written informed consent.

### Exposures

#### Distance to a major road (DMR)

Straight-line distances from each participant's residence to the nearest major road in 2002 and 2012 proband studies were calculated using ArcGIS 10.1 software (Redlands, CA). Major roads were defined using public sector mapping agencies, and Australian transport hierarchy codes 301 and 302.<sup>11</sup> Participants were categorized into two groups: (i) living <200m; or (ii) living [?]200m from a major road. Major traffic pollutant concentrations tend to decay as the distance to major roads (DMR) increases, with most components of TRAP reaching near background concentrations at approximately 200m.<sup>12</sup>

#### Nitrogen dioxide (NO<sub>2</sub>)

A satellite-based land-use regression model was used to assign mean annual NO<sub>2</sub> exposures for the 2002 and 2012 proband studies.<sup>13</sup> Briefly, the land-use regression model-predicted mean annual NO<sub>2</sub> levels were based on tropospheric NO<sub>2</sub> columns derived from satellite observations in combination with other predictors such as land use and roads, to estimate ground-level NO<sub>2</sub> across Australia.<sup>13</sup> As more than half of the ambient NO<sub>2</sub> is attributed to on-road sources, NO<sub>2</sub> is a reasonable proxy for TRAP.<sup>14</sup> The model's development and validation are described in detail elsewhere, and it explained 81% of spatial variability in measured annual NO<sub>2</sub> at all regulatory monitoring sites in Australia.<sup>13</sup> Mean annual residential exposures to outdoor NO<sub>2</sub> were estimated and assigned based on participants' geocoded addresses at baseline (2002 proband study) and follow-up (2012 proband study).

#### Φινε παρτικυλατε ματτερ ωιτη αν αεροδψναμικ διαμετερ <2.5 μμ (PM<sub>2.5</sub>)

The methods are explained in more detail elsewhere.<sup>15</sup> In brief, satellite-based estimates for Australia of ground-level PM<sub>2.5</sub> were used as a land-use regression predictor, with other spatial predictors of PM<sub>2.5</sub>. This model explained 63% of spatial variability in measured annual PM<sub>2.5</sub> (RMSE: 1 μg/m<sup>3</sup>).<sup>15</sup> The mean annual residential exposures to outdoor PM<sub>2.5</sub> were estimated and assigned based on participants' geocoded addresses at baseline and follow-up. In Australia, traffic-related sources of PM<sub>2.5</sub> are estimated to account for only 17% of ambient PM<sub>2.5</sub> mass, while the majority of ambient PM<sub>2.5</sub> is from other anthropogenic sources (i.e. wood heaters, power stations and non-road combustion).<sup>16</sup>

## Outcomes

### Prevalent eczema at 53 years

Prevalent eczema at age 53 (2012 proband study) was determined using the International Study of Asthma and Allergies in Childhood (ISAAC) definition of eczema.<sup>17</sup> Participants were classified as having prevalent eczema if they reported “yes” to all three questions: ‘have you had an itchy rash in the past 12 months?’, ‘Have you ever had an itchy rash coming and going for at least six months?’, and ‘Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?’

### Incident current eczema at 53 years

Incident current eczema at 53 years was defined as eczema newly arising between the two proband studies i.e. between 43 and 53 years. The participants were classified as having Incident eczema if they answered “no” to “Have you ever had eczema or any skin allergy?” at baseline (2002 proband study), but reported eczema based on the ISAAC definition<sup>17</sup> and having eczema for the first time after baseline at “How old were you when you first had this itchy rash?” at the follow-up (2012 proband study).

### Persistent current eczema

Persistent current eczema was defined as prevalent eczema at baseline that persisted to follow-up. Participants were classified as having persistent current eczema if they answered “yes” to “Have you ever had eczema or any skin allergy?” at baseline and reported eczema based on the ISAAC definition<sup>17</sup> at follow-up.

### Atopic status

Subclassification as AE or NAE was based on skin prick testing (SPT) results at age 53 years.<sup>10</sup> In the 2012 proband study, SPTs were performed for eight aeroallergens: *Dermatophagoides pteronyssinus*, cat pelt, *Cladosporioides*, *Alternaria tenuis*, *Penicillium* mix, *Aspergillus fumigatus*, mixed grass pollen No. 7 (which included Kentucky bluegrass, orchard, redbtop, Timothy, sweet vernal grass, meadow fescue and perennial ryegrass). Histamine was used as the positive control and normal saline as the negative control. After 10 to 15 mins, the wheal diameters were measured in two perpendicular directions in millimetres and an average was derived. A valid SPT was determined by a positive control or allergen wheal equal to or greater than 3 mm in size and a negative control wheal equal to or less than 3 mm in size. A positive SPT was defined as a wheal size of at least 3 mm greater than the negative control and was considered to indicate sensitisation to that allergen.<sup>18</sup> Atopy was defined as sensitization to at least one of the allergens tested.

## Statistical Analysis

Associations between markers of ambient air pollution and the following outcome measures were assessed: 1) Prevalent eczema, 2) Incident current eczema, 3) Persistent eczema, 4) Prevalent and incident eczema sub grouped by atopic status (neither, atopy alone, non-atopic and atopic eczema) and 5) Sensitisation (regardless of eczema status). Second, in accordance with the eczema and atopy classification used in the SALIA cohort study<sup>6</sup>, we examined NAE incidence and prevalence using three increasingly restricted subgroups: 1) all participants, 2) participants without hay fever ever, 3) participants without hay fever ever and negative SPT.

Logistic regression and multinomial models were fitted to estimate the associations between baseline ambient air pollution and each outcome. The coefficients represented the estimated effect per interquartile range (IQR) increase of air pollutant exposure and were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A directed acyclic graph (DAG) (supplementary figure 1) was developed to specify the hypothesized causal relationships and to determine which confounders to include in the model (supplementary table 1). The potential presence of non-linearity of these associations was assessed using Stata’s “fracpoly”

command; no evidence of non-linearity of associations between ambient air pollution markers and eczema was identified. Potential effect modification by sex was explored using likelihood ratio tests and a p value < 0.1 was considered as significant. A sensitivity analysis was performed, where associations were assessed only in the participants who did not change residential address during follow-up period. All analyses were carried out using the statistical software Stata (release 16; Stata Corporation, College Station, TX).

## Results

Of 8583 Tasmanian school children enrolled in 1968 at age 7 years, 5729 were included in the 2002 proband study (figure 1), of whom 338 were excluded because the participant did not provide a residential address allowing ambient air pollution exposure to be estimated. Of the remaining 5391 participants, 2238 were excluded because they did not participate in the 2012 proband study. Of the 3153 with data from both the 2002 and 2012 proband studies, 2369 had a valid SPT result. There were no important differences between those followed and those lost to follow-up, except that those lost were more likely to be smokers or exposed to smoke, less likely to report hay fever and being from lower socioeconomic status (Supplementary table 2).

The mean age at the 2012 follow-up was 53 years and 50.3% were males (Table 1). At 53 years 281 participants (8.96%) of the participants had prevalent eczema, 115 participants (3.67%) had incident current eczema and 201 participants (6.38%) had persistent eczema (supplementary table 3). When comparing baseline and follow-up concentrations, ambient air pollution markers decreased slightly over time (table 1).

### Association between ambient air pollution and prevalent eczema at age 53.

There was evidence that sex modified the association (P for interaction<0.1) between NO<sub>2</sub> and prevalent eczema (table 2). Thus, in males, baseline exposure to NO<sub>2</sub> was associated with increased risk of having prevalent eczema at follow-up (adjusted odds ratio (aOR): 1.15 [95%CI 0.98-1.36] per IQR [2.27ppb] NO<sub>2</sub> increase), while higher exposure in females was associated with reduced risk of prevalent eczema (aOR: 0.83 [95%CI 0.67-1.03 per 2.27 ppb NO<sub>2</sub>increase).

Likewise, associations also differed by sex when prevalent eczema was classified by atopy status (table 3). In males, baseline NO<sub>2</sub> exposure was associated with increased risk of having both NAE (aOR 1.39 [95%CI 1.02-1.90]) and AE (aOR 1.26 [1.00-1.59]) per 2.27 ppb NO<sub>2</sub> increase, while baseline PM<sub>2.5</sub> was associated with increased risk of having AE (aOR 1.47 [1.04-2.06]) per 1.56 µg/m<sup>3</sup>PM<sub>2.5</sub> increase. By contrast, in females, higher NO<sub>2</sub> exposure at baseline was associated with a reduced risk of having AE (aOR 0.65 [95% CI 0.43-0.99]) per 2.27 ppb NO<sub>2</sub> increase. A similar trend was seen at follow-up, NO<sub>2</sub> was associated with increased risk of prevalent NAE (aOR 1.37 [95%CI 1.03-1.83] per 2.27 ppb) in males while in females it was a protective of NAE (aOR 0.67 [0.44-1.01]) per 2.21 ppb increase (Table 3). When the same associations were assessed restricting only to those who did not changed their address (non-movers), only negligible variation of the estimated effects were shown (supplementary table 4).

### Association between ambient air pollution at baseline and incident current eczema.

There was weak evidence of associations, nor effect modification by sex, between baseline ambient air pollution markers at baseline and incident current eczema (Table 2). Similarly, when incident current eczema was classified by atopy groups (Table 4), there was weak evidence of association.

## Association between ambient air pollution at baseline and persistent current eczema.

There was evidence that sex modified the association ( $P$  for interaction  $< 0.1$ ) between  $\text{NO}_2$  exposure and as a result, increased risk of persistent eczema was stronger in males than females (Table 2). Likewise, when persistent eczema was classified by atopy status (Table 5), there was evidence of interaction by sex ( $P$  for interaction  $< 0.1$ ). As such,  $\text{NO}_2$  exposure in males was found to increase persistent AE risk (aOR 1.25 [95% CI 0.95-1.65] per 2.27 ppb  $\text{NO}_2$  increase, while in females, the association tended towards reduced risk of persistent AE (aOR 0.57 [0.36-0.91] per 2.27 ppb  $\text{NO}_2$  increase). Similarly,  $\text{PM}_{2.5}$  exposure in males increased the risk of persistent AE (aOR 1.53 [1.04-2.25] per 1.56  $\mu\text{g}/\text{m}^3\text{PM}_{2.5}$  increase) and in females the risk of persistent AE was reduced (aOR 0.71 [0.49-1.02] per 1.56  $\mu\text{g}/\text{m}^3\text{PM}_{2.5}$  increase).

## Restricted definition of non-atopic eczema

When using the same analytic approach as the SALIA cohort study<sup>6</sup> there were no significant associations between ambient air pollution markers at baseline and incident NAE with increasing the strictness (i.e. those participants without hay fever and SPT negative) of the definition (supplementary table 5). However, a non-significant trend between DMR at follow-up and increased risk of prevalent NAE was seen, and this effect became stronger when the NAE definition became stricter (supplementary table 5). Furthermore, when the analyses were restricted to women, there was an association between DMR at follow-up and increased risk of prevalent eczema (supplementary table 6).

Association between ambient air pollution at baseline and aeroallergen sensitisation at age 53 years.

At baseline, increased exposure to  $\text{PM}_{2.5}$  was associated with increased odds of being sensitized to aeroallergens (aOR 1.15 [95% CI 1.03-1.30] per 1.56  $\mu\text{g}/\text{m}^3\text{PM}_{2.5}$  increase) at age 53 (supplementary table 7). Furthermore, there were associations between ambient air pollution markers and specific aeroallergen sensitisations that are described in more detail in supplementary table 8.

## Discussion

In this cohort of participants followed from 43 to 53 years of age, based in Australia where pollution levels are generally low, we observed that in males, higher exposure to ambient air pollution was associated with increased risk of prevalent eczema (both atopic and non-atopic). In contrast, for females, higher exposure to  $\text{NO}_2$  was associated with a paradoxical protective effect of prevalent eczema (both atopic and non-atopic). Additionally, there was evidence that increased levels of  $\text{PM}_{2.5}$  exposure were associated with increased risk of allergic sensitisation, in both males and females.

There are a limited number of previous studies that have considered the association between ambient air pollution exposure and eczema prevalence or incidence, and the results were inconsistent. Two paediatric studies<sup>19,20</sup> showed no association between ambient air pollution and increased risk of eczema, while other studies suggested increased eczema risk from ambient air pollution in children<sup>7</sup> and adults.<sup>21,22</sup> A study by Kim et al<sup>23</sup> found similar results in that  $\text{NO}_2$  was associated with the prevalence of AE in male but not in female, however the study population were children. The reason for these sex specific effects is not clear, but may be partly be due to differences in skin morphology, occupational exposures in adults and behaviour.<sup>24</sup> As has been reported previously in this age group,<sup>25</sup> women tend to spent more time indoors compared to men, with men reported spending almost twice the amount of time outside compared to women (supplementary file 9). Additionally, women are more likely to care about skin issues and avoid exposure to irritants compared to men.<sup>26</sup> Therefore, residual confounding may have introduced the sex-specific interaction in the association estimates. On the other hand, Gilmour et al.<sup>27</sup> observed that not all oxidative stress responses on the epithelial barrier are injurious and a lower level of oxidative stress might be paradoxically protective. To further elucidate the possible reasons for these sex specific effects, we recommend focused exploration of

the physiological, barrier function and immune responses to ambient air pollution at low levels in men and women.

We were unable to replicate the results from the SALIA cohort of elderly women study.<sup>6</sup> However, we saw similar non-significant trends of associations between ambient air pollution markers at follow-up and NAE prevalence which may warrant further investigation. There are several reasons why we may not have observed the same associations. First, we used SPT results and hay fever rather than blood IgE levels and hay fever, to determine atopic sensitisation. However given the strong association between SPT and IgE<sup>28</sup>, this would be unlikely to explain the differences in results between these studies. Second, our cohort was younger (baseline at 43 years followed-up to 53 years) than those in SALIA (baseline at 53 years followed-up to 73 years of age), making this a different time in women's reproductive lives, and changes in sex hormone levels may help explain the differences in results seen between these studies. Third, we included both sexes in our main analyses, whereas the SALIA study included only women. However, we did not observe increased risk in women with higher ambient air pollution exposures. Finally, the sources of ambient PM<sub>2.5</sub><sup>16</sup> are different between Australia (mainly from wood heaters, power stations and off-road sources) and Germany (mainly on-road traffic) where the study was conducted.<sup>6</sup>

Our findings suggest an association between PM<sub>2.5</sub> and aeroallergen sensitisation, agreeing with other studies.<sup>29,30</sup> In a study with adult participants; living close to busy roads was associated with a higher risk of sensitisation to pollen.<sup>29</sup> Furthermore, a previous cross-sectional analysis using data from this cohort reported, in this low pollution setting, that increased levels of ambient air pollution conferred an increased risk of atopy.<sup>30</sup> Of two studies that have not observed an association between ambient air pollution and an increased risk of allergic sensitisation, one study had a relatively small sample size and low power.<sup>31</sup> Another, in an adult population, reported a cross sectional association with DMR and NO<sub>2</sub> and aeroallergen sensitisation, but did not assess PM<sub>2.5</sub>.<sup>32</sup>

It has been proposed that air pollutants may lead to eczema and sensitisation via inflammatory oxidative stress leading to skin barrier dysfunction.<sup>3</sup> Ambient air pollution may drive these effects either through direct percutaneous absorption or indirectly through inhalation and subsequent systemic inflammation.<sup>3</sup> These air pollutants produce reactive oxygen species (ROS) and nitrogen species that lead to damage of proteins, lipids, and DNA.<sup>33</sup> Air pollutants can also act as irritants and immunomodulators leading to elevated levels of serum IgE.<sup>34</sup> Specifically, PM<sub>2.5</sub> may activate the aryl hydrocarbon receptor to promote cell metabolism and inflammation.<sup>34</sup> Other proposed mechanisms are by altering trans-epidermal water loss, increasing inflammatory signals and modifying the skin pH and microbiome.<sup>35</sup> Our results support an effect of ambient air pollution on immune function, even in this low ambient air pollution setting, with relatively higher exposure levels being associated with eczematous skin symptoms in males and overall increased aeroallergen sensitisation risk in the sample population.

Our study has both strengths and limitations. Strengths include access to a large population-based prospective cohort study with long follow-up allowing for a 10 year assessment period, well-characterized definitions of eczema with objective measures of SPT and land-use regression models. While the questions and definitions used were well validated,<sup>36</sup> a limitation is the reliance on self-reporting. Unfortunately, there were no data on the frequency or severity of symptoms and the aero-allergen SPT data were only available at follow-up, which may lead to some misclassification of atopy in the eczema subgroups. It is possible that residual confounding could have been an issue. As such, further replication of these findings is required. Given the exploratory nature of these data with multiple associations being assessed, we have attempted to interpret the pattern of associations, rather than relying on any arbitrary p value threshold to draw conclusions. Finally, as almost all the participants were Caucasian and Anglo-Celtic, the findings may not be generalizable to other ethnicities.



## Conclusion

Our findings suggest that higher ambient air pollution exposure is associated with greater risk of NAE and AE in adult men and an increased risk of aeroallergen sensitisation in both sexes. Ongoing efforts to reduce ambient air pollution exposure are likely to have a range of health benefits. Nevertheless, further research is needed to identify the components of ambient air pollution that exert the major effects, the extent of exposure required to increase risk of eczema and the factors that determine individual susceptibility. Further efforts are required to harmonize measurement of ambient air pollution markers, case definitions, study designs, and assessment of confounding factors to aid in replication of findings in this area.

### List of abbreviations

Atopic eczema (AE)

Directed acyclic graph (DAG)

Distance to major roads (DMR)

Fine particulate matter with an aerodynamic diameter of 2.5  $\mu\text{m}$  or less mass ( $\text{PM}_{2.5}$ )

International Study of Asthma and Allergies in Childhood (ISAAC)

Interquartile range (IQR)

Nitrogen dioxide ( $\text{NO}_2$ ) exposure

Non-atopic eczema (NAE)

Odds ratios (ORs)

Skin prick testing (SPT)

Study on the influence of air pollution and lung function, inflammation and Aging (SALIA)

Tasmanian Longitudinal Health STUDY (TAHS)

### Declarations section

#### *Ethics approval and consent to participate*

The 2002 and 2012 proband studies were approved by the Human Research Ethics Committee of the University of Melbourne, Melbourne. All participants provided written informed consent.

#### *Availability of data and materials:*

The data that support the findings of this study are available from the TAHS cohort 5<sup>th</sup> and 6<sup>th</sup> follow-up studies but restrictions apply to the availability of these data, which were used under authorization from the TAHS investigators for the current study, and so are not publicly available. Data are however available from the TASH investigators upon reasonable request.

#### *Competing interests:*

MJA holds investigator-initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has also undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has received a speaker's fee from GSK. The other authors declare that they have no competing interests.

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### References

1. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy*. 2018;73(6):1284-1293.
2. Fu T, Keiser E, Linos E, et al. Eczema and sensitization to common allergens in the United States: a multiethnic, population-based study. *Pediatric dermatology*. 2014;31(1):21-26.
3. Ahn K. The role of air pollutants in atopic dermatitis. *The Journal of allergy and clinical immunology*. 2014;134(5):993-999.
4. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *The Journal of allergy and clinical immunology*. 2004;113(5):832-836.
5. Tanei R, Hasegawa Y. Atopic dermatitis in older adults: A viewpoint from geriatric dermatology. *Geriatrics & gerontology international*. 2016;16 Suppl 1:75-86.
6. Huls A, Abramson MJ, Sugiri D, et al. Nonatopic eczema in elderly women: Effect of air pollution and genes. *The Journal of allergy and clinical immunology*. 2019;143(1):378-385.e379.
7. Annesi-Maesano I, Moreau D, Caillaud D, et al. Residential proximity fine particles related to allergic sensitisation and asthma in primary school children. *Respiratory Medicine*. 2007;101(8):1721-1729.
8. Niwa Y, Sumi H, Kawahira K, Terashima T, Nakamura T, Akamatsu H. Protein oxidative damage in the stratum corneum: Evidence for a link between environmental oxidants and the changing prevalence and nature of atopic dermatitis in Japan. *The British journal of dermatology*. 2003;149(2):248-254.
9. Sticozzi C, Belmonte G, Pecorelli A, et al. Cigarette smoke affects keratinocytes SRB1 expression and localization via H2O2 production and HNE protein adducts formation. *PLoS One*. 2012;7(3):e33592.
10. Matheson MC, Abramson MJ, Allen K, et al. Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS). *International journal of epidemiology*. 2017;46(2):407-408i.
11. Bowatte G, Lodge CJ, Knibbs LD, et al. Traffic related air pollution and development and persistence of asthma and low lung function. *Environment International*. 2018;113:170-176.
12. Karner AA, Eisinger DS, Niemeier DA. Near-Roadway Air Quality: Synthesizing the Findings from Real-World Data. *Environmental Science & Technology*. 2010;44(14):5334-5344.
13. Knibbs LD, Hewson MG, Bechle MJ, Marshall JD, Barnett AG. A national satellite-based land-use regression model for air pollution exposure assessment in Australia. *Environmental Research*. 2014;135:204-211.
14. EPA N. Air emissions inventory for the greater metropolitan region in New South Wales. 2008 Calendar Year. *Consolidated Natural and Human-Made Emissions: Results*. 2012;1.
15. Knibbs LD, van Donkelaar A, Martin RV, et al. Satellite-Based Land-Use Regression for Continental-Scale Long-Term Ambient PM2.5 Exposure Assessment in Australia. *Environ Sci Technol*. 2018;52(21):12445-12455.
16. Broome RA, Powell J, Cope ME, Morgan GG. The mortality effect of PM2.5 sources in the Greater Metropolitan Region of Sydney, Australia. *Environment International*. 2020;137:105429.

17. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J.* 1995;8(3):483-491.
18. Smith W. Skin Prick Testing for the Diagnosis of Allergic Disease—A Manual for Practitioners. Australasian Society of Clinical Immunology and Allergy (ASCI). In:2019.
19. Anderson HR, Ruggles R, Pandey KD, et al. Ambient particulate pollution and the world-wide prevalence of asthma, rhinoconjunctivitis and eczema in children: Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC). *Occup Environ Med.*2010;67(5):293-300.
20. Watanabe M, Noma H, Kurai J, et al. Association of Short-Term Exposure to Ambient Fine Particulate Matter with Skin Symptoms in Schoolchildren: A Panel Study in a Rural Area of Western Japan.*Int J Environ Res Public Health.* 2017;14(3):299.
21. Montnemery P, Nihlén U, Göran Löfdahl C, Nyberg P, Svensson A. Prevalence of self-reported eczema in relation to living environment, socio-economic status and respiratory symptoms assessed in a questionnaire study. *BMC Dermatol.* 2003;3:4-4.
22. Tang KT, Ku KC, Chen DY, Lin CH, Tsuang BJ, Chen YH. Adult atopic dermatitis and exposure to air pollutants—a nationwide population-based study. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.*2017;118(3):351-355.
23. Kim Y-M, Kim J, Han Y, Jeon B-H, Cheong H-K, Ahn K. Short-term effects of weather and air pollution on atopic dermatitis symptoms in children: A panel study in Korea. *PLoS One.* 2017;12(4):e0175229.
24. Lee Y-L, Su H-J, Sheu H-M, Yu H-S, Guo YL. Traffic-Related Air Pollution, Climate, and Prevalence of Eczema in Taiwanese School Children. *Journal of Investigative Dermatology.*2008;128(10):2412-2420.
25. Brasche S, Bischof W. Daily time spent indoors in German homes – Baseline data for the assessment of indoor exposure of German occupants.*International Journal of Hygiene and Environmental Health.*2005;208(4):247-253.
26. Bannister MJ, Freeman S. Adult-onset atopic dermatitis.*Australasian Journal of Dermatology.* 2000;41(4):225-228.
27. Gilmour MI, Jaakkola MS, London SJ, Nel AE, Rogers CA. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ Health Perspect.* 2006;114(4):627-633.
28. Wagner N, Rudert M. Sensitivity and specificity of standardised allergen extracts in skin prick test for diagnoses of IgE-mediated respiratory allergies. *Clinical and Translational Allergy.*2019;9(1):8.
29. Wyler C, Braun-Fahrlander C, Kunzli N, et al. Exposure to motor vehicle traffic and allergic sensitization. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team.*Epidemiology (Cambridge, Mass).* 2000;11(4):450-456.
30. Bowatte G, Lodge CJ, Knibbs LD, et al. Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age. *The Journal of allergy and clinical immunology.* 2017;139(1):122-129 e121.
31. Mortimer K, Neugebauer R, Lurmann F, Alcorn S, Balmes J, Tager I. Early-lifetime exposure to air pollution and allergic sensitization in children with asthma. *J Asthma.* 2008;45(10):874-881.
32. Pujades-Rodríguez M, McKeever T, Lewis S, Whyatt D, Britton J, Venn A. Effect of traffic pollution on respiratory and allergic disease in adults: cross-sectional and longitudinal analyses. *BMC Pulmonary Medicine.* 2009;9(1):42.
33. Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. *The Journal of allergy and clinical immunology.*2002;110(3):349-356.

34. Liu Q, Wu J, Song J, et al. Particulate matter 2.5 regulates lipid synthesis and inflammatory cytokine production in human SZ95 sebocytes. *Int J Mol Med.* 2017;40(4):1029-1036.
35. Hendricks AJ, Eichenfield LF, Shi VY. The impact of airborne pollution on atopic dermatitis: a literature review. *British Journal of Dermatology.* 2020;183(1):16-23.
36. Flohr C, Weinmayr G, Weiland SK, et al. How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. *The British journal of dermatology.*2009;161(4):846-853.

**Tables** (each table complete with title and footnotes);

Table 1. Characteristics of participants included. (N=3153)

Co-variates
Age (years). Mean (SD); min-max
Male. %(n/N)
Body mass index (kg/m <sup>2</sup> ). Mean (SD); min-max
Heating by indoor combustion of solid+ or gas fuel. %(n/N)
Cooking by indoor combustion of solid+ or gas fuel. %(n/N)
Years of education. %(n/N) < Grade 12 Grade 12 or equivalent > Grade 12
Occupation. %(n/N) Managers and Professionals Associate Professionals Tradespersons and Advanced Clerical Intermediat
Smoking status. %(n/N) Never Former Current
Current second-hand smoke. %(n/N)
Hay fever ever. %(n/N)
Living <200m from a major road
NO <sub>2</sub> (ppb) median [IQR; 25-75%le]
PM <sub>2.5</sub> (µg/m <sup>3</sup> ) median [IQR; 25-75%le]

+ Solid fuels are coal and wood.

Table 2. Adjusted+ associations between ambient air pollution markers at baseline and prevalent eczema at 53 years, incident current eczema++ and persistent current eczema stratified by gender.

	<b>Eczema prevalence (281/3,135)</b>	<b>Eczema prevalence (281/3,135)</b>	<b>Eczema incidence (115/3,152)</b>	<b>Eczema persistence (201/3150)</b>
Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline
	aOR (95%CI) + p	aOR (95%CI) + p	aOR (95%CI) + p	aOR (95%CI) + p
DMR<200m	1.10 (0.83-1.45) 0.514	1.15 (0.76-1.75) 0.518	1.15 (0.76-1.75) 0.518	1.06 (0.76-1.48) 0.722
Males	1.17 (0.77-1.77)	0.88 (0.48-1.63)	0.88 (0.48-1.63)	1.26 (0.78-2.03)
Females	1.04 (0.71-1.53)	1.55 (0.86-2.79)	1.55 (0.86-2.79)	0.91 (0.57-1.44)
P for interaction	0.653	0.145	0.145	0.675
NO <sub>2</sub> §	1.01 (0.88-1.15) 0.890	1.10 (0.90-1.33) 0.781	1.10 (0.90-1.33) 0.781	0.96 (0.82-1.13) 0.604
Males	1.15 (0.98-1.36)	1.13 (0.88-1.43)	1.13 (0.88-1.43)	1.15 (0.94-1.40)
Females	0.83 (0.67-1.03)	1.02 (0.74-1.41)	1.02 (0.74-1.41)	0.75 (0.58-0.98)
P for interaction	<b>0.018*</b>	0.530	0.530	<b>0.033</b>

	<b>Eczema prevalence (281/3,135)</b>	<b>Eczema prevalence (281/3,135)</b>	<b>Eczema incidence (115/3,152)</b>	<b>Eczema persistence (201/3150)</b>
PM <sub>2.5</sub> §	0.97 (0.84-1.13)	1.17 (0.92-1.47)	1.17 (0.92-1.47)	0.84 (0.71-1.00)
	0.740	0.195	0.195	0.048
Males	0.96 (0.77-1.20)	1.21 (0.88-1.66)	1.21 (0.88-1.66)	0.91 (0.70-1.18)
Females	1.00 (0.82-1.23)	1.11 (0.79-1.56)	1.11 (0.79-1.56)	0.80 (0.63-1.01)
P for interaction	0.809	0.686	0.686	0.685

\*P for interaction with p<0.1 are bolded

+Adjusted for: age, sex, household cooking by indoor combustion of solid and gas fuels, household cooking by indoor combustion of solid and gas fuels, occupation, highest education level, smoking and second-hand smoking.

++ORs (95% CIs) are given per an IQR increase in air pollution marker

Table 3. Adjusted associations between ambient air pollution exposure at the baseline and prevalent eczema at 53 years by atopy with stratified results by gender.

	<b>No atopy or eczema (972/2,360)</b>	<b>Atopy alone (1,172/ 2,360)</b>	<b>Non-atopic Eczema (83 / 2,360)</b>	<b>Atopic Eczema (132 / 2,360)</b>
Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline
	<i>aOR (95%CI) +</i>	<i>aOR (95%CI) +</i>	<i>aOR (95%CI) +</i>	<i>aOR (95%CI) +</i>
DMR++	Ref group	1.15 (0.95-1.41)	1.46 (0.90-2.38)	0.93 (0.60-1.44)
		0.150	0.128	0.837
Males	Ref group	1.09 (0.82-1.46)	1.41 (0.59-3.41)	1.05 (0.58-1.90)
Females	Ref group	1.22 (0.93-1.61)	1.54 (0.85-2.81)	0.81 (0.42-1.56)
P for interaction		0.541	0.908	0.613
NO <sub>2</sub> ++	Ref group	1.06 (0.96-1.16)	1.11 (0.88-1.41)	1.02 (0.84-1.25)
		0.246	0.375	0.810
Males	Ref group	1.09 (0.96-1.25)	1.39 (1.02-1.90)	1.26 (1.00-1.59)
Females	Ref group	1.03 (0.90-1.18)	0.89 (0.63-1.25)	0.65 (0.44-0.98)
P for interaction		0.954	<b>0.081</b>	<b>0.005</b>
PM <sub>2.5</sub> ++	Ref group	1.05 (0.95-1.18)	0.93 (0.70-1.23)	1.07 (0.84-1.36)
		0.320	0.611	0.577
Males	Ref group	1.17 (0.99-1.9)	1.11 (0.64-1.92)	1.47 (1.04-2.06)
Females	Ref group	0.99(0.85-1.15)	0.86 (0.61-1.20)	0.82 (0.59-1.14)
P for interaction	Ref group	0.317	0.800	<b>0.018</b>
Air pollution markers at follow-up	Air pollution markers at follow-up	Air pollution markers at follow-up	Air pollution markers at follow-up	Air pollution markers at follow-up
DMR++	Ref group	1.23 (1.01-1.51)	1.50 (0.91-2.46)	0.85 (0.54-1.34)
		0.043	0.107	0.486
Males	Ref group	1.37 (1.03-1.83)	2.09 (0.9-4.83)	0.97 (0.53-1.79)
Females	Ref group	1.14 (0.86-1.51)	1.34 (0.71-2.51)	0.73 (0.37-1.47)
P for interaction	Ref group	0.435	0.479	0.567

	No atopy or eczema (972/ 2,360)	Atopy alone (1,172/ 2,360)	Non-atopic Eczema (83 / 2,360)	Atopic Eczema (132 / 2,360)
NO <sub>2</sub> ++	Ref group	1.05 (0.96-1.16) 0.293	1.10 (0.87-1.40) 0.428	0.86 (0.68-1.08) 0.176
Males	Ref group	1.06 (0.93-1.21)	1.37 (1.01-1.86)	0.98 (0.74-1.29)
Females	Ref group	1.04 (0.91-1.20)	0.86 (0.60-1.24)	0.67 (0.44-1.01)
P for interaction	Ref group	0.551	<b>0.099</b>	<b>0.097</b>
PM <sub>2.5</sub> ++	Ref group	1.18 (1.04-1.33) 0.010	1.03 (0.76-1.41) 0.833	1.00 (0.77-1.29) 0.986
Males	Ref group	1.26 (1.01-1.51)	0.97 (0.57-1.63)	1.22 (0.84-1.75)
Females	Ref group	1.13 (0.95-1.35)	1.09 (0.73-1.62)	0.83 (0.57-1.21)
P for interaction	Ref group	0.756	0.420	0.162

\*P for interaction with p<0.1 are bolded ++ORs (95% CIs) per an IQR increase in air pollution marker

+Adjusted for: age, sex, household cooking by indoor combustion of solid and gas fuels, household cooking by indoor combustion of solid and gas fuels, occupation, highest education level, smoking and second-hand smoking.

Table 4. Adjusted associations between ambient air pollution exposure at the baseline and incident of current eczema by atopy with stratified results by gender.

	No atopy or eczema (1,018/2,273)	Atopy alone (1,263/2,273)	Non-atopic Eczema (41/2,273)	Atopic Eczema (47/2,273)
Air pollution markers at baseline	Air pollution markers at baseline <i>aOR (95%CI) +</i>	Air pollution markers at baseline <i>aOR (95%CI) +</i>	Air pollution markers at baseline <i>aOR (95%CI) +</i>	Air pollution markers at baseline <i>aOR (95%CI) +</i>
DMR++	Ref group	1.09 (0.89-1.32) 0.407	0.95 (0.46-1.97) 0.884	1.30 (0.67-2.47) 0.441
Males	Ref group	1.06 (0.80-1.40)	0.63 (0.18-2.29)	0.88 (0.36-2.11)
Females	Ref group	1.10 (0.84-1.43)	1.20 (0.48-2.98)	2.68 (0.91-7.83)
P for interaction	Ref group	0.841	0.506	0.117
NO <sub>2</sub> ++	Ref group	1.04 (0.95-1.14) 0.380	0.94 (0.63-1.40) 0.763	1.11 (0.83-1.48) 0.474
Males	Ref group	1.08 (0.95-1.23)	0.99 (0.55-1.79)	1.18 (0.86-1.61)
Females	Ref group	1.01 (0.88-1.15)	0.89 (0.53-1.50)	0.75 (0.35-1.59)
P for interaction	Ref group	0.916	0.822	0.143
PM <sub>2.5</sub> ++	Ref group	1.06 (0.95-1.18) 0.321	0.85 (0.57-1.27) 0.426	1.25 (0.85-1.83) 0.253
Males	Ref group	1.19 (1.01-1.40)	1.15 (0.57-2.33)	1.43 (0.88-2.33)
Females	Ref group	0.98 (0.85-1.13)	0.74 (0.45-1.22)	1.10 (0.54-2.21)
P for interaction	Ref group	0.188	0.645	0.338

\*P for interaction with p<0.1 are bolded

+Adjusted for: age, sex, household cooking by indoor combustion of solid and gas fuels, household cooking by indoor combustion of solid and gas fuels, occupation, highest education level, smoking and second-hand

smoking.

++ORs (95% CIs) per an increase of 1 IQR in air pollution marker

Table 5. Adjusted associations between ambient air pollution exposure at the baseline and persistent eczema by atopy with stratified results by gender.

	No atopy or eczema (1,005/2,368)	Atopy alone (1,207/2,368)	Non-atopic Eczema (54/2,368)	Atopic Eczema (102/2,368)
Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline	Air pollution markers at baseline
	aOR (95%CI) + p	aOR (95%CI) + p	aOR (95%CI) + p	aOR (95%CI) + p
DRM<200m	Ref group	1.15 (0.96-1.42) 0.131	1.65 (0.92-2.96) 0.092	0.74 (0.44-1.25) 0.266
Males	Ref group	1.10 (0.82-1.46)	1.88 (0.66-5.31)	1.02 (0.51-2.03)
Females	Ref group	1.23 (0.84-1.61)	1.66 (0.81-3.40)	0.51 (0.22-1.17)
P for interaction		0.547	0.882	0.225
NO <sub>2</sub> §	Ref group	1.07 (0.97-1.17) 0.161	1.25 (0.96-1.63) 0.099	0.95 (0.75-1.20) 0.671
Males	Ref group	1.10 (0.97-1.26)	1.58 (1.12-2.32)	1.25 (0.95-1.65)
Females	Ref group	1.41 (0.91-1.19)	1.00 (0.68-1.47)	0.57 (0.36-0.91)
P for interaction		0.937	0.137	<b>0.011</b>
PM <sub>2.5</sub> §	Ref group	1.06 (0.95-1.18) 0.332	0.77 (0.55-1.08) 0.131	1.00 (0.77-1.31) 0.986
Males	Ref group	1.17 (0.99-1.38)	0.94 (0.48-1.87)	1.53 (1.04-2.25)
Females	Ref group	0.99 (0.85-1.15)	0.780 (0.47-1.05)	0.71 (0.49-1.02)
P for interaction		0.296	0.645	<b>0.009</b>

\*P for interaction with p<0.1 are bolded

+Adjusted for: age, sex, household cooking by indoor combustion of solid and gas fuels, household cooking by indoor combustion of solid and gas fuels, occupation, highest education level, smoking and second-hand smoking.

++ORs (95% CIs) per an increase of 1 IQR in air pollution marker

Figure legend

Figure 1. Participant flow chart.

xi. *Supplementary files*

*Supplementary figure 1 (.jpg)*

Directed acyclic graph (DAG)

*Supplementary table 1 (Microsoft Word Document (.docx))*

Confounder table of definitions

*Supplementary table 2 (Microsoft Word Document (.docx))*

Loss to follow-up SPT analysis

*Supplementary table 3 (Microsoft Word Document (.docx))*

Prevalence and incidence of eczema and their subclasses at 2012 survey.

*Supplementary table 4 (Microsoft Word Document (.docx))*

Adjusted associations between ambient air pollution exposure at the baseline and prevalent eczema at 53 years by atopy with stratified results by gender and for participants that did not change their address.

*Supplementary table 5 (Microsoft Word Document (.docx))*

Description of air pollution exposures at 2002 and 2012 survey.

*Supplementary table 6 (Microsoft Word Document (.docx))*

Associations between air pollutants at baseline and incident symptoms of eczema after age 43 years following exclusion of atopic subjects, with increasing strictness from left to right (SALIA cohort analytical approach)

*Supplementary table 7 (Microsoft Word Document (.docx))*

Adjusted associations between ambient air pollution markers and aeroallergen sensitisation with stratified results by gender.

*Supplementary table 8 (Microsoft Word Document (.docx))*

Adjusted associations between air pollutants and specific aeroallergen

*Supplementary table 9 (Microsoft Word Document (.docx))*

Average outside time at 2012 follow-up by gender



### Participant Flow Chart

