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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$_2$], fine particulate matter with an aerodynamic diameter ≤2.5 µm [PM$_{2.5}$]) 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 IgE 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$_2$ was associated with increased odds of prevalent eczema (OR=1.15 [95%CI 0.98-1.36]) and prevalent 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$^3$ increase in PM$_{2.5}$ 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 odds of eczema, only in males, and aeroallergen sensitisation in both genders.

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

Word count: 247
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.\(^1\) Eczema has a heterogeneous presentation, which varies in terms of severity, age of onset, and response to treatment.\(^2\)

The World Allergy Organization has recognized at least two types of eczema.\(^3\) An atopic type (AE) with skin inflammation driven by T-cell responses and Th\(_2\) 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.\(^4\) The second form, non-atopic eczema (NAE), is characterized by normal levels of total IgE and lack of sensitisation to environmental allergens.\(^4\) The pathophysiology of NAE is poorly understood,\(^3\) and, particularly in older patients and those with chronic eczema, other non-atopic inflammatory mechanisms might be involved.\(^4\)

There have been relatively few studies of the risk factors for eczema in adults.\(^5\) In paediatric studies, higher levels of ambient air pollutants have been associated with increased eczema prevalence.\(^6\) It has been proposed that air pollutants may generate reactive oxygen species which damage the outermost layer of the skin through oxidative stress.\(^7\) 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.\(^8\) 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\(_2\), NO\(_x\), PM\(_{2.5}\), and PM\(_{10}\)) were significantly associated with increased odds of incident eczema over a 19-year follow-up period, these associations being stronger for NAE.\(^5\) 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 intervention 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. Several follow-up surveys have subsequently been conducted and study methodology has been reported in detail elsewhere. The data for this analysis came from participants of the 2002 and 2012 proband studies when participants had a mean age of 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. These included freeways, highways and arterial roads, which were likely to have high volumes of traffic. 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.

**Nitrogen dioxide (NO₂)**

A satellite-based land-use regression model was used to assign mean annual NO₂ exposures for the 2002 and 2012 proband studies. Briefly, the land-use regression model-predicted mean annual NO₂ levels were based on tropospheric NO₂ columns derived from satellite observations in combination with other predictors such as land use and roads, to estimate ground-level NO₂ across Australia. As more
than half of the ambient NO\textsubscript{2} is attributed to on-road sources, NO\textsubscript{2} is a reasonable proxy for TRAP.\textsuperscript{13} The model’s development and validation are described in detail elsewhere, and it explained 81% of spatial variability in measured annual NO\textsubscript{2} at all regulatory monitoring sites in Australia.\textsuperscript{12} Mean annual residential exposures to outdoor NO\textsubscript{2} were estimated and assigned based on participants’ geocoded addresses at baseline (2002 proband study) and follow-up (2012 proband study).

Fine particulate matter with an aerodynamic diameter <2.5 µm (PM\textsubscript{2.5})

The methods are explained in more detail elsewhere.\textsuperscript{14} In brief, satellite-based estimates for Australia of ground-level PM\textsubscript{2.5} were used as a land-use regression predictor, with other spatial predictors of PM\textsubscript{2.5}. This model explained 63% of spatial variability in measured annual PM\textsubscript{2.5} (RMSE: 1 µg/m\textsuperscript{3}).\textsuperscript{14} The mean annual residential exposures to outdoor PM\textsubscript{2.5} were estimated and assigned based on participants’ geocoded addresses at baseline and follow-up. In Australia, traffic-related sources of PM\textsubscript{2.5} are estimated to account for only 17% of ambient PM\textsubscript{2.5} mass, whereas the majority of ambient PM\textsubscript{2.5} is from other anthropogenic sources (i.e. wood heaters, power stations, etc).\textsuperscript{15}

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.\textsuperscript{16} 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 eczema at 53 years

Incident 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\textsuperscript{16} 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 at follow-up.

Atopic status

Subclassification as AE or NAE was based on skin prick testing (SPT) results at age 53 years. In the 2012 proband study, SPTs were performed for eight aeroallergens: *Dermatophagoides pteronyssinus*, cat pelt, *Cladosporoides*, *Alternaria tenuis*, *Penicillium mix*, *Aspergillus fumigatus*, mixed grass pollen No. 7. 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. Atopy was defined as sensitisation 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 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, 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. To detect outliers and influential data points, we separated the main multinomial regression models into sets of logistic regression models and plotted their residuals. 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 2002-08 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 and being from lower socioeconomic status, less likely to report hay fever. (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 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\textsubscript{2} and prevalent eczema (Table 2). Thus, in males, baseline exposure to NO\textsubscript{2} was associated with increased odds of having prevalent eczema at follow-up (adjusted odds ratio (aOR): 1.15 [95%CI 0.98-1.36] per IQR [2.27 ppb] NO\textsubscript{2} increase), while higher exposure in females was associated, although non significantly, with reduced odds of prevalent eczema (aOR: 0.83 [95%CI 0.67-1.03] per 2.27 ppb NO\textsubscript{2} increase). Additional adjustment for family history of allergic disease did not materially alter the results.

Likewise, associations also differed by sex when prevalent eczema was classified by atopy status (Table 3). In males, baseline NO\textsubscript{2} exposure was associated with increased odds of having AE (aOR 1.26 [1.00-1.59]) per 2.27 ppb NO\textsubscript{2} increase, while baseline PM\textsubscript{2.5} was associated with increased odds of having AE (aOR 1.47 [1.04-2.06]) per 1.56 µg/m\textsuperscript{3} PM\textsubscript{2.5} increase. By contrast, in females, higher NO\textsubscript{2} exposure at baseline was associated with a reduced odds of having AE (aOR 0.65 [95% CI 0.43-0.99]) per 2.27 ppb NO\textsubscript{2} increase. A similar trend was seen at follow-up, NO\textsubscript{2} was associated with a reduced odds of AE (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 change 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 eczema.

There was weak evidence of associations, nor effect modification by sex, between baseline ambient air pollution markers at baseline and incident eczema (Table 2). Similarly, when incident eczema was classified by atopy groups (Supplementary Table 5), 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 NO\textsubscript{2} exposure and as a result, increased odds 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, baseline NO\textsubscript{2} exposure in males was found to increase persistent AE odds (aOR 1.25 [95% CI 0.95-1.65] per 2.27 ppb NO\textsubscript{2} increase, while in females, the association tended towards reduced odds of persistent AE (aOR 0.57 [95% CI 0.36-0.91] per 2.27 ppb NO\textsubscript{2} increase). Similarly, baseline PM\textsubscript{2.5} exposure in males increased the odds of persistent AE (aOR 1.53 [1.04-2.25] per 1.56 µg/m\textsuperscript{3} PM\textsubscript{2.5} increase) and in females the odds of persistent AE was reduced (aOR 0.71 [0.49-1.02] per 1.56 µg/m\textsuperscript{3} PM\textsubscript{2.5} increase).

Restricted definition of non-atopic eczema

When using the same analytic approach as the SALIA cohort study\textsuperscript{5} 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 6). However, a non-significant trend between DMR at follow-up and increased odds of prevalent NAE was seen, and this effect became stronger when the NAE definition became stricter (Supplementary Table 6). Furthermore, when the analyses were restricted to women, there was an association between DMR at follow-up and increased odds of prevalent eczema (Supplementary Table 7).

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

At baseline, increased exposure to PM\textsubscript{2.5} was associated with increased odds of being sensitized to aeroallergens (aOR 1.15 [95% CI 1.03-1.30] per 1.56 µg/m\textsuperscript{3} PM\textsubscript{2.5} increase) at age 53 (Table 4). 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 odds of prevalent atopiceczema. In contrast, for females, higher exposure to NO$_2$ was associated with a paradoxical reduced odds of prevalent atopiceczema. Furthermore, the absence of associations between ambient air pollution and incidence of eczema might be due to the reduction in ambient air pollution concentrations over time. Additionally, there was evidence that increased levels of PM$_{2.5}$ exposure were associated with increased odds 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$^{18,19}$ showed no association between ambient air pollution and increased risk of eczema, while other studies suggested an association between ambient air pollution and increased eczema prevalence in children$^6$ and adults.$^{20,21}$ A study by Kim et al.$^{22}$ found similar results in that 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 due to differences in skin morphology, occupational exposures in adults and behaviour.$^{23}$ As has been reported previously in this age group,$^{24}$ women tend to spend more time indoors compared to men, with men reported spending almost twice the amount of time outside compared to women (Supplementary Table 9). Additionally, women are more likely to care about skin issues and avoid exposure to irritants compared to men.$^{25}$ Therefore, residual confounding may have introduced the sex-specific interaction in the association estimates. On the other hand, Gilmour et al.$^{26}$ 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.$^5$ 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\(^27\) 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\(_{2.5}\)\(^15\) 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.\(^5\)

Our findings suggest an association between PM\(_{2.5}\) and aeroallergen sensitisation, agreeing with other studies.\(^28,29\) In a study with adult participants; living close to busy roads was associated with a higher risk of sensitisation to pollen.\(^28\) 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 a higher development of atopy.\(^29\) Of two studies that have not observed an association between ambient air pollution and allergic sensitisation, one study had a relatively small sample size and low power.\(^30\) Another, in an adult population, reported a cross sectional association with DMR and NO\(_2\) and aeroallergen sensitisation, but did not assess PM\(_{2.5}\).\(^31\)

It has been proposed that air pollutants may lead to eczema and sensitisation via inflammatory oxidative stress leading to skin barrier dysfunction.\(^32\) Ambient air pollution may drive these effects either through direct percutaneous absorption or indirectly through inhalation and subsequent systemic inflammation.\(^32\) These air pollutants produce reactive oxygen species (ROS) and nitrogen species that lead to damage of proteins, lipids, and DNA.\(^33\) Air pollutants can also act as irritants and immunomodulators leading to elevated levels of serum IgE.\(^34\) Specifically, PM\(_{2.5}\) may activate the aryl hydrocarbon receptor to promote cell metabolism and inflammation.\(^34\) Other proposed mechanisms are by altering trans-epidermal water loss, increasing inflammatory signals and modifying the skin pH and microbiome.\(^32\) Our results support an effect of ambient air pollution on immune function, even in this low ambient air pollution setting.

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,\(^36\) a limitation is the reliance on self-reporting.

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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. Although lost to follow-up tend to be more pronounced among the less advantaged participants, this differential loss to follow-up generally does not lead to selection bias in the measurement of exposure-outcome associations. As such, while we cannot exclude this possibility, it seems unlikely. Also, 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 odds of AE in adult men and an increased odds 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 µm or less mass (PM$_{2.5}$)

International Study of Asthma and Allergies in Childhood (ISAAC)

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Interquartile range (IQR)

Nitrogen dioxide (NO2) 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 5th and 6th 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 TAHS investigators upon reasonable request.

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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


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### Tables (each Table complete with title and footnotes);

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

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<th>2012 Survey</th>
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</tr>
<tr>
<td>Cooking by indoor combustion of solid† or gas fuel. %%(n/N)</td>
<td>24.1 (757/3,153)</td>
<td>28.7 (886/3,081)</td>
</tr>
<tr>
<td>Years of education. %%(n/N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Grade 12</td>
<td>34.7 (1,093/3,153)</td>
<td>32.7 (1,020/3,153)</td>
</tr>
<tr>
<td>Grade 12 or equivalent</td>
<td>9.5 (300/3,153)</td>
<td>7.8 (242/3,153)</td>
</tr>
<tr>
<td>&gt; Grade 12</td>
<td>55.8 (1,755/3,153)</td>
<td>59.6 (1,860/3,153)</td>
</tr>
<tr>
<td>Occupation. %%(n/N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managers and Professionals</td>
<td>30.9 (970/3,135)</td>
<td>35 (1,087/3,105)</td>
</tr>
<tr>
<td>Associate Professionals</td>
<td>11.4 (357/3,135)</td>
<td>14.1 (439/3,105)</td>
</tr>
<tr>
<td>Tradespersons and Advanced Clerical</td>
<td>20.7 (648/3,135)</td>
<td>18.8 (585/3,105)</td>
</tr>
<tr>
<td>Intermediate clerical and production</td>
<td>18 (563/3,135)</td>
<td>18 (558/3,105)</td>
</tr>
<tr>
<td>Elementary clerical, laborers and related</td>
<td>19 (597/3,135)</td>
<td>14 (436/3,105)</td>
</tr>
<tr>
<td>Smoking status. %%(n/N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>44.5 (1,404/3,143)</td>
<td>44.5 (1,402/3,120)</td>
</tr>
<tr>
<td>Former</td>
<td>31.6 (995/3,143)</td>
<td>38.4 (1,211/3,120)</td>
</tr>
<tr>
<td>Current</td>
<td>23.6 (744/3,143)</td>
<td>16.1 (507/3,120)</td>
</tr>
<tr>
<td>Current second-hand smoke. %%(n/N)</td>
<td>11.6 (358/3,096)</td>
<td>7.8 (244/3,153)</td>
</tr>
<tr>
<td>Hay fever ever. %%(n/N)</td>
<td>53 (1,660/3,153)</td>
<td>55.8 (1,757/3,153)</td>
</tr>
<tr>
<td>Living &lt; 200m from a major road</td>
<td>813 / 3,153 (25.78%)</td>
<td>787 / 3,048 (25.82%)</td>
</tr>
<tr>
<td>NO₂ (ppb) median [IQR; 25-75%le]</td>
<td>4.24 [2.27; 3.43-5.7]</td>
<td>2.72 [2.21; 1.93-4.14]</td>
</tr>
<tr>
<td>PM₂.₅ (µg/m³) median [IQR; 25-75%le]</td>
<td>6.48 [1.49; 5.76-7.26]</td>
<td>6.4 [1.56; 5.63-7.19]</td>
</tr>
</tbody>
</table>

† Solid fuels are coal and wood.

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

<table>
<thead>
<tr>
<th></th>
<th>Eczema prevalence (281/3,135) §</th>
<th>Eczema incidence (115/3,152) §</th>
<th>Eczema persistence (201/3150) §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air pollution markers at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>DMR&lt;200m</th>
<th>aOR (95%CI) †</th>
<th>p</th>
<th>aOR (95%CI) †</th>
<th>p</th>
<th>aOR (95%CI) †</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1.10 (0.83-1.45)</td>
<td>0.514</td>
<td>1.15 (0.76-1.75)</td>
<td>0.518</td>
<td>1.06 (0.76-1.48)</td>
<td>0.722</td>
</tr>
<tr>
<td>Females</td>
<td>1.17 (0.77-1.77)</td>
<td>0.88 (0.48-1.63)</td>
<td>1.26 (0.78-2.03)</td>
<td>0.91 (0.57-1.44)</td>
<td>0.675</td>
<td></td>
</tr>
<tr>
<td>P for interaction</td>
<td>0.653</td>
<td>0.145</td>
<td>0.722</td>
<td>0.675</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NO₂‡</th>
<th>aOR (95%CI) †</th>
<th>p</th>
<th>aOR (95%CI) †</th>
<th>p</th>
<th>aOR (95%CI) †</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1.01 (0.88-1.15)</td>
<td>0.890</td>
<td>1.10 (0.90-1.33)</td>
<td>0.781</td>
<td>0.96 (0.82-1.13)</td>
<td>0.604</td>
</tr>
<tr>
<td>Females</td>
<td>1.15 (0.98-1.36)</td>
<td>1.13 (0.88-1.43)</td>
<td>1.15 (0.94-1.40)</td>
<td>0.75 (0.58-0.98)</td>
<td>0.675</td>
<td></td>
</tr>
<tr>
<td>P for interaction</td>
<td>0.018*</td>
<td>0.530</td>
<td>0.033</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PM₂.⁵‡</th>
<th>aOR (95%CI) †</th>
<th>p</th>
<th>aOR (95%CI) †</th>
<th>p</th>
<th>aOR (95%CI) †</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>0.97 (0.84-1.13)</td>
<td>0.740</td>
<td>1.17 (0.92-1.47)</td>
<td>0.195</td>
<td>0.84 (0.71-1.00)</td>
<td>0.048</td>
</tr>
<tr>
<td>Females</td>
<td>0.96 (0.77-1.20)</td>
<td>1.21 (0.88-1.66)</td>
<td>0.91 (0.70-1.18)</td>
<td>0.80 (0.63-1.01)</td>
<td>0.685</td>
<td></td>
</tr>
<tr>
<td>P for interaction</td>
<td>0.809</td>
<td>0.686</td>
<td>0.685</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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

§Few missing observations

Table 3. Adjusted associations between ambient air pollution exposure at the baseline and prevalent eczema at 53 years by atopy with stratified results by sex.
<table>
<thead>
<tr>
<th>Air pollution markers at baseline§</th>
<th>aOR (95%CI) †</th>
<th>aOR (95%CI) †</th>
<th>aOR (95%CI) †</th>
<th>aOR (95%CI) †</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMR</td>
<td></td>
<td>1.15 (0.95-1.41)</td>
<td>1.46 (0.90-2.38)</td>
<td>0.93 (0.60-1.44)</td>
</tr>
<tr>
<td>Males</td>
<td>Ref group</td>
<td>0.150</td>
<td>0.128</td>
<td>0.837</td>
</tr>
<tr>
<td>Females</td>
<td>Ref group</td>
<td>1.09 (0.82-1.46)</td>
<td>1.41 (0.59-3.41)</td>
<td>1.05 (0.58-1.90)</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td>0.541</td>
<td>0.908</td>
<td>0.613</td>
</tr>
<tr>
<td>NO₂‡</td>
<td></td>
<td>1.06 (0.96-1.16)</td>
<td>1.11 (0.88-1.41)</td>
<td>1.02 (0.84-1.25)</td>
</tr>
<tr>
<td>Males</td>
<td>Ref group</td>
<td>0.246</td>
<td>0.375</td>
<td>0.810</td>
</tr>
<tr>
<td>Females</td>
<td>Ref group</td>
<td>1.09 (0.96-1.25)</td>
<td>1.17 (0.77-1.77)</td>
<td>1.26 (1.00-1.59)</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td>0.954</td>
<td><strong>0.081</strong></td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>PM₂₅‡</td>
<td></td>
<td>1.05 (0.95-1.18)</td>
<td>0.93 (0.70-1.23)</td>
<td>1.07 (0.84-1.36)</td>
</tr>
<tr>
<td>Males</td>
<td>Ref group</td>
<td>0.320</td>
<td>0.611</td>
<td>0.577</td>
</tr>
<tr>
<td>Females</td>
<td>Ref group</td>
<td>1.17 (0.99-1.9)</td>
<td>1.11 (0.64-1.92)</td>
<td>1.47 (1.04-2.06)</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td>0.99(0.85-1.15)</td>
<td>0.86 (0.61-1.20)</td>
<td>0.82 (0.59-1.14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.317</td>
<td>0.800</td>
<td><strong>0.018</strong></td>
</tr>
</tbody>
</table>

Air pollution markers at follow-up

| DMR                               |               | 1.23 (1.01-1.51) | 1.50 (0.91-2.46) | 0.85 (0.54-1.34) |
| Males                             | Ref group     | 0.043         | 0.107         | 0.486         |
| Females                           | Ref group     | 1.37 (1.03-1.83) | 2.09 (0.9-4.83) | 0.97 (0.53-1.79) |
| P for interaction                 |               | 0.435         | 0.479         | 0.567         |
| NO₂‡                              |               | 1.05 (0.96-1.16) | 1.10 (0.87-1.40) | 0.86 (0.68-1.08) |
| Males                             | Ref group     | 0.293         | 0.428         | 0.176         |
| Females                           | Ref group     | 1.06 (0.93-1.21) | 1.17(0.78-1.75) | 0.98 (0.74-1.29) |
| P for interaction                 |               | 0.86 (0.60-1.24) | 0.67 (0.44-1.01) |
| PM₂₅‡                             |               | 1.18 (1.04-1.33) | 1.03 (0.76-1.41) | 1.00 (0.77-1.29) |

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### Table 4. Adjusted associations between ambient air pollution markers and aeroallergen sensitisation with stratified results by sex

<table>
<thead>
<tr>
<th>Aerosol allergen sensitisation (1,218 / 2,207)</th>
<th>Air pollution markers at baseline</th>
<th></th>
<th>Air pollution markers at follow-up</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR (95%CI) †</td>
<td>p</td>
<td>aOR (95%CI) †</td>
<td>p</td>
</tr>
<tr>
<td>DRM</td>
<td>1.09 (0.91-1.32)</td>
<td>0.350</td>
<td>1.45 (0.95-1.39)</td>
<td>0.168</td>
</tr>
<tr>
<td>Males</td>
<td>1.07 (0.81-1.41)</td>
<td>0.322</td>
<td>1.27 (0.96-1.67)</td>
<td>0.630</td>
</tr>
<tr>
<td>Females</td>
<td>1.12 (0.86-1.45)</td>
<td>0.769</td>
<td>1.06 (0.81-1.39)</td>
<td>0.398</td>
</tr>
<tr>
<td>P for interaction</td>
<td>0.765</td>
<td>0.573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO₃‡</td>
<td>1.04 (0.96-1.14)</td>
<td>0.93-1.12</td>
<td>1.02 (0.93-1.12)</td>
<td>0.630</td>
</tr>
<tr>
<td>Males</td>
<td>1.09 (0.96-1.23)</td>
<td>0.215</td>
<td>1.03 (0.90-1.16)</td>
<td>0.573</td>
</tr>
<tr>
<td>Females</td>
<td>1.01 (0.89-1.15)</td>
<td>1.03 (0.90-1.18)</td>
<td>0.93-1.12</td>
<td>0.630</td>
</tr>
<tr>
<td>P for interaction</td>
<td>0.765</td>
<td>0.573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM₂.₅‡</td>
<td>1.07 (0.96-1.19)</td>
<td>0.15 (0.93-1.30)</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1.19 (1.01-1.40)</td>
<td>1.36 (1.06-1.50)</td>
<td>0.93-1.29</td>
<td>0.630</td>
</tr>
<tr>
<td>Females</td>
<td>0.99 (0.86-1.15)</td>
<td>1.09</td>
<td>0.93-1.29</td>
<td>0.630</td>
</tr>
</tbody>
</table>

*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.

‡An influential outlier was removed from this regression model.
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<table>
<thead>
<tr>
<th>No atopy or eczema (1,005/2,368)</th>
<th>Atopy alone (1,207/2,368)</th>
<th>Non-atopic Eczema (54/2,368)</th>
<th>Atopic Eczema (102/2,368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aOR (95%CI) †</td>
<td>aOR (95%CI) †</td>
<td>aOR (95%CI) †</td>
<td>aOR (95%CI) †</td>
</tr>
<tr>
<td>p</td>
<td>p</td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>DRM</td>
<td>Ref group</td>
<td>1.15 (0.96-1.42)</td>
<td>1.65 (0.92-2.96)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td>0.131</td>
<td>0.092</td>
</tr>
<tr>
<td>Females</td>
<td>Ref group</td>
<td>1.10 (0.82-1.46)</td>
<td>1.88 (0.66-5.31)</td>
</tr>
<tr>
<td>P for interaction</td>
<td></td>
<td>0.547</td>
<td>1.66 (0.81-3.40)</td>
</tr>
<tr>
<td>0.178</td>
<td>0.092</td>
<td>0.225</td>
<td>0.671</td>
</tr>
<tr>
<td>*P-value less than 0.05</td>
<td>†Adjusted for: age, sex, household cooking by indoor combustion of solid or gas fuels, occupation, highest education level, smoking and second-hand smoking.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡ORs (95% CI) per an IQR increase in air pollution marker</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Adjusted associations between ambient air pollution exposure at the baseline and persistent eczema by atopy with stratified results by sex.
<table>
<thead>
<tr>
<th>Females</th>
<th>Ref group</th>
<th>1.41 (0.91-1.19)</th>
<th>1.00 (0.68-1.47)</th>
<th>0.57 (0.36-0.91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P for interaction</td>
<td>0.937</td>
<td>0.137</td>
<td>0.011</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Males</th>
<th>Ref group</th>
<th>1.17 (0.99-1.38)</th>
<th>0.94 (0.48-1.87)</th>
<th>1.53 (1.04-2.25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>Ref group</td>
<td>0.99 (0.85-1.15)</td>
<td>0780 (0.47-1.05)</td>
<td>0.71 (0.49-1.02)</td>
</tr>
<tr>
<td>P for interaction</td>
<td>0.296</td>
<td>0.645</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>

*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

*Supplementaryfigure 1 (.jpg)*

*Directed acyclic graph (DAG)*

*SupplementaryTable 1 (Microsoft Word Document (.docx))*

*Confounder Table of definitions*

*SupplementaryTable 2 (Microsoft Word Document (.docx))*

Summary statistics and predictors of loss to follow-up between baseline (2002 proband study) and follow-up (2012 proband study) stratified by sex

*SupplementaryTable 3 (Microsoft Word Document (.docx))*

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Prevalence, incidence and persistence 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 sex and for participants that did not change their address.

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

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

**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))**

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

**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 sex.
Participant Flow Chart

8893 Tasmanian school children enrolled in 1988, cohort born in 1981

Multiple follow-up conducted in 1974, 1979 and 1991

7312 traced in 5th survey

5729 responded the 5th survey

358 respondents without air pollution data

5501 completed 5th survey and have air pollution data

2238 participants did not complete the 6th survey

3153 completed 5th and 6th survey and have air pollution data

2369 have a valid SPT result at 6th survey
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

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

Date:
2021-08

Citation:

Persistent Link:
http://hdl.handle.net/11343/265942