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

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Abstract

Background:There is limited information on risk factors for eczema in adults.Recent evidence suggeststhat air pollution may be associated with increased incidence of eczema in adults. We aimed to assess this possible association.

Methods:Ambientair 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 persistencewere assessed from surveys, while IgE sensitisation was assessed using skin prick tests. The presence or absence of eczema and sensitisationwas 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 betweenambient 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 oddsof prevalent eczema (OR=1.15 [95%CI 0.98-1.36])and prevalent atopiceczema (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 oddsof eczema, only inmales, and aeroallergen sensitisation in both genders.

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

Word count: 247

Introduction

Eczema, also known as atopicdermatitis, is a chronic inflammatory skin condition, characterized by defective skin barrier function and itaffectsaround 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_2cytokines 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 pollutantshave beenassociated with increasedeczema prevalence.[6]It has been proposed that air pollutants may generate reactive oxygen species which damage the outer-most layer of the skin through oxidative stress.[7]This processmay 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 ofambient air pollution on the prevalence and incidence of eczema in adultshas received less attention.

A recent longitudinal analysis of middle aged Germanwomen, whichinvestigated the influence of traffic related air pollutionon lung function, inflammation and Aging (SALIA) found thatbaseline concentrations of traffic-related air pollution (TRAP) markers (NO_2, NO_x, $PM_{2.5}$ and PM_{10}) were significantly associated withincreased odds of incident eczema over a 19-year follow-upperiod,these associations being stronger for NAE.[5] Therefore, environmental factors, includingair 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 pollutionon adult eczemamay lead totargeted interventionstopreventeczema.Using data from a large established longitudinal health study, we

investigated whether exposure to ambient air pollutionwas associated with the incidence and prevalence of AE or NAE in middle-aged adultsof both sexes.

Methods

Study population

The Tasmanian Longitudinal Health study (TAHS) is a population-based prospective cohortstudy, 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.[9]Several follow-up surveys have subsequently been conducted and study methodology has been reported in detail elsewhere.[9]The data for this analysiscame from participants ofthe2002 and 2012proband studies when participantshad a mean age of43 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 in2002 and 2012 proband studieswere 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.[10]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.[11]

Nitrogen dioxide (NO_2)

A satellite-based land-use regression model was used to assign mean annual NO_2 exposures for the 2002 and 2012 proband studies.[12]Briefly, theland-use regression model-predicted mean annual NO_2 levels were based on tropospheric NO_2 columns derived from satellite observations in combination with other predictors such as land use and roads, to estimate ground-level NO_2 across Australia.[12] As more

than half of the ambient $NO_2$is attributedto on-road sources, NO_2 is a reasonable proxy for TRAP.[13]The model's development and validation are described in detail elsewhere, and it explained 81% of spatial variability in measured annual NO_2 at all regulatory monitoring sites in Australia. [12] Mean annual residential exposures to outdoor NO_2 were estimated and assigned based on participants' geocoded addresses atbaseline (2002 proband study) andfollow-up (2012 proband study).

Fine particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$)

The methods are explained in more detail elsewhere.[14] In brief, satellite-based estimates for Australia of ground-level $PM_{2.5}$ were used as a land-use regression predictor, with other spatial predictors of $PM_{2.5}$. This model explained 63% of spatial variability in measured annual $PM_{2.5}$ (RMSE: 1 $\mu g/m^3$).[14] The mean annual residential exposures to outdoor $PM_{2.5}$ were estimated and assigned based on participants' geocoded addresses at baseline and follow-up.In Australia,traffic-related sources of $PM_{2.5}$are estimated to account foronly 17%of ambient $PM_{2.5}$mass, whilethe majority of ambient $PM_{2.5}$is from other anthropogenic sources (i.e. wood heaters, power stations, etc).[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.[16]Participants were classified as having prevalent eczema if they reported "yes" to allthree 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 twoproband studiesi.e. between 43 and 53 years.The participants were classified as having Incident eczema if theyanswered "no" to ''Have you ever had eczema or any skin allergy?'' at baseline(2002 proband study), but reported eczema based on theISAAC definition[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 baselineand reported eczema based on the ISAAC definition[16] at follow-up.

Atopic status

Subclassification as AE or NAE was based on skin prick testing (SPT) results at age 53 years.[9] 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. Histamine was used asthe positive control and normal saline as the negative control. After 10 to 15 mins, the wheal diameters were measured in two perpendicular directions in millimetresand 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.[17]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) Prevalenteczema,2) Incident eczema,3) Persistent eczema, 4)Prevalent and incident eczema sub grouped by atopic status (neither, atopy alone, non-atopic and atopic eczema) and5) Sensitisation (regardless of eczema status). Second, in accordance with the eczema and atopy classification usedin the SALIA cohort study[5], we examined NAE incidence and prevalence using three increasinglyrestricted 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 pollutionand each outcome. The coefficientsrepresented 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) (Supplementaryfigure 1) was developed to specify the hypothesized causal relationships and to determinewhich confounders to include in the model(SupplementaryTable 1).Thepotential presence of non-linearity of theseassociations 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 sexwas 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 2002-08proband study (figure 1), of whom 338 were excluded because the participantdid not provide a residential address allowingambient air pollutionexposure to be estimated. Of the remaining 5391participants, 2238 were excluded because they did not participate in the 2012 proband study. Of the 3153 with data from both the 2002 and 2012proband 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 smokeand being from lower socioeconomic status, less likely to report hay fever.(SupplementaryTable 2).

The mean age at the 2012 follow-up was 53 yearsand 50.3% were males (Table 1).At 53 years 281 participants (8.96%)of the participantshad prevalent eczema, 115 participants (3.67%)had incident eczema and 201 participants(6.38%) had persistent eczema(SupplementaryTable 3).When comparing baseline and follow-up concentrations, ambient air pollution markers decreasedslightly 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 $NO_2$and prevalent eczema (Table 2).Thus,in males,baseline exposure to $NO_2$was associated with increased oddsof having prevalent eczema at follow-up (adjusted odds ratio (aOR):1.15 [95%CI 0.98-1.36] per IQR [2.27ppb] NO_2 increase), while higher exposure in females wasassociated, although non significantly,with reducedoddsofprevalent eczema(aOR:0.83 [95%CI 0.67-1.03 per 2.27 ppb NO_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_2exposure was associated with increased oddsof having AE (aOR 1.26 [1.00-1.59])per 2.27 ppb NO_2 increase, while baseline $PM_{2.5}$ was associated with increased odds of having AE (aOR 1.47 [1.04-2.06])per 1.56 µg/m^3 $PM_{2.5}$ increase.By contrast, infemales, higher NO_2exposure at baseline was associated with a reduced odds of having AE (aOR0.65 [95% CI 0.43-0.99])per 2.27 ppb NO_2 increase.A similar trend was seen at follow-up,$NO_2$was associated witha reduced odds of AE (aOR0.67 [0.44-1.01]) per 2.21 ppb increase (Table3).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 (SupplementaryTable4).

Association between ambient air pollution at baseline and incidenteczema.

There wasweak evidence of associations, nor effect modification by sex, between baselineambient air pollution markers at baseline and incidenteczema (Table 2). Similarly,when incident eczema was classified by atopy groups(Supplementary Table5),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_2 exposure and as a result, increased oddsofpersistent eczema was stronger in males thanfemales (Table 2). Likewise, when persistent eczema was classified by atopy status (Table5), there was evidence of interaction by sex (P for interaction<0.1). As such, baseline NO_2 exposurein males was found to increase persistent AE odds(aOR1.25 [95% CI 0.95-1.65]per 2.27 ppb NO_2 increase, while in females, the association tended towards reduced odds of persistent AE (aOR0.57 [95% CI 0.36-0.91] per 2.27 ppb NO_2 increase). Similarly, baseline $PM_{2.5}$ exposure in males increased the odds of persistent AE (aOR 1.53 [1.04-2.25] per 1.56 μg/m^3 $PM_{2.5}$ increase) and in females the odds of persistent AE was reduced (aOR 0.71 [0.49-1.02] per 1.56 μg/m^3 $PM_{2.5}$ increase).

Restricted definition of non-atopic eczema

When using the same analytic approach as the SALIA cohort study[5]there were no significant associations between ambient air pollution markers at baselineand incident NAEwith increasing the strictness (i.e. those participants without hay fever and SPT negative) of the definition (SupplementaryTable6).However,a non-significant trend between DMR at follow-up and increasedodds of prevalent NAE was seen,and thiseffect became stronger when the NAE definition becamestricter (SupplementaryTable6). Furthermore,when the analyses were restricted to women, there wasan associationbetween DMR at follow-up and increasedodds of prevalent eczema(SupplementaryTable7).

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

At baseline, increased exposure to $PM_{2.5}$ was associated with increased odds of being sensitized to aeroallergens (aOR 1.15 [95% CI 1.03-1.30])per 1.56 μg/m^3 $PM_{2.5}$ increase) at age 53 (Table4). Furthermore, there were associations between ambient air pollution markers and specific aeroallergen sensitisations that are described in more detail in SupplementaryTable8.

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 ofprevalent atopiceczema.In contrast,forfemales, higher exposure to $NO_2$was associated with a paradoxicalreduced oddsof 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 ofallergic 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 betweenambient air pollution and increased eczema prevalencein 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 be due to differences in skin morphology, occupational exposures in adults andbehaviour.[23]As has been reported previously in this age group,[24] women tend tospent more time indoors compared to men, with men reported spending almost twice the amount of time outside compared to women (SupplementaryTable 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 thephysiological, 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 similarnon-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 sexhormone 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)andGermany (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 sensitisationvia inflammatory oxidative stress leading to skin barrier dysfunction.[32]Ambient air pollutionmay 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.[35]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. Strengthsincludeaccess to alarge population-based prospective cohort study with long follow-up allowing for a 10-year assessment period, well-characterizeddefinitions of eczema with objective measures ofSPTand land-use regression models.While the questions and definitions used were well validated,[36] alimitation is the reliance on self-reporting.

Unfortunately, there were no data on the frequency or severity of symptomsandthe 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.[37]As such, while we cannot exclude this possibility, it seems unlikely. Also,it is possible thatresidual 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 CaucasianandAnglo-Celtic, the findings may not be generalizable to other ethnicities.

Conclusion

Our findings suggest thathigher ambient air pollution exposure is associated with greater oddsof AE in adult men and an increased oddsof 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)

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 theTAHS 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.

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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Tables (each Table complete with title and footnotes);

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

Co-variates	2002 Survey	2012 Survey
Age (years). Mean (SD); min-max	43 (0.82); 41-44	53 (0.95); 50.94-55.58
Male. %(n/N)	50.3 (1,586/3,153)	
Body mass index (kg/m^2). Mean (SD); min-	26.27 (4.61); 16.31- 52.33	28.4 (5.48); 16.9-58.86

max		
Heating by indoor combustion of solid† or gas fuel. %(n/N)	53.2 (1,679/3,153)	43.8 (1,383/3,153)
Cooking by indoor combustion of solid† or gas fuel. %(n/N)	24.1 (757/3,153)	28.7 (886/3,081)
Years of education. %(n/N)		
< Grade 12	34.7 (1,093/3,153)	32.7 (1,020/3,153)
Grade 12 or equivalent	9.5 (300/3,153)	7.8 (242/3,153)
>Grade 12	55.8 (1,755 /3,153)	59.6 (1,860/3,153)
Occupation. %(n/N)		
Managers and Professionals	30.9 (970/3,135)	35 (1,087/3,105)
Associate Professionals	11.4 (357/3,135)	14.1 (439/3,105)
Tradespersons and Advanced Clerical	20.7 (648/3,135)	18.8 (585/3,105)
Intermediate clerical and production	18 (563/3,135)	18 (558/3,105)
Elementary clerical, laborers and related	19 (597/3,135)	14 (436/3,105)
Smoking status. %(n/N)		
Never	44.5 (1,404 /3,143)	44.5 (1,402/3,120)
Former	31.6 (995/3,143)	38.4 (1,211/3,120)
Current	23.6 (744 /3,143)	16.1 (507 /3,120)
Current second-hand smoke. %(n/N)	11.6 (358 / 3,096)	7.8 (244/3,153)
Hay fever ever. %(n/N)	53 (1,660/3,153)	55.8 (1,757/3,153)
Living <200m from a major road	813 /3,153 (25.78%)	787 /3,048 (25.82%)
NO_2 (ppb) median [IQR; 25-75%le]	4.24 [2.27; 3.43-5.7]	2.72 [2.21; 1.93-4.14]
$PM_{2.5}$ ($\mu g/m^3$) median [IQR; 25-75%le]	6.48 [1.49; 5.76-7.26]	6.4 [1.56; 5.63-7.19]

† Solid fuels are coal and wood.

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

	Eczema prevalence (281/3,135) §	**Eczema incidence** (115/3,152) §	**Eczema persistence** (201/3150) §
Air pollution markers at baseline			

	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	1.06 (0.76-1.48) 0.722
Males	1.17 (0.77-1.77)	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)	0.91 (0.57-1.44)
P for interaction	0.653	0.145	0.675
NO_2‡	1.01 (0.88-1.15) 0.890	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)	1.15 (0.94-1.40)
Females	0.83 (0.67-1.03)	1.02 (0.74-1.41)	0.75 (0.58-0.98)
P for interaction	**0.018***	0.530	**0.033**
$PM_{2.5}$‡	0.97 (0.84-1.13) 0.740	1.17 (0.92-1.47) 0.195	0.84 (0.71-1.00) 0.048
Males	0.96 (0.77-1.20)	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)	0.80 (0.63-1.01)
P for interaction	0.809	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

§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.

	No atopy or eczema (972/ 2,360)	**Atopy alone** (1,172/ 2,360)	**Non-atopic Eczema** (83 / 2,360)	**Atopic Eczema** (133 / 2,360)

Air pollution markers at baseline§				
	aOR (95%CI) †	aOR (95%CI) †	aOR (95%CI) †	aOR (95%CI) †
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_2‡	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)	1.17 (0.77-1.77)	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	**0.081**	**0.005**
$PM_{2.5}$‡	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	**0.018**
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_2‡	Ref group	1.05 (0.96-1.16)	1.10 (0.87-1.40)	0.86 (0.68-1.08)
		0.293	0.428	0.176
Males	Ref group	1.06 (0.93-1.21)	1.17(0.78-1.75)	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	**0.099**	**0.097**
$PM_{2.5}$‡	Ref group	1.18 (1.04-1.33)	1.03 (0.76-1.41)	1.00 (0.77-1.29)

		0.010	0.833	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.

§An influential outlier was removed from this regression model

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

	Aeroallergen sensitisation (1,218 / 2,207)	
	Air pollution markers at baseline	Air pollution markers at follow-up
	aOR (95%CI) † p	aOR (95%CI) † p
DRM	1.09 (0.91-1.32) 0.350	1.45 (0.95-1.39) 0.168
Males	1.07 (0.81-1.41)	1.27 (0.96-1.67)
Females	1.12 (0.86-1.45)	1.06 (0.81-1.39)
P for interaction	0.769	0.398
NO_2‡	1.04 (0.96-1.14) 0.322	1.02 (0.93-1.12) 0.630
Males	1.09 (0.96-1.23)	1.03 (0.90-1.16)
Females	1.01 (0.89-1.15)	1.03 (0.90-1.18)
P for interaction	0.765	0.573
$PM_{2.5}$‡	1.07 (0.96-1.19) 0.215	1.15 (1.03-1.30) **0.017**
Males	1.19 (1.01-1.40)	1.36 (1.06-1.50)
Females	0.99 (86-1.15)	1.09 (*0.93-1.29)

P for interaction	0.178	0.456

*P-value less than 0.05

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

‡ORs (95% CIs) per an IQR increase 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 sex.

	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				
	aOR (95%CI) † p	aOR (95%CI) † p	aOR (95%CI) † p	aOR (95%CI) † p
DRM	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_2‡	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	**0.011**
$PM_{2.5}$‡	Ref group	1.06 (0.95-1.18)	0.77 (0.55-1.08)	1.00 (0.77-1.31)
		0.332	0.131	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)	0780 (0.47-1.05)	0.71 (0.49-1.02)
P for interaction		0.296	0.645	**0.009**

*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))

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

SupplementaryTable 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 sexand for participants that did not change their address.

SupplementaryTable 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

SupplementaryTable 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)

SupplementaryTable7 (Microsoft Word Document (.docx))

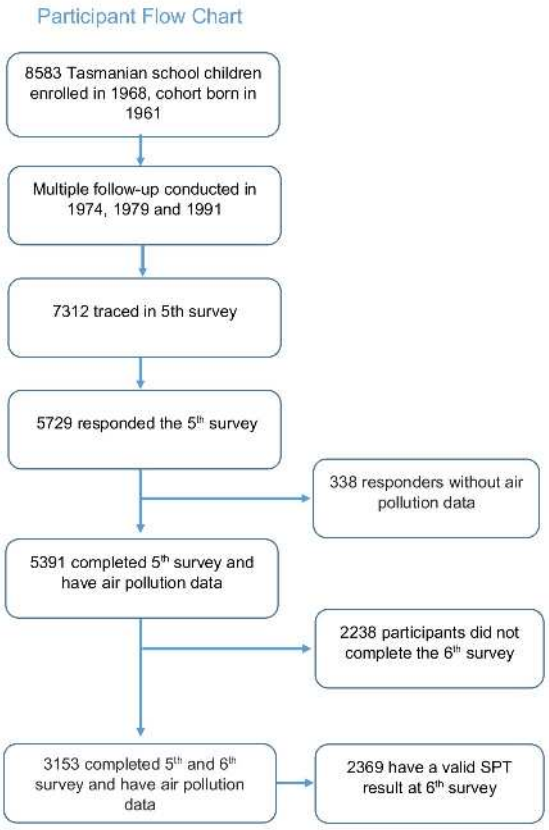
Associations between ambient air pollution at baseline and incident symptoms of eczema after age 43 years following exclusion of atopic subjects, with increasing strictness from left to right in females only (SALIA cohort analytical approach).

SupplementaryTable8 (Microsoft Word Document (.docx))

Adjusted associations between air pollutants and specific aeroallergen

SupplementaryTable 9 (Microsoft Word Document (.docx))

Average outside time at 2012 follow-up by sex



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