# Proposal to use TAHS dataset

**Title:** Association of non-atopic eczema and traffic-related air pollution (TRAP) in adulthood/middle age

# Project synopsis:

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. There is limited information on risk factors for eczema in adults. In paediatric studies, higher levels of ambient air pollutants have been associated with increased eczema prevalence. It has been proposed that air pollutants may generate reactive oxygen species which damage the outer-most layer of the skin through oxidative stress compromising the structural integrity of the epidermal barrier. Better understanding of the potential effects of ambient air pollution on adult eczema may lead to targeted interventions to prevent eczema. We aim to investigate whether exposure to ambient air pollution was associated with the incidence and prevalence of eczema in middle-aged adults. Ambient air pollution exposures (distance from a major road, nitrogen dioxide [NO2], fine particulate matter with an aerodynamic diameter ≤2.5 µm [PM2.5]) will be 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 will be assessed from surveys, while IgE sensitisation was assessed using skin prick tests. The presence or absence of eczema and sensitisation will be classified into four groups: no atopy or eczema, atopy alone, non-atopic eczema, and atopic eczema. Adjusted logistic and multinomial regression models will be fitted to estimate associations between ambient air pollution and eczema, and interaction by sex was assessed.

# Rationale:

Eczema is characterised by defective skin barrier function, and the World Allergy Organization has recognised at least two types of disease. An atopic type with skin inflammation driven by T-cell responses and TH2 cytokines in the initiating phase, which is usually associated with IgE-mediated sensitisation to environmental allergens and high levels of total IgE and allergen-specific IgE. And a nonatopic type of eczema with normal levels of total IgE and a lack of sensitisation to environmental allergens. [1] In older patients, particularly those with chronic eczema, other nonatopic inflammatory mechanisms might be involved. [2] Further studies have been recommended into the causes and mechanisms of this nonatopic eczema. [3]

One recent study analysed the association between traffic-related air pollutants and incident and prevalent nonatopic eczema in middle-aged women from the SALIA cohort which was conducted in the Ruhr area and Southern Münsterland, Germany. [4] Venous blood was drawn in a subsample of participants and assayed for total serum IgE at baseline by using nephelometry or ELISA and at follow-up, ImmunoCAP was used. Exposure to air pollution was assessed by using land-use regression models according to the European Study of Cohorts for Air Pollution Effects (ESCAPE) protocols, to estimate annual concentrations of nitrogen dioxide (NO2), oxides of nitrogen (NOx), fine particulate matter with an aerodynamic diameter of 2.5 µm or less (PM2.5) mass, and particulate matter with an aerodynamic diameter of less than 10 µm (PM10) at participants’ residential addresses. Baseline concentrations of pollution markers were associated with significantly increased odds of incident eczema symptoms after 55 years of age (between baseline and follow-up investigation), and associations were stronger for nonatopic eczema. These analyses revealed that eczema in the elderly differed from atopic eczema, especially its association with air pollution. The authors proposed that environmental factors, such as air pollution, might be more relevant for eczema in middle aged individuals than in children, especially for a nonatopic type of eczema. As this was the first study to report such associations, replication is required for these findings.

Accordingly, this study aims to replicate these findings by examining whether exposure to air pollution was associated with the incidence of nonatopic eczema in adulthood by using a cohort of middle-aged adults. We plan to use the Tasmanian Longitudinal Health Study (TAHS) to achieve this aim.

# Research Questions:

1. Is exposure to air pollution (NO2, NOx, PM10 and PM2.5) associated with the prevalence of atopic-eczema and/or non-atopic-eczema in middle age individuals?
2. Is exposure to air pollution (NO2, NOx, respirable particles (PM10), and fine particles (PM2.5)) associated with the incidence of eczema in middle aged individuals?
   1. Does this association vary according to eczema type (atopic versus non-atopic eczema)?

# Methods

## Study population

The Tasmanian Longitudinal Health STUDY (TAHS) is a population-based prospective cohort study, which has been followed up since 1968 by recruiting (98.7%, n=8583) of 7 year old children attending schools in the state of Tasmania, Australia. [5] Several follow-up surveys have been conducted since its beginning. This study will use data from the probands of follow ups in 2002 and 2012. [6, 7] Participants at the 2002 follow-up had a mean age of ~43 years, and at the 2012 follow-up they had about 53 years, which will provide a 10-year follow-up period.

Sample from TAHS:

Follow up in 2002-08, n = 5,729 probands completed questionnaires mean age of 43 years and 1405 probands performed laboratory testing.

Follow up in 2012, n = 3609 probands completed the survey and 2443 probands performed laboratory testing and have skin prick test data available.

Participants completed a self-administered postal survey that collected sociodemographic, occupational, residential, health service use, medical diagnoses, smoking, family history, reproductive data, and symptoms of diseases, both at baseline and at the clinical follow-up examination,.

## Variables:

Air pollution exposure variables: 1) Distance to major roads (**DMR** - living<200m from a major road), annual concentrations of 2) nitrogen dioxide (**NO2**), and 3) fine particulate matter with an aerodynamic diameter of 2.5 µm or less mass (**PM2.5**).

**DMR.**  Distance from each participant's residence to the nearest major road at the 45 year follow up was calculated using ArcGIS 10.1 software (Environmental Systems Research Institute, Redlands, CA). Major roads were deﬁned using public sector mapping agencies (PSMA), Australia transport hierarchy codes 301 and 302. [8] Participants were categorised into two groups: (i) living <200m; and (ii) living >200m from a major road.

**NO2.** A satellite based land use regression (LUR) model was used to assign mean annual NO2 exposures at the 45year follow up. [9] Brieﬂy, this LUR model predicted mean annual NO2 levels 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. [9] Mean annual residential exposures to outdoor NO2 were estimated and assigned based on participants' geocoded addresses at 45 years.

**PM2.5** will soon be available for the TAHS using land use regression models.

Primary outcome variable: Prevalence of eczema at age 53 will be based on the participant report of current “itchy rash in the past 12 months” and this will be divided into current atopic and non-atopic eczema based on skin prick test results.

Secondary outcome variable: Incidence of eczema between 43 and 53 years of age. This will be based on self-reported prevalent eczema presence or absence at each time point. At age of 43 years, the question ‘‘Have you ever had eczema or any kind of skin allergy?’’ to identify and exclude anyone with a prior history of eczema. The incidence of eczema symptoms at the 53-year follow-up examination will be defined by the following question: ‘‘have you ever had an itchy rash that was coming and going for at least 6 months? ’’ and ‘‘Have you had this itchy rash at any time in the last 12 months?’’ which corresponded to newly developed eczema symptoms after age 43 years (between baseline and follow-up investigation). This will then be further categorised into atopic and non-atopic eczema based on the SPT at age 53 years .

Covariates: age, body mass index, highest educational status of participant or spouse, household heating by indoor combustion of fossil fuels, smoking (categorized as current, former, or never smoking), and exposure to second-hand smoke at home or occupational exposures (as defined by an asthma “Job Exposure Matrix”. Final model adjustments will be decided using causal diagrams (DAGS).

## Statistical Analysis:

For the primary analyses, only participants who are eczema free at baseline (age 43 years) will be included. Logistic regression models will be fitted to the incident eczema outcomes. Coefficients will be estimated per interquartile range (IQR) of air pollutants and expressed as odds ratios (ORs) with 95% CIs. Potential non-linearity of associations will be assessed using Stata’s “fracpoly” command. Potential effect modification by sex, FLG null mutations, and GST polymorphisms will be explored using likelihood ratio tests.

# Data display:

Table 1. Demographic characteristics of included sample based on responses at 6th decade follow-up

|  |  |  |
| --- | --- | --- |
| Age at second follow-up | Mean(SD); minimum-maximum | 53 (0.95); 50.79-55.58 |
| Participant sex  Female  Male | n/N (%)  n/N (%) | 1,842/3,609 (51.04%)  1,767/3,609 (48.96%) |
| Age at incident eczema symptoms during adulthood after age 50 | Mean (SD) ; minimum-maximum | 51.17 (1.18); 50-54 |
| Body mass index (kg/m2) | Mean (SD); minimum-maximum | U2 and U3 required |
| Residential heating  Gas  Coal or wood fire  Electricity  Reverse cycle air-conditioning | n/N (%)  n/N (%)  n/N (%)  n/N (%) | 344/3,609 (9.53%)  1,313/3,609 (36.38%)  1,087/3,609 (30.12%)  1,706 /3,609 (47.27%) |
| Residential cooking facility  Gas  Electricity  Coal, coke or wood | n/N (%)  n/N (%)  n/N (%) |  |
| Years of education  <10 y  10 y  >10 y | n/N (%)  n/N (%)  n/N (%) |  |
| Smoking  Never  Former  Current | n/N (%)  n/N (%)  n/N (%) |  |
| Second-hand smoke ever | n/N (%) |  |
| Hay fever ever | n/N (%) |  |

Table 2. Description of eczema

|  |  |
| --- | --- |
| All participants with eczema  Prevalence of itchy rash in the last 12 months  Prevalence of itchy rash that was coming and going for at least 6 months  Prevalence of recurring rash that also impacted on the flexures  -SPT positive  -SPT negative | n/N (%)  n/N (%)  n/N (%)  n/N (%)  n/N (%)  n/N (%) |

TABLE 3. Description of air pollution exposures

|  |  |  |
| --- | --- | --- |
| Air pollution exposures | 45 year follow up | 53 year follow up |
| Living <200m from a major road | n/N (%) | n/N (%) |
| NO2 (ppb) | mean [SD] | mean [SD] |
| - Fine particulate matter with an aerodynamic diameter of 2.5 µm or less mass (PM2.5) | mean [SD] | mean [SD] |

TABLE 4. Associations between air pollutants at baseline and prevalence of eczema at age 53 years

|  |  |  |  |
| --- | --- | --- | --- |
|  | Eczema | Atopic-Eczema | Non-atopic Eczema |
| N | n/N | n/N | n/N |
| DRM<200m | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| NO2 | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| PM2.5 | OR (95% CI) | OR (95% CI) | OR (95% CI) |

Adjusted for: ….

Table 5. Associations between air pollutants at follow-up and incident symptoms of eczema after age 43 years

|  |  |  |  |
| --- | --- | --- | --- |
|  | Eczema | Atopic-Eczema | Non-atopic Eczema |
| N | n/N | n/N | n/N |
| DRM<200m | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| NO2 | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| PM2.5 | OR (95% CI) | OR (95% CI) | OR (95% CI) |

Adjusted for: ….

# References

1. Tanei R, Hasegawa Y: Atopic dermatitis in older adults: A viewpoint from geriatric dermatology. *Geriatrics & gerontology international* 2016, 16 Suppl 1:75-86.

2. Bieber T, D'Erme AM, Akdis CA, Traidl-Hoffmann C, Lauener R, Schappi G, Schmid-Grendelmeier P: Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go? *The Journal of allergy and clinical immunology* 2017, 139(4s):S58-s64.

3. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J *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.

4. Hüls A, Abramson MJ, Sugiri D, Fuks K, Kramer U, Krutmann J, Schikowski T: Nonatopic eczema in elderly women: Effect of air pollution and genes. *The Journal of allergy and clinical immunology* 2019, 143(1):378-385.e379.

5. Matheson MC, Abramson MJ, Allen K, Benke G, Burgess JA, Dowty JG, Erbas B, Feather IH, Frith PA, Giles GG *et al*: Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS). *International journal of epidemiology* 2017, 46(2):407-408i.

6. Wharton C, Dharmage S, Jenkins M, Dite G, Hopper J, Giles G, Abramson M, Walters EH: Tracing 8,600 participants 36 years after recruitment at age seven for the Tasmanian Asthma Study. *Australian and New Zealand Journal of Public Health* 2006, 30(2):105-110.

7. Bowatte G, Erbas B, Lodge CJ, Knibbs LD, Gurrin LC, Marks GB, Thomas PS, Johns DP, Giles GG, Hui J *et al*: Traffic-related air pollution exposure over a 5-year period is associated with increased risk of asthma and poor lung function in middle age. *European Respiratory Journal* 2017, 50(4):1602357.

8. The Intergovernmental Committee of S, Mapping: Assessing the Feasibility of a National Road Classification. Report to ICSM on National Road Classification Developments. 2006.

9. 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.