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Cohort profile

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Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS)

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Why was the cohort set up?

The Tasmanian Longitudinal Health Study (TAHS), originally named the Tasmanian Asthma Survey, was initiated to examine the prevalence and natural history of asthma in childhood.[1] In 1967 the Tasmanian Health Minister, who was the head of the School Health Service, gave his approval to carry out the survey on all children born in 1961 and attending school in the island state of Tasmania, Australia. The original aims of the survey were to provide an epidemiological description of childhood asthma, which has a variable natural history requiring: (i) an estimate of its prevalence among children of a suitable age; (ii) an estimate of the probability that an individual will change disease status during any given period; and (iii) an estimate of any secular trend, specifically any tendency for the incidence to vary over time.

The original study cohort consisted of all Tasmanian school children born in 1961, who would be aged 7 years at the time of the baseline survey. This was: (i) to ensure that participants were old enough to adequately perform spirometry manoeuvres; (ii) to ensure that participants were young enough to allow for follow-up of at least 7 years through the school system; and (iii) to reduce parental recall error of early life exposures and symptoms by limiting the recall time to a maximum of 7 years. At the baseline survey, questionnaires on both parents and all siblings were also collected, making the TAHS one of the first and largest family studies of respiratory disease in the world. Since the baseline survey, the cohort has been followed up several times as outlined below. The original study investigators planned to recruit another cohort of 7-year-old children in 4 years from the 1968 study, to investigate secular trends in asthma incidence, but this was never undertaken.

Who is in the cohort, how often have they been followed up, and what is attrition like?

The TAHS is a population-based prospective cohort study, which has been followed up from 1968 until the current follow-up when participants are in their sixth decade of life. Details of these follow-ups have been described previously.[1–3] Figure 1 outlines the follow-up over the past five decades, which is described in detail in the sections below.

The TAHS 1968 baseline study

The names of children born in 1961 were obtained from the School Health Service records. This included all public schools in Tasmania, and the private schools in Tasmania also agreed to participate and provided the names of all 1961-born children. A set of questionnaires relating to the medical history of the child and his/her parents and siblings were distributed by schools to a total of 8683 children. These questionnaires were accompanied by a letter to the parents of each child explaining the survey and included a detachable section seeking parental consent for the child to participate. A completed survey was returned by the parents of 8583 (98.8%) children. Once the questionnaires were returned, the children were invited to participate in a medical examination with particular emphasis on clinical symptoms of the upper and lower respiratory airways and spirometry.[1] Of the 8583 children who completed the survey, 93.5% ($n = 8022$) completed lung function tests.

Subsequent studies of TAHS probands

Proband 1974 study

In 1974 (average age 12 years) a follow-up survey of all children from the 1968 cohort was undertaken. A total of 7380 (87.3%) were traced and completed another respiratory survey. Of these 7380, a stratified random sample of 851 was selected according to symptoms of cough and wheeze in 1968 and 1974 (wheeze only, cough only, both wheeze and cough, and neither symptom in both surveys) for a clinical follow-up including spirometry. Of this sample of 851, more than 98% (837) with an average age of 13 years completed the clinic visit.

Proband 1979 study

In 1979 (average age 18 years) another survey was conducted of the stratified random sample from 1974. Of the 851 who were eligible, 85% (723) were traced to an address and, of these traced participants, 658 (91%) completed brief postal questionnaires. Those respondents were then invited for a clinical study that included a detailed respiratory questionnaire and clinical examination, which included the performance of spirometry. Of the 658 invited for the clinical study, only 218 (33%) completed the full study (spirometry and questionnaires); 92 (14%) completed the questionnaire only; and the remaining 348 (53%) declined the invitation.

Proband 1991 study

The next follow-up was undertaken in the period 1991–93 (average age 30 years) when a stratified sample was selected.[4] A total of 2000 participants were selected based on their asthma status in 1968 (1000 with asthma in 1968 and 1000 without asthma in 1968). Of these, approximately 86% were traced to an address and sent a detailed respiratory questionnaire on respiratory symptoms and lifestyle factors including smoking history and level of education. Completed questionnaires were returned by 87%

of the traced participants (1501). A clinical examination was not conducted at this follow-up.

Proband 2002 study

This follow-up study occurred in the 2002–08 period when participants were in their 5th decade of life (Figure 1). It involved a postal survey of all participants traced from the original 1968 cohort (average age 42.8 years) and a clinical study of a sub-sample of participants (average age 44.9 years). We traced 7562 (88.1%) of the original 1968 cohort to an address[3] and achieved a response of 5729 (78.4%) to a postal survey. A subgroup of these respondents, enriched for cases of asthma or cough reported in childhood or adulthood, were invited to participate in a more detailed laboratory study. Of 2387 invited, 1405 (58.9%) took part in a full laboratory visit; 346 (14.5%) completed the laboratory questionnaire over the phone; and 636 (26.6%) declined to participate.

Proband 2010 study

This study was conducted between 2010 and 2012 by inviting the participants from the 2002 clinical study to undertake another clinical study that included bronchial hyperreactivity (BHR) testing. Of the 1405 eligible participants from the 2002 clinical study, a small number of participants had died before the study commenced ($n = 12$, 0.9%) or had withdrawn from the TAHS cohort before the study started ($n = 18$, 1.3%). Therefore of the 1375 remaining participants, 840 (61.1%) took part in a full laboratory visit, 286 (20.8%) declined to participate and 249 (18.1%) were not located. The average age of participants at this follow-up was 49.6 years.

Proband 2012 study

At the time of writing this profile, we are coming to the end of a follow-up of the cohort, which began in 2012. This follow-up is a full clinical study, of all living and traceable probands of the cohort including lung function testing and questionnaires. The participants will have an average age between 51 and 54 years at attendance.

Subsequent studies of TAHS siblings

Sibling 2007 study

The first and only sibling follow-up thus far commenced in 2007 and involved a postal survey of all traced siblings from the original 1968 cohort (21 036) and a clinical study of a sub-sample of participants. For this study, over 80% of the cohort were traced ($n = 17\,844$, 80.2%) to an address and a response rate of 71.6% ($n = 12\,073$) was achieved to a postal survey. A subgroup of these respondents, enriched for cases of asthma or cough reported in childhood or adulthood, were invited to participate in a more detailed laboratory study conducted between 2007 and 2010. Of 2662 invited, 1596 (60%) took part in a full laboratory visit including questionnaires and clinical examination; a further 205 (7.7%) completed a telephone questionnaire or the laboratory visit only; and 861 (32.3%) declined to participate. The mean age of the respondents at the postal survey was 49.2 years [standard deviation (SD): ± 5.4 years) (age range 39.3–71.2), and at the clinical study the mean age was 50.7 years (SD: ± 5.4 years) (age range 40–73).

Subsequent studies of TAHS parents

Parent 2010 study

As for the siblings, the first and only follow-up study of the parent members of the TAHS cohort started in 2010. This study attempted to trace all parents of the TAHS probands ($n = 16\,221$). Out of the 16 221 parents, 353 had no listed name from the original 1968 database. Of the remaining 15 868 parents with recorded names, 5334 (33.6%) were deceased, 6682 (42.1%) were traced to an address, 561 (3.5%) withdrew, 364 (2.3%) were lost and 2927 (18.4%) were not able to be traced. Of those alive and traced to an address, 5111 (70.3%) responded to a postal survey done between 2010 and 2013, and this response represents 31.5% of the original parent population. The mean age of the respondents at the postal survey was 76.6 years (SD: 5.2 years) (age range 63–100 years).

What has been measured?

Key measures are summarized in Tables 1–3. The phenotype (Table 1) and environmental data (Table 2) comprise parent-completed and self-completed questionnaires of probands, siblings and parents, as well as clinical assessments (Table 3). The TAHS resource contains key respiratory phenotypes, collected at multiple time points, allowing the assessment of lung function and growth trajectories over childhood and into middle age. Current data collection focuses on the critical period in middle age when lung function decline is beginning to accelerate, but other major chronic diseases have not yet developed.

The TAHS biological samples and genetic resource

DNA samples have been collected for 1226 of the probands and 1644 of the siblings. The probands and siblings have been genotyped for five common Caucasian filaggrin (*FLG*) gene mutations, and probands have also been

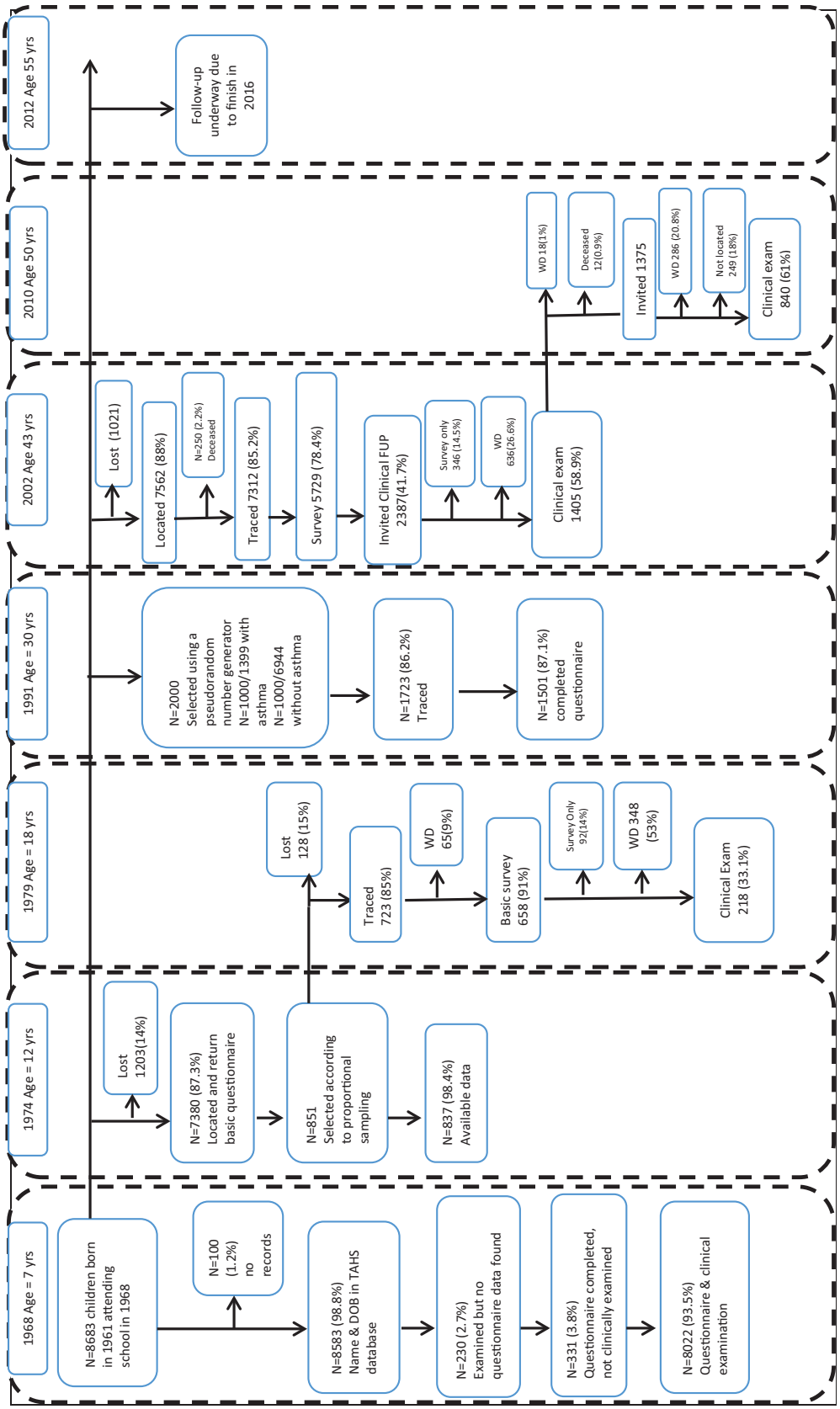

Figure 1 Follow-up and response rates of the TAHS probands from 1968 to 2012.
WD = Withdrawn, DOB = date of birth, yrs = years.

Table 1. Questionnaire outcome data in the TAHS cohort

TAHS Group	Probands									Siblings		Parents	
Year of study	1968	1974	1974	1979	1991	2002	2002	2010	2012	1968	2007	1968	2010
Study Type	Survey & Clinical Study	Survey	Clinical Study	Clinical Study	Survey	Survey	Clinical Study	Clinical Study	Clinical Study	Survey	Clinical Study	Survey	Survey
Respiratory Outcomes													
Asthma – Parent-reported	✓	✓	✓							✓			✓
– Self-reported				✓	✓	✓	✓	✓	✓		✓	✓	✓
– Doctor diagnosed											✓		✓
Eczema – Parent-reported	✓				✓	✓	✓	✓	✓	✓			
– Self reported											✓	✓	✓
Rhinitis – Parent-reported	✓									✓			
– Self reported			✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Food allergy – Parent-reported	✓												
– Self reported						✓		✓	✓		✓		✓
COPD						✓	✓	✓	✓		✓		✓
Chronic Bronchitis						✓	✓	✓	✓		✓	✓	✓
Emphysema						✓	✓	✓	✓		✓	✓	✓
Respiratory symptoms	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Sleep disordered breathing[1]								✓	✓				
Non-respiratory/allergy outcomes					✓			✓	✓		✓		✓

[1]Stop BANG, Berlin & obstructive sleep apnoea 50 (OSA50) Questionnaires.

genotyped for a selection of single nucleotide polymorphisms (SNPs) in other genes of interest in relation to chronic respiratory diseases and allergies (Table 4). Genome-wide data have been obtained for 400 of the probands with asthma, using the Illumina 610K array. We have also measured the levels of six cytokines [interleukin (IL)-4, IL-5, IL-6, IL-8, IL-10 and tumour necrosis factor-alpha (TNF-α)] in the serum of the probands from the 2002 clinical study follow-up.[5]

What has TAHS found? Key findings and publications

To date, 42 articles have been published using data from the TAHS cohort. Details of these can be found on the TAHS study website [http://tahs.mdhs.unimelb.edu.au/]. Below is a summary of the key contributions of TAHS.

Eczema is known to be the starting point for the 'atopic march',[6] a term classically used to describe the progression from atopic dermatitis (AD) to allergic rhinitis and finally asthma. TAHS was the first population-based study to explore the potential causal role of early life eczema in allergic rhinitis and asthma. This investigation was possible because of the unique family design of TAHS, which enabled us to explore the atopic march with a paired sibling design, allowing the disentanglement of childhood environment, adult environment and genetic factors. This analysis found that eczema in infancy might have a causal effect on hay fever that is associated with and without asthma, but not in asthma that is not associated hay fever.[7] TAHS has also been the first population-based study to show that early childhood allergies march towards asthma by middle age, specifically atopic asthma.[8] Thus, we observed that individuals with early childhood AD and allergic rhinitis were at greater risk of incident asthma throughout life.[8,9] More recently we have also observed an association between childhood AD only and asthma in adults who were atopic.[10]

The TAHS cohort has been followed from early life into middle age, which has enabled us to explore the longer-term impacts of early life risk factors on respiratory disease. We have been able to examine the effects of childhood infections (measles, mumps, chickenpox, rubella, pertussis, diphtheria and pneumonia) on the risk of asthma in middle age, and found that some of these childhood infectious diseases in general protected against asthma persisting in later life.[11] We have also explored those factors that may reduce the number of infections and have immune-modulatory effects, such as breastfeeding and immunization, and whether they modulate the risk of allergy development. We found no association between immunization and increased risk of allergic disease at any time point.[12] Exclusively breastfed babies with a maternal history of atopy were less likely to develop asthma before the age of 7 years, but more likely to develop asthma after the age of 7 years.[13] We hypothesized that this may be due to a protective effect of breastfeeding on risk of infections. We have also studied other markers of microbial exposure

Table 2. Questionnaire data and data linkage in the TAHS cohort

TAHS Group				Probands						Siblings		Parents	
Year of study	1968	1974	1974	1979	1991	2002	2002	2010	2012	1968	2007	1968	2010
Study Type	Survey & Clinical Study	Survey	Clinical Study	Clinical Study	Survey	Survey	Clinical Study	Clinical Study	Clinical Study	Survey	Clinical Study	Survey	Survey
Home environment and pets													
Cats – current, number							✓	✓	✓		✓		
Dogs– current, number								✓					
Indoor-House structure, carpets, mould				✓		✓	✓	✓	✓		✓		
Childhood environment													
Childhood cats								✓	✓		✓		✓
Parental smoking	✓							✓	✓		✓		✓
Day care/bedroom sharing								✓	✓		✓		✓
Farming	✓							✓	✓	✓	✓		✓
Sun exposure/Air pollution													
Sun exposure – Tanning, Outdoor activity									✓				
Traffic Noise									✓		✓		
Address data/geocoding	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Green index	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
General Health													
Dental Hygiene									✓				
Other Conditions					✓			✓	✓		✓		✓
Women's Health													
Menarche/Pregnancy					✓	✓			✓		✓		✓
Contraception					✓	✓			✓		✓		✓
Menopause									✓		✓		✓
Lifestyle and Nutritional factors													
Personal Smoking (current, pack years)			✓	✓	✓	✓		✓	✓		✓	✓	✓
Diet (Dietary Fat Q)								✓	✓				
Alcohol (ACCVFFQ)					✓				✓				
Breast feeding	✓												
Physical activity(IPAQ)									✓				
Snoring/Sleep								✓	✓				✓
Mental Health													
Generalized anxiety disorder 7 (GAD-7)									✓				
Patient Health Questionnaire 9 (PHQ-9)									✓				
Depression and/or anxiety					✓				✓		✓		✓

(Continued)

Table 2. Continued

TAHS Group				Probands						Siblings		Parents	
Year of study	1968	1974	1974	1979	1991	2002	2002	2010	2012	1968	2007	1968	2010
Study Type	Survey & Clinical Study	Survey	Clinical Study	Clinical Study	Survey	Survey	Clinical Study	Clinical Study	Clinical Study	Survey	Clinical Study	Survey	Survey
Other Characteristics													
Ethnicity	✓								✓				
SES - Main Occupation					✓	✓	✓	✓	✓		✓	✓	✓
SES - SEIFA	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓
SES – Education level					✓	✓	✓		✓		✓		✓
Childhood SES – Father's Occupation	✓									✓			
Marital status					✓			✓	✓				✓
Occupation (Work History Calendar)				✓	✓		✓		✓		✓		
Health services utilisation for asthma							✓	✓	✓		✓		
Family History asthma or COPD	✓						✓	✓	✓		✓		
Medication Use asthma or COPD			✓	✓	✓		✓	✓	✓		✓		
Data linkage													
National Death Index						✓							
Tasmanian State Archives													
School Medical Records[1]	✓												
Tasmanian Hospitals[2] labour & baby ward records	✓												

[1]School Medical Records contained parental occupation at starting school, immunisation record, common childhood infection record, height and weight annually during school years;
[2]Records include birth weight and gestation obtained from nine Tasmanian hospitals;
ACCVFFQ - Anti-Cancer Council of Victoria food frequency questionnaire;
IPAQ - International Physical Activity Questionnaire;
SEIFA - Socio-Economic Indexes for Areas

Table 3. Clinical assessments in the TAHS cohort

TAHS Group			Probands				Siblings
Year of study	1968	1974	1979	2002	2010	2012	2007
Study Type	Survey & Clinical Study	Clinical Study	Clinical Study	Clinical Study	Clinical Study	Clinical Study	Clinical Study
Anthropometric measures							
Height & Weight	✓	✓	✓	✓	✓	✓	✓
Waist circumference				✓	✓	✓	✓
Neck circumference					✓	✓	
Lung function measurements							
Spirometry: Pre - bronchodilator	✓	✓	✓	✓	✓	✓	✓
Post - bronchodilator				✓		✓	✓
Transfer factor of the lung for carbon monoxide				✓		✓	
TLco (post bronchodilator)							
Lung Volumes & Capacities (post bronchodilator)				✓			
Bronchial Hyper-reactivity (BHR)					✓		
Skin prick tests							
Aero-allergens[1]				✓		✓	✓
Food allergens[2]						✓	
Sleep studies (Apnealink™)							
Respiratory effort, Pulse, Oxygen saturation,						✓[3]	
Nasal flow & Snoring							
Biosamples							
Blood sample				✓	✓	✓	✓
DNA sample				✓			✓
GWAS - subsample of 400 asthmatics				✓			
SNPs – 32 SNPs in 21 genes				✓			✓[4]
Immunology – 6 cytokines from serum				✓			

[1] Aero Allergens - Dermatophagoides pteronyssinus, cat pelt, Cladosporioides, Alternaria tenuis, penicillium mix, Aspergillus fumigatus, mixed grasses No. 7 (which included Kentucky bluegrass, orchard, redtop, Timothy, sweet vernal grass, meadow fescue and perennial ryegrass).

[2] Food allergens – Egg, Milk, shrimp, peanut.

[3] subsample of n = 400.

[4] Genotyped for 5 FLG SNPs only.

(such as day care and, farming environment) and have found that having siblings before the age of two years and also increasing number of viral infections was protective against early-onset hay fever.[14] Furthermore, this work demonstrated an important critical window for the protective effect of exposure to siblings being in the first two years of life, after which time the protective effect wanes.

The population-based family structure of TAHS has made it an extremely useful resource for the study of genetic risk factors of chronic respiratory diseases. Familial aggregation of asthma has been explored in TAHS using the data from 7394 of the TAHS nuclear families (41 506 individuals).[15] Parental and sibling asthma was a strong predictor of a child's risk for ever having asthma [mother odds ratio (OR) = 3.13, 95% confidence interval (CI) 2.82–3.48; father OR = 2.99, 2.69–3.32; sibling OR = 3.47, 3.23–3.72]. The observed familial aggregation best fitted a co-dominant model, but the strong sibship association indicates that there are significant household environmental factors that play an important role in explaining part of the observed familial aggregation.

Over the past 5 years, the number of genome-wide association studies (GWAS) has dramatically increased, with the aim of identifying common variants for complex diseases such as chronic respiratory diseases and allergies. TAHS was one of the founding members of the Australian Asthma Genetics Consortium (AAGC), which has brought together asthma studies from around Australia to perform a GWAS. This consortium of Australian studies pooled a GWAS data from 2669 individuals with physician-diagnosed asthma and 4528 asthma-free controls. From this original GWAS, we identified two new genetic variants that increased the risk of asthma: IL6R and chromosome 11q13.5.[16] The association with IL6R raised the possibility that IL6R antagonists could be effective in prophylaxis against asthma in high-risk groups. Following on from this, we were able to contribute our data to larger international meta-analysis GWAS, resulting in several

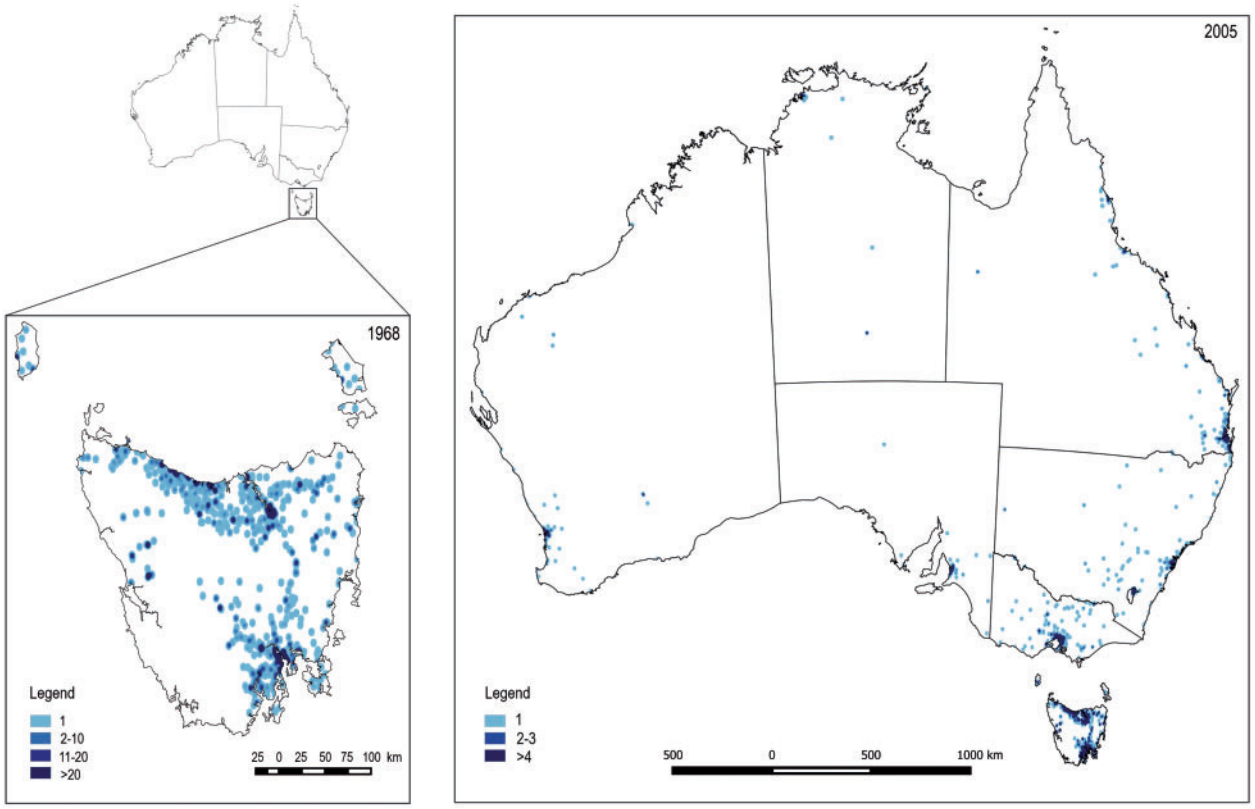

Figure 2. TAHS population density map of probands at baseline in 1968 and their geographical spread in the 2002 follow-up study. In the 2002 follow-up of the probands, 72.9% were still living in Tasmania, and the remainder had spread mainly up the east coast of Australia (VIC: 7.4%, NSW: 5.9%, QLD: 7.8%, WA: 3.1%, NT: 0.7% and SA: 1.5%). A similar spread was also found for the 2007 follow-up of the sibling members of the cohort.

publications, that reported on new genetic variants involved in atopic dermatitis,[17] severe asthma[18] and allergic sensitization.[19]

TAHS has recently added to the body of evidence on the role of life-time asthma in the development of chronic obstructive pulmonary disease (COPD). TAHS has confirmed the concept that current asthma in middle age is associated with spirometrically-defined COPD and, further, this was independent of personal smoking.[20] Compared with non-asthmatics, early-onset current asthmatics had a 3.7-fold increase in the odds of having COPD (95% CI 1.5–9.3), similar to the risk of COPD associated with a smoking history of 33 pack-years (OR = 3.7, 1.5–9.3). Late-onset current asthmatics had half these odds, similar to the risk of COPD associated with a smoking history of 24 pack-years. It also confirmed an interaction between the effects of asthma and active smoking on post-bronchodilator airflow obstruction, which was most relevant to those with current asthma symptoms, regardless of age of asthma onset. Furthermore, this effect was more pronounced for those with atopic sensitization.

Interestingly, until relatively recently asthma and COPD were considered to be mutually exclusive conditions. However, a TAHS publication helped lead to the recognition of the 'asthma-COPD overlap syndrome' (ACOS) by the international committees of the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[21] As suggested by the accompanying editorial to our publication, our work contributed substantially to developing consensus on the use of a COPD classification that includes a subgroup of 'smokers with asthma'.[22]

What are the main strengths and weaknesses of Tahs?

The major strengths of TAHS are the long follow-up period (five decades to date), excellent response rates at each follow-up, repeated lung function measurements over the lifespan including in childhood and into middle age, and the prospectively collected data on a range of risk factors and outcomes throughout the follow-ups. TAHS is one of only three population-based longitudinal studies of respiratory disease internationally that have followed a cohort of individuals from childhood into the sixth decade of life.[23] The planned ongoing follow-up of the cohort into older age has the potential to shed important insights into lung ageing, decline and chronic respiratory diseases.

TAHS is also rare among studies of respiratory disease because it was originally conceived as a family cohort, with all the family members surveyed at baseline. This provides a rare platform on which sibship and family studies can be developed to concurrently examine genetics, the shared childhood environment of siblings, and the adult environment for change in chronic respiratory disease risk.

As with all longitudinal studies, TAHS has had attrition overtime. As reported above and shown in Figure 2, the tracing rates have been very high, over 85% for all follow-ups, and survey response rates have ranged between 78% and 91%. Participation in the clinical studies has been more variable, with participation rates ranging between 33% and 98%. Our lowest participation rate of 33% was for the 1979 clinical study, which was attributed to the less rigorous recruitment process due to the age of the participants, and logistic difficulties. However, this participation rate was similar across symptom categories and was not associated with sex or socio-demographic factors.[24] For the 1991 study, the response rate to the postal survey was also independent of age, gender and asthma status at baseline. The first full cohort follow-up was conducted nearly 40 years after the baseline follow-up and we have been able to achieve high tracking and participation rates. We have conducted subgroup follow-ups, which were enriched for symptoms. However, we have adjusted for sampling fractions to ensure our results are generalizable.

The main limitation of the TAHS is the stratified random sampling at several time points. This has resulted in small number of participants with lung function through the adolescent growth period and with data on near peak lung volume in late adolescence. Unfortunately no biological samples or skin prick testing for allergy was conducted in the baseline study.

Can I get hold of the data? Where can I find out more?

We welcome applications to use the TAHS datasets or biological samples, and such applications can be submitted to the TAHS steering committee via Professor Shyamali Dharmage at [s.dharmage@unimelb.edu.au].

Tahs in a nutshell

- TAHS is the world's largest longitudinal population-based family study of respiratory health.
- TAHS was commenced in 1968 when all children born in 1961 and attending school in Tasmania, Australia (called probands) were recruited ($n = 8583$). The parents ($n = 16\,221$) and siblings ($n = 21\,035$) of these children were also surveyed at baseline in 1968.
- There have been follow-up studies of the probands at the ages of 12, 18, 30, 43, 50 and 54 years. The siblings and parents have also been followed up recently.
- The TAHS data comprise repeated prospective measures of respiratory and allergy outcomes including lung function measurements. TAHS also has biological samples and genetic information, and has been linked to archival health records.
- Requests for collaboration or use of the TAHS datasets or biological samples can be directed to the TAHS steering committee via Professor Shyamali Dharmage at [s.dharmage@unimelb.edu.au].

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