Received: 14 November 2023 | Revised: 17 April 2024 | Accepted: 8 May 2024

DOI: 10.1111/all.16184

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Childhood infections, asthma and allergy trajectories, and chronic rhinosinusitis in middle age: A prospective cohort study across six decades

Jennifer L. Perret[1,2,3] | N. Sabrina Idrose[1] | E. Haydn Walters[1,4] | Dinh S. Bui[1] | Adrian J. Lowe[1] | Caroline J. Lodge[1] | Anne R. Fernandez[1,5] | Vivian Yao[1] | Iain Feather[6] | Xiao-Wen Zeng[7] | Bruce R. Thompson[8] | Bircan Erbas[9] | Michael J. Abramson[10] | Shyamali C. Dharmage[1]

[1]Allergy and Lung Health Unit, Centre of Epidemiology and Biostatistics, The University of Melbourne, Melbourne, Victoria, Australia

[2]The Institute for Breathing and Sleep (IBAS), Melbourne, Victoria, Australia

[3]Department of Respiratory and Sleep Medicine, Austin Hospital, Melbourne, Victoria, Australia

[4]School of Medicine, University of Tasmania, Hobart, Tasmania, Australia

[5]School of Medicine, Deakin University, Geelong, Victoria, Australia

[6]Gold Coast University Hospital, Southport, Queensland, Australia

[7]Department of Occupational and Environmental Health, School of Public Health, Sun Yat-sen University, Guangzhou, China

[8]School of Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia

[9]School of Psychology and Public Health, La Trobe University, Melbourne, Victoria, Australia

[10]School of Public Health & Preventive Medicine, Monash University, Melbourne, Victoria, Australia

Correspondence
Jennifer L. Perret, Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Vic. 3010, Australia.
Email: jennifer.perret@unimelb.edu.au

Funding information
GlaxoSmithKline; Royal Hobart Hospital Research Foundation; Helen MacPherson Smith Trust; Asthma Foundation of Queensland; Clifford Craig Medical Research Trust of Tasmania; University of Melbourne; Asthma Foundation of Tasmania; Asthma Foundation of Victoria; National Health and Medical Research Council (NHMRC) of Australia, Grant/Award Number: 299901, 566931 and 1021275

Abstract

Introduction: Evidence on the early life risk factors of adult CRS, and the history of asthma and allergies across the life course, is limited.

Aim: To investigate relationships between respiratory infective/allergic conditions in childhood, and asthma and allergies across the life course and CRS in middle age.

Methods: Data were from the population-based Tasmanian Longitudinal Health Study (TAHS) cohort, first studied in 1968 when aged 6–7 years ($n = 8583$) and serially followed into middle age ($n = 3609$). Using a well-accepted epidemiological definition, participants were assigned a CRS-severity subtype at age 53: no sinusitis/CRS (reference); past doctor diagnosis only; current symptoms without doctor diagnosis; and doctor-diagnosed CRS with current symptoms. Relationships with infective/allergic respiratory illnesses at age 7, and previously published asthma-allergy trajectories from 7 to 53 years, were examined using multinominal regression.

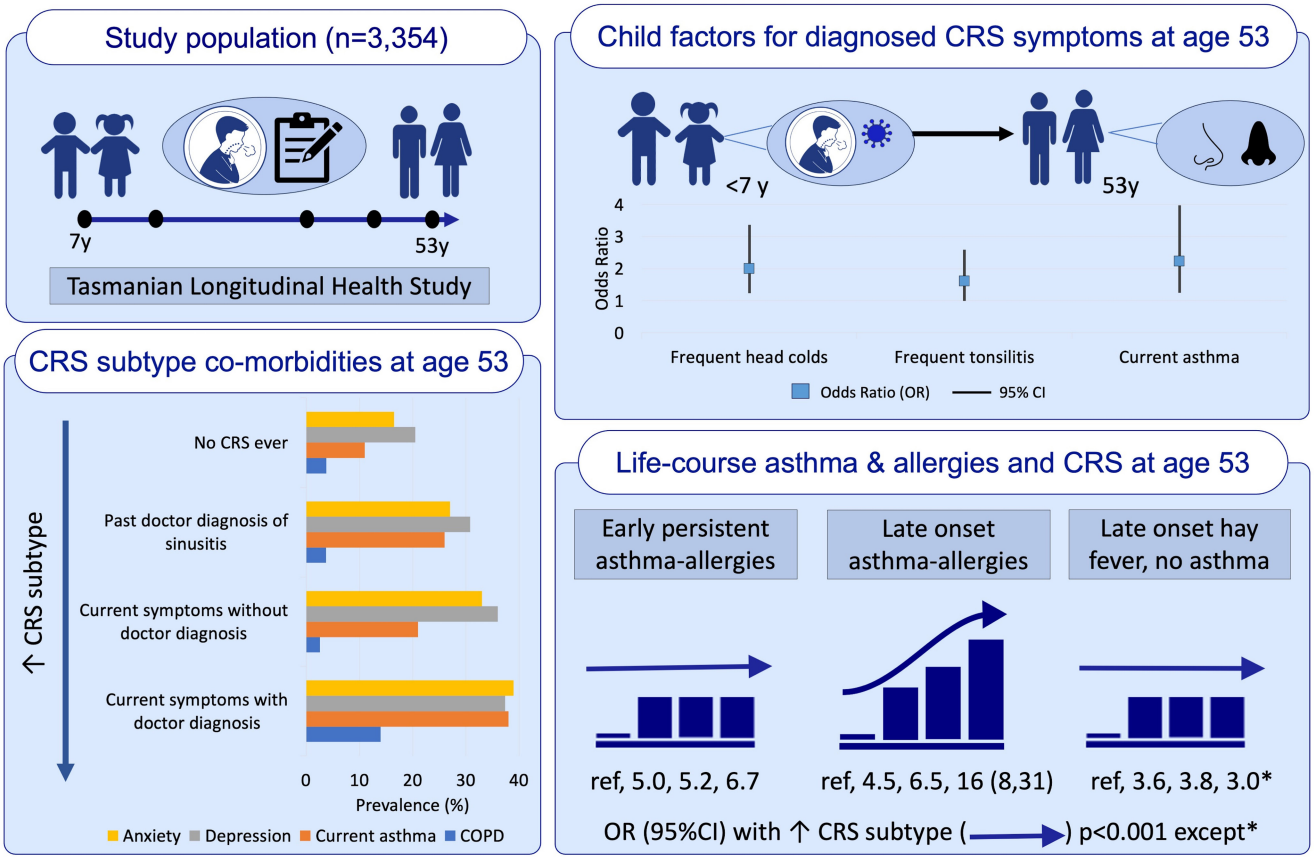
Results: In middle age, 5.8% reported current CRS symptoms with 2.5% doctor-diagnosed. Childhood conditions associated with symptomatic doctor-diagnosed CRS

Michael J. Abramson and Shyamali C. Dharmage are equal senior authors.

included frequent head colds (multinomial odds ratio [mOR] = 2.04 (95% confidence interval [95% CI]: 1.24, 3.37)), frequent tonsillitis (mOR = 1.61 [95% CI: 1.00, 2.59]) and current childhood asthma (mOR = 2.23 [95% CI: 1.25, 3.98]). Life course trajectories that featured late-onset or persistent asthma and allergies were associated with all CRS subtypes in middle age; early-onset persistent asthma and allergies (mOR = 6.74, 95% CI: 2.76, 16.4); late-onset asthma allergies (mOR = 15.9, 95% CI: 8.06, 31.4), and late-onset hayfever (mOR = 3.02, 95% CI: 1.51, 6.06) were associated with symptomatic doctor-diagnosed CRS.

Conclusion: Current asthma, frequent head colds and tonsillitis at age 7 could signal a susceptible child who is at higher risk for CRS in mid-adult life and who might benefit from closer monitoring and/or proactive management. Concurrent asthma and allergies were strongly associated and are potential treatable traits of adult CRS.

KEYWORDS
allergies, asthma, chronic rhinosinusitis, head colds, tonsillitis, trajectories



GRAPHICAL ABSTRACT

In this epidemiological study, mid-life doctor-diagnosed CRS was a symptom-based definition that was linked to lower airways disease (atopic asthma, worse asthma severity, COPD) and poorer mental health. Childhood upper airway infections (frequent head colds and tonsillitis) were linked to symptomatic doctor-diagnosed CRS in middle age. Late-onset allergic asthma was strongly associated with symptomatic doctor-diagnosed CRS in middle age. Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; OR, odds ratio

1 | INTRODUCTION

Adult chronic rhinosinusitis (CRS) is an inflammatory condition of the mucosal lining of the nasal cavity and paranasal sinuses associated with detrimental effects on overall wellbeing, quality of life and daily functioning. The cardinal symptoms of nasal blockage and/or discharge can predispose to headaches, poor sleep and fatigue, reduced work capacity and loss of income and productivity from excessive work absences at a substantial cost to individuals, families and society.[1,2]

To reduce the risk of symptomatic CRS in later life, identifying earlier opportunities to intervene could aid the timelier implementation of preventive strategies and/or proactive management. However, most studies on the risk factors have been cross-sectional or case–control studies,[3,4] whereas prospective cohort studies that provide more robust evidence of the spectrum of associations relevant to general populations are relatively few. These population-based cohort studies have documented relationships between asthma/allergies and the development of CRS into early adulthood,[5,6] and between CRS and the development of asthma.[5] However, no previous study has investigated CRS into middle age and documented the history of asthma/allergies over the life course retrospectively, and few have examined whether CRS has origins in early life.[7] The sole longitudinal study that spanned from childhood to 32 years found that physician-diagnosed childhood sinusitis (age 6 years), presumed 'head colds' and allergic conditions predicted adult sinusitis.[6] However, this study comprised a small sample of 772 participants and did not investigate other potential early life factors of likely infective origin such as childhood tonsillitis.

In this paper, we used the epidemiological definition for CRS as recommended by the European Academy of Allergology and Clinical Immunology (EAACI)/ European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS),[8] and data from the population-based Tasmanian Longitudinal Health Study (TAHS) cohort between ages 7 and 53 years. Although this definition could not differentiate between CRS with or without nasal polyps, our aims were to: (1) describe middle age CRS subtypes in terms of prevalence, history of allergic rhinitis (AR) and current asthma, and skin-prick-test positivity; (2) investigate associations between childhood allergic/infective conditions and CRS subtypes in middle age as potential early life indicators; and (3) investigate associations between life-time asthma and allergy trajectories with CRS subtypes in middle age that could highlight links between these diseases.

2 | METHODS

2.1 | Study design and population

Data were from TAHS, details of which have been published elsewhere.[9–11] In brief, TAHS is a population-based prospective cohort study which began in 1968 when 98.8% of Tasmanian school children born in 1961 ($n = 8583$), were enrolled in a respiratory study. Their parents completed a questionnaire for the 7-year-old children who also underwent a clinical examination including spirometry but no skin-prick or blood tests at that time. Participants were serially followed-up until 2012–16 at mean age 53 years (see Figure S1). At this last follow-up, 42.0% ($n = 3609$) of the original cohort completed an online, postal or interviewer-assisted questionnaire and 30.6% ($n = 2629$) underwent lung function and skin-prick testing. The analytical sample was limited to participants who had both outcome and confounder data available ($n = 3364$ for the main analysis) and were assigned an asthma-allergy trajectory between ages 7 and 53 years ($n = 3112$).

2.2 | Clinical definitions

2.2.1 | Chronic Rhinosinusitis at mean age 53

Based on the EPOS epidemiological definition,[8] current CRS was defined by having at least two symptoms of nasal blockage, discharge, pain and reduced/absent smell at mean age 53, of which one was related to either nasal blockage or discharge.

Doctor-diagnosed CRS ever by age 53 was defined by an affirmative response to the following question: 'Has a doctor ever told you that you have chronic sinusitis?'

Adult CRS combined these two definitions and comprised the following four subtypes:

1. No history of sinusitis/CRS (reference group)
2. Doctor-diagnosed sinusitis-ever without fulfilling EAACI/EPOS main criteria[8] for current CRS (i.e. past sinusitis diagnosis)
3. Current CRS symptoms without being diagnosed by a doctor
4. Doctor-diagnosed CRS with current symptoms

2.2.2 | Childhood exposures at age 7

The childhood exposures were defined by affirmative parental responses from the original 1968 survey that questioned the presence of frequent head colds (>2 episodes/year); tonsillitis/sore throats (>2 episodes last 12 months) and/or tonsillectomy; hay fever-ever; asthma/wheezing that was recurrent (≥2 episodes of asthma and/or wheezing) and/or current (episode within the last 12 months); doctor-diagnosed pneumonia and/or pleurisy; and recurrent bronchitis (≥2 episodes of 'loose, rattly or chesty' cough).

2.2.3 | Asthma and allergies

Five trajectories of asthma and allergy have been previously developed by latent class analysis methodology,[12] which incorporated data on recent eczema, food allergy and symptoms of asthma,

rhinitis and/or conjunctivitis from typical allergic triggers at ages 7, 45 and 53 years when data were available (Methods S2). Specific to this analytical sample ($n = 3112$), these included: (1) minimal asthma and allergies (reference category, 49.0%); (2) early-onset persistent asthma and allergies, characterized by a high probability of early-onset asthma and other allergic diseases in mid-adulthood (5.8%); (3) early-onset remitted asthma and allergies, characterized by a low probabilities of asthma/allergies in mid-adulthood (6.2%); (4) late-onset asthma and allergies, with a high probability of asthma/allergies in mid-adulthood (8.6%); and (5) the relatively common late-onset hay fever without asthma, characterized by a high probability of only allergies in mid-adulthood (30.4%).[12]

Current doctor-diagnosed asthma was defined by a self-reported past medical diagnosis and asthma-related symptom/s, medication and/or health care utilization in the last 12 months. Asthma symptom severity was based on the frequency of symptoms and exacerbations irrespective of treatment, as informed by previous TAHS publications (Table S1).[13,14] Atopic sensitization was defined by skin-prick test positivity as described in Methods S2E. Atopic conditions were defined by self-reported asthma, rhinitis and/or conjunctivitis plus atopic sensitization. Allergic conditions were defined by symptoms of asthma, rhinitis and/or conjunctivitis associated with typical allergic triggers, regardless of evidence of atopic sensitization.

Definitions of asthma, atopy, childhood exposures and confounders, and co-morbidities in middle age have been further outlined in Methods S2.

2.3 | Statistical analysis

All analyses were performed using Stata v16 or 17 (StataCorp, College Station, TX, USA). Comparisons across adult CRS subtypes were assessed using Chi-squared and trend tests,[15] and associations assessed by multinominal regression with no sinusitis/CRS as the reference category. Potential confounding variables were considered separately using directed acyclic graphs via Daggity,[16] and a minimum set of confounders were selected (Methods S3). For the early life exposure analysis, baseline adjustments included participant sex, rurality of school, paternal occupation (as a measure of socio-economic status), number of siblings, as well as parental asthma/allergies, head colds and bronchitis for the corresponding childhood exposures. Models were additionally adjusted for parental smoking at age 7 but were included as supplementary results because childhood exposures could have occurred earlier. For the asthma-allergy trajectory analyses, models were additionally adjusted for childhood upper airway infections (frequent head colds and tonsillitis). Complete case analysis was used.

Effect modification of the relationships by current asthma, allergic rhinitis and smoking at age 53 was examined using likelihood ratio tests, and stratified results included in the supplement. A conventional cut-off of $p < .05$ was defined statistical significance for associations and $p < .1$ for interactions.

2.4 | Ethics

This study was approved by the Human Research Ethics Committees at the University of Melbourne (040375) and University of Tasmania (H0012710). Written consent was provided by all participants.

3 | RESULTS

Of 3364 participants, 2.5% (95% CI: 2.0, 3.0%) had doctor-diagnosed CRS with current symptoms, 3.4% (2.8, 4.1%) had current CRS symptoms but no doctor diagnosis, 4.3% (3.7, 5.1%) had a past diagnosis of chronic sinusitis only, and 90% comprised the reference group of no sinusitis/CRS (Table 1). Among those with current CRS symptoms, participants who were doctor-diagnosed had a significantly higher prevalence of facial pain/pressure (87.9%, [95%CI: 79, 94]) compared with those without a doctor diagnosis (62.8%, [53, 71]). Of those with past sinusitis, 14.5% still had reduced/absent smell.

There was little difference (0.4%–2.3%) in the prevalence of childhood factors between TAHS participants who had complete data and those excluded due to incomplete data (Table S2). Increasing prevalence of multiple CRS-related co-morbidities have been shown across CRS-severity subtypes in Table 1. These include 'lower airways diseases' (asthma, COPD, pneumonia), gastro-oesophageal reflux disorder (GORD), obesity, snoring and mental health disorders. More specifically, the prevalence of concurrent doctor-diagnosed asthma with or without SPT positivity was markedly increased across the CRS subtypes in mid-life, where current doctor-diagnosed asthma occurred in over one-third (37.8%) of those with doctor-diagnosed symptomatic CRS in contrast with 12.7% among all study participants (Figure 1). More concurrent clinical asthma symptoms, symptomatic COPD, pre- and post-bronchodilator airflow obstruction, but not current smoking, were also increased across the CRS subtypes (Table 1).

Regarding employment, compared with no CRS/sinusitis, a lower proportion of those with symptomatic CRS ± past doctor-diagnosed sinusitis was currently employed in their early-to-mid-fifties. And a lower proportion with a past diagnosis was in full-time employment, regardless of symptoms (Table 1).

3.1 | Early life factors

In this study, the prevalence of frequent childhood head colds, childhood asthma, maternal smoking and other parental factors differed across adult CRS subtypes (Table 2). There was a female predominance for those who had a past doctor diagnosis, with or without current symptoms.

Three early life exposures (frequent head colds, frequent tonsillitis, current childhood asthma) were significantly associated with the most severe subtype of symptomatic doctor-diagnosed CRS in middle age, with and without adjustment for parental smoking (Table 3

TABLE 1 Clinical features and co-morbidities of chronic rhinosinusitis[a], by CRS subtype in the middle-aged TAHS cohort.

Clinical feature at mean age 53	Total cases (% *n*)	CRS at mean age 53 [*N* = 3364, % (*n*)][b]				χ^2 *p*-value
		No CRS, 89.80% (*n* = 3021)	Past sinusitis diagnosis, 4.34% (*n* = 146)	Current CRS without diagnosis, 3.39% (*n* = 114)	Current CRS with diagnosis, 2.47% (*n* = 83)	
Components of the CRS definition[a]						
Nasal blockage[c]	6.7 (225)	2.1 (64)	2.7 (4)	78.1 (89)	81.9 (68)	<.001
Nasal discoloured discharge[c]	6.9 (232)	1.9 (58)	2.7 (4)	51.8 (59)	65.1 (54)	<.001
Facial pain/pressure[c]	5.2 (175)	2.5 (76)	8.2 (12)	62.8 (71)	87.9 (73)	<.001
Reduced/absence of smell sense[c]	6.9 (233)	3.4 (101)	14.5 (21)	56.1 (64)	56.6 (47)	<.001
Concurrent co-morbidities, % (*n*)						
Dr-diagnosed asthma (recalled)	25.4 (851)	23.5 (707)	39.0 (57)	35.4 (40)	56.6 (47)	<.001
Dr-diagnosed current asthma, regardless of SPT results	12.7 (424)	11.1 (331)	26.2 (38)	21.4 (24)	37.8 (31)	<.001
Dr-diagnosed current atopic (SPT+) asthma (*N* = 2304)[b]	9.5 (218)	8.3 (175)	20.9 (19)	14.3 (9)	31.3 (15)	<.001
Asthma symptom severity (*N* = 3325)[b]						<.001
No asthma	79.4 (2640)	81.1 (2423)	67.6 (98)	66.4 (75)	55.7 (44)	–
Asymptomatic or intermittent	14.8 (493)	14.1 (422)	22.1 (32)	22.1 (25)	17.7 (14)	–
Mild persistent	2.9 (95)	2.5 (75)	5.5 (8)	5.3 (6)	7.6 (6)	–
Moderate-to-severe persistent	2.9 (97)	2.3 (68)	4.8 (7)	6.2 (7)	19.0 (15)	–
COPD with respiratory symptom(s) (*N* = 2456)[b]	4.0 (97)	3.8 (84)	3.7 (4)	2.6 (2)	14.0 (7)	.003
Pre-BD airflow obstruction only	8.2 (202)	7.8 (174)	8.3 (9)	13.0 (10)	17.7 (9)	.029
Post-BD airflow obstruction only	4.6 (112)	4.5 (99)	3.7 (4)	2.6 (2)	14.0 (7)	.011
Current smoking at mean age 53	17.5 (586)	17.3 (521)	13.0 (19)	28.1 (32)	16.9 (14)	.012
Inhalers for 'breathing' last 12 months	11.8 (390)	10.6 (315)	18,9 (27)	18.5 (20)	35.9 (28)	<.001
Dr-diagnosed anxiety-ever	18.0 (605)	16.5 (496)	27.4 (40)	32.5 (37)	38.6 (32)	<.001
GAD-7 ≥ 10 (current)	9.1 (301)	8.3 (245)	10.6 (15)	21.6 (24)	21.0 (17)	<.001
Dr-diagnosed depression-ever	21.9 (736)	20.5 (619)	30.8 (45)	36.0 (41)	37.4 (31)	<.001
PHQ-9 ≥ 10 (current)	7.2 (234)	6.3 (186)	8.3 (12)	18.0 (20)	20.0 (16)	<.001
Dr-diagnosed sleep apnoea (recalled)	4.9 (164)	4.7 (140)	9.7 (14)	6.3 (7)	3.7 (3)	.044

(Continues)

TABLE 1 (Continued)

Clinical feature at mean age 53	Total cases (% *n*)	CRS at mean age 53 [*N* = 3364, % (*n*)][b]				
		No CRS, 89.80% (*n* = 3021)	Past sinusitis diagnosis, 4.34% (*n* = 146)	Current CRS without diagnosis, 3.39% (*n* = 114)	Current CRS with diagnosis, 2.47% (*n* = 83)	χ^2 *p*-value
Self-reported snoring (yes)	74.0 (2470)	73.4 (2200)	75.2 (109)	87.6 (99)	74.7 (63)	.009
Snoring at least as loud as talking	44.6 (1494)	43.8 (1318)	45.5 (66)	58.4 (66)	53.0 (44)	.026
Obesity (BMI ≥30 kg/m^2)	32.3 (1074)	31.8 (9510)	30.1 (43)	38.7 (43)	45.7 (37)	.025
Dr-diagnosed pneumonia (recalled)	18.2 (609)	17.6 (528)	22.8 (33)	23.4 (26)	26.5 (22)	.035
Dr-diagnosed GORD (recalled)	10.8 (364)	10.1 (304)	15.1 (22)	18.4 (21)	20.5 (17)	<.001
Employment (*n* = 2380)[b] – Full time	63.2 (2072)	64.1 (1887)	50.7 (73)	66.7 (74)	45.8 (38)	<.001
Part-time	17.9 (586)	17.7 (520)	27.1 (39)	12.6 (14)	15.7 (13)	–
Casual	6.5 (213)	6.6 (195)	4.2 (6)	1.8 (2)	12.1 (10)	–
Not employed[d]	12.5 (309)	11.6 (340)	18.1 (26)	18.9 (21)	26.5 (22)	–

Abbreviations: BMI, body mass index; CRS, chronic rhinosinusitis; GAD-7, generalized anxiety disorder scale; GORD, gastro-oesophageal reflux disease; IQR, interquartile range; IHD, ischaemic heart disease; PHQ-9, patient health questionnaire; SPT, skin-prick-test; TAHS, Tasmanian Longitudinal Health Study.

[a]CRS defined by the European Position Paper on Rhinosinusitis and Nasal Polyps,[8] which required 2 or more of the 4 symptoms AND either nasal blockage or nasal discharge to be present.

[b]Participant numbers in the headings refer to the asthma variable at age 7 which has excluded 245 participants with missing data on sex, rurality of school, paternal occupation, and sibling number; reduced total numbers reporting on employment status, asthma severity and undertaking lung function and skin-prick-tests are as indicated.

[c]Nasal symptoms lasting >12 weeks in the past year.

[d]Includes those nominating the reasons of studying (*n* = 17, 0.5%) or retirement (*n* = 83, 2.5%).

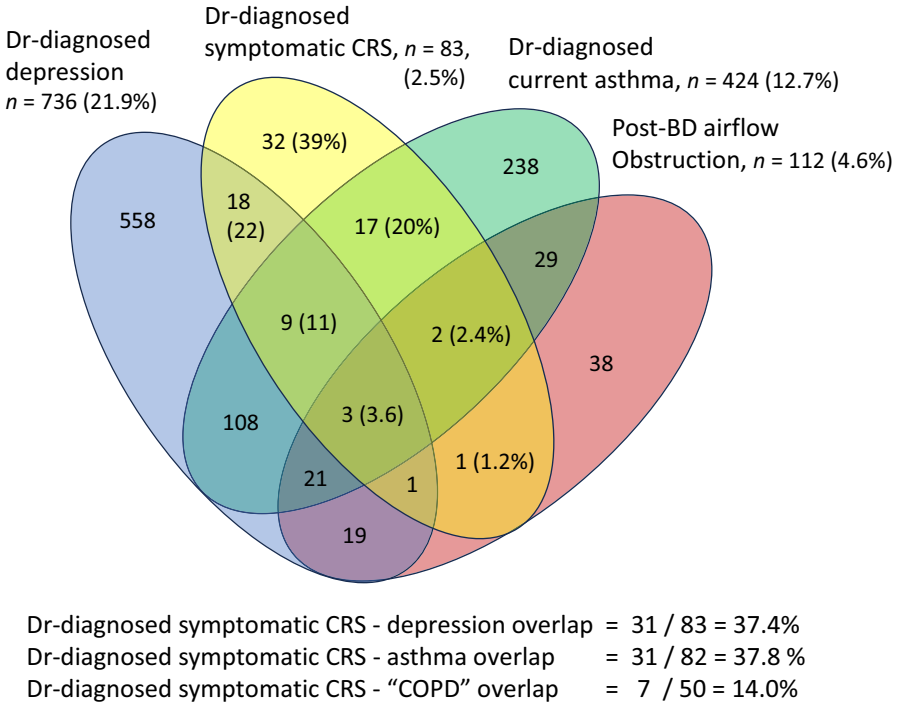


FIGURE 1 Common co-morbidities of CRS in middle age and the overlaps, with comparisons against the prevalence among all study participants. CRS was defined using the EAACI-EPOS epidemiological definition. Total $N = 3364$ who had confounder data but there was a restricted sample of $n = 2456$ who underwent post-bronchodilator spirometry to confirm a label of COPD. Case numbers are also included in Table 1. COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; EAACI-EPOS, European Academy of Allergy and Clinical Immunology-European Position Paper on Rhinosinusitis and Nasal Polyps.

and Table S3). Specifically, frequent childhood head colds were associated with a two-fold increase in the odds for symptomatic doctor-diagnosed CRS in middle age ([95% CI: 1.24, 3.37], $p = .005$, Table 3). This was especially so for those who had concurrent asthma in middle age (mOR 3.47, [1.47, 8.17]; $p = .004$) compared with no current asthma (mOR 1.34, [0.71, 2.53]) when stratified by current asthma status but the p-interaction value was not significant (p-interaction = .25, Table S4). Frequent childhood tonsillitis was associated with a 1.61-fold increase ([1.00, 2.59], $p = .049$) in the odds for symptomatic doctor-diagnosed CRS in middle age, and current childhood asthma was associated with a 2.23-fold increase ([1.25, 3.98], $p = .007$, Table 3). While there were no clear interactions between the effects of these three exposures and either current allergic rhinitis (Table S5) or ever-smoking on CRS in middle age (Table S6, p-interaction value > .1), the main associations were significant among non-smokers but not ever smokers (Table S6).

There was some evidence of association between the early life factors and the milder subtype of current CRS but no doctor diagnosis, which did not reach statistical significance.

Notwithstanding small numbers, there was a modest protective main association between doctor-diagnosed childhood pneumonia/pleurisy and past sinusitis that remained following adjustment for parental smoking (mOR = 0.48, [0.24, 0.95]; $p = .036$, Table S3), and was especially seen for non-smokers ($n = 3$, Table S6).

3.2 | Current asthma, allergic rhinitis (AR) and SPT positivity across CRS subtypes

Compared with no sinusitis/CRS, the prevalence of AR-ever by age 7 was similar across all CRS subtypes (12.8%–16.3%) but increased many-fold to 88.9%–94.0% for each of the three CRS subtypes by age 53 years (Table 4). The prevalence of AR-ever substantially increased between childhood and early adolescence (12.8% at age seven to 81.2% at age 13 years) for the severe subtype who had doctor-diagnosed symptomatic CRS in middle age (2.5%), compared with early adulthood for the less severe CRS subtypes (Table 4). The increase in prevalence of current asthma was between early adolescence and early adulthood for all three CRS subtypes (Table 4).

Regarding atopic sensitization, significant trends were seen for any skin-prick allergen across CRS subtypes (p-trend = .048, Table 5). Compared with no sinusitis/CRS, the prevalence was consistently highest for those who had symptomatic doctor-diagnosed CRS for the allergens, *D. pteronyssinus* (58.2% compared with 40.2%), peanut (20.0% vs. 8.1%), and cow's milk (10.0% vs. 3.5%). A similar trend for *D. pteronyssinus* was also seen at age 45 (Table S7). Few participants reporting past sinusitis or current CRS symptoms were skin-prick-test positive to moulds.

3.3 | Asthma-allergy trajectories between ages 7 and 53 years

Compared with the reference exposure group who had minimal asthma allergies, all symptomatic asthma-allergy trajectories other than the early-onset remitted trajectory were associated with each of the CRS subtypes (Table 6). For participants belonging to the trajectory that featured both late-onset asthma and allergies (8.6%), there was a clear pattern of increasing strength of association across the severity of CRS subtypes. The early-onset persistent asthma and allergy trajectory (5.8%), and the more common late-onset hay fever without asthma trajectory (30.4%) were similarly associated

TABLE 2 Participant demographics, childhood conditions and parental characteristics of the TAHS participants at age seven.

Clinical characteristics		CRS history at mean age 53 [$N = 3364$, % (n)][a]				
At age 7 (in 1968)	Cases (n)	No CRS, 89.80% ($n = 3021$)	Past sinusitis diagnosis, 4.34% ($n = 146$)	Current CRS without diagnosis, 3.39% ($n = 114$)	Current CRS with diagnosis, 2.47% ($n = 83$)	χ^2 p-value[b]
Demographics [%(n)]						
Sex						
Male	1649	50.8 (1534)	24.0 (35)	44.7 (51)	35.0 (29)	<.001
Female	1715	49.2 (1487)	76.0 (111)	55.3 (63)	65.0 (54)	
Rurality of school						
Inner regional	1970	58.9 (1779)	52.7 (77)	61.4 (70)	53.0 (44)	.104
Outer regional	1284	37.8 (1141)	46.6 (68)	33.3 (38)	44.6 (37)	
Remote	110	3.3 (101)	0.7 (1)	5.3 (6)	2.4 (2)	
Paternal occupation						
Level 1 (highest)	837	24.6 (743)	33.6 (49)	19.3 (22)	27.7 (23)	.071
Level 2	249	7.3 (220)	6.9 (10)	10.5 (12)	8.4 (7)	
Level 3	964	28.6 (865)	21.2 (31)	36.0 (41)	32.5 (27)	
Level 4	912	27.6 (835)	26.7 (39)	21.9 (25)	15.7 (13)	
Level 5	402	11.9 (358)	11.6 (17)	12.3 (14)	15.7 (13)	
Number of siblings						
Median (IQR)	–	2 (1, 3)	2 (1, 3)	2 (1, 3)	2 (1, 3)	.893[b]
Participant illness [%(n)]						
Frequent head colds	801	23.7 (702)	24.7 (35)	29.4 (32)	40.0 (32)	.005
Tonsillitis						
≥2 episodes in last year	779	23.8 (686)	24.8 (34)	29.1 (32)	33.8 (27)	.125
Tonsillectomy	549	16.5 (491)	19.7 (28)	15.3 (17)	16.1 (13)	.764
Either	1183	35.9 (1043)	41.6 (57)	40.0 (44)	48.2 (39)	.062
Hay fever	453	13.6 (402)	16.3 (23)	16.2 (18)	12.8 (10)	.704
Asthma/wheezing						
1–5 episodes	249	7.6 (224)	7.7 (11)	8.1 (9)	6.2 (5)	.622
≥6 episodes	284	8.4 (247)	9.1 (13)	11.7 (13)	13.7 (11)	
Current at age 7	366	11 (318)	11 (16)	14 (16)	19 (16)	.055
Pneumonia/pleurisy	439	13.5 (401)	7.0 (10)	15.4 (17)	13.4 (11)	.140
Bronchitis						
1–5 episodes	932	28.0 (831)	31.0 (44)	31.2 (35)	27.2 (22)	.144
≥6 episodes	631	18.9 (560)	23.2 (33)	19.6 (22)	19.7 (16)	
Parental history [%(n)]						
Smoking at age 7						
Maternal smoking	1100	33.8 (984)	26.8 (37)	41.3 (45)	42.0 (34)	.044
Paternal smoking	1889	58.5 (1691)	58.4 (80)	62.0 (67)	64.8 (51)	.702
Parental head cold	808	24.1 (693)	31.6 (43)	31.8 (34)	34.6 (27)	.017
Parental asthma-hay fever	1046	36.9 (1062)	38.7 (53)	34.9 (37)	39.7 (31)	.527
Parental bronchitis	889	18.6 (535)	19.7 (27)	22.9 (25)	30.4 (24)	.001

Abbreviations: CRS, chronic rhinosinusitis; IQR, interquartile range; TAHS, Tasmanian Longitudinal Health Study.

[a]Maximum participant numbers in the heading refer to the current asthma variable at age 7 which has excluded 245 participants with missing data on sex, rurality of school, paternal occupation, and sibling number.

[b]Chi-squared tests otherwise non-parametric trend test as indicated.

TABLE 3 Multivariable associations between childhood factors and adult chronic rhinosinusitis in middle age, unadjusted for parental smoking.

Childhood factors up to age 7[a,b]	Chronic rhinosinusitis at mean age 53 years[c,d]					
	Past sinusitis diagnosis, *N* = 146/3364		Current CRS without diagnosis, *N* = 114/3364		Current CRS with diagnosis, *N* = 83/3364	
	n	mOR (95% CI)	*n*	mOR (95% CI)	*n*	mOR (95% CI)
Frequent head colds[b]	35	0.88 (0.58, 1.36)	32	1.22 (0.77, 1.94)	32	2.04 (1.24, 3.37)**
Tonsillitis[a]						
Frequent	34	0.98 (0.65, 1.46)	32	1.31 (0.86, 2.00)	27	1.61 (1.00, 2.59)*
Tonsillectomy[d]	28	1.33 (0.86, 2.06)	17	0.89 (0.52, 1.52)	13	1.08 (0.59, 2.01)
Either	57	1.26 (0.88, 1.79)	44	1.18 (0.80, 1.75)	39	1.76 (1.12, 2.76)*
Hay fever[b]	23	1.38 (0.85, 2.24)	18	1.22 (0.71, 2.12)	10	0.93 (0.46, 1.85)
Asthma/wheezing[b]						
≥2 episodes	19	1.08 (0.64, 4.47)	19	1.22 (0.72, 2.08)	16	1.51 (0.85, 2.69)
Current, age 7	16	1.22 (0.70, 2.15)	16	1.46 (0.82, 2.59)	16	2.23 (1.25, 3.98)**
Pneumonia and/or pleurisy[a]	10	0.52 (0.27, 1.00)^	17	1.20 (0.70, 2.03)	11	1.04 (0.54, 1.99)
Bronchitis ≥2 episodes[b]	59	1.12 (0.79, 1.61)	47	1.09 (0.73, 1.62)	36	1.15 (0.72, 1.83)

Note: ^$p = .05$, *$p < .05$, **$p < .01$.

Abbreviations: AR, allergic rhinitis; CRS, chronic rhinosinusitis; mOR, multinominal odds ratio; *p*-int, *p*-value for-interaction.

[a]Adjusted for sex, rurality of school, paternal occupation, number of siblings at age 7.

[b]Adjusted for sex, rurality of school, paternal occupation, number of siblings at age 7, and parental history (head colds, asthma/hay fever or bronchitis).

[c]Reference group are participants without either current CRS symptoms or a past doctor's diagnosis of sinusitis; complete case analysis was used.

[d]Total regression numbers *N* = 3364 and *n* correspond to Model 1 and asthma/wheezing as complete cases were used. Model 2 additionally adjusted for parental smoking has a maximum of *N* = 3203.

across all CRS subtypes. However, the late-onset asthma allergies trajectory was more strongly associated with symptomatic doctor-diagnosed CRS than the late-onset hay fever *without* asthma given the 95% CIs did not overlap (Table 6). These relationships did not appreciably change when additionally adjusting for parental smoking (Table S8).

4 | DISCUSSION

Our prospective study that spans the first-to-sixth decade of life has shown that an epidemiological definition of CRS is clinically relevant in middle age given the markedly increased prevalence of doctor-diagnosed asthma, including current atopic asthma, and links to other CRS-related co-morbidities.[3] Using this definition, we have documented temporal associations between multiple childhood factors –frequent childhood head colds, tonsillitis and current asthma at age 7—and doctor-diagnosed CRS with current symptoms at age 53. We have also shown trends in skin-prick-test positivity across adult CRS subtypes of increasing severity, especially for *D. pteronyssinus*, peanut and cow's milk. Strong main associations were observed between our novel trajectories of asthma and allergies from childhood and CRS in middle age, especially for the profile of 'late-onset asthma and allergies'. For the first time, we have documented the history of asthma and allergic rhinitis-ever within each CRS subtype where the prevalence increased substantially between childhood and early adulthood, except for symptomatic doctor-diagnosed CRS in which the prevalence of allergic rhinitis-ever increased from adolescence onwards. This was not totally unexpected, as this pattern resembles a typical 'atopic march' sequence.[17]

Specifically, we have linked three trajectories of asthma and allergies between ages 7–53 years to CRS in middle age, which suggests that asthma, hay fever and allergies are potentially treatable traits of CRS. A common feature of these trajectories was the presence of asthma and/or allergies at the time of CRS symptoms which may reflect the presence of increased type II inflammation in the airways at the time of the reported CRS, that is a T-lymphocyte type-2 endotype, which also strengthens evidence that the recency of asthma and allergies is important.[3,18] Given our study did not confirm CRS by radiology or endoscopy, we hypothesize that our highest-risk trajectory of late-onset asthma and allergies may have been related to the major phenotype of chronic rhinosinusitis with nasal polyposis (CRSwNP),[18] or the combined phenotype-endotype, T2wNP, reflecting both CRSwNP and a T-lymphocyte type-2 endotype.[19] The treatment of specific endotypes of this 'united airways disease (UAD)'[20] with biological therapies has become accepted for severe asthma, where the co-presence of CRS is predictive of their effectiveness, with or without nasal polyposis.[21] More evidence is needed around the early active treatment of concurrent allergic-type conditions to reduce symptoms, disease activity and the substantial burden of illness from adult CRS.[22,23]

TABLE 4 Longitudinal current asthma, allergies, and their trajectories from childhood to middle age in TAHS participants, by chronic rhinosinusitis status.

Clinical feature	*N*	CRS at mean age 53 [%(*n*)][a,b]				χ^2 *p*-value
		No CRS, 90%[a]	Past sinusitis diagnosis, 4.3%[a]	Current CRS without diagnosis, 3.4%[a]	Current CRS with diagnosis 2.5%[a]	
Allergic rhinitis-ever[*N* = 3275 (*n*), %(*n*)]		*2945*	*141*	*111*	*78*	
At age 7	453	13.6 (402)	16.3 (23)	16.2 (18)	12.8 (10)	.704
At age 13[c]	105	26.6 (90)	26.7 (4)	18.2 (2)	81.2 (9)	.001
At age 31[c]	375	47.5 (316)	82.1 (23)	76.7 (23)	65.0 (13)	<.001
At age 43	1625	49.9 (1382)	75.4 (104)	79.6 (82)	80.3 (57)	<.001
At age 53	2212	62.9 (1900)	88.9 (129)	92.1 (105)	94.0 (78)	<.001
Current at age 53	1344	35.9 (1082)	67.1 (96)	83.2 (94)	86.8 (72)	<.001
Current asthma [*N* = 3364 (*n*), %(*n*)][a]		*3021*	*146*	*114*	*83*	
At age 7	366	10.5 (318)	11.0 (16)	14.0 (16)	19.3 (16)	.055
At age 13	206	6.4 (175)	11.2 (14)	8.1 (8)	11.8 (9)	.045
At age 31[c]	145	17.5 (116)	35.7 (10)	41.4 (12)	36.8 (7)	<.001
At age 43	514	15.4 (424)	25.4 (35)	31.1 (32)	31.9 (23)	<.001
At age 45[c]	266	20.6 (202)	38.9 (21)	34.0 (17)	68.4 (26)	<.001
At age 53	381	9.8 (295)	21.9 (32)	20.3 (23)	37.4 (31)	<.001
Asthma and allergy trajectories [%(*n*)]		*3016*	*146*	*114*	*83*	
Minimal or least asthma and allergies	1646	52.1 (1570)	25.3 (37)	21.1 (24)	18.1 (15)	<.001
Early-onset persistent asthma and allergies	205	5.5 (167)	10.3 (15)	10.5 (12)	13.3 (11)	
Early-onset remitted asthma and allergies	212	6.7 (202)	2.1 (3)	4.4 (5)	2.4 (2)	
Late-onset asthma and allergies	288	7.1 (213)	15.8 (23)	18.4 (21)	37.4 (31)	
Late-onset hay fever, no asthma	1008	28.7 (864)	46.6 (68)	45.6 (52)	28.9 (24)	

Abbreviations: AR, allergic rhinitis; CRS, chronic rhinosinusitis; SPT, skin-prick tests; TAHS, Tasmanian Longitudinal Health Study.

[a]Maximum participant numbers for the current asthma variable at age 7 which has excluded 245 participants with missing data on sex, rurality of school, paternal occupation, and sibling number are shown in italics; reduced participant numbers for hay fever-ever and the asthma and allergy trajectories are also shown in italics.

[b]As each follow-up collected data on different numbers of participants, the percentage is given first (numbers are in brackets).

[c]These follow-ups were enriched for participants with a history of asthma.

To contrast the only previous population-based study from childhood to early adulthood,[6] we adopted the EAACI/EPOS epidemiological definition of CRS.[8] This symptom-based definition of CRS has been described as being stable and reasonably reliable for epidemiological assessment in large populations,[24] given objective radiological or endoscopic confirmation or phenotypic characterization of CRSwNP and CRSsNP is rarely feasible.[8] While an overlap between symptoms of CRS and allergic rhinitis may occur,[25] symptoms alone have an excellent sensitivity as a diagnostic metric,[26] with its absence able to largely 'rule out' the diagnosis. Thus, symptoms remain the mainstay of diagnosis in primary care patients, and more importantly, they drive patients to seek medical care.[8] Symptoms have also been found to have excellent sensitivity and specificity when using an expert panel consensus as the diagnostic gold standard.[26]

Symptoms comprise the epidemiological definition of CRS as recommended by the last 3 EAACI/EPOS documents,[8,27,28] which for adults, state that 'questions on allergic symptoms (i.e. sneezing, watery rhinorrhoea, nasal itching, and itchy watery eyes) should be included'. Our finding of a strong relationship between late-onset asthma and allergies suggests that this diagnostic formulation should also mention allergic asthma alongside allergic rhinitis and conjunctivitis. Alternatively, late-onset allergic asthma as a distinct CRS phenotype could be used in epidemiological studies.

TABLE 5 Concurrent atopic sensitization by chronic rhinosinusitis subtype in middle age.

Atopic sensitization at age 53[a]		CRS at mean age 53 [%(*n*)][b,c]				
Allergen ($N = 2528$)	Positive	No CRS, 90.1% (2289)[b]	Past sinusitis diagnosis, 4.3% (110)[b]	Current CRS, no diagnosis, 3.4% (75)[b]	Current CRS with diagnosis 2.5% (54)[b]	χ^2 *p*-value
Any skin-prick-test positivity	1382	53.8 (1232)	60.9 (67)	61.3 (46)	68.5 (37)	.006
D. pteronyssinus	1039	40.2 (922)	44.6 (49)	48.7 (36)	58.2 (32)	.002
Cat pelt	374	14.2 (326)	15.5 (17)	30.7 (23)	14.6 (8)	.018
C. cladosporioides	150	5.7 (131)	12.7 (14)	4.1 (3)	3.6 (2)	.883
Alternaria	237	9.2 (212)	11.8 (13)	10.8 (8)	7.4 (4)	.844
Penicillium	91	3.7 (84)	1.8 (2)	5.4 (4)	1.9 (1)	.689
Aspergillus	127	4.8 (111)	7.3 (8)	5.4 (4)	7.3 (4)	.284
Rye grass	749	29.1 (666)	33.9 (37)	40.5 (30)	29.1 (16)	.132
Mixed grass	748	29.2 (669)	33.0 (36)	35.6 (26)	30.9 (17)	.267
Egg	32	1.7 (27)	1.3 (1)	4.2 (2)	5.4 (2)	.058
Peanut	165	8.1 (145)	5.9 (5)	12.7 (7)	20.0 (8)	.015
Shellfish	83	4.5 (73)	6.5 (5)	2.1 (1)	11.4 (4)	.194
Cows' milk	73	3.5 (61)	3.5 (3)	9.1 (5)	10.0 (4)	.005

Abbreviations: AR, allergic rhinitis; CRS, chronic rhinosinusitis; SPT, skin-prick tests; TAHS, Tasmanian Longitudinal Health Study.

[a]Reduced numbers undergoing SPT at age 53; aeroallergen data at age 45 included in Table S6.

[b]Maximum participant numbers for the current follow-up (N = 3364) which has excluded 245 participants with missing data on sex, rurality of school, paternal occupation, and sibling number; fewer numbers underwent skin prick testing.

[c]As each follow-up collected data on different numbers of participants, the percentage is given first (numbers are in brackets).

Interestingly, there were trends of increasing atopic sensitization to *D. pteronyssinus*, peanut and cow's milk across CRS subtypes, that were highest for the group with doctor-diagnosed symptomatic CRS and this is consistent with previous reports in the literature.[29–32] We did not see links between CRS subtype and pollen aero-allergens which is the main driver for seasonal allergic rhinitis, raising the possibility that perennial rhinitis could be more strongly associated with CRS.

Regarding early life upper respiratory tract infections (URTIs), we found a temporal association between childhood tonsillitis ± tonsillectomy and doctor-diagnosed current CRS in middle age, which has rarely been mentioned previously.[3] The association between frequent annual 'head colds' in childhood and CRS in mid-adult life existed despite adjustment for parental head colds, and previous studies have only shown an association up to early adulthood.[6] Such infections in children at day care, nursery or school are very common and can be recurrent and complicated by a secondary bacterial infection of the paranasal sinuses.[33] While our data cannot tell us about the adequacy of treatment of these infections or exclude a predisposition to altered mucosal responses from infection due to genetic and other host factors, these childhood infections may reflect susceptibility to sinonasal disease, as much as risk factors for later disease. However, we do not have data to untangle this. Nonetheless, our findings suggest that frequent URTIs in early childhood by age 7 years could be considered as a 'red flag' for closer monitoring and/or active management by health care providers.

The initiation and persistence of CRS may be attributable to biofilms,[34,35] where the epithelial lining of nasal cavity and paranasal sinuses is destroyed and impaired mucociliary clearance may lead to stasis and biofilm formation. Essentially, these are layers of live, immobile bacteria embedded in their own matrix that become protected from immune host defences. Synthesized endotoxins within the crypts of the tonsils can lead to chronic inflammation, and when local environmental conditions are favourable, bacteria in the biofilm become motile, resulting in re-infection[36–38] This persistence of bacteria within the biofilm in the sinuses[36] is a negative prognostic indicator for recurrent sinusitis[37] which may relate to an upregulation of epithelial adhesion sites from oxidative insults such as ongoing airway inflammation.[39] It has been postulated that some cases of persistent CRS associated with neutrophilic inflammation (which is usually caused by acute bacterial infection) may evolve into a late 'maladaptive-eosinophilic' stage of disease, which is the predominant type of inflammation seen in adult CRS.[40]

Unexpectedly, we found a modest reduction in the odds for a past diagnosis of sinusitis among participants with childhood pneumonia and/or pleurisy so further studies are needed to clarify this finding. While the biological plausibility is not entirely clear, *Streptococcus pneumoniae* is a cause of both sinusitis and pneumonia like *Haemophilus influenzae* infection, and it is notable that the use of pneumococcal-conjugated vaccines led to a 66% lower risk of hospitalization for sinusitis and 19% lower risk of hospitalization for pneumonia in children in Sweden.[41,42]

TABLE 6 Multivariable associations between life course asthma-allergy trajectories and adult chronic rhinosinusitis in middle age.

Asthma-allergy trajectories age 7–53 years ($N = 3112$)		Chronic rhinosinusitis at mean age 53 years[a,b,c]					
			Past sinusitis diagnosis, $n = 132$		Current CRS, no diagnosis, $n = 104$		Current CRS with diagnosis, $n = 78$
	n (%)	Case *n*	mOR (95% CI)	Case *n*	mOR (95% CI)	Case *n*	mOR (95% CI)
Minimal or least asthma and allergies	1526 (49.0)	40	Reference	26	Reference	15	Reference
Early-onset persistent asthma and allergies	180 (5.8)	17	5.00 (2.46, 10.1)***	13	5.18 (2.37, 11.3)***	12	6.74 (2.76, 16.4)***
Early-onset remitted asthma and allergies	193 (6.2)	4	[d]	5	[d]	2	[d]
Late-onset asthma and allergies	267 (8.6)	24	4.52 (2.51, 8.14)***	25	6.48 (3.47, 12.1)***	35	15.9 (8.06, 31.4)***
Late-onset hay fever, no asthma	946 (30.4)	71	3.64 (2.34, 5.66)***	57	3.82 (2.29, 6.38)***	27	3.02 (1.51, 6.06)**

Note: *$p < .05$, **$p < .01$, ***$p < .001$.

Abbreviations: AR, allergic rhinitis; CRS, chronic rhinosinusitis; mOR, multinominal odds ratio; *p*-int, *p*-value for-interaction.

[a]Reference group are participants without either current CRS symptoms or a past doctor's diagnosis of sinusitis; complete case analysis was used.

[b]Adjusted for sex, rurality of school, paternal occupation, number of siblings at age 7, childhood head colds and tonsillitis, parental asthma and hay fever.

[c]Total regression numbers $N = 3112$ using complete cases.

[d]Estimates suppressed as five or fewer cases in cell.

4.1 | Strengths and limitations

There are several strengths to our study: Firstly, this was a large whole-of-population cohort (99% of all children born in 1961 at school in Tasmania in 1968) which has been serially followed for over five decades into middle age. Therefore, our prevalence estimates across the life course are largely representative of the general population, as opposed to the more common clinic-based recruitment. Similarly, we could investigate several childhood conditions as exposures and adjust for several parental factors, that is from data on parental 'head colds' and allergic predisposition collected in 1968 also. While we did not have objective radiological or endoscopic confirmation available to distinguish between the major CRS phenotypes with or without nasal polyposis, symptoms have been shown to be both sensitive and specific,[26] and we performed skin-prick-testing concurrently in middle age.

Regarding the limitations of a symptom-based diagnosis of CRS that may not 'rule out' people with AR, our population-based findings have limited direct relevance to specialist clinical practice, as we did not collect data on either the radiological/endoscopic appearance or aspirin-exacerbated respiratory disease. Furthermore, parent-reported information about past childhood health events was collected only when the TAHS participants were aged 6–7 years. This could have introduced some recall bias if parents suffered from frequent URTIs or chronic sinusitis themselves.[43] Similarly, those with current asthma/allergies in middle age could over-report or more accurately report CRS symptoms or a past sinusitis diagnosis (i.e. recall bias, as we did not have prior cohort data or healthcare records to provide more accurate historical information), pushing the point estimate either towards or away from the null to an uncertain degree.[44] There was also potential for attrition bias, although little difference was seen when comparing childhood factors between TAHS participants and non-participants in this analysis.

Our CRS-outcome variable incorporated whether the diagnosis had been made by a doctor. However, we did not collect descriptive data on CRS phenotype, other severity measures, social burden, or disease impact (i.e. workdays lost, quality of life). As this CRS-outcome was only available at the latest follow-up, the temporality of the association between asthma, allergies and CRS could not be definitively established given the potential for a bidirectional relationship.[5] We also neither had sufficient data on immunological biomarkers to subtype our CRS cases by endotypes, nor collected specific data on anatomical variants or childhood CRS to exclude potential confounding bias or investigate a potential mediating effect. Similarly, we were unable to investigajectories across the life course as the whole cohort was only surveyed about current AR symptoms at ages 7 and 53 years. Finally, Australia is a country with one of the highest prevalence of asthma and allergies worldwide and the study participants were almost exclusively of European ethnicity, so generalization of our findings to other populations should be cautious, given the global variation in CRS endotypes.[45]

5 | CONCLUSION

Our prospective population-based epidemiological study has found current asthma at age 7 and upper respiratory infective illnesses (frequent head colds and tonsillitis) to be temporally associated with symptomatic doctor-diagnosed CRS in middle age. Such conditions could be a sign of a susceptible child who is at

higher risk for CRS in mid-adult life and who might benefit from closer monitoring and/or proactive management. The markedly increased prevalence of doctor-diagnosed asthma including current atopic asthma across CRS subtypes, and the strong association especially between late-onset allergic asthma profile and symptomatic doctor-diagnosed CRS suggest that asthma and allergy are potential treatable traits of CRS. Thus, mentioning concurrent symptoms of allergic asthma alongside allergic rhinitis and conjunctivitis in the epidemiological definition of the current EAACI/EPOS document[8] would be encouraged.

AUTHOR CONTRIBUTIONS

Funding acquisition: SCD, EHW, MJA, JLP, BE. Data curation and resources: SCD, EHW, MJA, IF, BRT. Conceptualization: JLP, SCD, EHW, MJA. Data access and verification: JLP. Data interpretation: JLP, ARF, XZ, VY, EB, CJL, AJL, SCD, EHW, MJA. Formal analysis: JLP, ARF, VY. Manuscript writing – original draft: JLP, ARF, VY, SI. Manuscript writing – review & editing: all authors, led by JLP. Supervision: JLP, SCD, XZ, NSI, DSB. Project administration: SCD.

ACKNOWLEDGEMENTS

We acknowledge the TAHS study participants and previous investigators, Drs Heather Gibson, Bryan Gandevia, Harold Silverstone and Norelle Lickiss. We thank Professors Mark Jenkins (Centre for Epidemiology & Biostatistics, VIC), Alan James (Sir Charles Gardner Hospital, WA), Peter Frith (Flinders University, SA), Paul Thomas (University of NSW, NSW), Graham Giles (Cancer Council Victoria), A/Prof David Johns (University of Tasmania, TAS) and Richard Wood-Baker (Royal Hobart Hospital, TAS), and Drs Melanie Matheson (University of Melbourne, VIC), James Markos (Launceston General Hospital, TAS) and Geza Benke (Monash University, VIC), who are investigators of TAHS but not co-authors of this manuscript, for their assistance with obtaining funds and data collection. We also acknowledge all the study site co-ordinators and respiratory scientists who collected data in the lung function laboratories of Tasmania, Victoria, Queensland, and New South Wales; the research interviewers and data entry operators; and the organizational roles of Ms Cathryn Wharton and Dr Desiree Mészáros. Furthermore, we thank the late Dr Stephen Morrison (University of Queensland) for his assistance with obtaining funds/data collection. Finally, we thank the Archives Office of Tasmania for providing data from the 1968 and 1974 TAHS questionnaires and copies of the school medical records. Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

The TAHS was supported by the National Health and Medical Research Council (NHMRC) of Australia, research grants 299901, 566931 and 1021275; the University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; the Victorian, Queensland and Tasmanian Asthma Foundations; Royal Hobart Hospital; Helen MacPherson Smith Trust; and GlaxoSmithKline. JLP, AJL, CJL and SCD have been funded through the NHMRC of Australia. These sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST STATEMENT

SCD, JLP, EHW, MJA, DSB, AJL and CJL hold an investigator-initiated grant from GlaxoSmithKline for unrelated research, and SCD and JLP have a partnership grant with AstraZeneca for unrelated research. MJA additionally holds investigator-initiated grants from Pfizer, Boehringer-Ingelheim and Sanofi for unrelated research; undertaken an unrelated consultancy for Sanofi; and received a speaker's fee from GlaxoSmithKline. BRT has been a medical advisor for Chiesi Pharmaceuticals, NDD Medical Technologies and GlaxoSmithKline. AJL has received a grant from Sanofi and non-financial support from Primus Pharmaceuticals for unrelated research. No other authors reported financial disclosures.

DATA AVAILABILITY STATEMENT

TAHS is a cohort study with data that has been prospectively collected since 1968 and will be an ongoing resource for future epidemiological analyses. Data collection protocols have been detailed in the TAHS cohort profile paper published in 2016 (Matheson et al. 2016 doi: 10.1093/ije/dyw028). The raw data have not been made widely available, but expressions of interest can be discussed with the corresponding author, Dr J Perret, and/or principal investigator, Prof S Dharmage, on an individual basis.

ORCID

Jennifer L. Perret https://orcid.org/0000-0001-7034-0615
N. Sabrina Idrose https://orcid.org/0000-0002-7079-3670
E. Haydn Walters https://orcid.org/0000-0002-0993-4374
Dinh S. Bui https://orcid.org/0000-0002-4388-784X
Adrian J. Lowe https://orcid.org/0000-0002-4691-8162
Caroline J. Lodge https://orcid.org/0000-0002-2342-3888
Anne R. Fernandez https://orcid.org/0000-0002-7082-6073
Vivian Yao https://orcid.org/0000-0003-2781-0479
Iain Feather https://orcid.org/0009-0006-7306-6598
Xiao-Wen Zeng https://orcid.org/0000-0003-3918-1841
Bruce R. Thompson https://orcid.org/0000-0002-5885-0652
Bircan Erbas https://orcid.org/0000-0001-9597-418X
Michael J. Abramson https://orcid.org/0000-0002-9954-0538
Shyamali C. Dharmage https://orcid.org/0000-0001-6063-1937

REFERENCES

1. Liu T, Cooper T, Earnshaw J, Cervin A. Disease burden and productivity cost of chronic rhinosinusitis patients referred to a tertiary centre in Australia. *Aust J Otolaryngol*. 2018;1:5.
2. Caulley L, Thavorn K, Rudmik L, Cameron C, Kilty SJ. Direct costs of adult chronic rhinosinusitis by using 4 methods of estimation: results of the US medical expenditure panel survey. *J Allergy Clin Immunol*. 2015;136(6):1517-1522.

3. Tan BK, Chandra RK, Pollak J, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. *J Allergy Clin Immunol*. 2013;131:1350-1360.
4. Chen YT, Chien CY, Tai SY, Huang CM, Lee CT. Asthma associated with chronic rhinosinusitis: a population-based study. *Int Forum Allergy Rhinol*. 2016;6(12):1284-1293.
5. Ryu G, Min C, Park B, Choi HG, Mo JH. Bidirectional association between asthma and chronic rhinosinusitis: two longitudinal follow-up studies using a national sample cohort. *Sci Rep*. 2020;10(1):9589.
6. Chang EH, Stern DA, Willis AL, Guerra S, Wright AL, Martinez FD. Early life risk factors for chronic sinusitis: a longitudinal birth cohort study. *J Allergy Clin Immunol*. 2018;141(4):1291-1297 e1292.
7. Min JY, Tan BK. Risk factors for chronic rhinosinusitis. *Curr Opin Allergy Clin Immunol*. 2015;15(1):1-13.
8. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on Rhinosinusitis and nasal polyps 2020. *Rhinology*. 2020;58(Suppl S29):1-464.
9. Matheson MC, Abramson MJ, Allen K, et al. Cohort profile: the Tasmanian longitudinal health study (TAHS). *Int J Epidemiol*. 2017;46(2):407-408i.
10. Perret JL, Lodge CJ, Lowe AJ, et al. Childhood pneumonia, pleurisy and lung function: a cohort study from the first to sixth decade of life. *Thorax*. 2020;75(1):28-37.
11. Perret JL, Vicendese D, Simons K, et al. Ten-year prediction model for post-bronchodilator airflow obstruction and early detection of COPD: development and validation in two middle-aged population-based cohorts. *BMJ Open Respir Res*. 2021;8(1):e001138.
12. Bui DS, Lodge CJ, Perret JL, et al. Trajectories of asthma and allergies from 7 years to 53 years and associations with lung function and extrapulmonary comorbidity profiles: a prospective cohort study. *Lancet Respir Med*. 2021;9(4):387-396.
13. Kandane-Rathnayake RK, Matheson MC, Simpson JA, et al. Adherence to asthma management guidelines by middle-aged adults with current asthma. *Thorax*. 2009;64(12):1025-1031.
14. Tan DJ, Burgess JA, Perret JL, et al. Non-pharmacological management of adult asthma in Australia: cross-sectional analysis of a population-based cohort study. *J Asthma*. 2020;57(1):105-112.
15. Cuzick J. A Wilcoxon-type test for trend. *Stat Med*. 1985;4(1):87-90.
16. Textor J, van der Zander B, Gilthorpe MK, Liskiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol*. 2016;45(6):1887-1894.
17. Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol*. 2010;105(2):99-106; quiz 107–109, 117.
18. Won HK, Kim YC, Kang MG, et al. Age-related prevalence of chronic rhinosinusitis and nasal polyps and their relationships with asthma onset. *Ann Allergy Asthma Immunol*. 2018;120(4):389-394.
19. Kato A, Peters AT, Stevens WW, Schleimer RP, Tan BK, Kern RC. Endotypes of chronic rhinosinusitis: relationships to disease phenotypes, pathogenesis, clinical findings, and treatment approaches. *Allergy*. 2022;77(3):812-826.
20. Braunstahl GJ. United airways concept: what does it teach us about systemic inflammation in airways disease? *Proc Am Thorac Soc*. 2009;6(8):652-654.
21. Wechsler ME, Scelo G, Larenas-Linnemann DES, et al. Association between T2-related comorbidities and effectiveness of biologics in severe asthma. *Am J Respir Crit Care Med*. 2024;209(3):262-272.
22. Mullol J, Maldonado M, Castillo JA, et al. Management of united airway disease focused on patients with asthma and chronic rhinosinusitis with nasal polyps: a systematic review. *J Allergy Clin Immunol Pract*. 2022;10(9):2438-2447 e2439.
23. Hopkins C, Surda P, Bast F, Hettige R, Walker A, Hellings PW. Prevention of chronic rhinosinusitis. *Rhinology*. 2018;56(4):307-315.
24. Tomassen P, Newson RB, Hoffmans R, et al. Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis – a GA2LEN study. *Allergy*. 2011;66(4):556-561.
25. Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. *Otolaryngol Head Neck Surg*. 2010;143:147-151.
26. Dixon AE, Sugar EA, Zinreich SJ, et al. Criteria to screen for chronic sinonasal disease. *Chest*. 2009;136(5):1324-1332.
27. Fokkens W. Evidence based diagnosis and treatment of rhinosinusitis and nasal polyps. *Rhinology*. 2005;43(1):1.
28. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology*. 2012;50(1):1-12.
29. Gutman M, Torres A, Keen KJ, Houser SM. Prevalence of allergy in patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2004;130(5):545-552.
30. Sedaghat AR, Phipatanakul W, Cunningham MJ. Characterization of aeroallergen sensitivities in children with allergic rhinitis and chronic rhinosinusitis. *Allergy Rhinol (Providence)*. 2014;5(3):143-145.
31. Lill C, Loader B, Seemann R, et al. Milk allergy is frequent in patients with chronic sinusitis and nasal polyposis. *Am J Rhinol Allergy*. 2011;25(6):e221-e224.
32. Corey JP, Gungor A. In vitro testing for immunoglobulin E-mediated food allergies. *Otolaryngol Head Neck Surg*. 1996;115(4):312-318.
33. Fireman P. Diagnosis of sinusitis in children: emphasis on the history and physical examination. *J Allergy Clin Immunol*. 1992;90(3):433-436.
34. Foreman A, Jervis-Bardy J, Wormald PJ. Do biofilms contribute to the initiation and recalcitrance of chronic Rhinosinusitis? *Laryngoscope*. 2011;121:1085-1091.
35. Vestby LK, Gronseth T, Simm R, Nesse LL. Bacterial biofilm and its role in the pathogenesis of disease. *Antibiotics (Basel)*. 2020;9(2):59.
36. Kilty SJ, Desrosiers MY. The role of bacterial biofilms and the pathophysiology of chronic rhinosinusitis. *Curr Allergy Asthma Rep*. 2008;8:227-233.
37. Karunasagar A, Garag SS, Appannavar SB, Kulkarni RD, Naik AS. Bacterial biofilms in chronic rhinosinusitis and their implications for clinical management. *Indian J Otolaryngol Head Neck Surg*. 2018;70(1):43-48.
38. Kostic M, Ivanov M, Babic SS, et al. Analysis of tonsil tissues from patients diagnosed with chronic tonsillitis-microbiological profile, biofilm-forming capacity and histology. *Antibiotics (Basel)*. 2022;11(12):1747.
39. Shukla SD, Hansbro PM, Walters EH. Upregulated pneumococcal adhesion molecule (platelet-activating factor receptor) may predispose COPD patients to community-acquired pneumonia. *Int J Chron Obstruct Pulmon Dis*. 2017;12:3111-3113.
40. Hamilos DL. Pediatric chronic rhinosinusitis. *Am J Rhinol Allergy*. 2015;29(6):414-420.
41. Department of Health & Human Services, State Government of Victoria, Australia. Vaccine history timeline. 2019. Accessed September 12, 2019. https://www2.health.vic.gov.au/public-health/immunisation/immunisation-schedule-vaccine-eligibility-criteria/vaccine-history-timeline
42. Lindstrand A, Bennet R, Galanis I, et al. Sinusitis and pneumonia hospitalization after introduction of pneumococcal conjugate vaccine. *Pediatrics*. 2014;134:e1528-e1536.
43. Rajmil L, Fernández E, Gispert R, et al. Influence of proxy respondents in children's health interview surveys. *J Epidemiol Community Health*. 1999;53:38-42.
44. Alexander LK, Lopes B, Ricchetti-Masterson K, Yeatts KB. Sources of systematic error or bias: information bias. In: The University of North Carolina, ed. *Eric Notebook*. 2nd ed. Gillings School of Global Public Health, Department of Epidemiology; 2014.

45. Sedaghat AR, Kuan EC, Scadding GK. Epidemiology of chronic rhinosinusitis: prevalence and risk factors. *J Allergy Clin Immunol Pract*. 2022;10(6):1395-1403.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Perret JL, Idrose NS, Walters EH, et al. Childhood infections, asthma and allergy trajectories, and chronic rhinosinusitis in middle age: A prospective cohort study across six decades. *Allergy*. 2024;00:1-15. doi:10.1111/all.16184