



Allergic diseases and long-term risk of autoimmune disorders: longitudinal cohort study and cluster analysis

Mamidipudi Thirumala Krishna ^{1,2}, Anuradhaa Subramanian³, Nicola J. Adderley³, Dawit T. Zemedikun ³, Georgios V. Gkoutos^{4,5} and Krishnarajah Nirantharakumar^{3,5}

Affiliations: ¹Dept of Allergy and Immunology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. ²Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK. ³Institute of Applied Health Research, University of Birmingham, Birmingham, UK. ⁴Institute of Cancer and Genomics, University of Birmingham, Birmingham, UK. ⁵Midlands Health Data Research UK, Birmingham, UK.

Correspondence: Mamidipudi Thirumala Krishna, Dept of Allergy and Immunology, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham, B9 5SS, UK. E-mail: mtkrishna@yahoo.com



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This study has shown that the long-term risk of autoimmune disorders is significantly higher in patients with allergic diseases. Allergic diseases and autoimmune disorders co-occur, and show an age- and sex-related clustering pattern. <http://bit.ly/33tqkZn>

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ABSTRACT

Introduction: The association between allergic diseases and autoimmune disorders is not well established. Our objective was to determine incidence rates of autoimmune disorders in allergic rhinitis/conjunctivitis (ARC), atopic eczema and asthma, and to investigate for co-occurring patterns.

Methods: This was a retrospective cohort study (1990–2018) employing data extracted from The Health Improvement Network (UK primary care database). The exposure group comprised ARC, atopic eczema and asthma (all ages). For each exposed patient, up to two randomly selected age- and sex-matched controls with no documented allergic disease were used. Adjusted incidence rate ratios (aIRRs) were calculated using Poisson regression. A cross-sectional study was also conducted employing Association Rule Mining (ARM) to investigate disease clusters.

Results: 782 320, 1 393 570 and 1 049 868 patients with ARC, atopic eczema and asthma, respectively, were included. aIRRs of systemic lupus erythematosus (SLE), Sjögren's syndrome, vitiligo, rheumatoid arthritis, psoriasis, pernicious anaemia, inflammatory bowel disease, coeliac disease and autoimmune thyroiditis were uniformly higher in the three allergic diseases compared with controls. Specifically, aIRRs of SLE (1.45) and Sjögren's syndrome (1.88) were higher in ARC; aIRRs of SLE (1.44), Sjögren's syndrome (1.61) and myasthenia (1.56) were higher in asthma; and aIRRs of SLE (1.86), Sjögren's syndrome (1.48), vitiligo (1.54) and psoriasis (2.41) were higher in atopic eczema. There was no significant effect of the three allergic diseases on multiple sclerosis or of ARC and atopic eczema on myasthenia. Using ARM, allergic diseases clustered with multiple autoimmune disorders. Three age- and sex-related clusters were identified, with a relatively complex pattern in females ≥ 55 years old.

Conclusions: The long-term risks of autoimmune disorders are significantly higher in patients with allergic diseases. Allergic diseases and autoimmune disorders show age- and sex-related clustering patterns.

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Introduction

Autoimmune disorders and allergic diseases are characterised by an immune dysregulated state [1, 2]. From an immunological viewpoint, it has been suggested that these conditions are largely polarised with disparate mechanisms, with autoimmune disorders and allergic diseases primarily mediated by a T-helper (Th)1 and Th2 cellular immune response, respectively [3, 4]. Both have a complex aetio-pathogenesis and occur as a consequence of a complex interplay between multiple genetic and environmental factors with other possible variables hitherto unknown [5].

Western countries have been challenged with an “allergy epidemic” during the last three to four decades, resulting in a very high burden of allergic rhinitis, allergic conjunctivitis, atopic eczema and asthma [6, 7]. In particular, the UK ranks as one of the highest countries with respect to the prevalence of allergic diseases worldwide [7]. Interestingly, there has been a parallel increase in the incidence rates of several autoimmune disorders, including multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis and systemic lupus erythematosus (SLE), during the same period [5]. The biological plausibility and causality hypothesis has linked these observations to the possible involvement of common triggers such as infection, genetic foci, environmental factors, reduced biodiversity and birth by caesarean section [8]. Furthermore, there is some emerging evidence regarding an enhanced risk of autoimmune disorders such as SLE, rheumatoid arthritis, Sjögren’s syndrome, multiple sclerosis, coeliac disease and myasthenia gravis in patients with allergic diseases and *vice versa* [9–12]. Studies carried out in South Asian immigrants in Western countries have shown higher rates of both allergic diseases and autoimmune disorders, with a positive association with the duration of settlement away from their native country and with an enhanced risk in their offspring [13–15]. These studies have, however, been limited by relatively small sample size, methodological issues, selection bias, focus on a single or limited number of allergic diseases and/or autoimmune disorders, and some by not accounting for important confounders such as smoking history. Nonetheless, the evidence generated from these studies has challenged the Th1/Th2 paradigm [4, 16].

The main aim of this study was to test the hypothesis that an underlying allergic disease such as allergic rhinitis/conjunctivitis (ARC), atopic eczema or asthma enhances the risk of development of an autoimmune disorder. In a large population-based study, we determined adjusted incidence rate ratios (aIRRs) of common autoimmune disorders in patients with and without ARC, atopic eczema and asthma, and investigated for clustering patterns between allergic diseases and autoimmune disorders.

Methods

Setting

Data were extracted from The Health Improvement Network (THIN), a database comprised of electronic medical records from UK general practices using Vision software (www.visionhealth.co.uk). It includes coded data recorded by the patient’s general practitioner for clinical and management purposes, capturing every consultation. Symptoms and diagnoses are recorded using Read Codes, a hierarchical coding system for structured storage information [17]. 15 million patients at 787 general practices across the UK have contributed data to THIN; there are approximately 3 million active patients comprising 6–7% of the population. The data extracted from THIN are generalisable to the UK population for major health conditions [18].

In order to ensure data quality and allow sufficient time to document important covariates, general practices were included in this study only if they met the following criteria: 1) 12 months after the practice reported an acceptable mortality rate [19] and 2) 12 months after date the practice began using electronic medical records, and study start date.

Ethics approval

The THIN data collection scheme and research carried out using THIN data were approved by the National Health Service (NHS) South-East Multicentre Research Ethics Committee in 2003. Under the terms of the approval, studies must undergo independent scientific review. Approval for this study was obtained from the Scientific Review Committee (for the use of THIN data) in August 2018 (SRC reference 18THIN64).

Study design

Incidence of autoimmune disorders

A longitudinal retrospective cohort study was carried out (January 1, 1990–January 17, 2018). Patients of all ages registered for at least 365 days prior to study entry were included.

The exposed cohort was defined as patients with a prevalent or incident diagnosis of any one or more of the three allergic diseases of interest: asthma, ARC and atopic eczema. Food allergy was not included in our analysis, as the diagnostic coding may not be accurate in primary care records, unless patients had undergone a review by an allergy specialist. In a sensitivity analysis, the exposed cohort was defined as

incident diagnoses only (newly diagnosed after registration with the practice). For patients with multiple allergic diseases, the earliest diagnosis was considered as the index condition. Diagnosis of all allergic diseases was indicated by the presence of a corresponding clinical (Read) code in the patient's medical record. Allergic rhinitis and allergic conjunctivitis were treated as a single exposure group (*i.e.* ARC) due to high rates of co-occurrence and as their inflammatory responses in the mucosa and conjunctiva unfold similarly [20, 21].

For each exposed patient, up to two controls were randomly selected within the same general practice from an age- (within 1 year) and sex-matched pool of patients with no allergic disease diagnosis. The following method was used to randomly select matched controls. Patients with an allergic disease were identified and their order was shuffled by randomly permuting the patient list (following the Fisher–Yates algorithm), using a linear congruential generator as the source of randomness. All permutations occur with equal likelihood. Following this, controls were selected. Shuffling ensures that all patients in the exposure group have an equal chance of being matched to a control in instances where that control could potentially be matched with more than one exposed patient. When the number of possible controls for a particular exposed patient exceeded the number required (*i.e.* $n=2$), a linear congruential generator was used to generate a random number between 1 and the number of potential controls; the potential control at the position of this random number was selected and the process was repeated for subsequent controls.

Outcomes were the following autoimmune disorders (considered separately): SLE, Sjögren's syndrome, vitiligo, rheumatoid arthritis, psoriasis, pernicious anaemia, myasthenia gravis, inflammatory bowel disease, coeliac disease, autoimmune thyroiditis (AIT) and multiple sclerosis.

The index date for exposed patients was the date of diagnosis of the first allergic disease recorded for newly diagnosed patients or date of study entry for patients with an existing diagnosis. Unexposed controls were assigned the same index date as their corresponding exposed patient to avoid immortal time bias [22]. Exposed and control patients were followed from the index date until the earliest of the following end-points: date of outcome recording (autoimmune disorder of interest), date of death, date patient left the practice, date the practice ceased contributing to THIN or study end date.

Read Codes

Read Code lists (see supplementary material) for each condition were compiled as follows: relevant codes were extracted from a database containing all current and past version 2 Read Codes; each code was reviewed and assessed for relevance; where available, code lists in previously published literature [23–26] were used to inform and validate code selection; in the case of uncertainty regarding the relevance of a code, consensus was reached in consultation with an experienced primary care physician.

Disease clusters

A cross-sectional study was performed with a census date of January 1, 2018. Patients of all ages who had been registered with the practice for at least 365 days were included.

Definitions of covariates

Age, sex, body mass index (BMI), deprivation quintile, ethnicity and smoking status were included as covariates in the cohort analyses. For BMI and smoking status, the last value recorded prior to the index date was used. BMI was categorised as $<18.5 \text{ kg}\cdot\text{m}^{-2}$ (underweight), $18\text{--}25 \text{ kg}\cdot\text{m}^{-2}$ (normal weight), $25\text{--}30 \text{ kg}\cdot\text{m}^{-2}$ (overweight) and $>30 \text{ kg}\cdot\text{m}^{-2}$ (obese). Smoking status was categorised as nonsmoker, ex-smoker and current smoker. Social deprivation was recorded as Townsend deprivation quintile [27]. Missing BMI, deprivation quintile, ethnicity and smoking data were handled by employing a “missing” category within the corresponding categorical variables.

Analysis

Incidence of autoimmune disorders

Baseline covariates were summarised for patients in the three separate exposure groups (asthma, atopic eczema and ARC) and their corresponding controls using appropriate descriptive statistics: mean with standard deviation and median (interquartile range (IQR)) for continuous variables, and number (percentage) for categorical variables. Incidence rates of each autoimmune disorder in each of the three allergic diseases were calculated by dividing the number of patients with a newly diagnosed autoimmune disorder (numerator) by the total number of person-years at risk (denominator) for the given allergic disease. Crude IRRs and aRRs together with their corresponding 95% confidence intervals were calculated using Poisson regression. Separate Poisson regression models were used for each allergic disease/autoimmune disorder combination. All models were adjusted for the following covariates: age, sex, BMI, ethnicity, Townsend deprivation quintile and smoking status. Two-sided *p*-values were calculated; $p<0.05$

was considered to indicate statistical significance. All analyses were performed in Stata/IC version 14 (StataCorp, College Station, TX, USA).

The study flow diagram is shown in figure 1.

Disease clusters

Association Rule Mining (ARM) was used to assess how the three allergic diseases associated with the 11 autoimmune disorders, as described by ZEMEDIKUN *et al.* [28]. This is a data mining technique used to investigate frequent co-occurring associations among variables in large databases. Association rules were created specifying allergic diseases as antecedent and autoimmune disorders as consequent so that the reverse associations were not detected. Significance was measured using three parameters: “support” (how frequently the disease combination appears in the dataset), “confidence” (the conditional probability that a subject with the antecedent disease will also have the consequent condition) and “lift” (the ratio of the observed support to that expected if the two events were independent). The minimum parameter thresholds for “support” and “confidence” were set at 0.0005 to extract sufficient number of association rules. “Lift”, also referred to as the interestingness measure, measures the importance of a relationship. Specifically, a “lift” of >1.0 indicates that the antecedent and consequent condition appear more often than expected, *i.e.* the antecedent (allergic disease) exerts a positive effect on the occurrence of the consequent (autoimmune disorder). ARM analysis was performed on the full cross-sectional dataset, and separately for age- and sex-restricted subgroups. ARM analysis was performed using R version 3.3.1 (www.r-project.org).

Results

Incidence of autoimmune disorders

782 320, 1 393 570 and 1 049 868 patients with ARC, atopic eczema and asthma, respectively, together with their matched controls, were included in the analyses (figure 1). Mean±SD age at baseline was 36.4±19.4, 29.8±25.3 and 35.6±21.3 years in patients with ARC, atopic eczema and asthma, respectively; 47.1%, 45.9% and 47.9% were male, respectively. Baseline sex, smoking status, BMI, ethnicity and Townsend deprivation quintile were similar between patients with each allergic disease and their respective controls, whereas

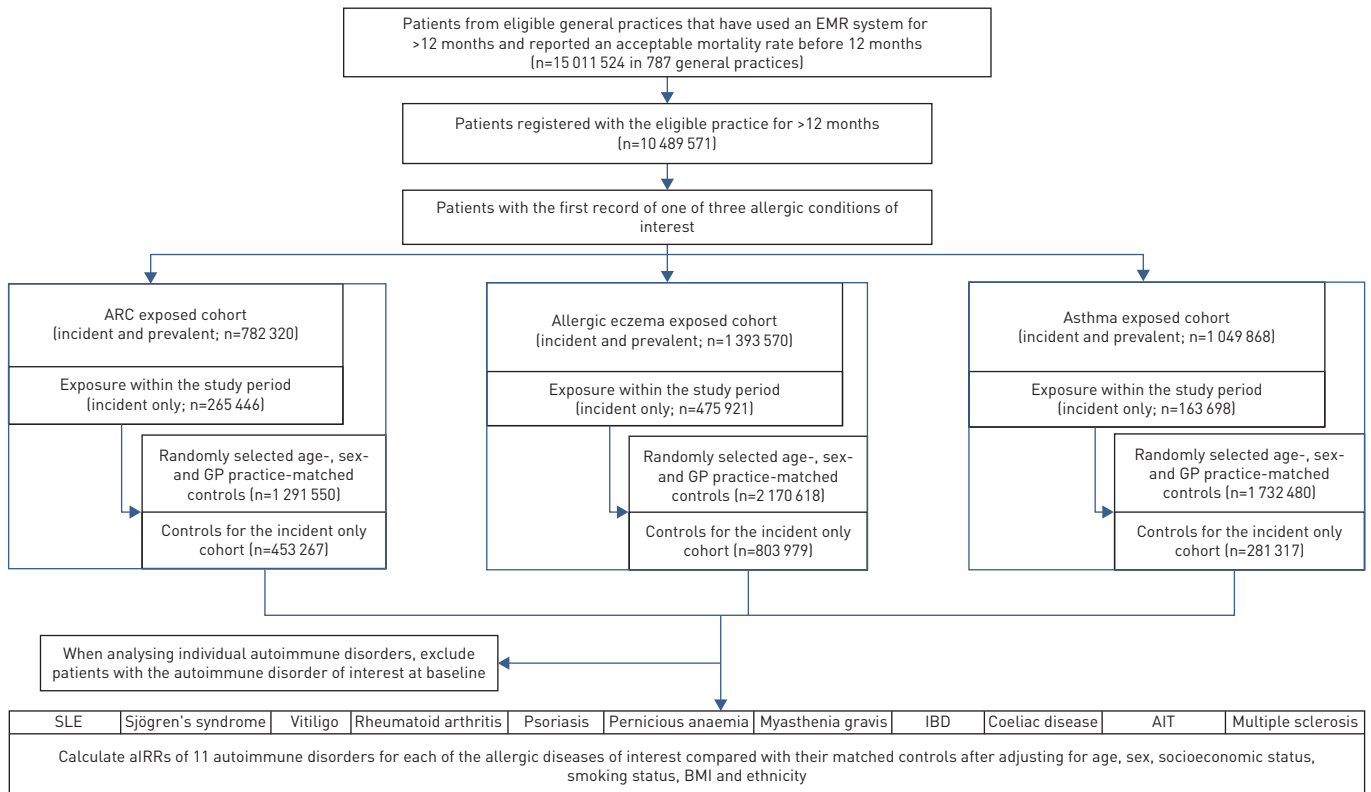


FIGURE 1 Flow diagram summarising study design. EMR: electronic medical record; ARC: allergic rhinitis/conjunctivitis; GP: general practitioner; SLE: systemic lupus erythematosus; IBD: inflammatory bowel disease; AIT: autoimmune thyroiditis; aIRR: adjusted incidence rate ratio; BMI: body mass index.

unexposed controls were slightly older than their corresponding exposure group (table 1); this arose as a result of incomplete matching of some patients due to lack of availability of matched controls within the same practice. Patients with allergic diseases had more autoimmune disorders at baseline.

TABLE 1 Baseline patient characteristics

	ARC		Atopic eczema		Asthma	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Subjects	782 320	1 291 550	1 393 570	2 170 618	1 049 868	1 732 480
Age at allergy diagnosis years	29.89±19.74		24.25±25.29		25.09±21.95	
Age years	36.44±19.44	38.14±19.11	29.77±25.30	32.74±25.45	35.61±21.26	37.98±20.91
Age categories						
0–9 years	56 995 [7.29]	78 503 [6.08]	443 272 [31.81]	602 343 [27.75]	110 635 [10.54]	142 078 [8.20]
10–19 years	97 289 [12.44]	125 135 [9.69]	152 580 [10.95]	191 030 [8.80]	146 137 [13.92]	184 127 [10.63]
20–29 years	156 848 [20.05]	247 795 [19.19]	176 608 [12.67]	277 761 [12.80]	218 329 [20.80]	356 637 [20.59]
30–39 years	165 941 [21.21]	292 551 [22.65]	157 265 [11.29]	272 643 [12.56]	178 980 [17.05]	323 138 [18.65]
40–49 years	115 694 [14.79]	209 110 [16.19]	126 174 [9.05]	226 457 [10.43]	126 552 [12.05]	234 123 [13.51]
50–59 years	78 520 [10.04]	141 956 [10.99]	10 9781 [7.88]	198 495 [9.14]	98 207 [9.35]	182 006 [10.51]
60–69 years	58 414 [7.47]	103 498 [8.01]	96 955 [6.96]	171 496 [7.90]	81 459 [7.76]	147 338 [8.50]
≥70 years	52 619 [6.73]	93 002 [7.20]	130 935 [9.40]	230 393 [10.61]	89 569 [8.53]	163 033 [9.41]
Sex						
Male	368 819 [47.14]	632 521 [48.97]	639 277 [45.87]	1 002 759 [46.20]	502 841 [47.90]	844 310 [48.73]
Female	413 501 [52.86]	659 029 [51.03]	754 293 [54.13]	1 167 859 [53.80]	547 027 [52.10]	888 170 [51.27]
BMI kg·m⁻²	25.94±5.26	25.82±5.31	26.14±5.43	25.98±5.33	26.74±6.01	25.83±5.35
BMI categories						
Underweight (<18.5 kg·m ⁻²)	13 778 [1.76]	24 658 [1.91]	18 525 [1.33]	32 012 [1.47]	18 722 [1.78]	32 606 [1.88]
Normal weight (18.5–25 kg·m ⁻²)	240 550 [30.75]	391 963 [30.35]	296 729 [21.29]	485 257 [22.36]	273 231 [26.03]	488 611 [28.20]
Overweight (25–30 kg·m ⁻²)	167 639 [21.43]	260 249 [20.15]	215 020 [15.43]	345 277 [15.91]	205 041 [19.53]	323 882 [18.69]
Obese (>30 kg·m ⁻²)	95 186 [12.17]	148 894 [11.53]	131 161 [9.41]	200 892 [9.26]	156 489 [14.91]	189 050 [10.91]
Missing	265 167 [33.89]	465 786 [36.06]	732 135 [52.54]	1 107 180 [51.01]	396 385 [37.76]	698 331 [40.31]
Smoker categories						
Nonsmoker	393 523 [50.30]	581 795 [45.05]	472 948 [33.94]	762 193 [35.11]	454 001 [43.24]	735 619 [42.46]
Ex-smoker	103 476 [13.23]	158 144 [12.24]	151 830 [10.90]	228 211 [10.51]	153 849 [14.65]	198 447 [11.45]
Current smoker	117 214 [14.98]	255 481 [19.78]	181 665 [13.04]	304 165 [14.01]	202 006 [19.24]	329 486 [19.02]
Missing	168 107 [21.49]	296 130 [22.93]	587 127 [42.13]	876 049 [40.36]	240 012 [22.86]	468 928 [27.07]
Ethnicity						
Caucasian	276 634 [35.36]	419 125 [32.45]	501 207 [35.97]	737 165 [33.96]	398 059 [37.92]	543 068 [31.35]
Black Afro-Caribbean	16 551 [2.12]	18 529 [1.43]	19 286 [1.38]	26 148 [1.20]	9 608 [0.92]	18 120 [1.05]
South Asian	23 375 [2.99]	27 075 [2.10]	33 686 [2.42]	38 714 [1.78]	15 577 [1.48]	25 656 [1.48]
Mixed Race/Chinese/Other	15 467 [1.98]	20 857 [1.61]	22 697 [1.63]	33 153 [1.53]	11 179 [1.06]	22 258 [1.28]
Missing	450 293 [57.56]	805 964 [62.40]	816 694 [58.60]	1 335 438 [61.52]	615 445 [58.62]	1 123 378 [64.84]
Townsend deprivation quintile						
1 (most affluent)	173 514 [22.18]	267 708 [20.73]	298 714 [21.44]	446 876 [20.59]	189 932 [18.09]	332 379 [19.19]
2	143 591 [18.35]	230 699 [17.86]	253 849 [18.22]	391 908 [18.06]	178 000 [16.95]	307 500 [17.75]
3	140 876 [18.01]	238 640 [18.48]	252 724 [18.14]	398 279 [18.35]	193 512 [18.43]	324 160 [18.71]
4	123 684 [15.81]	215 294 [16.67]	227 134 [16.30]	362 669 [16.71]	189 185 [18.02]	298 135 [17.21]
5 (most deprived)	87 912 [11.24]	154 989 [12.00]	160 308 [11.50]	256 742 [11.83]	189 185 [13.33]	212 347 [12.26]
Missing	112 743 [14.41]	184 220 [14.26]	200 841 [14.41]	314 144 [14.47]	159 252 [15.17]	257 959 [14.89]
Autoimmune disorders at baseline						
Systemic lupus erythematosus	791 [0.10]	1 195 [0.09]	1 445 [0.10]	1 610 [0.07]	1 064 [0.10]	1 514 [0.09]
Sjögren's syndrome	516 [0.07]	511 [0.04]	693 [0.05]	813 [0.04]	572 [0.05]	735 [0.04]
Vitiligo	2191 [0.28]	2516 [0.19]	3532 [0.25]	3519 [0.16]	1996 [0.19]	2895 [0.17]
Rheumatoid arthritis	3819 [0.49]	6122 [0.47]	6933 [0.50]	10 321 [0.48]	6310 [0.60]	8576 [0.50]
Psoriasis	20 077 [2.57]	28 648 [2.22]	40 319 [2.89]	39 147 [1.80]	24 362 [2.32]	35 489 [2.05]
Pernicious anaemia	1458 [0.19]	2095 [0.16]	2879 [0.21]	4101 [0.19]	2464 [0.23]	3166 [0.18]
Myasthenia gravis	180 [0.02]	256 [0.02]	251 [0.02]	460 [0.02]	273 [0.03]	349 [0.02]
Inflammatory bowel disease	5003 [0.64]	7030 [0.54]	7848 [0.56]	9537 [0.44]	6428 [0.61]	8843 [0.51]
Coeliac disease	1824 [0.23]	2141 [0.17]	2876 [0.21]	3221 [0.15]	2398 [0.23]	2770 [0.16]
Autoimmune thyroiditis	2069 [0.26]	2586 [0.20]	2528 [0.18]	3456 [0.16]	2291 [0.22]	3215 [0.19]
Multiple sclerosis	1479 [0.19]	2474 [0.19]	2204 [0.16]	3439 [0.16]	1519 [0.14]	3147 [0.18]

Data are presented as n, mean±SD or n (%). ARC: allergic rhinitis/conjunctivitis; BMI: body mass index.

In patients with ARC compared with patients with no diagnosed allergic disease, aIRRs were: SLE 1.45 (95% CI 1.27–1.67), Sjögren's syndrome 1.88 (95% CI 1.63–2.17), vitiligo 1.36 (95% CI 1.25–1.47), rheumatoid arthritis 1.21 (95% CI 1.15–1.28), psoriasis 1.38 (95% CI 1.34–1.42), pernicious anaemia 1.30 (95% CI 1.20–1.40), inflammatory bowel disease 1.33 (95% CI 1.26–1.41), coeliac disease 1.39 (95% CI 1.28–1.51) and AIT 1.18 (95% CI 1.08–1.29) (figure 2 and supplementary table E1).

In patients with atopic eczema, aIRRs were: SLE 1.86 (95% CI 1.66–2.09), Sjögren's syndrome 1.48 (95% CI 1.30–1.69), vitiligo 1.54 (95% CI 1.44–1.64), rheumatoid arthritis 1.28 (95% CI 1.22–1.34), psoriasis 2.41 (2.36–2.46), pernicious anaemia 1.25 (95% CI 1.18–1.33), inflammatory bowel disease 1.53 (95% CI 1.45–1.61), coeliac disease 1.41 (95% CI 1.32–1.50) and AIT 1.13 (95% CI 1.05–1.22) (figure 2 and supplementary table E1).

In patients with asthma, aIRRs were: SLE 1.44 (95% CI 1.27–1.62), Sjögren's syndrome 1.61 (95% CI 1.41–1.84), vitiligo 1.24 (95% CI 1.15–1.34), rheumatoid arthritis 1.44 (95% CI 1.37–1.50), psoriasis 1.39 (95% CI 1.36–1.43), pernicious anaemia 1.30 (95% CI 1.22–1.38), myasthenia gravis 1.56 (95% CI 1.29–1.88), inflammatory bowel disease 1.44 (95% CI 1.37–1.51), coeliac disease 1.44 (95% CI 1.34–1.55) and AIT 1.23 (95% CI 1.14–1.33) (figure 2 and supplementary table E1).

There was no statistically significant difference in incidence of multiple sclerosis in any of the allergic diseases or of myasthenia gravis in ARC and atopic eczema.

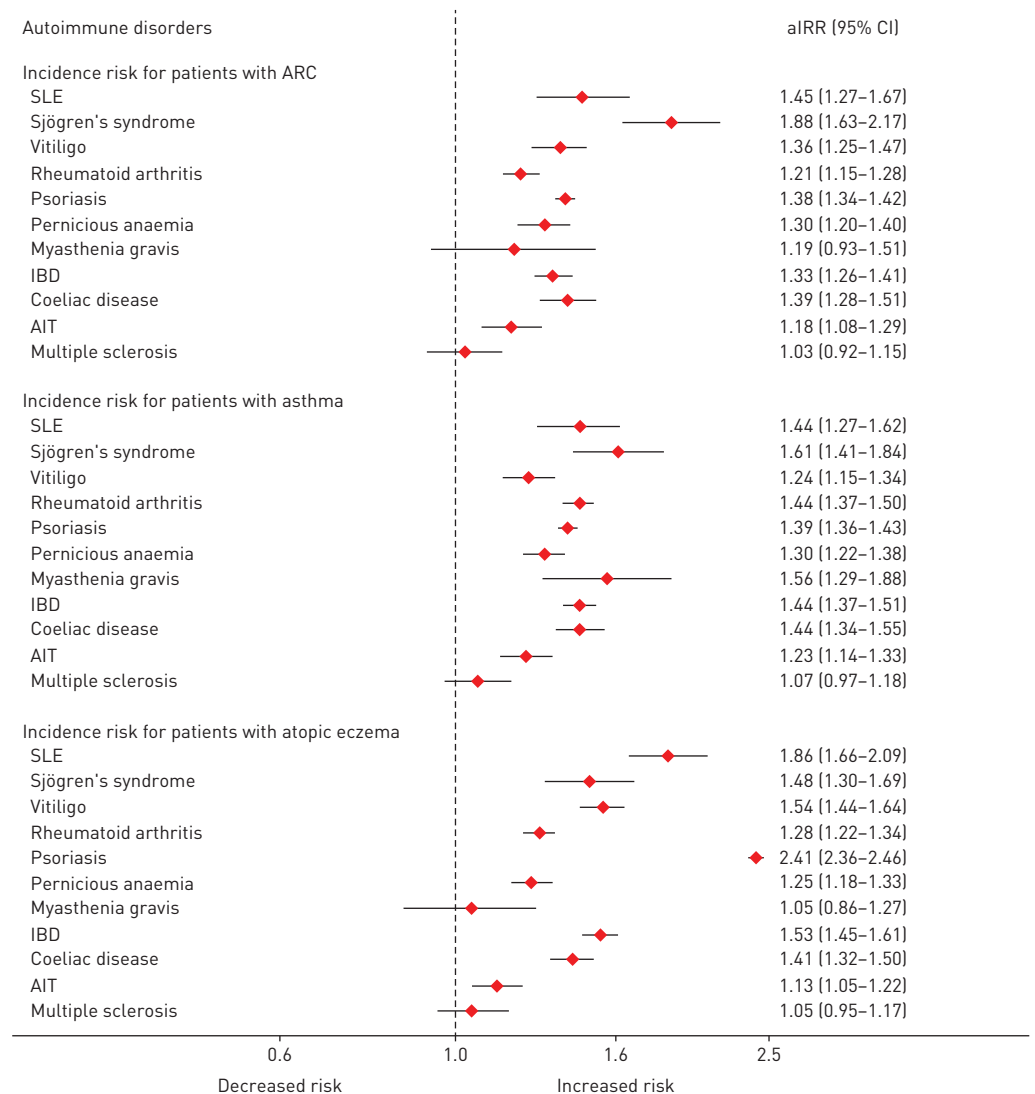


FIGURE 2 Forest plots summarising adjusted incidence rate ratios (aIRRs) of autoimmune disorders in each allergic disease (incident and prevalent cases). ARC: allergic rhinitis/conjunctivitis; SLE: systemic lupus erythematosus; IBD: inflammatory bowel disease; AIT: autoimmune thyroiditis.

Supplementary figure E1 summarises adjusted hazard ratios of autoimmune disorders in combinations of one, two and three allergic diseases. A sensitivity analysis including incident diagnoses of allergic diseases made only little difference to the results (supplementary table E2).

Disease clusters

In the ARM analysis of all ages and both sexes, all three allergic diseases clustered with psoriasis, coeliac disease and inflammatory bowel disease. ARC and atopic eczema clustered with vitiligo; ARC and asthma clustered with rheumatoid arthritis and AIT; and asthma and atopic eczema clustered with pernicious anaemia. The associations between ARC and vitiligo and between atopic eczema and psoriasis were particularly notable, with lifts of 1.583 and 1.414, respectively, indicating that the probability of vitiligo is 58% greater in the presence of ARC and the probability of psoriasis is 41% greater in the presence of atopic eczema. The latter association was strengthened when ARC, asthma or both were present (figure 3 and table 2).

Subgroup analysis highlighted three age- and sex-related clusters, <30, 30–54 and ≥55 years, with a relatively complex pattern of association in females ≥55 years (supplementary tables E3–E8, and supplementary figures E2 and E3). The three allergic diseases clustered with vitiligo, coeliac disease, psoriasis, pernicious anaemia, inflammatory bowel disease, AIT and rheumatoid arthritis. In males, the

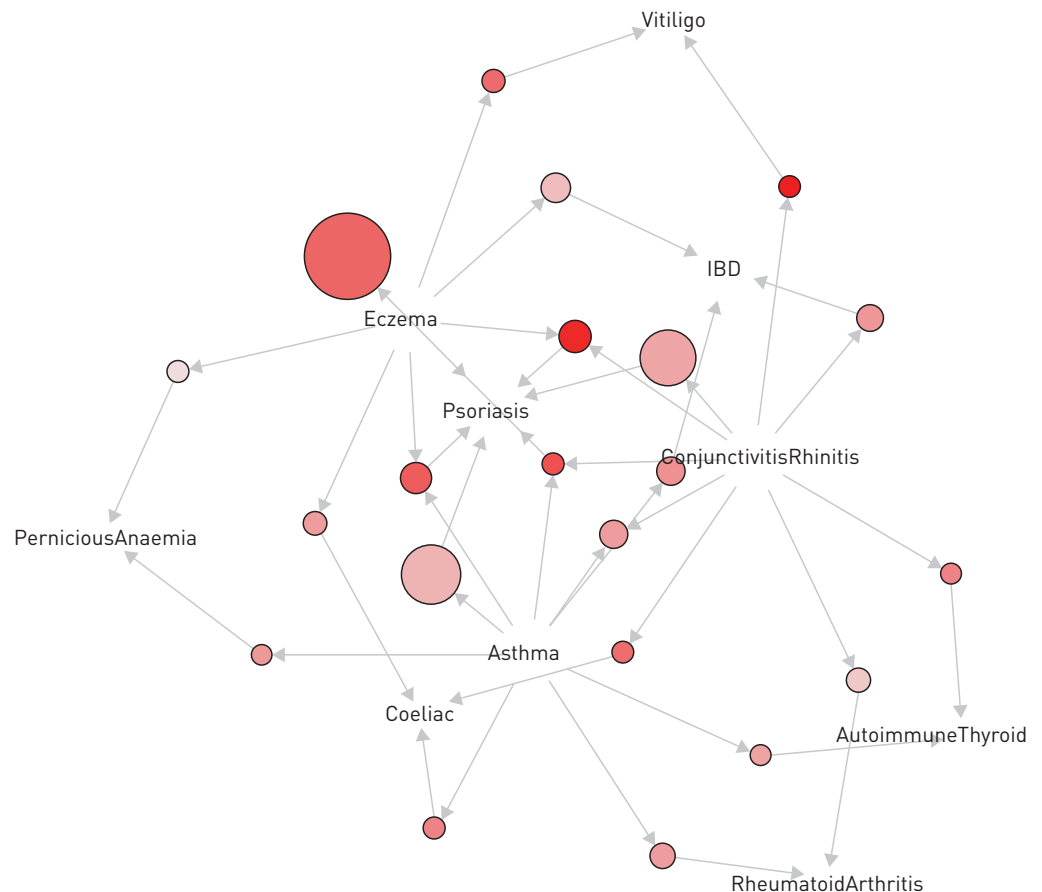


FIGURE 3 Association Rule Mining analysis of the entire study population illustrating clustering and association between allergic diseases and autoimmune disorders. IBD: inflammatory bowel disease. ConjunctivitisRhinitis corresponds to allergic rhinitis/conjunctivitis (ARC). This figure should be reviewed in conjunction with table 2. Each arrow connects an allergic disease (antecedent) with an autoimmune disorder (consequent) via nodes. The size and the intensity of colour within each node represent the level of "support" and level of "lift", respectively (i.e. the larger the node and darker the colour, the greater the "support" and "lift", respectively). For example, there is clustering between asthma, atopic eczema and psoriasis; asthma and ARC (but not atopic eczema) with rheumatoid arthritis; atopic eczema and ARC (but not asthma) with vitiligo. This suggests that these allergic diseases have a positive effect on the occurrence of the respective autoimmune disorders.

TABLE 2 Cluster analysis: association rules of allergic diseases and autoimmune disorders in the full cross-sectional dataset (in order of "lift")

Rule	Antecedent		Consequent	Support	Confidence	Lift
1	{ConjunctivitisRhinitis}	→	{Vitiligo}	0.0006	0.0050	1.5835
2	{Eczema,ConjunctivitisRhinitis}	→	{Psoriasis}	0.0020	0.0555	1.5547
3	{Asthma,Eczema,ConjunctivitisRhinitis}	→	{Psoriasis}	0.0007	0.0524	1.4654
4	{Asthma,Eczema}	→	{Psoriasis}	0.0018	0.0512	1.4340
5	{Eczema}	→	{Psoriasis}	0.0090	0.0505	1.4141
6	{Eczema}	→	{Vitiligo}	0.0008	0.0044	1.4019
7	{ConjunctivitisRhinitis}	→	{Coeliac}	0.0006	0.0054	1.3910
8	{ConjunctivitisRhinitis}	→	{AutoimmuneThyroid}	0.0006	0.0048	1.3427
9	{Asthma}	→	{Coeliac}	0.0007	0.0052	1.3386
10	{Asthma}	→	{IBD}	0.0014	0.0110	1.3114
11	{ConjunctivitisRhinitis}	→	{IBD}	0.0013	0.0109	1.2968
12	{Asthma}	→	{PerniciousAnaemia}	0.0006	0.0044	1.2939
13	{Asthma,ConjunctivitisRhinitis}	→	{Psoriasis}	0.0015	0.0459	1.2857
14	{Eczema}	→	{Coeliac}	0.0009	0.0049	1.2785
15	{Asthma}	→	{RheumatoidArthritis}	0.0012	0.0091	1.2768
16	{Asthma}	→	{AutoimmuneThyroid}	0.0006	0.0045	1.2527
17	{ConjunctivitisRhinitis}	→	{Psoriasis}	0.0052	0.0443	1.2403
18	{Asthma}	→	{Psoriasis}	0.0054	0.0423	1.1834
19	{Eczema}	→	{IBD}	0.0017	0.0095	1.1381
20	{ConjunctivitisRhinitis}	→	{RheumatoidArthritis}	0.0009	0.0078	1.0945
21	{Eczema}	→	{PerniciousAnaemia}	0.0006	0.0035	1.0136

IBD: inflammatory bowel disease. ConjunctivitisRhinitis corresponds to allergic rhinitis/conjunctivitis.

strongest associations were between ARC and vitiligo (<30 years) and between atopic eczema and psoriasis (>30 years). In females, the strongest associations were between asthma/other allergic diseases and psoriasis or inflammatory bowel disease.

Discussion

Strengths

To the best of our knowledge, this is the largest study conducted thus far to systematically investigate associations between each allergic disease independently with a range of common autoimmune disorders and to report multimorbidity and clustering patterns. Our data cover a wide geographical area of the UK and are generalisable to the British population [18]. Importantly, our study was conducted in a primary care setting, thereby reducing selection bias. Patients with missing data for some covariates were included in order to maximise the study population and ensure generalisability.

Limitations

First, the study involved retrospective data extraction. Second, multiple clinicians have contributed to the THIN database and differences in clinical practice, and changes in governance systems, service framework and clinical practice standards over three decades, are possible confounders. Third, there may be lack of standardisation with respect to diagnosis and management criteria in such a large population study involving a wide geographical area. Fourth, the majority of disorders investigated are heterogeneous in nature and it was not within the scope of this study to characterise them. Fifth, atopic status and autoimmune serology for autoimmune disorders could not be captured from the THIN database. Specifically, our data cannot differentiate between allergic asthma and nonallergic asthma in the asthma cohort. Sixth, this study did not specifically investigate the effect of parental allergy.

Interpretation of data

This study showed higher aIRRs of common autoimmune disorders in patients with ARC, asthma and atopic eczema compared with the control (unexposed) population. Furthermore, ARM analysis applied on the entire study population showed significant clustering between ARC, asthma and atopic eczema and autoimmune disorders including vitiligo, coeliac disease, psoriasis, pernicious anaemia, inflammatory bowel disease, AIT and rheumatoid arthritis. Further subgroup analysis highlighted three age- and sex-related clusters, *i.e.* <30, 30–54 and ≥55 years, with a relatively more complex pattern of association in older patients, females in particular. The clustering patterns could at least in part be influenced by known

demographic patterns involving autoimmune disorders, but it is plausible that patients with coexisting allergic diseases and autoimmune disorders represent a distinct phenotype with a specific genetic determinant(s).

While the aIRRs of both organ-specific and systemic autoimmune disorders were uniformly higher in patients with all allergic diseases, effect sizes were greatest in the atopic eczema cohort, with the effect most pronounced for psoriasis, SLE, Sjögren's syndrome, inflammatory bowel disease and vitiligo. Similarly, ARC was positively associated with all autoimmune disorders under consideration, but aIRRs were greatest for SLE and Sjögren's syndrome. A similar pattern was also noted in the asthma cohort, with aIRRs greatest for Sjögren's syndrome, rheumatoid arthritis, myasthenia gravis, coeliac disease and inflammatory bowel disease. The effects on respective autoimmune disorders were more pronounced in the presence of allergic comorbidity (*i.e.* two or more allergic diseases). Interestingly, aIRRs for multiple sclerosis were uniformly low across all allergic diseases and this is in keeping with a recent study by FAKIH *et al.* [29].

Comparison with previous studies

Strong associations with multiple autoimmune disorders and asthma have been reported in patients with coeliac disease [30]. Studies carried out using the National Health Insurance Research database in Taiwan reported a higher incidence of asthma in patients with Sjögren's syndrome [9]. Similar associations were also described between the three allergic diseases and SLE, and our findings are in keeping with these observations [10]. Another study from Taiwan showed a strong association between allergic conjunctivitis and myasthenia gravis [12]. A further study involving 155 311 patients with allergic rhinitis, atopic eczema and asthma (considered in a single group) showed positive associations with SLE, rheumatoid arthritis, Sjögren's syndrome, dermatomyositis/polymyositis and systemic sclerosis, with a particularly strong association with Sjögren's syndrome [11].

Biological plausibility

A number of common factors have been implicated in the aetio-pathogenesis of allergic diseases and autoimmune disorders, including reduced biodiversity, particularly of the gut microbiome, urbanisation, lifestyle factors, diet (including vitamin D status), and recently identified novel metabolic and immune dysregulatory pathways involving mitochondrial stress and intracellular and extracellular RNAs [8]. A meta-analysis of two genome-wide association studies [31] involving allergen sensitisation and self-reported allergy combined with publicly available genome-wide association study data on autoimmune disorders reported commonalities with respect to susceptibility foci, genetic pathways and genomic regulatory sites. Candidate genes have been reported between allergic diseases and autoimmune disorders [32–34]. There is some evidence for an “autoreactive” immunological state in atopic eczema [35], and for involvement of Th17 cells in allergic diseases and autoimmune disorders [36, 37].

Conclusions

The risk of autoimmune disorder(s) is significantly higher in patients with an underlying allergic disease. Allergic diseases and autoimmune disorders co-occur with an age- and sex-related clustering pattern. Further studies in well-characterised patients involving genomics are needed to confirm these observations and unravel novel mechanisms to pave the way for novel biomarkers, precision and personalised medicine, and primary and secondary prevention strategies in allergic diseases and autoimmune disorders.

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e-Table 1: Incidence rate ratios of autoimmune diseases in patients with allergic rhinitis/conjunctivitis, atopic eczema and asthma compared to controls with no allergic disease

	Allergic rhinitis/conjunctivitis		Atopic eczema		Asthma	
Autoimmune Disorders	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
SLE						
Outcome events, n (%)	445 (0.06)	395 (0.03)	701 (0.05)	473 (0.02)	541 (0.05)	531 (0.03)
Person-years	5,273,418	6,826,350	9,008,176	10,713,169	7,038,710	9,535,019
Crude IR per 1000 person-years	0.08	0.06	0.08	0.04	0.08	0.06
Follow-up years, median (IQR)	5.59 (2.35-10.33)	3.81 (1.42-8.10)	5.32 (2.19-9.85)	3.52 (1.28-7.44)	5.51 (2.13-10.46)	4.00 (1.46-8.64)
Unadjusted IRR (95% CI)	1.46 (1.27-1.67); p<0.001		1.76 (1.57-1.98); p<0.001		1.38 (1.22-1.56); p<0.001	
Adjusted IRR (95% CI)	1.45 (1.27-1.67); p<0.001		1.86 (1.66-2.09); p<0.001		1.44 (1.27-1.62); p<0.001	
Sjogren's						
Outcome events, n (%)	466 (0.06)	328 (0.03)	467 (0.03)	427 (0.02)	464 (0.04)	434 (0.03)
Person-years	5,275,513	6,830,374	9,014,747	10,717,723	7,042,642	9,540,365
Crude IR per 1000 person-years	0.09	0.05	0.05	0.04	0.07	0.05
Follow-up years, median (IQR)	5.59 (2.35-10.33)	3.81 (1.42-8.10)	5.32 (2.19-9.85)	3.52 (1.28-7.44)	5.51 (2.13-10.46)	4.00 (1.46-8.64)
Unadjusted IRR (95% CI)	1.84 (1.60-2.12); p<0.001		1.30 (1.14-1.48); p<0.001		1.45 (1.27-1.65); p<0.001	
Adjusted IRR (95% CI)	1.88 (1.63-2.17); p<0.001		1.48 (1.30-1.69); p<0.001		1.61 (1.41-1.84); p<0.001	
Vitiligo						
Outcome events, n (%)	1284 (0.16)	1137 (0.09)	2181 (0.16)	1580 (0.07)	1369 (0.13)	1426 (0.08)
Person-years	5,260,252	6,816,151	8,988,039	10,698,976	7,028,218	9,524,324
Crude IR per 1000 person-years	0.24	0.17	0.24	0.15	0.19	0.15
Follow-up years, median (IQR)	5.58 (2.34-10.33)	3.81 (1.42-8.09)	5.31 (2.18-9.84)	3.52 (1.28-7.43)	5.51 (2.13-10.46)	4.00 (1.46-8.64)
Unadjusted IRR (95% CI)	1.46 (1.35-1.58); p<0.001		1.64 (1.54-1.75); p<0.001		1.30 (1.21-1.40); p<0.001	
Adjusted IRR (95% CI)	1.36 (1.25-1.47); p<0.001		1.54 (1.44-1.64); p<0.001		1.24 (1.15-1.34); p<0.001	
Rheumatoid arthritis						
Outcome events, n (%)	2362 (0.30)	2749 (0.21)	3493 (0.25)	3829 (0.18)	3724 (0.36)	3898 (0.23)
Person-years	5,244,028	6,788,680	8,959,787	10,652,860	6,989,422	9,478,764
Crude IR per 1000 person-years	0.45	0.40	0.39	0.36	0.53	0.41
Follow-up years, median (IQR)	5.57 (2.34-10.31)	3.80 (1.42-8.08)	5.31 (2.18-9.83)	3.52 (1.28-7.42)	5.50 (2.12-10.46)	3.99 (1.46-8.62)
Unadjusted IRR (95% CI)	1.11 (1.05-1.18); p<0.001		1.08 (1.04-1.14); p<0.001		1.30 (1.24-1.36); p<0.001	
Adjusted IRR (95% CI)	1.21 (1.15-1.28); p<0.001		1.28 (1.22-1.34); p<0.001		1.44 (1.37-1.50); p<0.001	
Psoriasis						

Outcome events, n (%)	1024 (0.13)	1096 (0.09)	1247 (0.09)	1366 (0.06)	1310 (0.13)	1446 (0.08)
Person-years	5,261,982	6,815,772	8,998,819	10,699,191	7,028,030	9,522,181
Crude IR per 1000 person-years	0.19	0.16	0.14	0.13	0.19	0.15
Follow-up years, median (IQR)	5.58 (2.34-10.33)	3.81 (1.42-8.09)	5.32 (2.19-9.85)	3.52 (1.28-7.43)	5.51 (2.13-10.46)	4.00 (1.46-8.64)
Unadjusted IRR (95% CI)	1.21 (1.11-1.32); p<0.001		1.09 (1.01-1.17); p<0.001		1.23 (1.14-1.32); p<0.001	
Adjusted IRR (95% CI)	1.18 (1.08-1.29); p<0.001		1.13 (1.05-1.22); p<0.001		1.23 (1.14-1.33); p<0.001	
Multiple sclerosis						
Outcome events, n (%)	553 (0.07)	710 (0.06)	679 (0.05)	812 (0.04)	712 (0.07)	908 (0.05)
Person-years	5,267,880	6,816,872	9,003,555	10,701,390	7,035,374	9,524,161
Crude IR per 1000 person-years	0.10	0.10	0.08	0.08	0.10	0.10
Follow-up years, median (IQR)	5.59 (2.35-10.33)	3.81 (1.42-8.09)	5.32 (2.19-9.85)	3.52 (1.28-7.43)	5.51 (2.13-10.46)	4.00 (1.46-8.64)
Unadjusted IRR (95% CI)	1.01 (0.90-1.13); p=0.890		0.99 (0.90-1.10); p=0.906		1.06 (0.96-1.17); p=0.233	
Adjusted IRR (95% CI)	1.03 (0.92-1.15); p=0.649		1.05 (0.95-1.17); p=0.309		1.07 (0.97-1.18); p=0.171	

IR: incidence rate; IRR: incidence rate ratio; IQR: interquartile range; CI: confidence interval.

e-Table 2. Sensitivity analysis: IRRs of AIDs in patients with incident diagnoses of AR/AC, AE and asthma compared to controls with no ADs.

	Allergic rhinitis/conjunctivitis		Eczema		Asthma	
Automimmune disease	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
SLE						
Outcome events, n (%)	154 (0.06)	132 (0.03)	287 (0.06)	164 (0.02)	86 (0.05)	92 (0.03)
Person-years	1,701,938	2,221,393	2,898,378	3,761,282	1,101,923	1,483,542
Crude IR per 1000 person-years	0.09	0.06	0.10	0.04	0.08	0.06
Follow-up years, median (IQR)	5.60 (2.58-9.59)	3.67 (1.42-7.56)	5.24 (2.35-9.10)	3.52 (1.32-7.11)	5.87 (2.58-10.34)	3.97 (1.49-8.18)
Unadjusted IRR (95% CI)	1.52 (1.21-1.92); p<0.001		2.27 (1.87-2.75); p<0.001		1.26 (0.94-1.69); p=0.125	
Adjusted IRR (95% CI)	1.58 (1.25-1.99); p<0.001		2.40 (1.98-2.91); p<0.001		1.35 (1.00-1.82); p=0.050	
Sjogrens						
Outcome events, n (%)	166 (0.06)	125 (0.03)	174 (0.04)	166 (0.02)	83 (0.05)	72 (0.03)
Person-years	1,702,622	2,222,605	2,900,569	3,762,677	1,102,714	1,484,489
Crude IR per 1000 person-years	0.10	0.06	0.06	0.04	0.08	0.05
Follow-up years, median (IQR)	5.59 (2.58-9.59)	3.67 (1.42-7.56)	5.24 (2.35-9.10)	3.52 (1.32-7.11)	5.88 (2.59-10.34)	3.97 (1.49-8.18)
Unadjusted IRR (95% CI)	1.73 (1.37-2.19); p<0.001		1.36 (1.10-1.68); p=0.005		1.55 (1.13-2.13); p=0.006	
Adjusted IRR (95% CI)	1.86 (1.47-2.35); p<0.001		1.52 (1.22-1.88); p<0.001		1.83 (1.33-2.52); p<0.001	
Vitiligo						
Outcome events, n (%)	431 (0.16)	398 (0.09)	733 (0.15)	539 (0.07)	220 (0.13)	230 (0.08)
Person-years	1,697,699	2,217,853	2,891,844	3,756,071	1,100,534	1,482,456
Crude IR per 1000 person-years	0.25	0.18	0.25	0.14	0.20	0.16
Follow-up years, median (IQR)	5.59 (2.58-9.58)	3.67 (1.42-7.56)	5.23 (2.35-9.10)	3.52 (1.32-7.11)	5.87 (2.58-10.33)	3.97 (1.49-8.18)
Unadjusted IRR (95% CI)	1.41 (1.23-1.62); p<0.001		1.77 (1.58-1.97); p<0.001		1.29 (1.07-1.55); p=0.007	
Adjusted IRR (95% CI)	1.33 (1.16-1.53); p<0.001		1.67 (1.50-1.87); p<0.001		1.15 (0.96-1.39); p=0.138	
Rheumatoid arthritis						
Outcome events, n (%)	711 (0.27)	937 (0.21)	1345 (0.28)	1517 (0.19)	656 (0.40)	665 (0.24)
Person-years	1,692,662	2,207,941	2,880,181	3,736,621	1,094,323	1,474,136

Crude IR per 1000 person-years	0.42	0.42	0.47	0.41	0.60	0.45
Follow-up years, median (IQR)	5.59 (2.58-9.58)	3.66 (1.42-7.55)	5.23 (2.35-9.09)	3.52 (1.32-7.10)	5.86 (2.58-10.33)	3.96 (1.49-8.16)
Unadjusted IRR (95% CI)	0.99 (0.90-1.09); p=0.837		1.15 (1.07-1.24); p<0.001		1.33 (1.19-1.48); p<0.001	
Adjusted IRR (95% CI)	1.11 (1.00-1.22); p=0.042		1.31 (1.22-1.41); p<0.001		1.48 (1.32-1.65); p<0.001	
Psoriasis						
Outcome events, n (%)	2999 (1.16)	2961 (0.67)	9892 (2.14)	4507 (0.57)	1849 (1.16)	1914 (0.69)
Person-years	1,649,818	2,161,177	2,769,326	3,665,273	1,070,007	1,446,990
Crude IR per 1000 person-years	1.82	1.37	3.57	1.23	1.73	1.32
Follow-up years, median (IQR)	5.55 (2.56-9.56)	3.64 (1.41-7.53)	5.11 (2.26-8.97)	3.49 (1.31-7.06)	5.81 (2.55-10.26)	3.93 (1.48-8.13)
Unadjusted IRR (95% CI)	1.33 (1.26-1.40); p<0.001		2.90 (2.80-3.01); p<0.001		1.31 (1.23-1.39); p<0.001	
Adjusted IRR (95% CI)	1.38 (1.32-1.46); p<0.001		3.12 (3.01-3.24); p<0.001		1.31 (1.23-1.40); p<0.001	
Pernicious anaemia						
Outcome events, n (%)	422 (0.16)	440 (0.10)	725 (0.15)	874 (0.11)	327 (0.20)	383 (0.14)
Person-years	1,699,288	2,218,586	2,893,314	3,753,784	1,099,582	1,480,889
Crude IR per 1000 person-years	0.25	0.20	0.25	0.23	0.30	0.26
Follow-up years, median (IQR)	5.59 (2.58-9.58)	3.67 (1.42-7.56)	5.24 (2.35-9.10)	3.52 (1.32-7.11)	5.87 (2.58-10.33)	3.97 (1.49-8.17)
Unadjusted IRR (95% CI)	1.25 (1.10-1.43); p<0.001		1.08 (0.98-1.19); p=0.144		1.15 (0.99-1.33); p=0.064	
Adjusted IRR (95% CI)	1.41 (1.23-1.62); p<0.001		1.23 (1.11-1.35); p<0.001		1.28 (1.10-1.48); p=0.002	
Myasthenia gravis						
Outcome events, n (%)	46 (0.02)	53 (0.01)	70 (0.01)	104 (0.01)	34 (0.02)	33 (0.01)
Person-years	1,703,928	2,223,390	2,902,443	3,763,898	1,103,204	1,485,109
Crude IR per 1000 person-years	0.03	0.02	0.02	0.03	0.03	0.02
Follow-up years, median (IQR)	5.60 (2.58-9.59)	3.67 (1.42-7.56)	5.25 (2.35-9.11)	3.52 (1.32-7.11)	5.88 (2.59-10.34)	3.97 (1.49-8.18)
Unadjusted IRR (95% CI)	1.13 (0.76-1.68); p=0.537		0.87 (0.64-1.18); p=0.379		1.39 (0.86-2.24); p=0.181	
Adjusted IRR (95% CI)	1.30 (0.87-1.93); p=0.202		1.04 (0.76-1.41); p=0.814		1.70 (1.04-2.77); p=0.034	
Inflammatory bowel disease						
Outcome events, n (%)	758 (0.29)	735 (0.16)	1119 (0.24)	1042 (0.13)	476 (0.29)	448 (0.16)
Person-years	1,690,568	2,208,536	2,879,756	3,740,664	1,095,384	1,475,637

Crude IR per 1000 person-years	0.45	0.33	0.39	0.28	0.43	0.30
Follow-up years, median (IQR)	5.59 (2.57-9.58)	3.66 (1.42-7.55)	5.23 (2.35-9.09)	3.52 (1.32-7.10)	5.86 (2.58-10.33)	3.96 (1.49-8.17)
Unadjusted IRR (95% CI)	1.35 (1.22-1.49); p<0.001		1.39 (1.28-1.52); p<0.001		1.43 (1.26-1.63); p<0.001	
Adjusted IRR (95% CI)	1.38 (1.25-1.53); p<0.001		1.46 (1.34-1.59); p<0.001		1.44 (1.26-1.64); p<0.001	
Coeliac disease						
Outcome events, n (%)	439 (0.17)	409 (0.09)	760 (0.16)	724 (0.09)	265 (0.16)	299 (0.11)
Person-years	1,698,808	2,218,504	2,893,873	3,756,389	1,099,974	1,481,891
Crude IR per 1000 person-years	0.26	0.18	0.26	0.19	0.24	0.20
Follow-up years, median (IQR)	5.59 (2.58-9.58)	3.67 (1.42-7.56)	5.24 (2.35-9.10)	3.52 (1.32-7.11)	5.87 (2.58-10.33)	3.97 (1.49-8.18)
Unadjusted IRR (95% CI)	1.40 (1.23-1.60); p<0.001		1.36 (1.23-1.51); p<0.001		1.19 (1.01-1.41); p=0.036	
Adjusted IRR (95% CI)	1.39 (1.21-1.59); p<0.001		1.37 (1.24-1.52); p<0.001		1.26 (1.07-1.49); p=0.007	
Autoimmune thyroid disease						
Outcome events, n (%)	320 (0.12)	323 (0.07)	415 (0.09)	493 (0.06)	175 (0.11)	198 (0.07)
Person-years	1,698,383	2,218,157	2,895,224	3,755,315	1,100,647	1,481,515
Crude IR per 1000 person-years	0.19	0.15	0.14	0.13	0.16	0.13
Follow-up years, median (IQR)	5.59 (2.58-9.59)	3.67 (1.42-7.56)	5.24 (2.35-9.10)	3.52 (1.32-7.11)	5.87 (2.58-10.34)	3.97 (1.49-8.18)
Unadjusted IRR (95% CI)	1.29 (1.11-1.51); p=0.001		1.09 (0.96-1.24); p=0.187		1.19 (0.97-1.46); p=0.094	
Adjusted IRR (95% CI)	1.32 (1.13-1.54); p<0.001		1.14 (1.00-1.30); p=0.055		1.27 (1.03-1.56); p=0.026	
Multiple sclerosis						
Outcome events, n (%)	133 (0.05)	206 (0.05)	229 (0.05)	271 (0.03)	76 (0.05)	117 (0.04)
Person-years	1,700,866	2,218,576	2,896,668	3,757,131	1,101,981	1,482,101
Crude IR per 1000 person-years	0.08	0.09	0.08	0.07	0.07	0.08
Follow-up years, median (IQR)	5.60 (2.58-9.59)	3.67 (1.42-7.56)	5.24 (2.35-9.10)	3.52 (1.32-7.11)	5.88 (2.59-10.34)	3.97 (1.49-8.18)
Unadjusted IRR (95% CI)	0.84 (0.68-1.05); p=0.122		1.10 (0.92-1.31); p=0.307		0.87 (0.65-1.17); p=0.359	
Adjusted IRR (95% CI)	0.89 (0.72-1.12); p=0.323		1.15 (0.96-1.37); p=0.119		0.95 (0.70-1.27); p=0.710	

IR: incidence rate; IRR: incidence rate ratio; IQR: interquartile range; CI: confidence interval.

e-Table 3. Association rules extracted from the male population <30 years of age (in order of lift).

Rule	Antecedent	Consequent	Support	Confidence	Lift
1	{ConjunctivitisRhinitis}	=> {Vitiligo}	0.001	0.004	1.898
2	{Asthma}	=> {IBD}	0.001	0.005	1.745
3	{ConjunctivitisRhinitis}	=> {IBD}	0.001	0.005	1.737
4	{Eczema,ConjunctivitisRhinitis}	=> {Psoriasis}	0.001	0.019	1.736
5	{Asthma,Eczema}	=> {Psoriasis}	0.001	0.019	1.732
6	{Asthma,ConjunctivitisRhinitis}	=> {Psoriasis}	0.001	0.018	1.715
7	{ConjunctivitisRhinitis}	=> {Psoriasis}	0.002	0.017	1.568
8	{Asthma}	=> {Psoriasis}	0.002	0.017	1.544
9	{Eczema}	=> {Vitiligo}	0.001	0.003	1.417
10	{Eczema}	=> {Psoriasis}	0.003	0.014	1.284
11	{Eczema}	=> {Coeliac}	0.001	0.002	1.282
12	{Eczema}	=> {IBD}	0.001	0.003	1.222

e-Table 4. Association rules extracted from the male population ≥ 30 - 54 years of age (in order of lift).

Rule	Antecedent		Consequent	Support	Confidence	Lift
1	{Eczema}	=>	{Psoriasis}	0.008	0.068	1.688
2	{Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.002	0.066	1.660
3	{Eczema}	=>	{Vitiligo}	0.001	0.005	1.605
4	{ConjunctivitisRhinitis}	=>	{Vitiligo}	0.001	0.005	1.544
5	{Asthma,Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.001	0.060	1.493
6	{Asthma,Eczema}	=>	{Psoriasis}	0.002	0.060	1.488
7	{Eczema}	=>	{IBD}	0.001	0.013	1.424
8	{Asthma}	=>	{IBD}	0.002	0.012	1.305
9	{ConjunctivitisRhinitis}	=>	{IBD}	0.001	0.011	1.272
10	{Asthma,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.002	0.048	1.190
11	{ConjunctivitisRhinitis}	=>	{Psoriasis}	0.006	0.047	1.164
12	{Asthma}	=>	{Psoriasis}	0.006	0.045	1.119
13	{Asthma}	=>	{Vitiligo}	0.001	0.004	1.106

e-Table 5. Association rules extracted from the male population over ≥55 years of age (in order of lift).

Rule	Antecedent		Consequent	Support	Confidence	Lift
1	{Eczema}	=>	{Psoriasis}	0.012	0.093	1.741
2	{Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.002	0.092	1.720
3	{Asthma,Eczema}	=>	{Psoriasis}	0.002	0.090	1.679
4	{Asthma,Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.001	0.088	1.641
5	{Eczema}	=>	{Vitiligo}	0.001	0.005	1.572
6	{Eczema}	=>	{Coeliac}	0.001	0.006	1.549
7	{Eczema}	=>	{IBD}	0.002	0.018	1.370
8	{Eczema}	=>	{PerniciousAnaemia}	0.001	0.007	1.347
9	{Asthma}	=>	{RheumatoidArthritis}	0.001	0.014	1.345
10	{Asthma}	=>	{IBD}	0.002	0.016	1.261
11	{Asthma}	=>	{Coeliac}	0.001	0.005	1.244
12	{Asthma,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.001	0.066	1.242
13	{Eczema}	=>	{RheumatoidArthritis}	0.002	0.013	1.239
14	{Asthma}	=>	{PerniciousAnaemia}	0.001	0.007	1.222
15	{ConjunctivitisRhinitis}	=>	{IBD}	0.001	0.016	1.220
16	{ConjunctivitisRhinitis}	=>	{Psoriasis}	0.006	0.063	1.179
17	{Asthma}	=>	{Psoriasis}	0.006	0.060	1.129
18	{ConjunctivitisRhinitis}	=>	{PerniciousAnaemia}	0.001	0.006	1.126
19	{ConjunctivitisRhinitis}	=>	{RheumatoidArthritis}	0.001	0.011	1.071

e-Table 6. Association rules extracted from the female population <30 years of age (in order of lift).

Rule	Antecedent		Consequent	Support	Confidence	Lift
1	{Asthma,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.001	0.029	1.959
2	{Asthma,Eczema}	=>	{Psoriasis}	0.001	0.027	1.871
3	{Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.001	0.027	1.823
4	{Asthma}	=>	{Psoriasis}	0.003	0.024	1.655
5	{ConjunctivitisRhinitis}	=>	{Psoriasis}	0.002	0.024	1.613
6	{Eczema}	=>	{Vitiligo}	0.001	0.003	1.594
7	{Eczema}	=>	{Psoriasis}	0.005	0.020	1.372
8	{Eczema}	=>	{IBD}	0.001	0.003	1.261
9	{Eczema}	=>	{Coeliac}	0.001	0.004	1.210

e-Table 7. Association rules extracted from the female population ≥30 - 54 years of age (in order of lift).

Rule	Antecedent		Consequent	Support	Confidence	Lift
1	{Asthma,Eczema}	=>	{IBD}	0.001	0.017	1.625
2	{Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.003	0.071	1.574
3	{Eczema,ConjunctivitisRhinitis}	=>	{IBD}	0.001	0.017	1.573
4	{Eczema}	=>	{Psoriasis}	0.012	0.069	1.530
5	{Asthma,ConjunctivitisRhinitis}	=>	{IBD}	0.001	0.015	1.461
6	{Asthma,Eczema}	=>	{Psoriasis}	0.003	0.065	1.433
7	{Asthma,Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.001	0.064	1.431
8	{ConjunctivitisRhinitis}	=>	{Coeliac}	0.001	0.007	1.417
9	{Eczema}	=>	{Vitiligo}	0.001	0.005	1.406
10	{Asthma}	=>	{Coeliac}	0.001	0.007	1.357
11	{Eczema}	=>	{Coeliac}	0.001	0.007	1.345
12	{Eczema}	=>	{IBD}	0.002	0.014	1.338
13	{Eczema}	=>	{SLE}	0.001	0.003	1.286
14	{Asthma}	=>	{IBD}	0.002	0.013	1.270
15	{Asthma}	=>	{RheumatoidArthritis}	0.001	0.008	1.263
16	{ConjunctivitisRhinitis}	=>	{IBD}	0.002	0.013	1.257
17	{Asthma}	=>	{PerniciousAnaemia}	0.001	0.005	1.250
18	{ConjunctivitisRhinitis}	=>	{Vitiligo}	0.001	0.005	1.225
19	{ConjunctivitisRhinitis}	=>	{PerniciousAnaemia}	0.001	0.005	1.205
20	{Asthma,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.002	0.053	1.177
21	{ConjunctivitisRhinitis}	=>	{Psoriasis}	0.008	0.053	1.172
22	{Asthma}	=>	{AutoimmuneThyroid}	0.001	0.009	1.169
23	{ConjunctivitisRhinitis}	=>	{RheumatoidArthritis}	0.001	0.008	1.165
24	{ConjunctivitisRhinitis}	=>	{AutoimmuneThyroid}	0.001	0.009	1.133
25	{Asthma}	=>	{Psoriasis}	0.008	0.051	1.127
26	{Asthma}	=>	{MS}	0.001	0.005	1.112
27	{Eczema}	=>	{PerniciousAnaemia}	0.001	0.004	1.104
28	{Eczema}	=>	{AutoimmuneThyroid}	0.001	0.008	1.077
29	{Eczema}	=>	{MS}	0.001	0.005	1.064
30	{Eczema}	=>	{RheumatoidArthritis}	0.001	0.007	1.049
31	{ConjunctivitisRhinitis}	=>	{MS}	0.001	0.005	1.039

e-Table 8. Association rules extracted from the female population ≥55 years of age (in order of lift).

Rule	Antecedent		Consequent	Support	Confidence	Lift
1	{Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.003	0.094	1.825
2	{Asthma,Eczema}	=>	{Psoriasis}	0.003	0.092	1.786
3	{Asthma,Eczema,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.001	0.091	1.768
4	{Eczema}	=>	{Psoriasis}	0.014	0.091	1.766
5	{ConjunctivitisRhinitis}	=>	{Sjogrens}	0.001	0.006	1.673
6	{ConjunctivitisRhinitis}	=>	{Vitiligo}	0.001	0.006	1.503
7	{Asthma,Eczema}	=>	{IBD}	0.001	0.020	1.497
8	{Eczema}	=>	{Sjogrens}	0.001	0.005	1.448
9	{Eczema}	=>	{Vitiligo}	0.001	0.006	1.388
10	{Eczema,ConjunctivitisRhinitis}	=>	{IBD}	0.001	0.018	1.370
11	{Eczema}	=>	{SLE}	0.001	0.005	1.357
12	{Asthma}	=>	{Sjogrens}	0.001	0.005	1.352
13	{Asthma}	=>	{PerniciousAnaemia}	0.002	0.013	1.329
14	{Eczema}	=>	{Coeliac}	0.001	0.009	1.323
15	{Asthma,Eczema}	=>	{RheumatoidArthritis}	0.001	0.029	1.321
16	{ConjunctivitisRhinitis}	=>	{Coeliac}	0.001	0.009	1.318
17	{Asthma}	=>	{SLE}	0.001	0.005	1.294
18	{Asthma}	=>	{Coeliac}	0.001	0.009	1.285
19	{Asthma}	=>	{RheumatoidArthritis}	0.004	0.028	1.280
20	{ConjunctivitisRhinitis}	=>	{AutoimmuneThyroid}	0.001	0.012	1.278
21	{Asthma,ConjunctivitisRhinitis}	=>	{Psoriasis}	0.002	0.065	1.268
22	{Asthma,ConjunctivitisRhinitis}	=>	{IBD}	0.001	0.017	1.252
23	{Eczema,ConjunctivitisRhinitis}	=>	{RheumatoidArthritis}	0.001	0.027	1.250
24	{Eczema}	=>	{IBD}	0.003	0.016	1.243
25	{Asthma}	=>	{Vitiligo}	0.001	0.005	1.230
26	{Asthma}	=>	{IBD}	0.002	0.016	1.229
27	{Asthma}	=>	{AutoimmuneThyroid}	0.001	0.011	1.191
28	{ConjunctivitisRhinitis}	=>	{Psoriasis}	0.007	0.061	1.182
29	{ConjunctivitisRhinitis}	=>	{IBD}	0.002	0.015	1.160
30	{ConjunctivitisRhinitis}	=>	{SLE}	0.001	0.004	1.155
31	{Asthma}	=>	{Psoriasis}	0.008	0.059	1.145
32	{Eczema}	=>	{AutoimmuneThyroid}	0.002	0.010	1.144
33	{Asthma,ConjunctivitisRhinitis}	=>	{RheumatoidArthritis}	0.001	0.025	1.139
34	{Eczema}	=>	{RheumatoidArthritis}	0.004	0.025	1.133
35	{Eczema}	=>	{PerniciousAnaemia}	0.002	0.011	1.117
36	{ConjunctivitisRhinitis}	=>	{PerniciousAnaemia}	0.001	0.011	1.086
37	{ConjunctivitisRhinitis}	=>	{RheumatoidArthritis}	0.003	0.023	1.048
38	{Eczema}	=>	{MS}	0.001	0.006	1.020

e-Methods-1: Read code lists used to ascertain allergic diseases and autoimmune disorders

Allergic Rhinitis

medcode	description
H17..00	Allergic rhinitis
H17..11	Perennial rhinitis
H170.00	Allergic rhinitis due to pollens
H171.00	Allergic rhinitis due to other allergens
H172.00	Allergic rhinitis due to unspecified allergen
H17z.00	Allergic rhinitis NOS
Hyu2000	[X]Other seasonal allergic rhinitis
Hyu2100	[X]Other allergic rhinitis
H170.11	Hay fever - pollens
H170.12	Pollinosis
H171.11	Cat allergy
H171.12	Dander (animal) allergy
H171.13	Feather allergy
H171.14	Hay fever - other allergen
H171.15	House dust allergy
H171.16	House dust mite allergy
H171000	Allergy to animal
H171100	Dog allergy
H172.11	Hay fever - unspecified allergen

Allergic Conjunctivitis

medcode	description
F4C0600	Acute atopic conjunctivitis
F4C0611	Acute allergic conjunctivitis
F4C1411	Allergic conjunctivitis
F4C1300	Vernal conjunctivitis
F4A3100	Vernal conjunctivitis of limbus and cornea

Atopic Eczema

medcode	description
M111.00	Atopic dermatitis/eczema
M112.00	Infantile eczema
M113.00	Flexural eczema
M114.00	Allergic (intrinsic) eczema
M12z100	Eczema NOS
M12z300	Hand eczema
M12z400	Erythrodermic eczema
Myu2200	[X]Exacerbation of eczema
M11z.00	Atopic dermatitis NOS
M11..00	Atopic dermatitis and related conditions

Asthma

medcode	description
H33..00	Asthma
H33..11	Bronchial asthma
H330.00	Extrinsic (atopic) asthma
H330.11	Allergic asthma

H330.12	Childhood asthma
H330.13	Hay fever with asthma
H330.14	Pollen asthma
H330000	Extrinsic asthma without status asthmaticus
H330011	Hay fever with asthma
H330100	Extrinsic asthma with status asthmaticus
H330111	Extrinsic asthma with asthma attack
H330z00	Extrinsic asthma NOS
H331.00	Intrinsic asthma
H331.11	Late onset asthma
H331000	Intrinsic asthma without status asthmaticus
H331100	Intrinsic asthma with status asthmaticus
H331111	Intrinsic asthma with asthma attack
H331z00	Intrinsic asthma NOS
H332.00	Mixed asthma
H333.00	Acute exacerbation of asthma
H334.00	Brittle asthma
H335.00	Chronic asthma with fixed airflow obstruction
H33z.00	Asthma unspecified
H33z000	Status asthmaticus NOS
H33z011	Severe asthma attack
H33z100	Asthma attack
H33z111	Asthma attack NOS
H33z200	Late-onset asthma
H33zz00	Asthma NOS
H33zz11	Exercise induced asthma
H33zz12	Allergic asthma NEC
14B4.00	H/O: asthma
H312000	Chronic asthmatic bronchitis
H33z.11	Hyperreactive airways disease
H33zz13	Allergic bronchitis NEC

SLE

medcode	description
F371000	Polyneuropathy in disseminated lupus erythematosus
F396100	Myopathy due to disseminated lupus erythematosus
F4D3300	Eyelid discoid lupus erythematosus
H57y400	Lung disease with systemic lupus erythematosus
K01x400	Nephrotic syndrome in systemic lupus erythematosus
K01x411	Lupus nephritis
K0B4000	Renal tubulo-interstitial disorder in SLE
M154.00	Lupus erythematosus
M154000	Lupus erythematosus chronicus
M154100	Discoid lupus erythematosus
M154200	Lupus erythematosus migrans
M154300	Lupus erythematosus nodularis
M154400	Lupus erythematosus profundus
M154500	Lupus erythematosus tumidus
M154600	Lupus erythematosus unguium mutilans
M154700	Subacute cutaneous lupus erythematosus

M154z00	Lupus erythematosus NOS
Myu7800	[X]Other local lupus erythematosus
N000.00	Systemic lupus erythematosus
N000000	Disseminated lupus erythematosus
N000300	Systemic lupus erythematosus with organ or sys involv
N000400	Systemic lupus erythematosus with pericarditis
N000500	Neonatal lupus erythematosus
N000600	Cerebral lupus
N000611	Systemic lupus erythematosus encephalitis
N000z00	Systemic lupus erythematosus NOS
N000100	Libman-Sacks disease

Sjogren's Syndrome

medcode	description
N002.00	Sicca (Sjogren's) syndrome
F396700	Myopathy due to Sjogren's disease
H57y300	Lung disease with Sjogren's disease

Vitiligo

medcode	description
F4E5311	Vitiligo of eyelid
M295100	Vitiligo

Rheumatoid Arthritis

medcode	Description
N040.00	Rheumatoid arthritis and other inflammatory polyarthropathy
N040000	Inflammatory polyarthropathy
N040100	Other rheumatoid arthritis of spine
N040200	Rheumatoid arthritis of shoulder
N040300	Rheumatoid arthritis of sternoclavicular joint
N040400	Rheumatoid arthritis of acromioclavicular joint
N040500	Rheumatoid arthritis of elbow
N040600	Rheumatoid arthritis of distal radio-ulnar joint
N040700	Rheumatoid arthritis of wrist
N040800	Rheumatoid arthritis of MCP joint
N040900	Rheumatoid arthritis of PIP joint of finger
N040A00	Rheumatoid arthritis of DIP joint of finger
N040B00	Rheumatoid arthritis of hip
N040C00	Rheumatoid arthritis of sacro-iliac joint
N040D00	Rheumatoid arthritis of knee
N040E00	Rheumatoid arthritis of tibio-fibular joint
N040F00	Rheumatoid arthritis of ankle
N040G00	Rheumatoid arthritis of subtalar joint
N040H00	Rheumatoid arthritis of talonavicular joint
N040J00	Rheumatoid arthritis of other tarsal joint
N040K00	Rheumatoid arthritis of 1st MTP joint
N040L00	Rheumatoid arthritis of lesser MTP joint
N040M00	Rheumatoid arthritis of IP joint of toe
N040N00	Rheumatoid vasculitis
N040P00	Seronegative rheumatoid arthritis
N040Q00	Rheumatoid bursitis

N040R00	Rheumatoid nodule
N040S00	Rheumatoid arthritis - multiple joint
N040T00	Flare of rheumatoid arthritis
F371200	Polyneuropathy in rheumatoid arthritis
F396400	Myopathy due to rheumatoid arthritis
G5y8.00	Rheumatoid myocarditis
G5yA.00	Rheumatoid carditis
H570.00	Rheumatoid lung
N040.00	Rheumatoid arthritis
N040000	Rheumatoid arthritis of cervical spine
N041.00	Felty's syndrome
N042.00	Other rheumatoid arthropathy + visceral/systemic involvement
N042000	Rheumatic carditis
N042100	Rheumatoid lung disease
N042200	Rheumatoid nodule
N042z00	Rheumatoid arthropathy + visceral/systemic involvement NOS
N043.00	Juvenile rheumatoid arthritis - Still's disease
N043000	Juvenile rheumatoid arthropathy unspecified
N043100	Acute polyarticular juvenile rheumatoid arthritis
N043200	Pauciarticular juvenile rheumatoid arthritis
N043300	Monarticular juvenile rheumatoid arthritis
N043z00	Juvenile rheumatoid arthritis NOS
N047.00	Seropositive erosive rheumatoid arthritis
N04X.00	Seropositive rheumatoid arthritis, unspecified
N04y000	Rheumatoid lung
N04y011	Caplan's syndrome
N04y012	Fibrosing alveolitis associated with rheumatoid arthritis
Nyu1000	[X]Rheumatoid arthritis+involvement/other organs or systems
Nyu1100	[X]Other seropositive rheumatoid arthritis
Nyu1200	[X]Other specified rheumatoid arthritis
Nyu1G00	[X]Seropositive rheumatoid arthritis, unspecified
H571.00	Rheumatic pneumonia
N04..00	Rheumatoid arthritis and other inflammatory polyarthropathy

Psoriasis

medcode	description
M16..00	Psoriasis and similar disorders
M161.00	Other psoriasis
M161000	Psoriasis unspecified
M161100	Psoriasis annularis
M161200	Psoriasis circinata
M161300	Psoriasis diffusa
M161400	Psoriasis discoidea
M161500	Psoriasis geographica
M161600	Guttate psoriasis
M161700	Psoriasis gyrata
M161800	Psoriasis inveterata
M161900	Psoriasis ostracea
M161A00	Psoriasis palmaris
M161B00	Psoriasis plantaris

M161C00	Psoriasis punctata
M161D00	Pustular psoriasis
M161E00	Psoriasis universalis
M161F00	Psoriasis vulgaris
M161F11	Chronic large plaque psoriasis
M161H00	Erythrodermic psoriasis
M161J00	Flexural psoriasis
M161z00	Psoriasis NOS
M166.00	Palmoplantar pustular psoriasis
M16y.00	Other psoriasis and similar disorders
M16y000	Scalp psoriasis
M16z.00	Psoriasis and similar disorders NOS
Myu3000	[X]Other psoriasis
N045200	Juvenile arthritis in psoriasis
14F2.00	H/O: psoriasis
M160.00	Psoriatic arthropathy
M160.11	Psoriatic arthritis
M160000	Psoriasis spondylitica
M160100	Distal interphalangeal psoriatic arthropathy
M160200	Arthritis mutilans
M160z00	Psoriatic arthropathy NOS

Pernicious Anaemia

medcode	description
D010.00	Pernicious anaemia
F381500	Myasthenic syndrome due to pernicious anaemia
D010.11	Addison's anaemia

Myasthenia Gravis

medcodeeq	description
F380.00	Myasthenia gravis
F380000	Persistent neonatal myasthenia gravis
F380100	Juvenile or adult myasthenia gravis
F380z00	Myasthenia gravis NOS

Inflammatory Bowel Disease

medcode	description
J4...12	Inflammatory bowel disease
J40..00	Regional enteritis - Crohn's disease
J40..11	Crohn's disease
J400200	Crohn's disease of the terminal ileum
J400300	Crohn's disease of the ileum unspecified
J400400	Crohn's disease of the ileum NOS
J400500	Exacerbation of Crohn's disease of small intestine
J400z00	Crohn's disease of the small bowel NOS
J401200	Exacerbation of Crohn's disease of large intestine
J401z00	Crohn's disease of the large bowel NOS
J401z11	Crohn's colitis
J40z.11	Crohn's disease NOS
J41..12	Ulcerative colitis and/or proctitis
J410.00	Ulcerative proctocolitis

J410000	Ulcerative ileocolitis
J410100	Ulcerative colitis
J410200	Ulcerative rectosigmoiditis
J410300	Ulcerative proctitis
J410400	Exacerbation of ulcerative colitis
J410z00	Ulcerative proctocolitis NOS
J411.00	Ulcerative (chronic) enterocolitis
J412.00	Ulcerative (chronic) ileocolitis
J413.00	Ulcerative pancolitis
N031000	Arthropathy in ulcerative colitis
N031100	Arthropathy in Crohn's disease
N045300	Juvenile arthritis in Crohn's disease
N045400	Juvenile arthritis in ulcerative colitis
J41y.00	Other idiopathic proctocolitis
Jyu4000	[X]Other Crohn's disease
Jyu4100	[X]Other ulcerative colitis

Coeliac Disease

medcode	description
J690.00	Coeliac disease
J690.11	Coeliac rickets
J690.13	Gluten enteropathy
J690.14	Sprue - nontropical
J690.18	Gluten intolerance
J690100	Acquired coeliac disease
J690z00	Coeliac disease NOS
J690z00	Coeliac disease NOS

Autoimmune Thyroid Disease

medcode	description
C020.11	Basedow's disease
C020.12	Graves' disease
C046.00	Autoimmune myxoedema
C05..00	Thyroiditis
C050.00	Acute thyroiditis
C050000	Acute nonsuppurative thyroiditis
C050z00	Acute thyroiditis NOS
C051.00	Subacute thyroiditis
C051.11	De Quervain's thyroiditis
C052.00	Chronic lymphocytic thyroiditis
C052.11	Autoimmune thyroiditis
C052.12	Hashimoto's disease
C053.00	Chronic fibrous thyroiditis
C053.11	Riedel's thyroiditis
C05y.00	Other and unspecified chronic thyroiditis
C05y400	Chronic thyroiditis with transient thyrotoxicosis
C05z.00	Thyroiditis NOS
Cyu1400	[X]Other chronic thyroiditis
C020000	Toxic diffuse goitre with no crisis
C020100	Toxic diffuse goitre with crisis

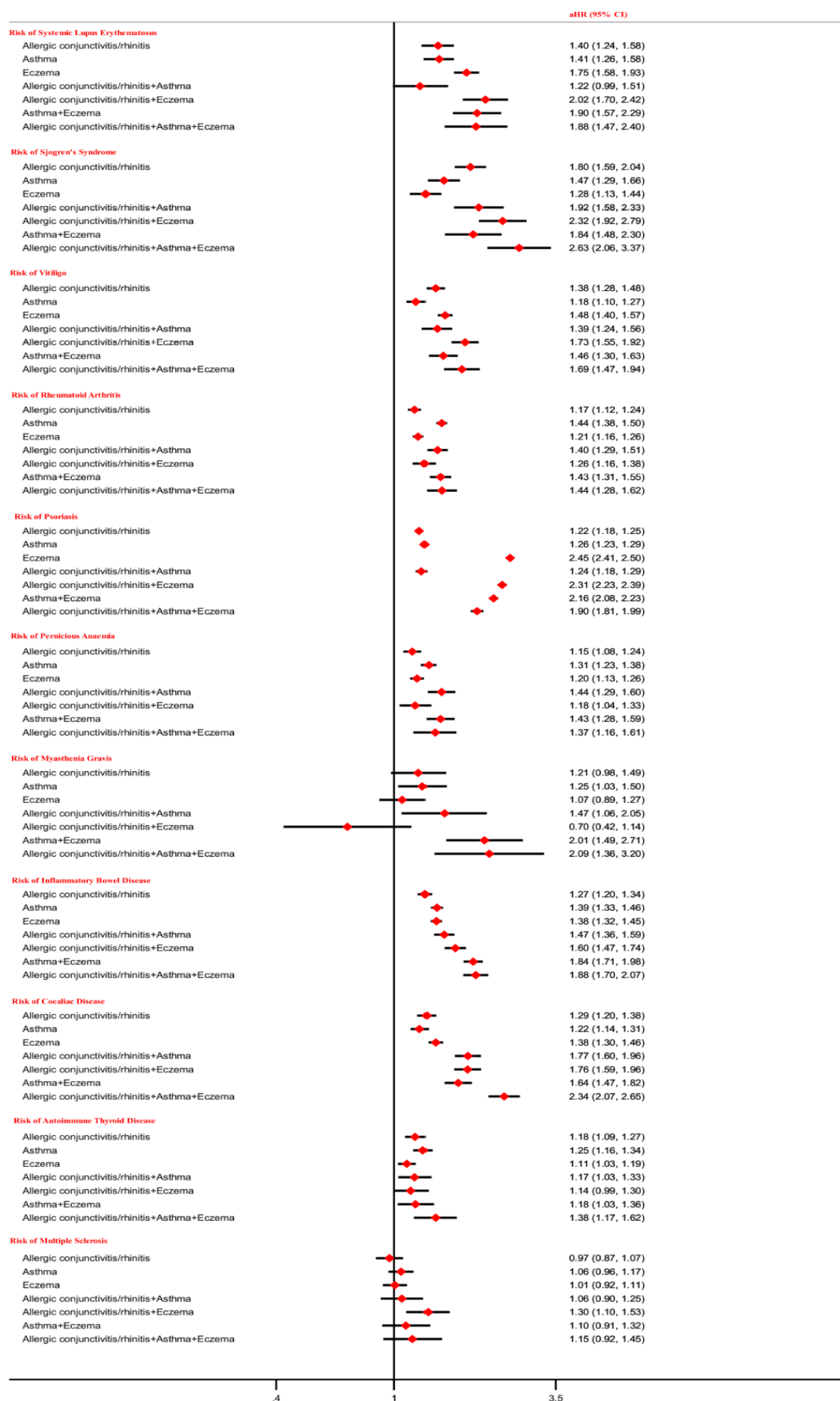
C020200	Thyroid-associated dermopathy
C020z00	Toxic diffuse goitre NOS

Multiple Sclerosis

medcode	description
F20..00	Multiple sclerosis
F200.00	Multiple sclerosis of the brain stem
F201.00	Multiple sclerosis of the spinal cord
F202.00	Generalised multiple sclerosis
F203.00	Exacerbation of multiple sclerosis
F206.00	Primary progressive multiple sclerosis
F207.00	Relapsing and remitting multiple sclerosis
F20z.00	Multiple sclerosis NOS
ZRVE.00	Kurtzke multiple sclerosis rating scale
F20..11	Disseminated sclerosis
F205.00	Malignant multiple sclerosis
F208.00	Secondary progressive multiple sclerosis

Figure E1: Adjusted hazard ratios of AIDs in combinations of ADs. Forest plot summarising adjusted hazard ratios (aHR) of AIDs in combinations of 1, 2 or 3 ADs. The figure illustrates an overall trend towards higher aHRs for respective AIDs in the presence of ≥ 2 ADs. aHRs calculated using Cox proportional hazards

Risk of AutoImmune Disorders



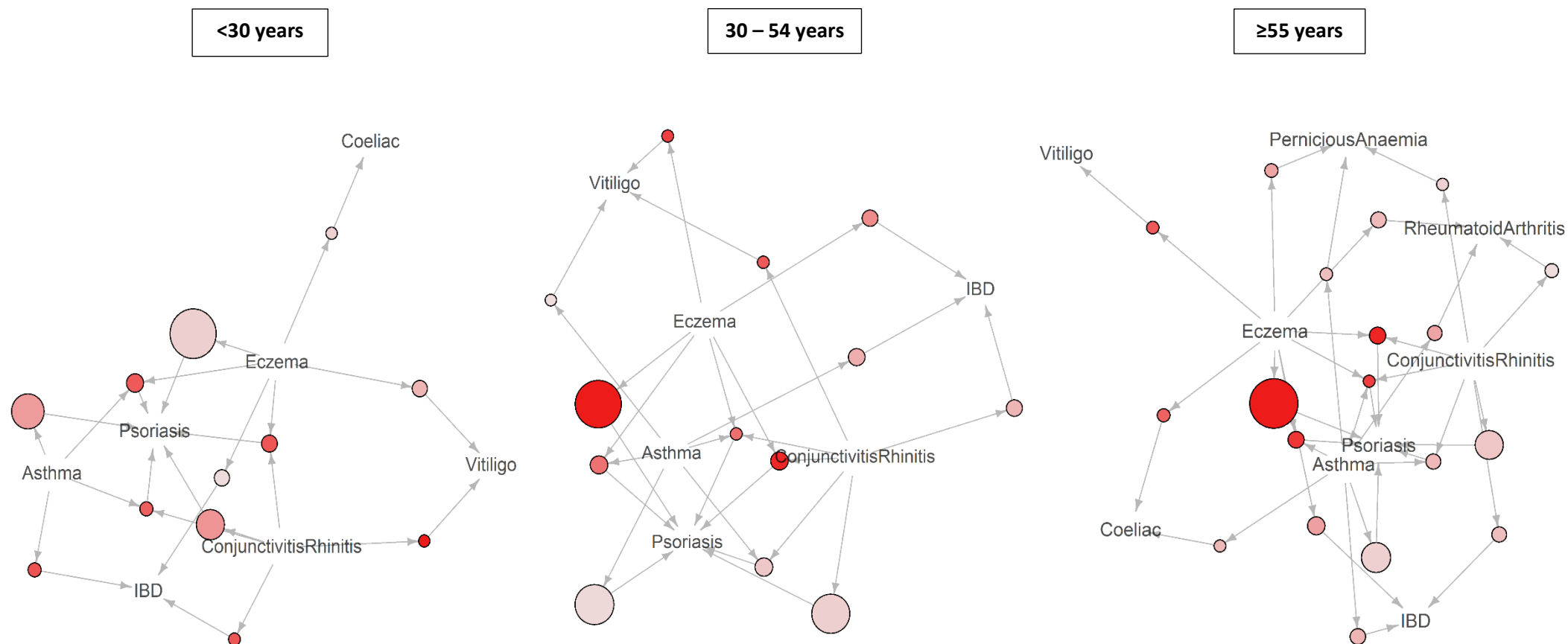


Figure E2: Sub-group ARM analysis by age in males. To be reviewed in conjunction with tables E3–E5. Each arrow connects an AD (antecedent) with an AID (consequent) via circles (or nodes). The size and the intensity of colour within each circle represent the level of 'support' and level of 'lift' respectively, *i.e.*, larger the circle and darker the colour, greater is the 'support' and 'lift' respectively.



Figure E3: Sub-group ARM analysis by age in females. To be reviewed in conjunction with tables E6–E8. Each arrow connects an AD (antecedent) with an AID (consequent) *via* circles (or nodes). The size and the intensity of colour within each circle represent the level of 'support' and level of 'lift' respectively, *i.e.*, larger the circle and darker the colour, greater is the 'support' and 'lift' respectively.



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Allergic diseases and long-term risk of autoimmune disorders: longitudinal cohort study and cluster analysis

Mamidipudi Thirumala Krishna ^{1,2}, Anuradhaa Subramanian³, Nicola J. Adderley³, Dawit T. Zemedikun ³, Georgios V. Gkoutos^{4,5} and Krishnarajah Nirantharakumar^{3,5}

Affiliations: ¹Dept of Allergy and Immunology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. ²Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK. ³Institute of Applied Health Research, University of Birmingham, Birmingham, UK. ⁴Institute of Cancer and Genomics, University of Birmingham, Birmingham, UK. ⁵Midlands Health Data Research UK, Birmingham, UK.

Correspondence: Mamidipudi Thirumala Krishna, Dept of Allergy and Immunology, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham, B9 5SS, UK. E-mail: mtkrishna@yahoo.com



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This study has shown that the long-term risk of autoimmune disorders is significantly higher in patients with allergic diseases. Allergic diseases and autoimmune disorders co-occur, and show an age- and sex-related clustering pattern. <http://bit.ly/33tqkZn>

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This single-page version can be shared freely online.

ABSTRACT

Introduction: The association between allergic diseases and autoimmune disorders is not well established. Our objective was to determine incidence rates of autoimmune disorders in allergic rhinitis/conjunctivitis (ARC), atopic eczema and asthma, and to investigate for co-occurring patterns.

Methods: This was a retrospective cohort study (1990–2018) employing data extracted from The Health Improvement Network (UK primary care database). The exposure group comprised ARC, atopic eczema and asthma (all ages). For each exposed patient, up to two randomly selected age- and sex-matched controls with no documented allergic disease were used. Adjusted incidence rate ratios (aIRRs) were calculated using Poisson regression. A cross-sectional study was also conducted employing Association Rule Mining (ARM) to investigate disease clusters.

Results: 782 320, 1 393 570 and 1 049 868 patients with ARC, atopic eczema and asthma, respectively, were included. aIRRs of systemic lupus erythematosus (SLE), Sjögren's syndrome, vitiligo, rheumatoid arthritis, psoriasis, pernicious anaemia, inflammatory bowel disease, coeliac disease and autoimmune thyroiditis were uniformly higher in the three allergic diseases compared with controls. Specifically, aIRRs of SLE (1.45) and Sjögren's syndrome (1.88) were higher in ARC; aIRRs of SLE (1.44), Sjögren's syndrome (1.61) and myasthenia (1.56) were higher in asthma; and aIRRs of SLE (1.86), Sjögren's syndrome (1.48), vitiligo (1.54) and psoriasis (2.41) were higher in atopic eczema. There was no significant effect of the three allergic diseases on multiple sclerosis or of ARC and atopic eczema on myasthenia. Using ARM, allergic diseases clustered with multiple autoimmune disorders. Three age- and sex-related clusters were identified, with a relatively complex pattern in females ≥ 55 years old.

Conclusions: The long-term risks of autoimmune disorders are significantly higher in patients with allergic diseases. Allergic diseases and autoimmune disorders show age- and sex-related clustering patterns.