

Alopecia areata and risk of atopic and autoimmune conditions: population-based cohort study

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Abstract

Background. Alopecia areata (AA) has features of both autoimmune and atopic pathogenesis, but information on the risk of people with AA developing autoimmune and atopic conditions is limited.

Objective. To assess the prevalence and incidence of atopic and autoimmune conditions in people with AA.

Methods. This was a population-based cohort study of 8051 adults with newly diagnosed AA (AA group) and 32 204 adults in the matched control group, using the UK Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network primary care database, 2009–2018 (trial registration number: NCT04239521). Baseline prevalence of common atopic and autoimmune conditions, and risk of new-onset atopic and autoimmune disease, were estimated.

Results. Atopic and autoimmune conditions were more prevalent in the AA group than the control group (atopic 37.2% vs. 26.7%, autoimmune 11.5% vs. 7.9%). The AA group were 43% more likely to develop any new-onset atopic condition [adjusted hazard ratio (aHR) 1.43, 95% confidence interval (CI) 1.28–1.61] and 45% more likely to develop any autoimmune condition (aHR 1.45, 95% CI 1.28–1.66) compared with the control group. When examining individual conditions, the AA group were at increased risk of atopic dermatitis (aHR 1.91, 95% CI 1.67–2.19), allergic rhinitis (aHR 1.32, 95% CI 1.14–1.54), autoimmune hypothyroidism (aHR 1.65, 95% CI 1.35–2.02), systemic lupus erythematosus (aHR 4.51, 95% CI 1.88–10.82) and vitiligo (aHR 2.39, 95% CI 1.49–3.82). There was no evidence for a higher incidence of other conditions examined.

Conclusion. People with AA have an increased burden of atopic and autoimmune comorbidity. This supports previous work suggesting that both T helper cell (Th)1 and Th2 immune responses may be implicated in the pathogenesis of AA.

Introduction

Alopecia areata (AA) is a chronic inflammatory dermatosis that affects hair follicles, leading to non-scarring hair loss.¹ The pathogenesis of AA remains incompletely understood but a central theory is that it is an autoimmune disease that results from a breakdown in the normal immune privilege of the anagen hair follicle.^{2,3}

Supporting this concept, previous studies have reported an increased risk of autoimmune conditions in patients with AA^{4–9}; however, population-based data are lacking. A recent systematic review and meta-analysis identified only two population-based analyses from Taiwan, which described an increased risk of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and psoriasis in people with AA.^{8–10}

There have been no large population-based studies in other ethnic groups.

Previous studies also suggest that atopic conditions occur more frequently in people with AA,^{4,5,8,11–14} but have not examined the temporal relationship between conditions. Larger studies include a US study that reported individuals with a history of any atopy have a twofold increased risk of having comorbid AA⁵; and a recent Israeli study that observed a higher prevalence of asthma, atopic dermatitis (AD), allergic rhinitis (AR) and allergic conjunctivitis amongst patients with AA, but did not examine incidence of new-onset atopic disease.¹³

We aimed to conduct the first large-scale population-based study of the prevalence and incidence of atopic and autoimmune conditions in a Western population of adult patients with AA.

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Method

The study protocol was registered as part of an observational study series of AA with ClinicalTrials.gov (NCT04239521).¹⁵

Data source

Patient-level information was extracted from the UK Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network database (Appendix S1; see [Supporting Information](#)).¹⁶

Study population

Adults (≥ 18 years) contributing data to RCGP RSC between 1 January 1999 and 31 December 2018.

Definition of people with alopecia areata

The primary cohort comprised people diagnosed with new-onset AA over the study period. AA was defined using diagnosis Read codes specific to the condition (Appendix S2; see [supporting Information](#)).¹⁵ People were considered to have AA if they had an AA diagnostic Read code and no Read code for an alternative diagnosis in the subsequent 365 days (Appendix S1; see [supporting Information](#)).

Definition of matched control group

For each patient with AA, we matched four control patients without AA by age, sex and time since practice registration. Individuals in the control group required at least 1 year of follow-up when matched to minimize the risk of a nonrecorded existing diagnosis of AA.

Atopic and autoimmune condition outcomes

We identified the following atopic and autoimmune outcomes using diagnostic codes (Appendix S1; see [supporting Information](#)). For atopic: AD, AR, asthma and a composite condition (one or more of AD, AR and asthma). For autoimmune: Crohn disease, ulcerative colitis, coeliac disease, pernicious anaemia, type 1 diabetes, autoimmune hypothyroidism (Hashimoto thyroiditis), Graves disease, psoriasis, psoriatic arthritis, RA, ankylosing spondylitis, SLE, polymyalgia rheumatica, Sjögren syndrome, vitiligo, multiple sclerosis (MS) and a composite condition (one or more of listed autoimmune conditions).

Recorded sociodemographic characteristics and clinical features

Ethnicity was grouped into major UK groups: white, black, Asian, mixed and others.¹⁷ Socioeconomic status was defined using national Index of Multiple Deprivation (IMD).¹⁸ Consultation history was defined as the number of primary care visits in the year prior to cohort entry. Clinical features comprised body mass index, smoking status, alcohol use and common comorbidities (Appendix S1; see [supporting information](#)).

Statistical analyses

Patients were followed up from cohort entry (date of diagnosis for each person with AA and their matched counterparts)

until the earliest of the date of diagnosis of the outcome of interest, practice deregistration, death, 10 years after cohort entry or 31 December 2018.

Prevalence of atopic and autoimmune conditions

We estimated the prevalence in the AA group and matched control group at cohort entry, overall and stratified by age category, sex, ethnicity and IMD.

Incidence of new-onset atopic and autoimmune conditions

We estimated incidence rates for new-onset atopic and autoimmune conditions within 10 years after cohort entry. Individuals in the AA group with a pre-existing condition of interest were excluded, together with their matched counterparts. Incidence rates were stratified by age category, sex, ethnicity and IMD. Cox proportional hazards models were used to estimate the association between AA and each outcome, adjusted for sociodemographic factors, clinical features and comorbidities (Appendix S1; see [supporting Information](#)). We did not adjust for multiple testing as our focus was on describing clinically relevant risk increases in people with AA (if observed) rather than statistical significance.

Sensitivity analysis

To evaluate the magnitude of potential bias from including general practitioner (GP) nonattendees, we repeated analysis of composite outcomes including only people in the control group with at least one primary care consultation in the year preceding cohort entry. To delineate the relationship between each atopic condition (AD, AR and asthma) and AA, we repeated the incidence analysis for each individual atopic condition excluding people that had any pre-existing atopic condition.

Statistical analyses were performed using R v3.4.1. The study was reported in-line with RECORD guidelines.

Results

In total, 8051 adults were diagnosed with new-onset AA over the study period and were matched to 32 204 people who acted as the control group (Supplementary Figure S1). Age (mean 39), sex (55% female) and socioeconomic status were similar in both groups (Table 1, and see also Supplementary Table S1).

Atopic and autoimmune conditions are more prevalent in alopecia areata

Atopic conditions were more prevalent in the AA group than the matched control group (overall atopic 37.2% vs. 26.7%, AD 15.7% vs. 7.8%, AR 16.1% vs. 11.6%, asthma 18.6% vs. 14.4%, Table 2). The higher prevalence of atopic conditions in the AA group was consistent across all sociodemographic subgroups except for asthma in ≥ 70 years age groups, where absolute numbers were low (Supplementary Table S2). Among the AA group, people of black ethnicity had the highest prevalence of atopic conditions (Supplementary Table S2).

Overall, a higher prevalence of autoimmune conditions was observed in the AA group (composite autoimmune

Table 1 Demographic characteristics of newly diagnosed patients in the alopecia areata group and matched control group without alopecia areata^a

Characteristic	AA group	Matched control group
Patients, <i>n</i>	8051	32 204
Age, mean (SD)	39.27 (14.28)	39.79 (15.16)
Age group, years		
18–29	2348 (29.2)	8756 (27.2)
30–39	2251 (28.0)	9947 (30.9)
40–49	1628 (20.2)	6114 (19.0)
50–59	990 (12.3)	3480 (10.8)
60–69	548 (6.8)	2161 (6.7)
70–79	223 (2.8)	1198 (3.7)
≥ 80	63 (0.8)	548 (1.7)
Sex		
Women	4398 (54.6)	17 569 (54.6)
Men	3653 (45.4)	14 635 (45.4)
Deprivation quintile ^b		
1 (most deprived)	1677 (21.2)	6451 (20.4)
2	1596 (20.2)	6131 (19.4)
3	1469 (18.6)	5894 (18.6)
4	1544 (19.6)	6355 (20.1)
5 (least deprived)	1607 (20.4)	6774 (21.4)
Ethnicity ^c		
White	4281 (69.7)	18 979 (79.4)
Asian	1313 (21.4)	3238 (13.5)
Black	254 (4.1)	997 (4.2)
Mixed	137 (2.2)	377 (1.6)
Other	157 (2.6)	315 (1.3)

Data are *n* (%) unless stated. ^aAdditional baseline clinical characteristics are reported in Supplementary Table S1. ^bDeprivation data missing for 158 in the alopecia areata (AA) group and 599 in the matched control group. ^cEthnicity data missing for 1909 in the AA group and 8298 in the matched control group.

outcome: AA group 11.5%, control group 7.9%, Table 2), and this was consistent across subgroups (Supplementary Table S2). For individual conditions, autoimmune hypothyroidism, SLE, psoriasis, vitiligo and MS were more prevalent in the AA group than the control group (Table 2).

People diagnosed with alopecia areata are also at increased risk of new atopic and autoimmune conditions

Unadjusted incidence of new-onset atopic and autoimmune conditions were higher in the AA group compared with the control group [overall atopic conditions unadjusted incidence rate per 1000 person-years 18.1, 95% confidence interval (CI) 16.5–19.8 in the AA group vs. 11.7, 95% CI 11.0–12.5 in the control group; overall autoimmune conditions 9.0, 95% CI 8.1–10.1 in the AA group vs. 5.9, 95% CI 5.5–6.3 in the control group] (Supplementary Table S3). For atopic conditions, overall incidence was higher in females than males (22.1, 95% CI 19.7–24.8 vs. 13.8, 95% CI 11.8–16.0) and in people of Asian ethnicity compared with white ethnicity (30.9, 95% CI 25.4–37.2 vs. 16.5, 95% CI 14.5–18.8) (Supplementary Table S4). The same pattern of difference by sex and ethnicity was observed for individual atopic conditions, except for asthma where there was no evidence of a difference by ethnicity (Supplementary Table S4).

Over a median 5.1 years of follow-up, 471 of 5055 eligible in the AA group without a history of atopy developed a new-onset atopic condition, and 340 of 7127 eligible in the AA group without a history of autoimmune disease developed a new-onset autoimmune condition. In unadjusted

Table 2 Prevalence of atopic and autoimmune conditions in the alopecia areata group (*n*=8051) and the matched control group without alopecia areata (*n*=32 204)

Condition	Number with condition		Prevalence (95% CI)		<i>P</i> -value
	AA group	Matched control group	AA group	Matched control group	
Atopic conditions					
Any atopic condition ^a	2996	8605	37.21 (36.16–38.27)	26.72 (26.24–27.21)	< 0.001
Atopic dermatitis	1266	2500	15.72 (14.95–16.54)	7.76 (7.48–8.06)	< 0.001
Allergic rhinitis	1294	3718	16.07 (15.29–16.89)	11.55 (11.20–11.90)	< 0.001
Asthma	1500	4625	18.63 (17.80–19.50)	14.36 (13.98–14.75)	< 0.001
Autoimmune conditions					
Any autoimmune condition ^b	924	2556	11.48 (10.80–12.19)	7.94 (7.65–8.24)	< 0.001
Crohn	19	109	0.24 (0.15–0.37)	0.34 (0.28–0.41)	0.18
Ulcerative colitis	30	147	0.37 (0.26–0.53)	0.46 (0.39–0.54)	0.36
Coeliac disease	22	77	0.27 (0.18–0.41)	0.24 (0.19–0.30)	0.67
Pernicious anaemia	12	63	0.15 (0.09–0.26)	0.20 (0.15–0.25)	0.47
Type 1 diabetes	40	114	0.50 (0.37–0.68)	0.35 (0.29–0.43)	0.08
Autoimmune hypothyroidism	366	858	4.55 (4.11–5.02)	2.66 (2.49–2.85)	< 0.001
Graves disease	18	51	0.22 (0.14–0.35)	0.16 (0.12–0.21)	0.27
Psoriasis	305	890	3.79 (3.39–4.23)	2.76 (2.59–2.95)	< 0.001
Psoriatic arthritis	20	61	0.25 (0.16–0.38)	0.19 (0.15–0.24)	0.36
Rheumatoid arthritis	46	146	0.57 (0.43–0.76)	0.45 (0.39–0.53)	0.20
Ankylosing spondylitis	10	36	0.12 (0.07–0.23)	0.11 (0.08–0.15)	0.91
Systemic lupus erythematosus	21	16	0.26 (0.17–0.40)	0.05 (0.03–0.08)	< 0.001
Polymyalgia rheumatica	27	96	0.34 (0.23–0.49)	0.30 (0.24–0.36)	0.67
Sjögren syndrome	6	19	0.07 (0.03–0.16)	0.06 (0.04–0.09)	0.80
Vitiligo	72	102	0.89 (0.71–1.12)	0.32 (0.26–0.38)	< 0.001
Multiple sclerosis	25	57	0.31 (0.21–0.46)	0.18 (0.14–0.23)	0.03

CI, confidence interval. ^aOne or more of atopic dermatitis, allergic rhinitis and asthma. ^bOne or more of Crohn disease, ulcerative colitis, coeliac disease, pernicious anaemia, type 1 diabetes, autoimmune hypothyroidism, Graves disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, polymyalgia rheumatica, Sjögren syndrome, vitiligo, multiple sclerosis.

(Figure 1 and Supplementary Table S5) and adjusted (Figure 2, Supplementary Table S5) analyses, associations between AA and increased relative risk of atopic and autoimmune composite outcomes were evident. For individual conditions, there was evidence of an increased relative risk of AD, AR, autoimmune hypothyroidism, SLE and vitiligo, but not asthma and other autoimmune conditions (Figure 2, Supplementary Table S5). Of those who developed a new-onset atopic condition ($n=471$), 25 developed both AD and AR, 10 developed both AD and asthma, and five developed all three atopic conditions.

Sensitivity analysis

When practice nonattendees were excluded (approximately 55% of the control group), findings were consistent with the primary analysis [composite atopic adjusted hazard ratio (aHR) 1.59, 95% CI 1.34–1.88; composite autoimmune aHR 1.79, 95% CI 1.47–2.19]. When we estimated the association between AA, and AD, AR and asthma individually, excluding people that had pre-existing AD, AR or asthma, findings were consistent with the primary analysis (Supplementary Table S6).

Discussion

In this large population-based study in England, we found patients with AA have a higher burden of atopic and autoimmune conditions compared with a matched control group. AA was associated with a 43% higher risk of new-onset atopic conditions, and 45% higher risk of new-onset autoimmune conditions. When assessing individual conditions, prevalence and incidence of AD, AR, autoimmune hypothyroidism,

SLE and vitiligo were higher in people with AA. The strongest association in our study was for SLE, with a 4.5-fold risk increase of incident SLE in people with AA.

When evaluating atopic conditions, new-onset AD was associated a larger risk increase in people with AA (aHR 1.91, 95% CI 1.67–2.19) than asthma (aHR 1.11, 95% CI 0.93–1.32) or AR (aHR 1.32, 95% CI 1.14–1.54). Similar findings were reported in Taiwan, where patients with AA were twice as likely to develop AD compared with the control group [odds ratio (OR) 2.24, 95% CI 1.95–2.58], with a modest risk increase for AR (OR 1.29, 95% CI 1.18–1.41) and no association for asthma (OR 1.07, 95% CI 0.93–1.22).⁸ Other studies have reported an association between AA and atopic conditions,^{5,6,13,19} but have not explored temporal associations. Although AD, asthma and AR are often grouped together to form an ‘atopic march’ because of similar pathogenesis involving T helper cell (Th)2-type inflammation in epithelial cells, distinct epithelial cells in different organs and environmental exposure occurring on skin but not airways, may partially explain the higher risk of AD over asthma or AR.⁸ The use of temporal associations to explore this further is recommended for future research.

The 45% increased risk we observed for new-onset autoimmune conditions is not dissimilar to that previously reported in Taiwanese patients (aHR 1.86, 95% CI 1.32–2.63).⁹ Our findings of an increased burden of SLE autoimmune thyroid disease, and vitiligo in people with AA are also concordant with Taiwanese data, where the greatest risk increase was also observed for SLE,^{8,9} and recent cross-sectional meta-analyses^{10,11} suggesting these associations may be generalizable across different ethnic groups. In contrast to the Taiwanese analysis, we found no evidence of an association between AA and either incident RA or psoriasis, although the effect sizes across the two studies are not

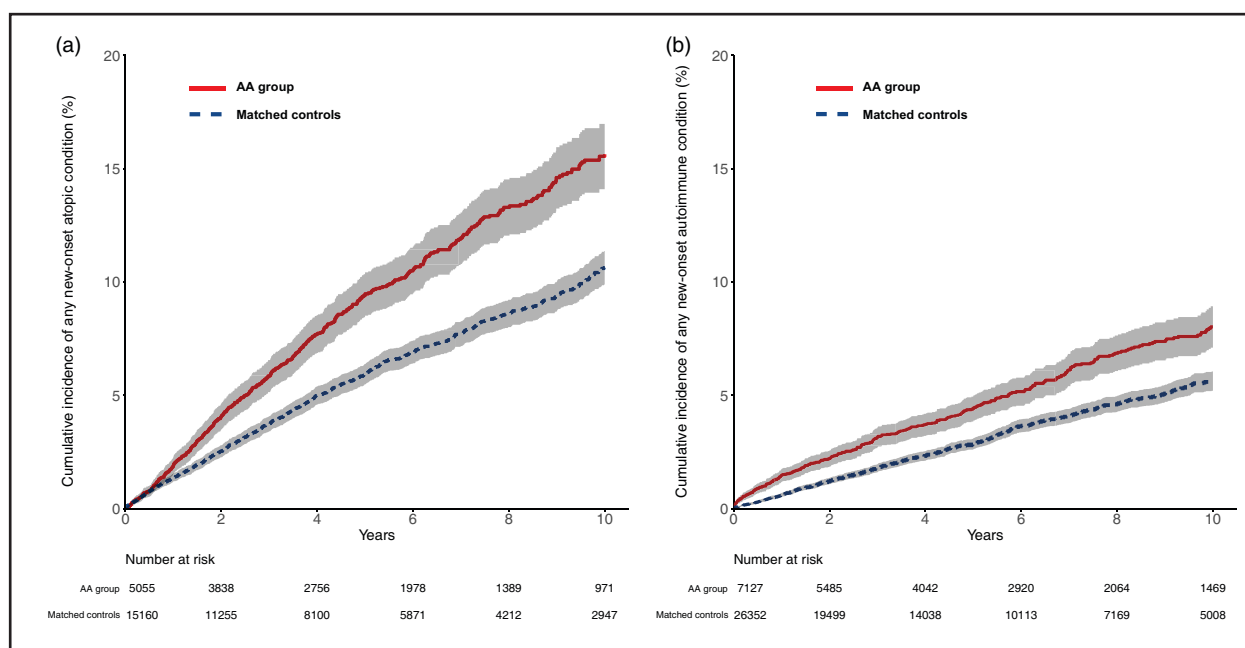


Figure 1 Cumulative incidence of (a) any atopic condition and (b) any autoimmune condition in people with alopecia areata (AA) and matched control group. Any atopic condition: one or more of atopic dermatitis, allergic rhinitis and asthma. Any autoimmune condition: one or more of Crohn disease, ulcerative colitis, coeliac disease, pernicious anaemia, type 1 diabetes, autoimmune hypothyroidism, Graves disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, polymyalgia rheumatica, Sjögren syndrome, vitiligo and multiple sclerosis.

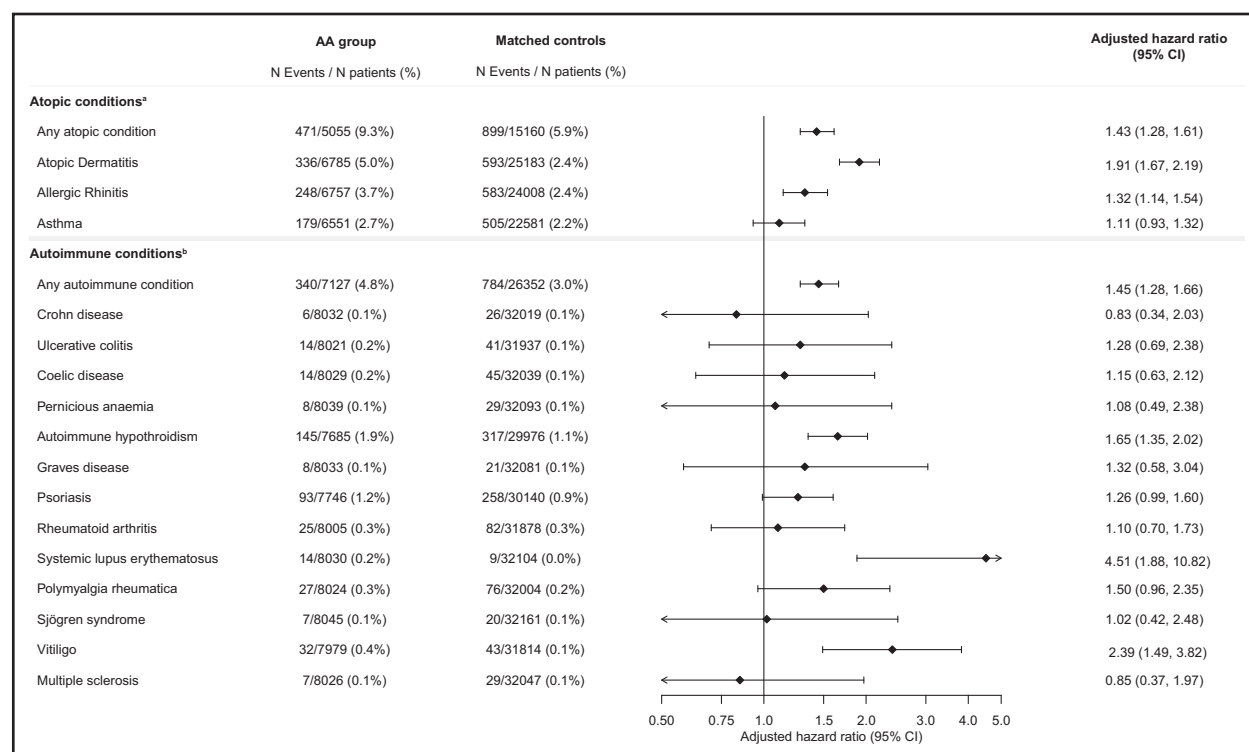


Figure 2 Associations between alopecia areata (AA) and atopic and autoimmune outcomes. Forest plot shows adjusted hazard ratios, with 95% confidence intervals (95% CI). A hazard ratio > 1 represents an increase in the risk of the condition in the AA group compared with the matched control group. Individual conditions where <5 new diagnoses were recorded over follow-up were not analysed (type 1 diabetes, psoriatic arthritis and ankylosing spondylitis). Models adjusted for age (restricted cubic spline 3 knot) sex, Index of Multiple Deprivation quintile, ethnicity, body mass index, smoking status, alcohol use category, number of visits in year prior to cohort entry, type 2 diabetes, hypertension, atrial fibrillation, angina, acute myocardial infarction, stroke, heart failure, chronic liver disease, dementia, chronic obstructive pulmonary disease, chronic kidney disease stage 3–5, malignancy, depression and hyperlipidaemia. ^aOne or more of atopic dermatitis, allergic rhinitis and asthma. ^bOne or more of Crohn disease, ulcerative colitis, coeliac disease, pernicious anaemia, type 1 diabetes, autoimmune hypothyroidism, Graves disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, polymyalgia rheumatica, Sjögren syndrome, vitiligo and multiple sclerosis.

discordant.⁹ Similar to previous studies,^{19,20} we found no evidence of an association between inflammatory bowel disease or coeliac disease and AA despite recently proposed links between autoimmune gut disorders and AA.²¹

In contrast to the traditional autoimmune theory for AA,²² our study provides epidemiological data that suggest AA may have features of atopic and autoimmune-mediated skin disease. This is an interesting finding and one consistent with a recent study demonstrating upregulation of Th1 (autoimmune disease) and Th2 (allergic disease) pathways in AA.²³ Kridin *et al.* describe how the strong Th2 upregulation seen in AA, in combination with the significant association with atopic comorbidities, particularly AD, suggests that the traditional view of AA as a primarily Th1-centred disease should be expanded.¹³ Genetic data have also identified that interleukin (IL-13) is both a susceptible locus for AA IL-13 loci and is associated with both atopic and autoimmune conditions.²⁴ Further supporting a pathogenic role of the Th2 axis in AA, a recent trial of dupilumab (which blocks IL-4/IL-13) demonstrated significant increased regrowth in participants with moderate-to-severe AA.²⁵

To our knowledge, our study is the first large population-based study to assess the prevalence and incidence of atopic and autoimmune conditions in a Western population, providing a more complete picture of temporal associations with AA. Strengths include the large

population-representative sample and the high data quality and completeness in RCGP RSC. A study limitation is that findings may not be generalizable to dissimilar populations to the UK. It is also possible that people with AA may have higher primary care contact, leading to an increased likelihood of detection bias, particularly for less severe conditions. As with all studies using routine clinical data, the possibility of incomplete coding means we may have missed or misidentified some cases. As a result of lack of GP coding granularity, the potential impact of AA severity on atopic and autoimmune morbidity was not evaluated. We were unable to use systemic immunomodulatory therapy prescriptions to identify patients with severe AA; these therapies are usually prescribed in secondary care and not automatically recorded in primary care records. We were also unable to reliably evaluate incidence of type 1 diabetes, psoriatic arthritis and ankylosing spondylitis because of low numbers of events in our study cohort.

Conclusion

We have shown a clinically relevant increase in the burden of atopic and autoimmune comorbidity in patients with AA. For atopic conditions, risk was increased for AD and AR, but not asthma. For autoimmune conditions, increased risk may

be confined to autoimmune hypothyroidism, vitiligo and, with by far the largest risk increase, SLE. These findings highlight the need for GPs and dermatologists to be alert to these conditions and consider screening for them among patients with AA. The observed associations for atopic and autoimmune conditions support previous work suggesting that both Th1 and Th2 immune responses may be implicated in the pathogenesis of AA. Further research is needed to understand the pathophysiological relationship between AA and atopic and autoimmune conditions.

What is already known about this topic?

- The pathogenesis of AA remains incompletely understood but it is hypothesized that it is an autoimmune disease.
- Only two population-based studies, both from Taiwan, have previously examined the co-occurrence of autoimmune comorbidity in people with AA. There have been no large population-based studies in other ethnic groups.

What does this study add?

- Adults newly diagnosed with AA in UK primary care ($n=8051$) have a higher prevalence of pre-existing atopic and autoimmune conditions than a population control group ($n=32\,204$).
- After diagnosis, people with AA are at 40% higher risk of being diagnosed with new-onset atopic and autoimmune conditions compared with a control group. Risk is highest for AD, AR, autoimmune hypothyroidism, SLE and vitiligo.
- Clinicians should be aware of this increased burden of atopic and autoimmune comorbidity in people with AA.

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Conflict of interest

S.deL. is Director of RCGP RSC, he had received funding for projects from Eli Lilly, Astra Zeneca, GSK, MSD, Seqirus, Daiichi Sankyo and Takeda – all through his universities and none related to this study. W.S.C. is an employee of Pfizer Ltd. S.H. and C.T. are investigators on the Pfizer-funded ALLEGRO clinical trial. S.H., M.H., A.E.M. and A.G.M. are members of the British Association of Dermatologists guidelines group for alopecia areata.

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Ethics statement

Ethics approval: study approval was granted by the Joint Research and Surveillance Centre Committee of the Oxford-RCGP RSC. The study did not meet the requirements for formal ethics board review as defined using the NHS Health Research Authority research decision tool (<http://www.hra-decisiontools.org.uk/research/>). Informed consent: not applicable.

Data availability

The RCGP RSC dataset is held securely at Oxford University and the University of Surrey and can be accessed by bone fide researchers. Approval is on a project-by-project basis (www.rcgp.org.uk/rsc). Ethical approval by an NHS Research Ethics Committee may be needed before any data release/other appropriate approval. Researchers wishing to directly analyse the patient-level pseudonymized data will be required to complete information governance training and work on the data from university secure servers. Patient-level data cannot be taken out of the secure network.

Supporting Information

Additional [Supporting Information](#) may be found in the online version of this article at the publisher's website.

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