Atopic dermatitis and the risk of developing rheumatoid arthritis - A population-based cohort study

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INTRODUCTION

- Atopic Dermatitis (AD), a prevalent and often persistent skin disease is associated with immune-mediated inflammation and skin barrier dysfunction. It is now recognized as a systemic disease linked to a larger issue of immune dysfunction.
- Data is scarce on its association with other chronic inflammatory conditions such as Rheumatoid Arthritis (RA), particularly in both adults and children

STUDY OBJECTIVES

- To assess the risk of RA in patients with AD, stratified by age, after adjusting for traditional risk factors, using a previously validated algorithm.

METHODS

Design: Cohort study (1994-Feb 2015)

Data Source: The Health Improvement Network (THIN)

Study Population: All patients in THIN at start date who had observation time in THIN after implementation of Vision software. analyses were stratified into pediatric (<18 years at baseline) and adult (>=18 years at baseline) cohorts

Exposed: All patients with a diagnosis of AD. Patients with AD were identified using a validated algorithm (PPV=86%) of at least one of five common diagnostic Read codes for AD *and* two AD-related therapy codes. AD severity was defined as a time-updated variable. All patients with AD are considered to have mild disease by default. They will be classified as having "moderate" AD at the first of: i) a second potent topical corticosteroid treatment within one year, or ii) a first topical calcineurin inhibitor treatment. AD patients were classified as "severe" at the first of i)systemic immunosuppressant treatment or ii)phototherapy use or iii) dermatology referral

Unexposed: Patients without a diagnostic code for AD. Up to 5 unexposed controls were matched for each patient with AD on age (+/- 5 years), general practice and an encounter within +/- 6 months of the index date for the AD patient (defined as latter of practice registration date and diagnosis date)

Outcomes: at least 1 diagnostic code for RA

Start Date: Latest of: date of AD diagnosis, practice registration date or implementation of Vision software. Unexposed controls received a "diagnosis date" corresponding to a GP visit the same calendar year of the AD diagnosis date.

End Date: Earliest of: patient developed outcome of interest, died, transferred out of THIN, or the end of data collection period was reached.

Analyses: Multivariate Cox Proportional Hazard models to estimate hazard ratios (HR)

Covariates: age, sex, Townsend index, allergic rhinitis, and asthma (for both age groups) and body mass index, smoking, and drinking (for ≥18y stratum).

RESULTS

Table 1a. Baseline characteristics of study cohort <18 strata

Characteristic, N (%)	Control	Mild AD	Moderate AD	Severe AD
	1809029	381678	22433	5320
Age, median (IQR), y	4 (2, 9)	4 (1, 8)	9 (4, 14)	5 (1, 10)
Sex				
Female	872279 (48.22)	184682 (48.39)	11054 (49.28)	2335 (43.89)
Male	936750 (51.78)	196996 (51.61)	11379 (50.72)	2985 (56.11)
Townsend deprivation index (average)	275,637 (20.54)	72164(20.0)	4229.6(20.0)	1000.6(20.0)
Missing	91508 (5.06)	20856 (5.46)	1285 (5.73)	317 (5.96)
Person time, median (IQR), y	4.99 (2.02 - 9.41)	5.22 (2.12 -9.74)	6.02 (2.57-10.18)	6.89 (2.68-12.62)
Allergic rhinitis	75050 (4.15)	23935 (6.27)	2870 (12.79)	521 (9.79)
Asthma	169679 (9.38)	49782 (13.04)	6094 (27.17)	1222 (22.97)
Rheumatoid Arthritis	436 (0.02)	51 (0.01)	10 (0.04)	30 (0.56)
Juvenile Rheumatoid Arthritis	365 (0.02)	44 (0.01)	5 (0.02)	26 (0.49)
Rheumatoid arthritis	114 (0.01)	9 (0.00)	5 (0.02)	8 (0.15)

Table 1b. Baseline characteristics of study cohort >=18 strata

Characteristic, N(%)	Control	Mild AD	Moderate AD	Severe AD
	N=2678888	N=410867	N=196101	N=18115
Age, median (IQR), y	47 (32, 64)	45 (30, 63)	50 (34, 68)	47 (32, 63)
Sex				
Female	1445589 (53.96)	256071 (62.32)	109404 (55.79)	10736 (59.27)
Male	1233299 (46.04)	154796 (37.68)	86697 (44.21)	7379 (40.73)
BMI				
Underweight (<18)	72655 (2.71)	11504 (2.80)	4150 (2.12)	525 (2.90)
Normal (18.5-24.9)	911449 (34.02)	152480 (37.11)	66015 (33.66)	6972 (38.49)
Overweight (25-29.9)	707292 (26.40)	109693 (26.70)	56021 (28.57)	4799 (26.49)
Obese (30-34.9)	285567 (10.66)	44998 (10.95)	24088 (12.28)	1900 (10.49)
Severely Obese (35-39.9)	94373 (3.52)	15720 (3.83)	8486 (4.33)	653 (3.60)
Morbidly Obese (>40)	44721 (1.67)	8341 (2.03)	4525 (2.31)	343 (1.89)
Missing/Unknown	562831 (21.01)	68131 (16.58)	32816 (16.73)	2923 (16.14)
Smoking status				
Never	1293811 (48.30)	206577 (50.28)	89588 (45.68)	8653 (47.77)
Current	576463 (21.52)	84855 (20.65)	44195 (22.54)	3914 (21.61)
Former	548828 (20.49)	92290 (22.46)	48636 (24.80)	4182 (23.09)
Missing/Unknown	259786 (9.70)	27145 (6.61)	13682 (6.98)	1366 (7.54)
Drinking status				
Never	300614 (11.22)	51208 (12.46)	24278 (12.38)	2338 (12.91)
Current	1655958 (61.82)	262008 (63.77)	125921 (64.21)	11525 (63.62)
Former	114596 (4.28)	19708 (4.80)	10187 (5.19)	965 (5.33)
Missing/Unknown	607720 (22.69)	77943 (18.97)	35715 (18.21)	3287 (18.15)
Townsend deprivation index	2310346 (20.0)	263,978 (20.0)	37,386 (20.0)	3437(20.0)
Missing/Unknown	110920 (4.14)	17973 (4.37)	9171 (4.68)	926 (5.11)
Person time, median (IQR), y	4.96 (2.09, 9.18)	4.94 (2.05, 9.24)	5.20 (2.204 9.44)	5.41 (2.14, 10.44)
Allergic rhinitis	266083 (9.93)	66023 (16.07)	29926 (15.26)	3062 (16.90)
Asthma	346024 (12.92)	80267 (19.54)	42608 (21.73)	4584 (25.30)
Rheumatoid Arthritis	24463 (0.91)	2635 (0.64)	1488 (0.76)	2788 (15.39)
Juvenile Rheumatoid Arthritis	855 (0.03)	124 (0.03)	53 (0.03)	60 (0.33)
Rheumatoid Arthritis	23838 (0.89)	2525 (0.61)	1441 (0.73)	2757 (15.22)

Table 2. Risk of of RA outcomes among patients with AD; adjusted Hazard's ratio (HR)

	Hazards Ratio (HR) [ref: non-AD]							
	Pediatric Cohort*				Adult Cohort**			
Outcome	Overall AD	Mild AD	Moderate AD	Severe AD	Overall AD	Mild AD	Moderate AD	Severe AD
Rheumatoid Arthritis	1.38 (1.14, 1.67)	1.16 (0.94, 1.444)	1.17 (0.72, 1.91)	8.35 (5.63, 12.38)	1.18 (1.13, 1.22)	0.95 (0.90, 1.01)	1.03 (0.97, 1.10)	5.64 (5.19, 6.133)

*Variables included in model: age, sex, townsend, history of allergic rhinitis and asthma

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CONCLUSIONS/DISCUSSION

Conclusions: Our findings from a large population-based cohort suggest an overall increased risk of RA in patients with AD, with the association primarily limited to patients with severe AD. This sets the stage for further studies on potential underlying mechanisms, such as overlapping therapies or shared pathophysiology.

Strengths: To our knowledge, this is the first large population-based cohort study to investigate the risk of RA in patients with AD. The algorithm used has been previously validated in THIN. Our results were robust to multiple sensitivity analyses.

Limitations: Observation bias and unmeasured confounder's

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