

Achalasia Is Associated With Atopy in Patients Younger Than 40 Years of Age

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INTRODUCTION: Case reports describe individuals with achalasia features subsequently diagnosed with eosinophilic esophagitis (an atopic disorder). We have examined associations between achalasia and atopic and autoimmune conditions.

METHODS: This is a UK cohort study of 2,593 subjects with achalasia matched to 10,402 controls.

RESULTS: At diagnosis, achalasia was associated with autoimmune conditions (odds ratio 1.39; 95% confidence interval 1.02–1.90) and atopic conditions (1.40; 1.00–1.95) in those aged younger than 40 years.

DISCUSSION: Our findings support an autoimmune etiology in achalasia but also suggest a possible atopic etiology in younger subjects.

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INTRODUCTION

Achalasia is an uncommon esophageal motility disorder of the esophagus (1), resulting from a loss of inhibitory ganglions in the lower esophageal myenteric plexus (2). Disease progression leads to dysphagia through absent peristalsis and failure of lower esophageal sphincter relaxation.

Immune-mediated ganglionitis appears central to the pathophysiology, with certain human leukocyte antigen alleles associated and viral mimicry implicated (3). Associations with autoimmune disorders have been described (4). However, activated eosinophilic infiltration in esophageal smooth muscle has been demonstrated in achalasia (5), and patients with features of achalasia subsequently diagnosed with eosinophilic esophagitis (EoE) and responding to glucocorticosteroids have been reported (6,7). EoE is associated with other atopic conditions including asthma, rhinitis, and eczema (8). If EoE has a role in the etiology of achalasia, then an association with atopy would be expected, but this has not been investigated (9).

The aim of this study was to examine associations between achalasia and atopic, autoimmune, and neurodegenerative diseases.

METHODS

A population-based retrospective cohort study using IQVIA Medical Research Data, a UK primary care database of over 15 million subjects, was performed to assess associations between achalasia and atopic (eczema, allergic rhinitis, asthma, and allergic conjunctivitis), autoimmune (psoriasis, type 1 diabetes mellitus, pernicious anaemia, inflammatory bowel disease, autoimmune thyroid disease, and rheumatoid arthritis), and

neurodegenerative (multiple sclerosis, Parkinson disease, and dementia) diseases. Motor neurone disease and scleroderma were excluded because of the misclassification risk, given their associations with dysphagia.

The study period was from January 1, 1995, to December 31, 2018. To ensure data quality, practices were included one year following the later of installation of electronic medical records or practice acceptable mortality recording date. Subjects became eligible for the study at the later of 1 year after joining an eligible practice or study start date.

Subjects with a coded diagnosis of achalasia were identified and matched to 4 controls by age (± 2 years) and sex. Outcomes of interest, as well as covariates relating to their development (including age, sex, Townsend deprivation quintile, body mass index, and smoking status), were collected at study entry. Subject index date (when follow-up begins) was the achalasia diagnosis date for incident achalasia cases (diagnosed during study period) or the date they became eligible for study entry for prevalent achalasia cases (diagnosed before the study period). To mitigate immortal time bias (11), the same index date was assigned to the corresponding matched control subjects. Subjects were followed from index date until the earliest of the following: study end, last data collection from practice, subject transferred practice, death, or outcome.

Statistical analysis

Multivariable logistic regression was used to describe the difference in odds ratio (OR) of pre-existing diagnoses of each outcome condition (autoimmune, atopic, or neurodegenerative) between

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Table 1. Cohort demographics

	Prevalent cohort		Incident cohort	
	Achalasia	Controls	Achalasia	Controls
No. of subjects	2,593	10,402	1,082	4,322
Median age (IQR)	57 (42–72)		44 (61–74)	
Person-year follow-up (IQR)	4 (2–8)		3 (1–7)	
Age category (%)				
<18 yr	46 (2)	182 (2)	24 (2)	90 (2)
18–30	163 (6)	681 (7)	70 (6)	282 (7)
30–40	339 (13)	1,338 (13)	112 (10)	452 (10)
40–50	389 (15)	1,572 (15)	139 (13)	559 (13)
50–60	454 (18)	1,818 (17)	175 (16)	690 (16)
60–70	444 (17)	1,792 (17)	196 (18)	796 (18)
70–80	382 (15)	1,514 (15)	175 (16)	690 (16)
>80	376 (15)	1,505 (14)	191 (18)	763 (18)
Female (%)	1,292 (50)	5,158 (50)	560 (52)	2,236 (52)
Townsend index (%)				
1—least deprived	606 (23)	2,202 (21)	253 (23)	957 (22)
2	525 (20)	2,091 (20)	200 (18)	886 (21)
3	479 (18)	1,944 (19)	220 (20)	791 (18)
4	394 (15)	1,666 (16)	179 (17)	673 (16)
5—most deprived	264 (10)	1,097 (11)	107 (10)	455 (11)
Missing	325 (13)	1,402 (13)	123 (11)	560 (13)
Smoking status (%)				
Current smoker	403 (16)	1,959 (19)	162 (15)	735 (17)
Nonsmoker	1,407 (54)	5,103 (49)	594 (55)	2,200 (51)
Ex-smoker	557 (21)	2,132 (21)	272 (25)	1,015 (23)
Missing	226 (9)	1,208 (12)	54 (5)	372 (9)
Body mass index (%)				
<25 kg/m ²	1,033 (40)	3,354 (32)	447 (41)	1,401 (32)
25–30 kg/m ²	674 (26)	3,002 (29)	290 (27)	1,338 (31)
>30 kg/m ²	361 (14)	1,672 (16)	178 (16)	749 (17)
Missing	525 (20)	2,374 (23)	167 (15)	834 (19)
Diseases at baseline				
Atopic	681 (29.0)	2,370 (24.5)	311 (32.3)	1,113 (28.4)
Autoimmune	162 (8.9)	486 (6.2)	66 (9.2)	205 (6.7)
Neurodegenerative	53 (2.0)	247 (2.4)	17 (1.6)	105 (2.4)
IQR, interquartile range.				

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subjects with incident achalasia and matched controls at baseline (for conditions where ≥ 10 individuals had a diagnosis). A subgroup analysis for atopic disease was undertaken in achalasia subjects younger than 40 years because atopic disease typically presents at a younger age and if atopy has an etiological role in achalasia, this is most likely in younger subjects (1,12).

To calculate the risk of subsequent diagnoses (during follow-up), subjects with a pre-existing diagnosis of the outcome of interest were excluded. Multivariable Poisson regression accounting for person-time at risk was used to calculate incidence rate ratios

(IRRs) for the development of atopic, autoimmune, and neurodegenerative conditions in subjects with achalasia (incident and prevalent cases) compared with controls. Logistic and Poisson models were adjusted for age, sex, Townsend deprivation, body mass index, and smoking status.

The use of the IQVIA Medical Research Data* is approved by the UK Research Ethics Committee (reference number: 18/LO/0441). The study protocol was reviewed and approved by an independent Scientific Review Committee in February 2019 (reference number: 17THIN033-A1).

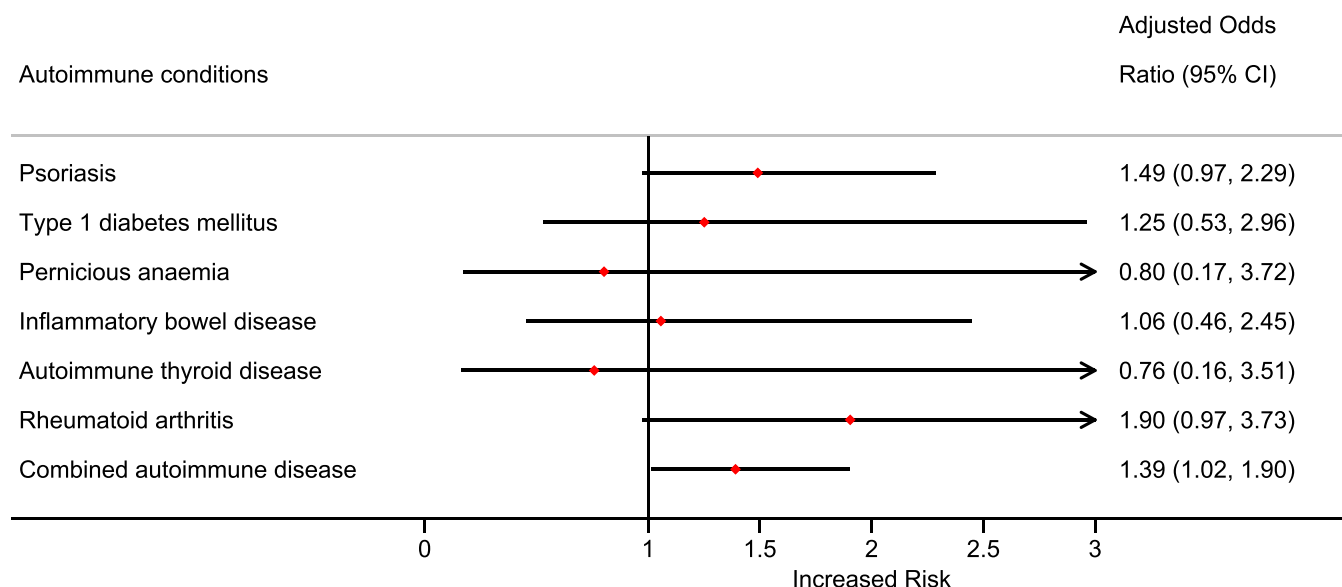


Figure 1. The association between achalasia and autoimmune conditions at achalasia diagnosis. CI, confidence interval; OR, odds ratio.

*IQVIA Medical Research Data incorporates data from The health Improvement Network, a Cegedim Database. Reference made to The health Improvement Network is intended to be descriptive of the data asset licensed by IQVIA. This work used deidentified data provided by patients as a part of their routine primary care.

RESULTS

There were 2,593 with achalasia identified (median age 57 years; 52% male) and were age/sex matched to 10,402 controls, including 1,082 incident achalasia subjects matched to 4,322 controls (Table 1).

Disease associations at achalasia diagnosis

At achalasia diagnosis, the incident achalasia cohort was less likely to have a neurodegenerative disease than controls: 17 achalasia subjects (1.6%) compared with 105 controls (2.4%);

adjusted OR 0.57 (95% CI 0.33–0.97, $P = 0.037$). By contrast, the achalasia cohort was more likely to have an autoimmune disease: 57 (9%) vs 176 (6%) in achalasia and control groups, respectively; OR 1.39 (1.02–1.90, $P = 0.039$) (Figure 1). At achalasia diagnosis, no association was observed with atopic conditions: 311 (32%) vs 1,133 (28%) in achalasia and control groups, respectively; OR 1.16 (0.99–1.35, $P = 0.066$). However, in the subgroup analysis, achalasia subjects younger than 40 years of age had a 40% increased risk of atopy: 76 (39%) vs 240 (30%) in achalasia and control groups, respectively; OR 1.40 (1.00–1.95, $P = 0.047$) (Figure 2).

Risk of developing atopic, autoimmune, and neurodegenerative diseases

During follow-up, few incident outcomes were observed. The risk of subsequent atopic, neurodegenerative, or autoimmune disease

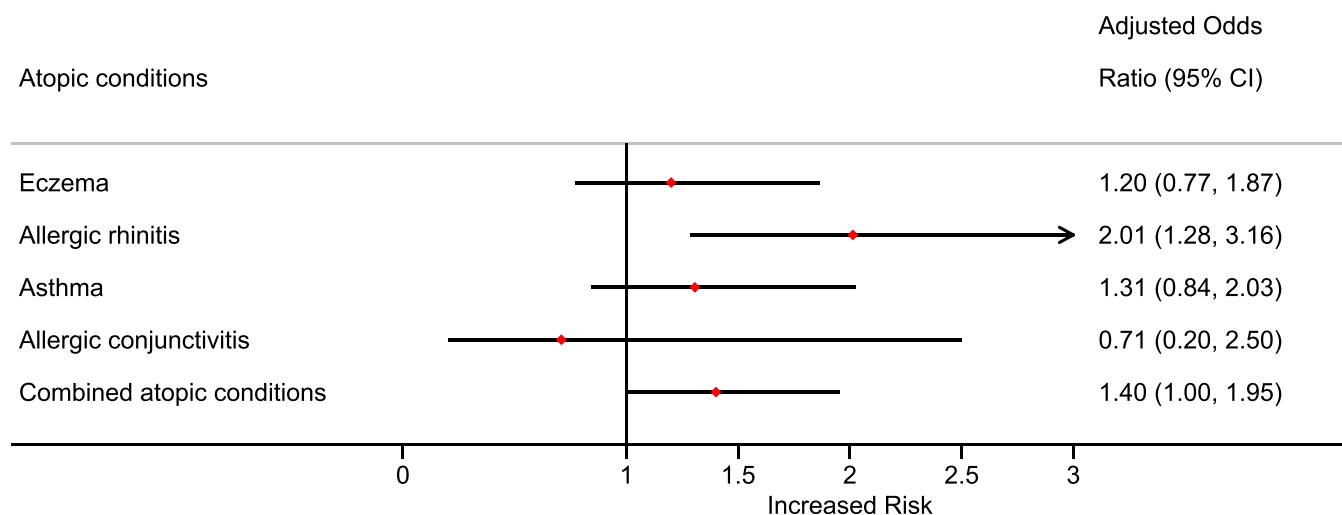


Figure 2. The association between achalasia and atopic conditions in subjects younger than 40 years at achalasia diagnosis. CI, confidence interval; OR, odds ratio.

in the achalasia and control groups was similar, with adjusted IRRs of 1.07 (95% CI 0.90–1.26), 1.10 (0.86–1.40), and 0.99 (0.72–1.37), respectively. However, specific associations were noted for rheumatoid arthritis (IRR 2.02 (1.16–3.50), $P = 0.012$) and vitiligo (3.21 (1.07–9.62), $P = 0.037$).

DISCUSSION

An association between achalasia and autoimmune conditions has been previously described (4,13). The reported effect sizes were similar to the 40% increase compared with matched controls found at baseline in the present study. However, for the first time in achalasia subjects younger than 40 years, a similar association was found with atopic conditions, increasing the possibility of an atopic etiology in some younger patients with achalasia.

EoE, similar to achalasia, is a rare diagnosis and unfortunately very few cases are recorded in the IQVIA Medical Research database, limiting any direct study of association between these 2 conditions. Spechler et al. speculated that a muscle-predominant eosinophilic infiltration of the esophagus may lead to some cases of achalasia and other motility disorders (9,14). Case reports of individual patients with manometry consistent with achalasia but with concurrent esophageal mucosal eosinophilia, and a symptomatic and manometric response to steroids has been described (9). However, whether these are isolated, rare patients with EoE or whether EoE is of wider significance in the etiology of achalasia is unclear.

Further research into this field is indicated with study of the prevalence of EoE on biopsy in patients with achalasia younger than 40 years. We would also suggest that in patients with achalasia or EoE, unresponsive to first-line treatment, esophageal biopsy in achalasia and manometry in EoE is considered to exclude potential alternative diagnoses.

CONFLICTS OF INTEREST

Guarantor of the article: Nigel Trudgill, MD.

Specific author contributions: Study concept and design was jointly conceived by D.K., T.T., J.C., N.B., N.A., K.N., and N.T. Data extraction was performed by D.K., and analysis was performed by D.K., J.C., N.A., and N.T. The manuscript was drafted by D.K. The data and manuscript were critically reviewed, revised, and approved by all authors.

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