

ORIGINAL ARTICLE

Specific IgE positivity against inhalant allergens and development of autoimmune disease

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Abstract

Background: Allergic and autoimmune diseases have been suggested to be inversely associated. We investigated the association between atopy and development of any and specific types of autoimmune disease. **Methods:** We included a total of 14 849 individuals from five population-based studies with measurements of atopy defined as specific IgE positivity against inhalant allergens. We followed the participants by linkage to the Danish National Patient Register (median follow-up time 11.2 years). Hazard ratio (HR) and 95% confidence interval (CI) of autoimmune disease were estimated by Cox regression. **Results:** The risk for atopics versus non-atopics was: for any autoimmune disease (HR = 0.99, 95% CI: 0.83, 1.18), thyrotoxicosis (HR = 0.69, 95% CI: 0.34, 1.37), type 1 diabetes (HR = 1.16, 95% CI: 0.84, 1.60), multiple sclerosis (HR = 1.97, 95% CI: 0.95, 4.11), iridocyclitis (HR = 0.82, 95% CI: 0.38, 1.74), Crohn's disease (HR = 1.03, 95% CI: 0.47, 2.25), ulcerative colitis (HR = 0.93, 95% CI: 0.52, 1.69), psoriasis vulgaris (HR = 1.50, 95% CI: 0.86, 2.62), seropositive rheumatoid arthritis (HR = 0.74, 95% CI: 0.48, 1.14) and polymyalgia rheumatica (HR = 0.79, 95% CI: 0.44, 1.44). **Conclusions:** We found no statistically significant associations between atopy and autoimmune disease, but we cannot exclude relatively small to moderate effects - protective or promotive - of atopy on autoimmune disease.

Keywords

Atopy, crohn's disease, iridocyclitis, multiple sclerosis, polymyalgia rheumatica, psoriasis vulgaris, rheumatoid arthritis, thyrotoxicosis

History

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Introduction

Atopic and autoimmune diseases share fundamentally important characteristics. At their broadest definition, they both result from hypersensitivity to seemingly harmless antigens. IgE-mediated sensitisation to autoantigens, also known as autosensitisation, characterises the development of autoimmune diseases and arises from an abnormal immune response against substances and tissues normally present in the body. It may be restricted to certain organs or involve a particular tissue in different places [1], e.g. multiple sclerosis, a chronic autoimmune disease where the antigenic target is central nervous system myelin and type 1 diabetes, an autoimmune disease caused by cell-mediated immunity against pancreatic islet beta cells [2,3]. The pathogenesis of autoimmune disease is largely unresolved; in some cases suggested to be caused by infection, in others thought to be protected by the same [4], but in general considered to be associated with a T helper cell 1 (Th1) deviation of the immune response [5]. By contrast, atopy that refers to a

tendency to develop immunoglobulin E (IgE) antibodies against common environmental allergens confers a high risk of allergic diseases and is associated with a Th2 response [6].

Atopy may, at least in theory, affect the risk of autoimmune disease. The two types of diseases have been suggested to be inversely associated because conditions favouring Th1- and Th2-activation should counteract each other [6]. Furthermore, accumulating evidence suggests that the mast cell that has long been implicated in atopic disease have an important role in autoimmunity as well [7]. Despite previous efforts to clarify the matter, the role of atopy in the development of autoimmune disease is, however, still unresolved [3,7–9]. We investigated the association between atopy, defined as specific IgE positivity against inhalant allergens, and the incidence of autoimmune diseases according to the *International Classification of Diseases* (ICD) in five Danish population-based studies.

Materials and methods

Ethics statement

The studies were approved by the Ethics Committee of Copenhagen and the Danish Data Protection Agency, and the recommendations of the Declaration of Helsinki were

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followed. Persons who participated gave their informed written consent.

Study populations

We used the five population-based studies, Monica1, Inter99, Health2006, the 1936-cohort and Allergy98 that were recruited from the Danish Central Personal Register as random samples of the population. The studies included questionnaires, blood tests and physical examinations. An overview of the studies in this area has previously been published [10]. In the Monica1 study (1982–1984), 4807 persons with Danish citizenship at 30, 40, 50 and 60 years of age were invited. The participation rate was 79% with 3785 participants [10].

In the Health2006 study, a sample of 7931 persons from 18 to 69 years of age was invited to a general health examination [11] and 3471 (43.8%) persons were examined during 2006–2008.

In the Inter99 study (1999–2001), 12 934 persons aged 30–60 years were invited. A total of 6784 persons participated, which gave a participation rate of 52.5% [12]. The study was a population-based randomised controlled trial (CT00289237, ClinicalTrials.gov) that investigated the effects of a lifestyle intervention on cardiovascular disease [13].

The Copenhagen Allergy study began in 1990 and included a group of persons randomly selected from the general population and a selected group of persons with allergic respiratory symptoms that was recruited from a random sample of the general population by a screening questionnaire. In the present study, we used data from the follow-up health examination in 1997–1998 (referred to as ‘Allergy98’) where a total of 1966 persons aged 15–77 years with Danish nationality were invited, and 1216 (61.9%) participated [13].

The 1936-cohort included 1200 randomly selected persons born in 1936 (aged 40 years at the time of the study). During 1976–1977, 1052 persons were examined (participation rate 87.7%). The 1936-cohort has previously been described [14,15].

From the five included studies, a total of 15 098 individuals had measurements of atopy (Monica1: 3481; Inter99: 5999; Allergy98: 1186; 1936-cohort: 989; Health2006: 3443). Of these, a total of 249 persons were included in more than one of the studies, and these persons were included only as a participant in the study in which they were first examined and excluded from the subsequent studies (Supplementary Figure 1). We thus included a total of 14 849 persons (Monica1: 3481; Inter99: 5961; Allergy98: 1172; 1936-cohort: 989; Health2006: 3246).

Assessment of atopy

In the Monica1 study and the 1936-cohort, serum-specific IgE positivity measurements were performed by the ADVIA Centaur Allergy Screen assay (Bayer HealthCare Diagnostics division, Tarrytown, NY) [16]. It is a multi-allergen assay for the qualitative detection of specific serum IgE antibodies against common inhalant allergens, and it includes 19 common inhalant allergens. Atopy was defined as a

positive result according to instructions provided by the manufacturer.

In the Health2006 and the Allergy98 study, measurements of serum specific IgE to mite (*Dermatophagoides* [D.] *pteronyssinus*), cat, grass and birch (in the Allergy98 study in addition dog and mugwort) were performed with the ADVIA Centaur sIgE assay (Bayer Corporation, New York, NY) [17]. In the Inter99 study, serum samples were analysed for specific IgE to mite (*D. pteronyssinus*), cat, grass and birch by the IMMULITE 2000 Allergy Immunoassay System [18]. In the Health2006, the Allergy98 and the Inter99 study, the analysis for specific IgE was defined as positive if the measurement was ≥ 0.35 kU/l. Specific IgE positivity, atopy, was defined as one or more positive tests for specific IgE to the allergens tested.

Registry-based diagnoses

In Denmark, it is possible to link data from Danish registers on an individual level since all persons living in Denmark have a unique and permanent personal civil registration number. Information on diseases according to the International Classification of Diseases (ICD) was obtained from the Danish National Patient Register [19]. The register holds information on admissions to Danish hospitals since 1978. Admissions are registered by one primary diagnosis and optionally one or more secondary diagnoses. The Danish Civil Registration System provided information on emigration and vital status [20]. The participants were followed until 31 December 2010.

The categorisation of diagnoses is summarised in Table 1. Before 1987, no distinction was made between insulin-dependent and non-insulin-dependent diabetes mellitus (ICD-8: 250 for both types of diabetes) [21]. From 1987 to 1998, insulin-dependent diabetes mellitus was coded as 249 (ICD-8; 1987–1993) or E10 (ICD-10; 1994–present). Most cases of type 1 and type 2 diabetes are likely coded as insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus, respectively. However, some patients with type 2 diabetes need insulin treatment and may thus be categorised as having insulin-dependent diabetes. Persons with a registry-based diagnosis of the event before baseline were excluded from the prospective analyses.

Covariates

The questionnaires provided information on the following covariates: smoking habits (never smokers; former smokers; current smokers <15 g/day; current smokers 15 – <25 g/day; ≥ 25 g/day); education/vocational training (no education beyond basic, education including students); alcohol consumption (drinks per week); and physical activity during leisure time (sedentary, light or moderate/vigorous). Body mass index (BMI) was calculated as weight divided by height squared.

The number of missing values was: smoking habits ($N_{\text{missing}} = 42$); education ($N_{\text{missing}} = 277$); alcohol consumption ($N_{\text{missing}} = 580$); physical activity during leisure time ($N_{\text{missing}} = 188$); BMI ($N_{\text{missing}} = 7$); and missing date of death ($n = 1$) giving a total of 880 persons (6.0%) with a missing value in at least one of the covariates (Supplementary Figure 1).

Table 1. Classification of autoimmune diseases according to ICD-8 and ICD-10 codes.

	ICD-8	ICD-10
Any autoimmune disease*	242.00, 249, 340, 364, 563.01, 563.19, 696.09–10, 696.19, 712.19, 712.39, 712.59, 446.30–31, 446.39, 281.0, 283.90–91, 446.49, 245.03, 255.1, 354, 571.93, 571.90, 269.00, 694, 694.05, 704.00, 709.01, 712.09, 446.29, 716, 733.09, 734.0, 734.19, 734.90, 712.49	E05.0, E10, G35, H20, K50, K51, L40, M05–M06, M31.5–6, M35.3, D51.0, D59.1, D69.3, E06.3, E27.1, G61.0, K75.4, K74.3, K90.0, L10, L12, L63, L80, M08, M31.3, M33, G70.0, M34, M32, M35.0, M45
Thyrotoxicosis	242.00	E05.0
Type 1 diabetes	249	E10
Multiple sclerosis	340	G35
Iridocyclitis	364	H20
Crohn's disease	563.01	K50
Ulcerative colitis	563.19	K51
Psoriasis vulgaris	696.09–10, 696.19	L40
Seropositive rheumatoid arthritis	712.19, 712.39, 712.59	M05–M06
Polymyalgia rheumatica	446.30–31, 446.39	M31.5–6, M35.3

*Including thyrotoxicosis, type 1 diabetes, multiple sclerosis, iridocyclitis, Crohn's disease, ulcerative colitis, psoriasis vulgaris, seropositive rheumatoid arthritis, polymyalgia rheumatica, pernicious anaemia (ICD-8: 281.0, ICD-10: D51.0), autoimmune haemolytic anaemia (ICD-8: 283.90–91, ICD-10: D59.1), idiopathic thrombocytopenic purpura (ICD-8: 446.49, ICD-10: D69.3), autoimmune thyroiditis (ICD-8: 245.03, ICD-10: E06.3), primary adrenocortical insufficiency (ICD-8: 255.1, ICD-10: E27.1), Guillain-Barre syndrome (ICD-8: 354, ICD-10: G61.0), autoimmune hepatitis (ICD-8: 571.93, ICD-10: K75.4), primary biliary cirrhosis (ICD-8: 571.90, ICD-10: K74.3), celiac disease (ICD-8: 269.00, ICD-10: K90.0), pemphigus (ICD-8: 694, ICD-10: L10), pemphigoid (ICD-8: 694.05, ICD-10: L12), alopecia areata (ICD-8: 704.00, ICD-10: L63), vitiligo (ICD-8: 709.01, ICD-10: L80), juvenile arthritis (ICD-8: 712.09, ICD-10: M08), Wegener's granulomatosis (ICD-8: 446.29, ICD-10: M31.3), dermatopolymyositis (ICD-8: 716, ICD-10: M33), myasthenia gravis (ICD-8: 733.09, ICD-10: G70.0), systemic sclerosis (ICD-8: 734.0, ICD-10: M34), systemic lupus erythematosus (ICD-8: 734.19, ICD-10: M32), Sjögren's syndrome (ICD-8: 734.90, ICD-10: M35.0) and ankylosing spondylitis (ICD-8: 712.49, ICD-10: M45).

Table 2. Baseline characteristics according to study population.

Study population	Mean (SD) or % (n)				
	Monica1	Allergy98	Inter99	Health2006	1936-cohort
Year of examination	1982–1984	1997–1998	1999–2001	2006–2008	1976–1977
Male gender	50.6 (1761)	45.7 (535)	49.2 (2930)	45.2 (1467)	46.7 (462)
Age (years)	45.0 (11.1)	40.0 (15.1)	46.1 (7.9)	49.0 (13.1)	40.4 (0.4)
BMI (kg/m ²)	24.6 (3.9)	25.7 (4.6)	26.3 (4.5)	25.9 (4.7)	23.9 (3.7)
Alcohol (drinks/week)	8.9 (11.5)	6.8 (8.0)	10.4 (13.5)	9.7 (10.3)	8.6 (11.2)
No education beyond basic	29.9 (1,041)	28.8 (336)	16.8 (962)	13.8 (440)	28.5 (282)
Never smokers	25.7 (895)	41.9 (492)	35.0 (2,087)	41.9 (1,345)	32.8 (324)
Low physical activity*	28.3 (985)	26.0 (303)	21.6 (1,257)	18.5 (595)	34.7 (343)
Atopy†	17.1 (594)	37.3 (437)	34.5 (2,058)	23.4 (758)	14.9 (147)
History of autoimmune disease	0.7 (24)	3.0 (35)	2.6 (155)	3.3 (107)	0.1 (1)

BMI, body mass index; SD, standard deviation.

*Sedentary leisure time physical activity.

†Serum-specific IgE positivity to inhalant allergens.

Statistical analyses

Analyses were performed with SAS, version 9.4 (SAS Institute Inc. Cary, NC). *p* Values were two-sided, and *p* values <0.05 were defined as statistically significant. Table 2 shows the baseline characteristics of the participants according to study population expressed as % (number) or mean (standard deviation, SD). Table 3 shows the baseline characteristics according to atopic status, expressed as % (number) or mean (standard deviation, SD) and compared with the Chi-square test or the Kruskal-Wallis test, respectively. Table 4 shows incident autoimmune diseases according to study population and atopic status and the results of crude Cox regression analyses with age as the underlying time axis (total number here was 14 848 persons since only 1 person was excluded due to missing date of death).

Multivariate Cox regression analyses were used to determine the association of atopy with the incidence of autoimmune disease (Table 5). Data from the five included study populations were pooled, we used delayed entry where persons contribute risk time from the date of baseline examination, and age was used as underlying time axis (which means that age is automatically adjusted for). Estimates are presented as hazard ratios, HR (95% confidence intervals, CI). The few participants lost to follow-up or deceased contributed risk time until the time of their last registered activity or date of death. Only persons with complete information on all considered variables were included in these Cox regression analyses. In model 1, we adjusted for gender and study population. In model 2, we further adjusted for education, physical activity, smoking habits, alcohol intake and BMI. There was no statistically

Table 3. Baseline characteristics according to atopic status.

	Non-atopic % (n) or mean (SD)	Atopic % (n) or mean (SD)	<i>p</i> Value*
Gender			
Male	46.1 (5006)	53.8 (2149)	<0.0001
Female	53.9 (5849)	46.2 (1845)	
Age (years)	46.3 (10.9)	43.7 (10.4)	<0.0001
Education			
No	22.3 (2380)	17.4 (681)	<0.0001
Yes	77.7 (8276)	82.6 (3235)	
Alcohol (drinks/week)	9.3 (11.9)	10.0 (11.9)	0.0003
Body mass index (kg/m ²)	25.5 (4.4)	25.8 (4.5)	<0.0001
Smoking habits			
Never smokers	32.7 (3545)	40.2 (1598)	<0.0001
Former smokers	24.2 (2621)	22.6 (901)	
Current smokers, <15 g/day	18.3 (1984)	16.0 (635)	
Current smokers, 15–<25 g/day	19.0 (2056)	16.1 (640)	
Current smokers, ≥25 g/day	5.8 (623)	5.1 (204)	
Physical activity			
Sedentary	24.1 (2585)	22.8 (898)	0.0026
Light	57.6 (6179)	56.4 (2219)	
Moderate/vigorous	18.3 (1963)	20.8 (817)	

SD, standard deviation.

*Chi-square or Kruskal-Wallis test.

Table 4. Incident autoimmune disease according to atopic status and study population.

	Non-atopics % (n)	Atopics % (n)	Atopics vs. non-atopics HR (95% CI)*	Inter99 % (n)	Health2006 % (n)	1936-cohort % (n)	Monica1 % (n)	Allergy98 % (n)
Any autoimmune disease†	6.2 (655)	4.6 (179)	0.98 (0.83, 1.16), <i>p</i> = 0.793	4.2 (241)	1.3 (40)	11.5 (114)	10.7 (370)	6.1 (69)
Thyrotoxicosis	0.5 (51)	0.3 (13)	0.78 (0.42, 1.44), <i>p</i> = 0.419	0.4 (25)	0.03 (1)	1.1 (11)	0.6 (21)	0.5 (6)
Type 1 diabetes	1.8 (190)	1.3 (53)	1.11 (0.82, 1.51), <i>p</i> = 0.502	1.0 (61)	0.1 (4)	3.8 (38)	3.7 (127)	1.1 (13)
Multiple sclerosis	0.2 (22)	0.3 (13)	1.72 (0.86, 3.43), <i>p</i> = 0.124	0.2 (13)	0.1 (2)	0.3 (3)	0.4 (15)	0.2 (2)
Iridocyclitis	0.3 (35)	0.2 (9)	0.88 (0.42, 1.85), <i>p</i> = 0.740	0.2 (12)	0.1 (2)	0.4 (4)	0.6 (19)	0.6 (7)
Crohn's disease	0.3 (27)	0.2 (9)	0.96 (0.45, 2.06), <i>p</i> = 0.923	0.3 (16)	0.1 (3)	0.4 (4)	0.3 (11)	0.2 (2)
Ulcerative colitis	0.5 (53)	0.4 (15)	0.93 (0.52, 1.66), <i>p</i> = 0.801	0.3 (19)	0.2 (5)	1.0 (10)	0.7 (24)	0.9 (10)
Psoriasis vulgaris	0.5 (50)	0.6 (22)	1.46 (0.88, 2.42), <i>p</i> = 0.143	0.5 (28)	0.1 (4)	0.7 (7)	0.7 (24)	0.8 (9)
Seropositive rheumatoid arthritis	1.2 (131)	0.7 (26)	0.71 (0.46, 1.08), <i>p</i> = 0.107	0.8 (45)	0.3 (8)	2.1 (21)	2.0 (69)	1.2 (14)
Polymyalgia rheumatic	0.7 (79)	0.3 (13)	0.77 (0.43, 1.39), <i>p</i> = 0.388	0.3 (15)	0.2 (7)	2.0 (20)	1.4 (47)	0.3 (3)

HR, hazard ratio; CI, confidence interval.

*Crude Cox regression analysis with age as underlying time axis.

†Including thyrotoxicosis, type 1 diabetes, multiple sclerosis, iridocyclitis, Crohn's disease, ulcerative colitis, psoriasis vulgaris, seropositive rheumatoid arthritis, polymyalgia rheumatica, pernicious anaemia, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, autoimmune thyroiditis, primary adrenocortical insufficiency, Guillain-Barre syndrome, autoimmune hepatitis, primary biliary cirrhosis, celiac disease, pemphigus, pemphigoid, alopecia areata, vitiligo, juvenile arthritis, Wegener's granulomatosis, dermatopolymyositis, myasthenia gravis, systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome and ankylosing spondylitis.

significant interaction between atopy and study population in the multivariable Cox regression analyses.

For meta-analyses of the study-specific estimates, we used Stata, version 12.1 (StataCorp LP, College Station, TX). We used the inverse variance method in fixed and random effects models (Supplementary Figures 2–11). Heterogeneity across studies was assessed by the I^2 -test. The meta-estimates are summarised in Figure 1 (fixed effect estimates in analyses where $I^2 = 0$, and random effect estimates where $I^2 > 0$).

Results

Baseline characteristics according to study population are summarised in Table 2. Persons with atopy were younger, more frequently male, drank more alcohol, were more educated, smoked less, and had higher BMI than persons

without atopy (Table 3). Table 4 shows cases of incident autoimmune disease according to atopic status – compared by crude Cox regression analyses with age as underlying time axis – and study population.

The median follow-up was 11.2 years (Monica1: 27.3; Inter99: 11.2; Allergy98: 12.6; 1936-cohort: 33.8; Health2006: 3.5 years). In multivariable Cox regression analyses, we found no statistically significant associations between atopy and any or specific autoimmune diseases, and the estimates changed little in stepwise adjustments (Table 5). The hazard ratio for atopics versus non-atopics for any autoimmune disease was HR = 0.99 (95% CI: 0.83, 1.18). The hazard ratio for atopics versus non-atopics was below 1 for thyrotoxicosis (HR = 0.69, 95% CI: 0.34, 1.37), iridocyclitis (HR = 0.82, 95% CI: 0.38, 1.74), ulcerative colitis (HR = 0.93, 95% CI: 0.52, 1.69), seropositive rheumatoid

Table 5. Hazard ratios and 95% confidence intervals of pooled analyses of incident autoimmune disease for atopics vs. non-atopics.

	Events (persons included)	Model 1† HR (95% CI), <i>p</i> value	Model 2‡ HR (95% CI), <i>p</i> value
Any autoimmune disease*	785 (13 690)	1 (reference)	1 (reference)
Non-atopic			
Atopic		0.98 (0.82, 1.16), <i>p</i> = 0.774	0.99 (0.83, 1.18), <i>p</i> = 0.936
Thyrotoxicosis	60 (13 949)	1 (reference)	1 (reference)
Non-atopic			
Atopic		0.65 (0.33, 1.31), <i>p</i> = 0.230	0.69 (0.34, 1.37), <i>p</i> = 0.287
Type 1 diabetes	227 (13 936)	1 (reference)	1 (reference)
Non-atopic			
Atopic		1.15 (0.83, 1.58), <i>p</i> = 0.403	1.16 (0.84, 1.60)
Multiple sclerosis	32 (13 944)	1 (reference)	1 (reference)
Non-atopic			
Atopic		1.96 (0.94, 4.09), <i>p</i> = 0.074	1.97 (0.95, 4.11), <i>p</i> = 0.070
Iridocyclitis	43 (13 952)	1 (reference)	1 (reference)
Non-atopic			
Atopic		0.84 (0.39, 1.78), <i>p</i> = 0.644	0.82 (0.38, 1.74), <i>p</i> = 0.603
Crohn's disease	34 (13 946)	1 (reference)	1 (reference)
Non-atopic			
Atopic		0.98 (0.45, 2.14), <i>p</i> = 0.958	1.03 (0.47, 2.25), <i>p</i> = 0.942
Ulcerative colitis	66 (13 922)	1 (reference)	1 (reference)
Non-atopic			
Atopic		0.90 (0.50, 1.63), <i>p</i> = 0.739	0.93 (0.52, 1.69), <i>p</i> = 0.821
Psoriasis vulgaris	61 (13 950)	1 (reference)	1 (reference)
Non-atopic			
Atopic		1.43 (0.82, 2.50), <i>p</i> = 0.208	1.50 (0.86, 2.62), <i>p</i> = 0.153
Seropositive rheumatoid arthritis	150 (13 930)	1 (reference)	1 (reference)
Non-atopic			
Atopic		0.73 (0.47, 1.12), <i>p</i> = 0.150	0.74 (0.48, 1.14), <i>p</i> = 0.173
Polymyalgia rheumatica	91 (13 955)	1 (reference)	1 (reference)
Non-atopic			
Atopic		0.81 (0.44, 1.46), <i>p</i> = 0.475	0.79 (0.44, 1.44), <i>p</i> = 0.446

Complete case analysis.

CI, confidence interval; HR, hazard ratio.

†Adjusted for study and gender (age is underlying time axis).

‡Further adjusted for education, season of blood sample, physical activity, smoking habits, alcohol intake and body mass index.

*Including thyrotoxicosis, type 1 diabetes, multiple sclerosis, iridocyclitis, Crohn's disease, ulcerative colitis, psoriasis vulgaris, seropositive rheumatoid arthritis, polymyalgia rheumatica, pernicious anaemia, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, autoimmune thyroiditis, primary adrenocortical insufficiency, Guillain-Barre syndrome, autoimmune hepatitis, primary biliary cirrhosis, celiac disease, pemphigus, pemphigoid, alopecia areata, vitiligo, juvenile arthritis, Wegener's granulomatosis, dermatopolymyositis, myasthenia gravis, systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome and ankylosing spondylitis.

arthritis (HR = 0.74, 95% CI: 0.48, 1.14) and polymyalgia rheumatica (HR = 0.79, 95% CI: 0.44, 1.44). The hazard ratio for atopics versus non-atopics was above 1 for type 1 diabetes (HR = 1.16, 95% CI: 0.84, 1.60), multiple sclerosis (HR = 1.97, 95% CI: 0.95, 4.11), Crohn's disease (HR = 1.03, 95% CI: 0.47, 2.25) and psoriasis vulgaris (HR = 1.50, 95% CI: 0.86, 2.62). The meta-analysed study-specific estimates also did not show any statistically significant associations of the same relations. However, the estimates were somewhat different for Crohn's disease, ulcerative colitis and polymyalgia rheumatica in particular (Figure 1).

Discussion

In a large prospective study of 14 849 persons from five study populations including a total of 834 cases of incident autoimmune disease, we found no statistically significant association between atopy and development of any or specific autoimmune diseases in either pooled data analyses or meta-analyses of study-specific estimates.

Our findings are somewhat in line with a large cross-sectional study using allergic and autoimmune disease information based on self-report and found no statistically

significant association between atopy and a history of autoimmune disease (thyroid disorder, rheumatoid arthritis or type 1 diabetes). Contradicting their *a priori* hypothesis, they found that having a history of physician-diagnosed allergic disease (hay fever or asthma) was associated with a 70% higher odds of having a physician-diagnosed autoimmune disease [9]. Our study extended these results by using a longitudinal design with standardised registry-based diagnoses and an objective marker of atopy on all included persons. Furthermore, we analysed several additional autoimmune diseases.

Regarding atopy and celiac disease, Zauli et al. screened 401 persons with atopy defined as a positive skin prick test to either inhalant allergens or food allergens with no clinical signs of malabsorption and found a prevalence of 1% of celiac disease which is higher than in the general population [8,22]. Our data were insufficient to confirm or refute this. In terms of atopy and type 1 diabetes, our results are in line with a study by Caffarelli et al. [5], who found no association between IgE sensitization and type 1 diabetes in children. Of note, we previously found no association between atopy and development of ischaemic heart disease, stroke or diabetes [23], development of any and different types of cancer [24], or

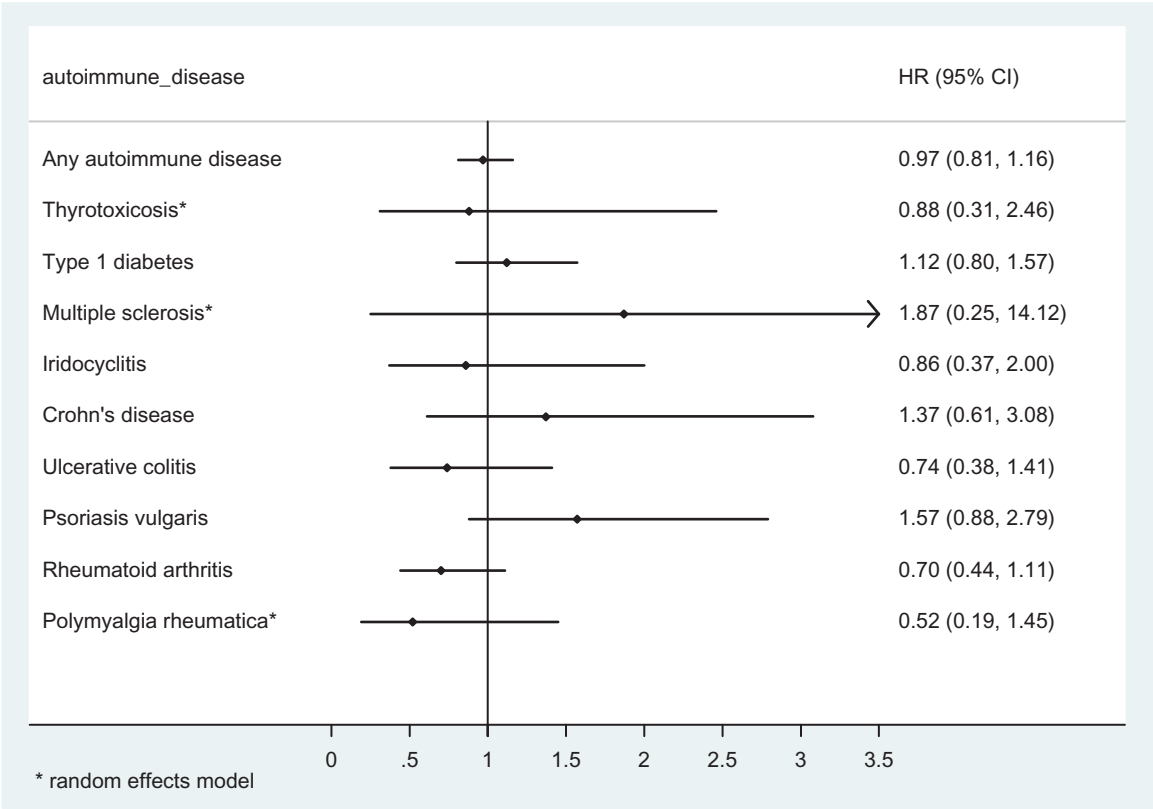


Figure 1. Summarisation of meta-analyses of the study-specific estimates of the association between atopy and risk of autoimmune disease.

cause-specific mortality [25] that also include disease entities with inflammatory elements.

The strengths of our study include the longitudinal design with long-term follow-up and the large population-based samples. We included standardised registry-based diagnoses with few lost to follow-up. Also, we used an accepted and objective marker of atopy, serum-specific IgE positivity to inhalant allergens. This was measured by commercially available immunoassays and was previously found to agree with skin prick test reactivity and a diagnosis of allergic respiratory disease [16,26].

The limitations of the study include the low number of events in some of the autoimmune disease categories. We may have lacked power to show small-moderate effects, and future meta-analyses should be undertaken, e.g. to investigate a possible link between atopy and multiple sclerosis. Also, the group of any autoimmune disease may include disease entities with different pathogenesis, where atopy might have a protective effect against some and a promoting effect on other and hence the effects may counteract each other. Also, it is a limitation that we only included atopy as the hypersensitivity response. However, we do not have reliable data on allergic disease diagnoses in the Danish registries.

Despite the sharing of important characteristics, the difference between atopic and autoimmune diseases is apparent when considering treatment options. Targeted treatment against the Th1 pathway, TNF- α in particular, has revolutionised the treatment of autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis [7]. By contrast, the development of immune tolerance with allergen-specific immunotherapy has long been successfully used in

the treatment of IgE-mediated allergic diseases whereas immunotherapy has been less promising in the treatment of autoimmune diseases [7].

In conclusion, we found no statistically significant association between atopy and development of any or specific autoimmune diseases. Our data implies that atopy is not associated with an altered risk of autoimmune disease, although we cannot exclude small to moderate effects - protective or promotive - of atopy on autoimmune disease.

Declaration of interest

The authors declare that they have no conflicts of interest.

References

1. Sozzani, S., M. P. Abbraccio, V. Annese, et al. 2014. Chronic inflammatory diseases: do immunological patterns drive the choice of biotechnology drugs? A critical review. *Autoimmunity*. 47: 287–306.
2. Fleiner, H. F., M. Radtke, L. Ryan, et al. 2014. Circulating immune mediators are closely linked in adult-onset type 1 diabetes as well as in non-diabetic subjects. *Autoimmunity*. 47: 530–537.
3. Rabin, R. L., and A. I. Levinson. 2008. The nexus between atopic disease and autoimmunity: a review of the epidemiological and mechanistic literature. *Clin. Exp. Immunol.* 153: 19–30.
4. Bach, J. F. 2005. [Infections and autoimmunity]. *Rev. Med. Intern.* 26: 32–34.
5. Caffarelli, C., G. Cavagni, R. Pierdomenico, et al. 2004. Coexistence of IgE-mediated allergy and type 1 diabetes in childhood. *Int. Arch. Allergy Immunol.* 134: 288–294.
6. Valenta, R., I. Mittermann, T. Werfel, et al. 2009. Linking allergy to autoimmune disease. *Trends Immunol.* 30: 109–116.
7. Shah, A. 2012. The pathologic and clinical intersection of atopic and autoimmune disease. *Curr. Allergy Asthma Rep.* 12: 520–529.

8. Zauli, D., A. Grassi, A. Granito, et al. 2000. Prevalence of silent coeliac disease in atopics. *Dig. Liver Dis.* 32: 775–779.
9. Sheikh, A., L. Smeeth, and R. Hubbard. 2003. There is no evidence of an inverse relationship between TH2-mediated atopy and TH1-mediated autoimmune disorders: lack of support for the hygiene hypothesis. *J. Allergy Clin. Immunol.* 111: 131–135.
10. Osler, M., A. Linneberg, C. Glumer, and T. Jorgensen. 2011. The cohorts at the Research Centre for Prevention and Health, formerly 'The Glostrup Population Studies'. *Int. J. Epidemiol.* 40: 602–610.
11. Berg, N. D., L. L. Husemoen, B. H. Thuesen, et al. 2012. Interaction between filaggrin null mutations and tobacco smoking in relation to asthma. *J. Allergy Clin. Immunol.* 129: 374–80.
12. Jorgensen, T., K. Borch-Johnsen, T. F. Thomsen, et al. 2003. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur. J. Cardiovasc. Prev. Rehabil.* 10: 377–386.
13. Husemoen, L. L., M. Fenger, N. Friedrich, et al. 2008. The association of ADH and ALDH gene variants with alcohol drinking habits and cardiovascular disease risk factors. *Alcohol Clin. Exp. Res.* 32: 1984–1991.
14. Drivsholm, T., L. F. Eplov, M. Davidsen, et al. 2006. Representativeness in population-based studies: a detailed description of non-response in a Danish cohort study. *Scand. J. Public Health.* 34: 623–631.
15. Linneberg, A., N. Friedrich, L. L. Husemoen, et al. 2010. Incidence and remission of specific IgE aeroallergen sensitization from age of 40 to 60 years, and association with alcohol consumption. *Int. Arch. Allergy Immunol.* 151: 142–148.
16. Linneberg, A., L. L. Husemoen, N. H. Nielsen, et al. 2006. Screening for allergic respiratory disease in the general population with the ADVIA Centaur Allergy Screen Assay. *Allergy.* 61: 344–348.
17. Petersen, A. B., P. Gudmann, P. Milvang-Gronager, et al. 2004. Performance evaluation of a specific IgE assay developed for the ADVIA centaur immunoassay system. *Clin. Biochem.* 37: 882–892.
18. Thuesen, B. H., L. L. Husemoen, L. Ovesen, et al. 2010. Atopy, asthma, and lung function in relation to folate and vitamin B(12) in adults. *Allergy.* 65: 1446–1454.
19. Andersen, T. F., M. Madsen, J. Jorgensen, et al. 1999. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan. Med. Bull.* 46: 263–268.
20. Pedersen, C. B. 2011. The Danish Civil Registration System. *Scand. J. Public Health.* 39: 22–25.
21. Nielsen, N. M., T. Westergaard, M. Frisch, et al. 2006. Type 1 diabetes and multiple sclerosis: a Danish population-based cohort study. *Arch. Neurol.* 63: 1001–1004.
22. Leonard, M. M., and B. Vasagar. 2014. US perspective on gluten-related diseases. *Clin. Exp. Gastroenterol.* 7: 25–37.
23. Skaaby, T., L. L. Husemoen, B. H. Thuesen, et al. 2014. The association of atopy with incidence of ischemic heart disease, stroke, and diabetes. *Endocrine.*
24. Skaaby, T., L. L. Husemoen, N. Roswall, et al. 2014. Atopy and development of cancer: a population-based prospective study. *JACI: In practice* 2: 779–785.
25. Skaaby, T., L. L. Husemoen, B. H. Thuesen, et al. 2014. Atopy and cause-specific mortality. *Clin. Exp. Allergy* 44: 1361–1370.
26. Petersen, A. B., P. Gudmann, P. Milvang-Gronager, et al. 2004. Performance evaluation of a specific IgE assay developed for the ADVIA centaur immunoassay system. *Clin. Biochem.* 37: 882–892.

Supplementary material available online
Supplementary Figures 1–11.