

The association of celiac disease and allergic disease in a general adult population

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Abstract

Background: The relationship between allergy and celiac disease (CD) is not clear.

Objective: The objective of this article is to investigate the association of CD and CD antibody positivity with hay fever, asthma and immunoglobulin (Ig)E sensitization in a general adult population.

Methods: A total of 2297 individuals were screened for CD antibodies and underwent allergy testing. CD antibody-positive participants were invited to undergo clinical evaluation including biopsies. Additionally, biobank blood samples from four population-based studies (6423, 973, 1718 and 1101 participants) with data on IgE sensitization to inhalant allergens were screened for CD antibodies. CD antibody-positive participants were screened for serum IgE against food allergens in three biobank studies. CD-antibody positivity was defined as IgA or IgG tissue transglutaminase ≥ 7 U/ml and/or IgG deamidated gliadin peptide ≥ 10 U/ml.

Results: The nine participants (0.4%) diagnosed with CD had significantly higher prevalence of IgE sensitization to wheat and dust mites. The prevalence of CD antibody positivity was 0.8% (18/2297), and these participants had a significantly higher prevalence of IgE sensitization to food allergens (Fv5), egg, dust mites and mugwort. In the biobank studies, the prevalence of CD antibody positivity was 0.8% to 1.2%. One study showed a positive association between CD antibody positivity and IgE sensitization for dog, horse and food allergens.

Conclusion: We found a possible association of CD and IgE sensitization to some food and inhalant allergens in the Health2006 study. In further studies, however, we could not consistently replicate these associations.

Keywords

Allergy, antibodies, asthma, celiac disease, epidemiology

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Key summary

Summarize the established knowledge on this subject:

- Celiac disease is a lifelong autoimmune disease caused by an abnormal immune response in genetically susceptible individuals, triggered by ingestion of gluten.
- Allergy is an exaggerated specific immune response against external proteins leading to allergic inflammation.
- The relationship between celiac disease and allergic diseases is not clear.

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What are the significant and/or new findings of this study?

- Our study indicated a possible association of celiac disease and immunoglobulin E sensitization to some food and inhalant allergens.
- Further studies in our research biobank cohorts could not consistently replicate these associations.

Introduction

Celiac disease (CD) is a lifelong autoimmune disease affecting about 1% of the population, although many cases of CD remain undiagnosed. CD is caused by an abnormal immune response, in genetically susceptible individuals, triggered by the ingestion of gluten proteins from wheat, rye and barley.^{1–3} CD primarily affects the small intestine, but the clinical manifestations are broad. The treatment of CD is a lifelong gluten-free diet. A small intestinal biopsy and detection of inflammation, crypt hyperplasia and/or villus atrophy is the gold standard for the diagnosis of CD in adults. However, since individuals with CD produce disease-specific antibodies, serology is more frequently used in the diagnostic process.^{4,5} In contrast to the abnormal immune response in autoimmune disease in which the immune system attacks itself, allergy is an exaggerated immune response against external proteins leading to allergic inflammation. Immunoglobulin (Ig) E-mediated allergic diseases include food allergies, allergic rhinitis and allergic asthma. Allergic reactions may occur in individuals IgE sensitized to allergens, primarily proteins. The genetic or acquired predisposition to production of IgE antibodies against environmental allergens and thus risk of IgE-mediated allergic disease is often referred to as “atopy” and the diseases therefore sometimes are labeled as “atopic diseases.”

Studies have found CD to be more frequent among individuals with atopic diseases,^{6–9} while others,¹⁰ but not all,¹¹ have found atopic diseases to be more common among individuals with CD. Ciacchi et al.¹² found no significant difference between individuals with CD compared with their relatives and spouses without CD with regard to allergy prevalence, but they found the prevalence of atopic dermatitis to be three times higher in individuals with CD. Enroth and colleagues found no association between self-reported allergy and CD-related autoantibodies.¹³ Pillon et al.¹⁴ found individuals with severe food allergy to have a five-fold increased risk of CD compared with controls. Asthma has also been found to be associated with CD; individuals with CD have increased risk of asthma^{15,16} and CD was increased in young individuals hospitalized with asthma,¹⁷ but the number of studies are limited.

Thus, the results are contradicting, and it is not clear whether CD is associated with increased risk of

IgE-mediated allergic disease or asthma. Therefore, we aimed to investigate the association of CD and CD antibody positivity with hay fever, asthma and IgE sensitization in a general population study of Danish adults who had been screened for CD, and if positive, were examined by a specialist and underwent intestinal biopsies. Confirmation of results was sought by measurements of CD antibodies in four additional population-based studies.

Methods

The Health2006 study

This study was based on the five-year follow-up of the Health2006 study, designed as a cross-sectional population-based study.¹⁸ A random sample living in the Southwestern part of Copenhagen aged 18–69 years were invited. All eligible participants in the Health2006 cohort were invited to a five-year follow-up examination including essentially the same study protocol^{19,20} with the addition of screening for CD by measurements of CD biomarkers. A total of 3405 participants were eligible for invitation, 2308 individuals (54.2% female) were reexamined (participation rate: 44.7%) and 2297 participants were screened for CD (11 were not included because of a missing blood sample or for technical reasons). The mean age at the five-year-follow-up examination was 55.7 years (range, 24–76 years). The study included structured self-administered questionnaires on general health, symptoms and diagnoses of disease, lifestyle and socioeconomic variables among other issues, physical examination and collection of blood samples.

Screening for CD. The screening for CD in the five-year follow-up of the Health2006 study has been described elsewhere.^{20,21} Briefly, 2297 individuals were screened for CD antibodies by the EliaTM Celikey[®] tissue transglutaminase (TTG) anti-IgA assay and deamidated gliadin peptide (DGP) anti-IgA and anti-IgG assays. Participants with undetectable levels of IgA-TTG were screened for IgG-TTG. The measurements were performed at Thermo Fisher Scientific, Immuno Diagnostics, Allerød, Denmark. Participants were defined as CD screen test positive and invited to a clinical examination if IgA-TTG ≥ 7.0 U/ml, IgA-DGP ≥ 10.0 U/ml and/or IgG-DGP ≥ 10.0 U/ml.

(None of the participants screened for IgG-TTG had levels ≥ 7.0 U/ml.)

For this current paper diagnosed cases of CD from the Health2006 study included the eight cases of screen-detected CD diagnosed by clinical evaluation and the one participant with known CD confirmed by International Classification of Diseases, 10th revision diagnosis code in the National Patient Register. Furthermore, after evaluating the screening²¹ we changed our definition of CD antibody positivity for this study to IgA-TTG ≥ 7.0 U/ml, IgG-TTG ≥ 7.0 U/ml and/or IgG-DGP ≥ 10.0 U/ml. Additionally, we conducted analyses in which CD antibody positivity was limited to IgA-TTG or IgG-TTG ≥ 10.0 U/ml.

Allergy. Serum samples were screened on a Phadia250 (ImmunoDiagnostics, Allerød, Denmark) for Phadiatop®, specific IgE to a panel of inhalant allergens, and serum-specific IgE to peanut, food mix Fx5 (a panel of food allergens), egg, soy, milk, cod, wheat, cat, horse, dog, *dermatophagoides (D.) pteronyssinus*, mold mix, grass, mugwort, birch and profilin birch. IgE positivity was defined as ≥ 0.35 kU/l.

Skin prick testing for a standard panel of aeroallergens: birch, timothy grass, mugwort, horse, cat, dog, two house dust mites (*D. pteronyssinus* and *D. farinae*), and two molds (*Cladosporium herbarum* and *Alternaria alternata*) was performed by the Soluprick SQ® test (ALK Abelló, Hørsholm, Denmark).

IgE sensitization to inhalant allergens was defined as a positive skin prick test to at least one of 10 allergens or one or more positive tests for serum-specific IgE against inhalant allergens.

Asthma and hay fever were defined as positive answers to the question “Has a doctor ever told you that you had asthma/hay fever?”

Confirmation of results in four additional studies

We aimed to confirm the association of CD antibodies and IgE sensitization against some inhalant allergens found in the Health2006 study. For this, we used our research biobank with serum samples from participants in previously performed studies. We screened four population-based studies (the Inter99 study,^{22,23} the 1936 cohort study,²⁴ the MONICA-I study²⁵ and the Allergy90 study^{26,27}) with information on allergy and IgE sensitization to inhalant allergens for CD antibodies. Information about the four biobank studies and the allergy testing is included in the Supplementary material. The biobank samples were screened for CD antibodies by the Elia™ Celikey® TTG anti-IgA and DGP anti-IgG assays at Thermo Fisher Scientific. Participants with undetectable levels of IgA-TTG were screened for IgG-TTG. CD antibody positivity

was defined as IgA-TTG ≥ 7.0 U/ml, IgG-TTG ≥ 7.0 U/ml and/or IgG-DGP ≥ 10.0 U/ml. Furthermore, we conducted analyses for which the CD antibody positivity only was defined as IgA-TTG or IgG-TTG ≥ 10.0 U/ml. Additionally, we screened serum samples from the CD antibody-positive participants in the 1936 cohort study, the Inter99 study and the Allergy90 study for specific IgE to a panel of food allergens (Fx5). If Fx5 positive, IgE specific to peanut, egg, milk and wheat were determined. IgE positivity was defined as positive when ≥ 0.35 kU/l. Prevalence of IgE positivity to food allergens in the CD antibody-positive individuals was compared with the prevalence of IgE positivity to food allergens in the CD antibody-negative individuals in the Health 2006 study.

Ethics

Informed written consent was obtained from all participants prior to participation. This study was approved by the local ethics committee (H-3-2011-081, September 6, 2011). Measurements of CD antibodies in stored blood samples were approved by the ethics committee of the Capital Region of Denmark (H-15014502, January 12, 2016). We followed the recommendations of the 1975 Declaration of Helsinki.

Statistical analyses

The association between variables was tested as appropriate: Wilcoxon test, Kruskal-Wallis tests and independent samples *t* test for continuous variables; and chi-squared test and Fisher exact test for categorical data. Complete case analyses were performed, thus the number of observations differs because of missing data. *P* values < 0.05 (two sided) were considered statistically significant. To adjust for multiple comparisons, the Bonferroni method was used. The Bonferroni adjusted significance level was 0.002 (27 outcomes). Statistical analyses were performed with software package SAS 9.4 (SAS Institute, NC, USA, USA), and the meta-analyses were performed with Stata 14 (StataCorp, College Station, TX). The study-specific estimates were combined using the inverse variance method both in fixed- and random-effects models; the results shown in Figure 1 are from the random-effects analyses. Heterogeneity across studies was assessed by the *I*² test.

Results

Table 1 shows the general characteristics of the participants stratified by CD antibody positivity, both in the Health2006 study and the four additional biobank

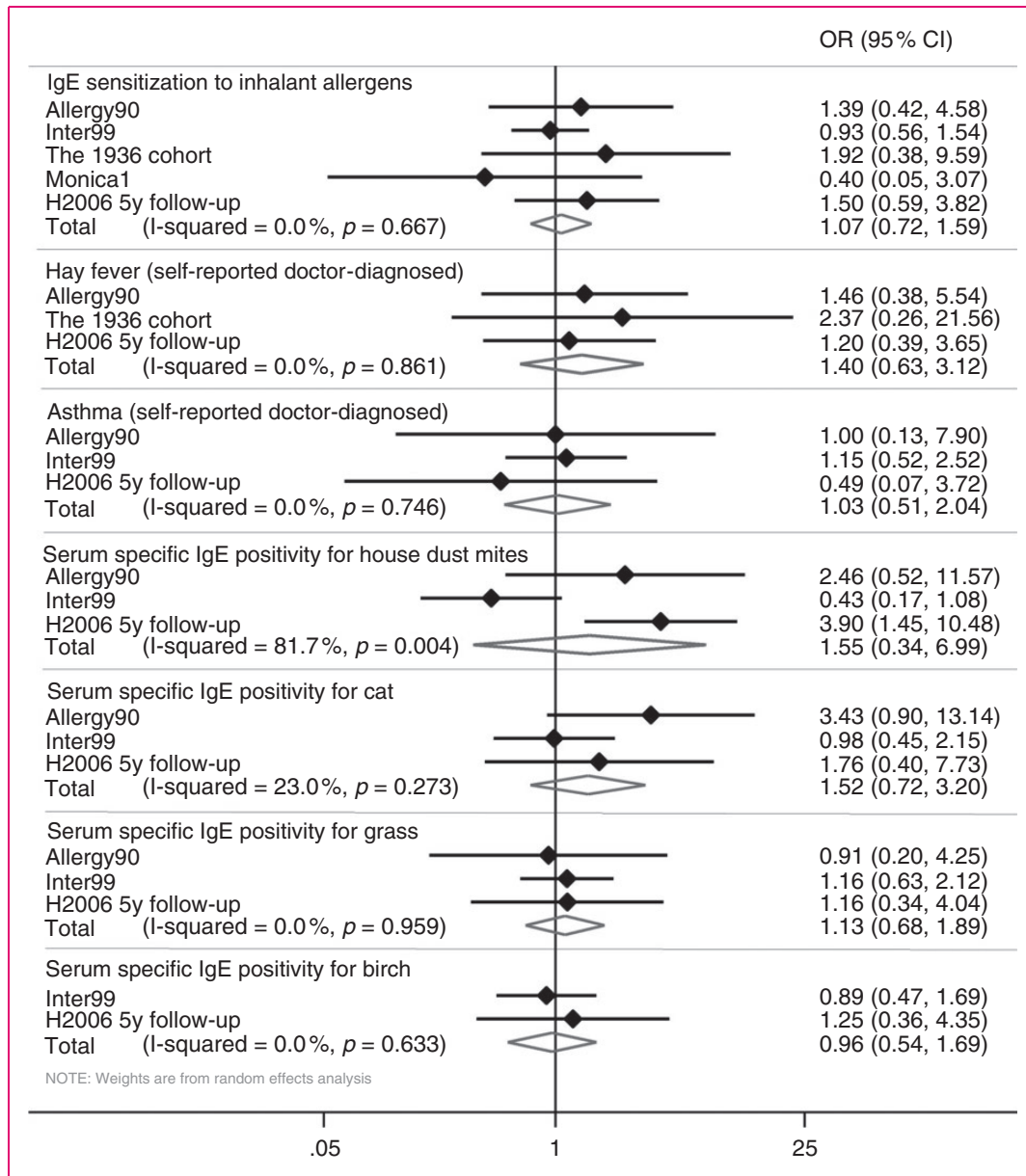


Figure 1. Meta-analyses of the different studies.
CI: confidence interval; IgE: immunoglobulin E; OR: odds ratio.

studies. There were no statistically significant differences between the CD antibody-negative and -positive participants.

The nine participants with diagnosed CD had a significantly higher prevalence of IgE sensitization to food allergens (fx5), wheat and house dust mites compared with individuals without CD. They also had significantly more skin prick reactivity for house dust mites (Table 2). When defining CD antibody positivity as IgA-TTG ≥ 7.0 U/ml, IgG-TTG ≥ 7.0 U/ml and/or IgG-DGP ≥ 10.0 U/ml, the prevalence of CD antibody positivity in Health2006 was 0.8% (18/2297). The 18 CD antibody-positive participants had significantly

higher prevalence of IgE sensitization to food allergens, egg, house dust mites and mugwort (Table 2). None of the other specific IgE tests were significantly different between the antibody-negative and -positive participants, nor was there IgE sensitization to inhalant allergens or skin prick test. There were no significant associations between CD or CD antibody positivity and asthma or hay fever. Results were essentially similar when CD antibody positivity was defined only by TTG antibodies, for which we found significant associations for IgE sensitization to food mix, egg, wheat and house dust mites and for skin prick test reactivity against the dust mite *D. pteronyssinus*.

Table 1. General characteristics of the participants stratified by celiac disease antibody positivity.

	The Health2006 study			The Inter99 study			p-value ^b	CD antibody negative participants ^a	CD antibody positive participants ^a	CD antibody negative participants	CD antibody positive participants ^a	p-value ^b
	Total	CD antibody negative participants	CD antibody positive participants ^a	Total	CD antibody negative participants	CD antibody positive participants ^a						
Number of participants	2297	2279	18	6423	6346	77						
Percentage CD antibody positive			0.8 % (18/2297)			1.2 % (77/6423)						
	%(<i>n/total N</i>)	%(<i>n/total N</i>)	%(<i>n/total N</i>)	%(<i>n/total N</i>)	%(<i>n/total N</i>)	%(<i>n/total N</i>)						
Sex							**0.728					**0.356
Male	45.9 (1055/2297)	45.9 (1046/2279)	50.0 (9/18)	49.3 (3168/6423)	49.3 (3126/6346)	54.6 (42/77)						
Female	54.1 (1242/2297)	54.1 (1233/2279)	50.0 (9/18)	50.7 (3255/6423)	50.7 (3220/6346)	45.5 (35/77)						
Education							*1.000					**0.176
Yes	92.5 (2107/2279)	92.4 (2090/2261)	94.4 (17/18)	83.4 (5152/6177)	83.5 (5097/6106)	77.5 (55/71)						
No	7.6 (172/2279)	7.6 (171/2261)	5.6 (1/18)	16.6 (1025/6177)	16.5 (1009/6106)	22.5 (16/71)						
Smoking							*0.199					**0.324
Current smoker	15.8 (361/2282)	15.9 (360/2264)	5.6 (1/18)	39.2 (2499/6371)	39.3 (2472/6295)	35.5 (27/76)						
Past smoker	39.5 (902/2282)	39.6 (897/2264)	27.8 (5/18)	25.4 (1619/6371)	25.5 (1603/6295)	21.1 (16/76)						
Never smoker	44.7 (1019/2282)	44.5 (1007/2264)	66.7 (12/18)	35.4 (2253/6371)	35.3 (2220/6295)	43.4 (33/76)						
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)						
Age at examination	55.0 (54.5-55.5)	55.0 (54.5-55.5)	54.8 (47.9-61.6)	46.1 (45.9-46.2)	46.0 (45.8-46.2)	47.6 (45.6-49.5)	‡0.941					‡0.121
Body mass index (BMI)	26.0 (25.8-26.2)	26.0 (25.8-26.2)	26.4 (24.3-28.6)	26.3 (26.2-26.4)	26.3 (26.2-26.4)	26.7 (25.6-27.9)	‡0.659					‡0.419
	Median (5%/95%)	Median (5%/95%)	Median (5%/95%)	Median (5%/95%)	Median (5%/95%)	Median (5%/95%)						
Alcohol consumption: Units per week	6.0 (0.0/27.0)	6.0 (0.0/27.0)	5.0 (0.0/26.0)	6.0 (0.0/32.8)	6.0 (0.0/32.5)	6.3 (0.0/35.5)	†0.756					†0.989
	The 1936 cohort study			The Monica-1 study, women			p-value ^b	CD antibody negative participants	CD antibody positive participants ^a	CD antibody negative participants	CD antibody positive participants ^a	p-value ^b
	Total	CD antibody negative participants	CD antibody positive participants ^a	Total	CD antibody negative participants	CD antibody positive participants ^a						
Number of participants	1035	1027	8	1839	1822	17						
Percentage CD antibody positive			0.8 % (8/1035)			0.9 % (17/1839)						
	%(<i>n/total N</i>)	%(<i>n/total N</i>)	%(<i>n/total N</i>)	%(<i>n/total N</i>)	%(<i>n/total N</i>)	%(<i>n/total N</i>)						
Sex							*0.727					N/A
Male	48.0 (497/1035)	48.1 (494/1027)	37.5 (3/8)	-	-	-						
Female	52.0 (538/1035)	51.9 (533/1027)	62.5 (5/8)	-	-	-						

(continued)

Table 1. Continued

	The 1936 cohort study				The Monica-1 study, women			
	Total	CD antibody negative participants	CD antibody positive participants ^a	p-value ^b	Total	CD antibody negative participants	CD antibody positive participants ^a	p-value ^b
Education								
Yes	72.0 (744/1033)	71.9 (737/1025)	87.5 (7/8)	*0.455	60.7 (1117/1839)	60.8 (1108/1822)	52.9 (9/17)	*0.619
No	28.0 (289/1033)	28.1 (288/1025)	12.5 (1/8)		39.3 (722/1839)	39.2 (714/1822)	47.1 (8/17)	
Smoking								
Current smoker	54.7 (566/1035)	54.7 (562/1027)	50.0 (4/8)	*0.106	53.8 (990/1839)	53.8 (980/1822)	58.8 (10/17)	*0.366
Past smoker	12.7 (131/1035)	12.5 (128/1027)	37.5 (3/8)		15.5 (285/1839)	15.4 (281/1822)	23.5 (4/17)	
Never smoker	32.7 (338/1035)	32.8 (337/1027)	12.5 (1/8)		30.7 (564/1839)	30.8 (561/1822)	17.7 (3/17)	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Age at examination	40.4 (40.3-40.4)	40.4 (40.3-40.4)	40.5 (40.3-40.8)	‡0.158	45.2 (44.7-45.7)	45.2 (44.7-45.7)	47.9 (41.7-54.2)	‡0.363
Body mass index (BMI)	23.9 (23.7-24.2)	23.9 (23.7-24.2)	23.2 (21.2-25.1)	‡0.390	23.9 (23.7-24.1)	23.8 (23.7-24.0)	25.8 (23.6-28.0)	‡0.079
	Median (5%/95%)	Median (5%/95%)	Median (5%/95%)		Median (5%/95%)	Median (5%/95%)	Median (5%/95%)	
Alcohol consumption: Units per week	5.0 (0.0/32.0)	5.0 (0.0/32.0)	6.0 (1.0/30.0)	†0.548	3.0 (0.0/16.0)	3.0 (0.0/16.0)	4.0 (0.0/11.0)	†0.549
The Allergy90 study								
	Total	CD antibody negative participants	CD antibody positive participants ^a	p-value ^b	TOTAL			
Number of participants	1101	1090	11					
Percentage CD antibody positive	%(<i>n</i> / <i>total N</i>)	%(<i>n</i> / <i>total N</i>)	%(<i>n</i> / <i>total N</i>)					
Sex								
Male	46.6 (513/1101)	46.3 (505/1090)	72.7 (8/11)	*0.126				**0.028
Female	53.4 (588/1101)	53.7 (585/1090)	27.3 (3/11)					
Education								
Yes	69.2 (762/1101)	69.0 (752/1090)	90.9 (10/11)					**<0.0001
No	30.8 (339/1101)	31.0 (338/1090)	9.1 (1/11)					
Smoking								
Current smoker	46.8 (515/1101)	46.8 (510/1090)	45.5 (5/11)					**<0.0001
Past smoker	20.0 (220/1101)	19.9 (217/1090)	27.3 (3/11)					
Never smoker	33.2 (366/1101)	33.3 (363/1090)	27.3 (3/11)	*0.852				

(continued)

Table 1. Continued

The Allergy90 study				TOTAL
Total	CD antibody negative participants	CD antibody positive participants ^a	p-value ^b	p-value for total ^c
Mean (95% CI)	Mean (95% CI)	Mean (95% CI)		
Age at examination	39.6 (38.8-40.4)	43.3 (37.2-49.3)	[‡] 0.205	[§] <0.0001
Body mass index (BMI)	24.8 (24.6-25.1)	27.7 (24.4-31.0)	[‡] 0.079	[§] <0.0001
Median (5%/95%)	Median (5%/95%)	Median (5%/95%)		
Alcohol consumption: Units per week	4.0 (0.0/25.0)	12.0 (0.0/98.0)	[‡] 0.055	[§] <0.0001

^aThe participants were screened for celiac disease antibodies by EliaTM Celikey[®] tissue transglutaminase (TTG) anti-IgA and anti-IgG assays and deamidated gliadin peptide (DGP) anti-IgG assays. Celiac disease (CD) antibody positive were defined as IgG-DGP ≥ 10.0 U/ml and/or IgA-TTG/IgG-TTG ≥ 7.0 U/ml.

^bp value between CD antibody negative and CD antibody positive

^cp value for the comparison of the five studies (Health2006, Inter99, The 1936 cohort, Monica-1 and Allergy90) totals, except for sex where Monica-1 is excluded from the analysis

*Fisher's Exact Test; [†] Wilcoxon Two-sample test; [‡] Independent samples t-test; [§] Kruskal-Wallis Test; **Chi-Square test

CD: Celiac disease

In the biobank studies, the prevalence of CD antibody positivity was 1% in total: 0.8% (8/1035) in the 1936 cohort study, 1.2% (77/6423) in the Inter99 study, 0.9% (17/1839) in the MONICA-1 study and 1.0% (11/1101) in the Allergy90 study (Table 1). These results are comparable to the percentages we found in the Health2006 study. There were no significant differences between the CD antibody-negative and -positive participants for IgE sensitization, asthma, hay fever or total IgE (Table 3). Only for the Allergy90 study, tested for additional allergens, did we find significant differences: The CD antibody-positive participants had a significantly higher prevalence of serum-specific IgE positivity against dog and skin prick test reactivity against horse. When limiting the CD antibody positivity to IgA-TTG/IgG-TTG ≥ 10.0 U/ml in the biobank studies, we found no statistically significant associations.

The analyses with measurements of IgE to food allergens did not reveal any significant differences for the 1936 cohort study or the Inter99 study (Table 4). For the Allergy90 study, however, we found that the CD antibody-positive participants had significantly more serum-specific IgE positivity against food mix and wheat than the CD antibody-negative participants in the Health2006 study.

When applying the Bonferroni adjusted significance level, none of the results remained statistically significant.

Figure 1 shows the results from the meta-analysis of the five studies; no significant associations were found.

Discussion

We found that individuals diagnosed with CD, or CD antibody-positive participants, had a significantly higher prevalence of IgE sensitization to some food and inhalant allergens. However, we could not replicate these associations of CD antibody positivity and IgE sensitization to inhalant allergens when screening blood samples in our research biobank from four different population-based studies for CD antibodies, although CD antibody positivity was significantly associated with a higher prevalence of IgE sensitization to dog, horse and food allergens in one study. In these five general Danish populations, the prevalence of CD antibody positivity, defined as IgA-TTG ≥ 7 U/ml, IgG-TTG ≥ 7 U/ml and/or IgG-DGP ≥ 10 U/ml., ranged between 0.8% and 1.2%.

We screened research biobank serum collected from 1976 through 2012 for CD antibodies and found no consistent increase in the prevalence of CD antibody positivity, although the prevalence steadily increased from 0.8% in 1976 to 1.2% in 2001, but in 2011–2012 (the Health2006 study) the prevalence was 0.8%. Earlier studies on the association of atopic diseases and CD have

Table 2. Allergy measurements stratified by celiac disease diagnosis and antibody status^a among participants in the Health2006 study.

	Participants without celiac disease % (n/total N)	Participants with celiac disease % (n/total N)	p value Fisher exact test	CD antibody-negative participants % (n/total N)	CD antibody-positive participants % (n/total N)	p value Fisher exact test
Number of participants	2288	9		2279	18	
IgE sensitization to inhalant allergens (serum IgE positivity or skin prick test reactivity to at least one allergen)	34.8 (795/2288)	55.6 (5/9)	0.291	34.8 (792/2279)	44.4 (8/18)	0.458
Asthma (self-reported doctor-diagnosed)	10.6 (241/2268)	11.1 (1/9)	1.000	10.7 (241/2259)	5.6 (1/18)	0.713
Hay fever (self-reported doctor-diagnosed)	19.3 (436/2264)	33.3 (3/9)	0.388	19.3 (435/2255)	22.2 (4/18)	0.764
Serum-specific IgE positivity						
Phadiatop ^b > 0.35	29.8 (682/2288)	55.6 (5/9)	0.138	29.8 (679/2279)	44.4 (8/18)	0.198
Peanut f13 > 0.35	4.2 (97/2288)	22.2 (2/9)	0.054	4.3 (97/2279)	11.1 (2/18)	0.180
Food mix ^c , Fx5	4.1 (93/2288)	22.2 (2/9) ^d	0.050	4.0 (92/2279)	16.7 (3/18) ^d	0.036
Egg, f1 > 0.35	1.3 (29/2288)	11.1 (1/9)	0.112	1.2 (28/2279)	11.1 (2/18) ^d	0.022
Soy, f14 > 0.35	1.3 (29/2288)	11.1 (1/9)	0.112	1.3 (29/2279)	5.6 (1/18)	0.211
Milk, f2 > 0.35	1.5 (35/2288)	0.0 (0/9)	1.000	1.5 (34/2279)	5.6 (1/18)	0.242
Cod, f3 > 0.35	0.2 (4/2288)	0.0 (0/9)	1.000	0.2 (4/2279)	0.0 (0/18)	1.000
Wheat, f4 > 0.35	2.0 (45/2288)	22.2 (2/9) ^d	0.014	2.0 (45/2279)	11.1 (2/18)	0.051
Cat, e1 > 0.35	6.6 (151/2288)	22.2 (2/9)	0.117	6.6 (151/2279)	11.1 (2/18)	0.340
Horse, e3 > 0.35	2.1 (49/2288)	0.0 (0/9)	1.000	2.2 (49/2279)	0.0 (0/18)	1.000
Dog, e5 > 0.35	6.0 (137/2288)	22.2 (2/9)	0.099	6.0 (137/2279)	11.1 (2/18)	0.298
<i>D. pteronyssinus</i> , d1 > 0.35	11.4 (261/2288)	44.4 (4/9) ^d	0.014	11.4 (259/2279)	33.3 (6/18) ^d	0.012
Mold mix, mx1 > 0.35	2.8 (65/2288)	11.1 (1/9)	0.231	2.8 (64/2279)	11.1 (2/18)	0.093
Grass, g6 > 0.35	14.6 (335/2288)	22.2 (2/9)	0.628	14.7 (334/2279)	16.7 (3/18)	0.739
Mugwort, w6 > 0.35	6.2 (141/2288)	22.2 (2/9)	0.104	6.1 (139/2279)	22.2 (4/18) ^d	0.022
Birch, t3 > 0.35	13.7 (314/2288)	33.3 (3/9)	0.116	13.8 (314/2279)	16.7 (3/18)	0.729
Profilin birch, t216 > 0.35	0.7 (16/2288)	11.1 (1/9)	0.065	0.7 (16/2279)	5.6 (1/18)	0.126
Skin prick test reactivity						
Skin prick test reactivity to at least one of 10 allergens	31.8 (720/2263)	44.4 (4/9)	0.478	31.9 (719/2255)	29.4 (5/17)	1.000
Birch	16.6 (376/2263)	33.3 (3/9)	0.178	16.7 (376/2255)	17.7 (3/17)	1.000
Grass	17.5 (395/2263)	33.3 (3/9)	0.198	17.5 (395/2255)	17.7 (3/17)	1.000
Mugwort	7.9 (179/2263)	0.0 (0/9)	1.000	7.9 (178/2255)	5.9 (1/17)	1.000
Horse	1.7 (38/2263)	11.1 (1/9)	0.145	1.7 (38/2255)	5.9 (1/17)	0.256
Cat	10.4 (235/2263)	33.3 (3/9)	0.059	10.4 (235/2255)	17.7 (3/17)	0.412
Dog	11.0 (249/2263)	33.3 (3/9)	0.068	11.0 (249/2255)	17.7 (3/17)	0.425
<i>D. pteronyssinus</i>	10.2 (231/2263)	44.4 (4/9) ^d	0.009	10.2 (231/2255)	23.5 (4/17)	0.090
<i>D. Farinae</i>	8.7 (197/2263)	33.3 (3/9) ^d	0.038	8.7 (197/2255)	17.7 (3/17)	0.184
Cladosporium	0.7 (15/2263)	0.0 (0/9)	1.000	0.7 (15/2255)	0.0 (0/17)	1.000
Alternaria	2.4 (55/2263)	11.1 (1/9)	0.202	2.4 (55/2255)	5.9 (1/17)	0.347

CD: celiac disease; Ig: immunoglobulin.

^aParticipants were screened for CD antibodies by EliaTM Celikey[®] tissue transglutaminase (TTG) anti-IgA and anti-IgG assays and deamidated gliadin peptide (DGP) anti-IgG assays. CD antibody positive was defined as IgG-DGP ≥ 10.0 U/ml and/or IgA-TTG/IgG-TTG ≥ 7.0 U/ml.^bPhadiatop[®] is a panel of inhalant allergens.^cFood mix is a panel of food allergens (egg (f1), milk (f2), cod (f3), wheat (f4), peanut (f13), soy (f14)).^dSignificantly different from antibody-negative participants, $p < 0.05$.

Table 3. Allergy measurements stratified by CD antibody status^a among participants in the MONICA-1, 1936 cohort, Allergy90 and Inter99 studies.

	CD antibody-negative participants % (n/total N)	CD antibody-positive participants % (n/total N)	p value
MONICA-1 study, women (n)	1822	17	
IgE sensitization to inhalant allergens	15.1 (257/1703)	6.7 (1/15)	0.713 ^c
1936 cohort study (n)	1027	8	
IgE sensitization to inhalant allergens	14.8 (143/965)	25.0 (2/8)	0.340 ^c
Asthma (self-reported doctor-diagnosed)	7.0 (46/661)	0.0 (0/5)	1.000 ^c
Hay fever (self-reported doctor-diagnosed)	9.5 (63/661)	20.0 (1/5)	0.398 ^c
Allergy90 study (n)	1090	11	
IgE sensitization to inhalant allergens	46.3 (505/1090)	54.6 (6/11)	0.763 ^c
Serum -specific IgE positivity			
Birch, t3 > 0.35	17.7 (192/1088)	0.0 (0/11)	0.228 ^c
Grass, g6 > 0.35	19.6 (213/1087)	18.2 (2/11)	1.000 ^c
Mugwort, w6 > 0.35	7.6 (83/1087)	0.0 (0/11)	1.000 ^c
Cat, e1 > 0.35	9.8 (107/1087)	27.3 (3/11)	0.089 ^c
Dog, e5 > 0.35	6.8 (74/1087)	27.3 (3/11) ^b	0.036 ^c
<i>D. pteronyssinus</i> , d1 > 0.35	8.3 (90/1087)	18.2 (2/11)	0.234 ^c
<i>D. farinae</i> , d2 > 0.35	14.6 (114/782)	33.3 (3/9)	0.135 ^c
Latex, k82 > 0.35	1.1 (12/1086)	0.0 (0/11)	1.000 ^c
Skin prick test reactivity			
Skin prick test reactivity to at least one of 10 allergens	38.4 (417/1086)	36.4 (4/11)	1.000 ^c
Birch	18.3 (199/1086)	0.0 (0/11)	1.000 ^c
Grass	19.9 (216/1086)	18.2 (2/11)	1.000 ^c
Mugwort	3.5 (38/1086)	0.0 (0/11)	1.000 ^c
Horse	2.5 (27/1086)	18.2 (2/11) ^b	0.032 ^c
Cat	9.3 (101/1086)	9.1 (1/11)	1.000 ^c
Dog	6.7 (73/1086)	9.1 (1/11)	0.538 ^c
<i>D. Pteronyssinus</i>	14.6 (158/1086)	27.3 (3/11)	0.211 ^c
<i>D. Farinae</i>	10.2 (111/1086)	0.0 (0/11)	0.615 ^c
Cladosporium	0.9 (10/1086)	0.0 (0/11)	1.000 ^c
Alternaria	4.1 (45/1086)	0.0 (0/11)	1.000 ^c
Asthma (self-reported doctor-diagnosed)	9.1 (99/1090)	9.1 (1/11)	1.000 ^c
Hay fever (self-reported doctor-diagnosed)	20.5 (223/1090)	27.3 (3/11)	0.706 ^c
Total IgE (Median (5%/95%))	30.0 (2.1/457.0)	44.1 (4.3/983)	0.129 ^d
Inter99 study (n)	6346	77	
IgE sensitization to inhalant allergens	32.9 (1888/5744)	30.9 (21/68)	0.796 ^c
Specific IgE			
IgE house dust mite	15.0 (895/5953)	7.1 (5/70)	0.065 ^c
IgE cat	9.8 (589/6042)	9.6 (7/73)	1.000 ^c
IgE grass	15.8 (956/6071)	17.8 (13/73)	0.628 ^c
IgE birch	16.4 (997/6075)	14.9 (11/74)	0.874 ^c
Asthma (self-reported doctor-diagnosed)	8.5 (518/6130)	9.6 (7/73)	0.672 ^c
Total IgE (Median (5%/95%))	28.5 (3.1/373.0)	34.1 (2.5/258.0)	0.713 ^d

CD: celiac disease; Ig: immunoglobulin; MONICA: Multinational MONItoring of Trends and Determinants in Cardiovascular Disease.

^aParticipants were screened for CD antibodies by EliaTM Celikey[®] tissue transglutaminase (TTG) anti-IgA and anti-IgG assays and deamidated gliadin peptide (DGP) anti-IgG assays. CD antibody-positive was defined as IgG-DGP $\geq$ 10.0 U/ml and/or IgA-TTG/IgG-TTG $\geq$ 7.0 U/ml.^bSignificantly different from antibody-negative participants, $p < 0.05$.^cFisher exact test.^dWilcoxon.

Table 4. Allergy measurements for food allergens among CD antibody-positive participants in the 1936 cohort, Inter99 and Allergy90 studies and CD antibody-negative participants in the Health2006 study.

	Health 2006 CD antibody- negative participants	1936 cohort CD antibody- positive participants	<i>p</i> value ^a	Inter99 CD antibody- positive participants	<i>p</i> value ^b	Allergy90 CD antibody- positive participants	<i>p</i> value ^c
n	2279	8		77		11	
Serum-specific IgE positivity							
Food mix ^d , Fx5	4.0 (92/2279)	0.0 (0/6)	1.000	2.7 (2/73)	1.000	27.3 (3/11)	0.009
Egg, f1 > 0.35	1.2 (28/2279)	0.0 (0/6)	1.000	0.0 (0/73)	1.000	0.0 (0/11)	1.000
Milk, f2 > 0.35	1.5 (34/2279)	0.0 (0/6)	1.000	0.0 (0/73)	0.625	0.0 (0/11)	1.000
Wheat, f4 > 0.35	2.0 (45/2279)	0.0 (0/6)	1.000	1.4 (1/73)	1.000	27.3 (3/11)	0.001
Peanut f13 > 0.35	4.3 (97/2279)	0.0 (0/6)	1.000	0.0 (0/73)	0.073	18.2 (2/11)	0.079

CD: celiac disease; Ig: immunoglobulin.

^aA *p* value for comparison of the CD antibody-positive participants in the 1936 cohort study and the CD antibody-negative participants from the Health2006 study, five-year follow-up by Fisher exact test.

^bA *p* value for comparison of the CD antibody-positive participants in the Inter99 study and the CD antibody-negative participants from the Health2006 study, five-year follow-up by Fisher exact test.

^cA *p* value for comparison of the CD antibody-positive participants in the Allergy90 study and the CD antibody-negative participants from the Health2006 study, five-year follow-up by Fisher exact test.

^dFood mix is a panel of food allergens.

been conflicting.^{6–13} We found a higher frequency of IgE sensitization between individuals with CD and CD antibody-positive participants, but no significant association between overall IgE sensitization to inhalant allergens and CD or CD antibody positivity. This tendency was not, however, consistent when screening the biobank studies. Moreover, we found CD antibody-positive participants to have a significantly higher prevalence of IgE sensitization to house dust mites and mugwort and individuals with CD to have a higher prevalence of IgE sensitization against house dust mites. These associations were not confirmed in the screening of biobank serum samples. In the Allergy90 study, however, we found significantly increased serum-specific IgE positivity against dog and significantly increased skin prick test reactivity against horse. The same tendency was seen in Health2006, although not statistically significant. Our results are not consistent, but might indicate a tendency toward more allergy among individuals with CD and CD antibody-positive participants.

Pillon et al. found individuals with severe food allergy (milk, egg and wheat allergy) to have increased risk of CD.¹⁴ In line with these findings, we found an association of IgE sensitization against food mix (Fx5), a panel of six food allergens, and CD and CD antibody positivity. Furthermore, we found significantly more serum-specific IgE positivity against egg among CD antibody-positive participants and significantly more serum-specific IgE positivity against wheat among individuals with CD. Also, CD antibody-positive participants had more specific IgE against wheat, although not statistically significant. However, the replication

studies based solely on serological measurements and not clinical diagnosis of CD did not consistently support that CD antibody-positive individuals are at increased risk of specific IgE positivity to food allergens, although one study (Allergy90) found a higher prevalence of IgE positivity to food mix and wheat among CD antibody-positive individuals. Thus, the results both from Pillon et al. and two of our studies suggest that screening for CD could be considered in individuals with food allergy. A mechanism behind this possible association might be an increased intestinal permeability in individuals with CD resulting in increased flow of dietary antigens¹⁴ that could lead to increased IgE sensitization. Other possible reasons for this association could be dysregulation of immune responses or common genetics. However, the pathogenesis of the two diseases are notably different and there is no obvious common pathway.

We could not reproduce the findings of an association of CD and asthma found in earlier studies.^{15–17} It is important to note, however, that in all our studies asthma was self-reported and some misclassification should be expected. Another important aspect is that the CD cases in our study were predominantly undiagnosed before the study and without substantial symptoms, probably related to low grade both of malnutrition and other possible consequences of symptomatic CD.

In the Health2006 study we screened both by using IgA-DGP and IgG-DGP, but after evaluating the screening²¹ we omitted IgA-DGP from the further screenings in the additional four population-based biobank studies to limit the proportion of false-negative

participants. We also included analyses for which the CD antibody positivity was limited to IgA-TTG or IgG-TTG ≥ 10 U/ml because this cutoff was found to have the highest positive predictive value, but no further significant differences were found. The prevalence of CD antibody positivity in these five study populations corresponds well to the pooled global seroprevalence of CD shown by Singh et al., while the CD prevalence in our study was lower than the pooled global prevalence of CD,²⁸ in line with registry studies documenting low prevalence of CD in Denmark.^{29,30}

The population-based design is a strength of our study. However, we cannot rule out that selection bias could influence our results if presence of both undiagnosed CD and allergy biomarkers were associated with participation in the included studies, although in the Health2006 study diagnosed CD recorded in the National Patient Register was not associated with participation.²⁰ Another strength is the variety of information and tests on allergic diseases, including serum-specific IgE positivity, skin prick test reactions and self-reported asthma and hay fever. Including many allergy outcomes may lead to a problem of multiple testing, however. It is thus important to note that when a Bonferroni significance level was applied to adjust for multiple testing, our results did not remain statistically significant. Nevertheless, as this is an explorative study and the Bonferroni method is very conservative, we reported the results with a significance level of 0.05. Furthermore, it is a major strength that we had the possibility to test our hypothesis in the biobank studies from the same region. However, it is a limitation, as mentioned above, that the biobank studies had information only on IgE sensitization to inhalant allergens. Moreover, our study might be limited by the slight uncertainty of the diagnosis of CD in the additional biobank analyses for which clinical diagnosis and biopsies were not possible. Nevertheless, we know from our earlier study²¹ that the positive predictive values of the chosen CD antibody positivity were high.

In conclusion, our study (the Health2006 study) indicated a possible association between CD and IgE sensitization to food and inhalant allergens. However, in additional analyses of other study populations we could not consistently replicate these associations between CD antibody positivity and IgE sensitization. Further research is needed to investigate the relationship between CD and allergic diseases and its possible clinical implications.

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Declaration of conflicting interests

None declared.

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Informed consent

Informed written consent was obtained from all participants prior to participation.

Ethics approval

The study was approved by the local ethics committee (H-3-2011-081, September 6, 2011). Measurements of CD antibodies in stored blood samples were approved by the ethics committee of the Capital Region of Denmark (H-15014502, January 12, 2016). We followed the recommendations of the 1975 Declaration of Helsinki.

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Supplemental Material

The biobank studies

The Inter99 study

The Inter99 study was a population-based intervention study (CT00289237, ClinicalTrials.gov).¹ We used baseline data; 6,784 individuals, aged 30–60 years, participated in a health examination during 1999–2001 (participation rate: 52%). Serum samples were analyzed for total IgE and specific IgE to mite (*Dermatophagoides (D.) pteronyssinus*), grass, cat, and birch by the IMMULITE 2000 Allergy Immunoassay System.² The specific IgE analysis was positive if the measurement was ≥ 0.35 kU/l. IgE sensitization was defined as a positive test for specific IgE against any of the allergens. Asthma was defined as a positive answer to the question: “Has a doctor ever told you that you had asthma?”

The 1936-cohort study

The 1936-cohort was a longitudinal population-based study based on a sample of 1,200 randomly selected individuals (aged 40 years in 1976), a total of 1,052 persons were examined (1976–1977) (participation rate: 88%). In 1995–1996 695 participants (aged 60 years) were re-examined (participation rate: 65%).^{3,4} Measurements of aeroallergen sensitization were performed using the ADVIA Centaur® Allergy Screen assay (Bayer HealthCare Diagnostics division, Tarrytown, N.Y., USA); a multi-allergen assay for the qualitative detection of specific serum IgE antibodies specific to serum levels of 19 common inhalant allergens. IgE sensitization to inhalant allergens was defined as a positive result of the binary assay output.⁴ Asthma and hay fever was defined as positive answers to the questions: “Has a doctor ever told you that you had asthma/allergic hay fever?” included in the questionnaire used in 1995–1996.

The Monica-I study

The Monica-I study was a part of an international World Health Organization (WHO) coordinated study, MONItoring of trends and determinants in CARDiovascular Diseases (MONICA). From 1982–1984, 3,785 (79%) individuals born in 1922, 1932, 1942 or 1952, participated in the Danish Monica-I survey.⁵ For this present study only women were included, because there was no remaining serum in the biobank from male participants in the study. In the Monica-I study, as for the 1936-cohort study, serum specific IgE positivity was tested using the ADVIA Centaur Allergy Screen assay.⁶ Asthma and hay fever was defined as positive answers to the questions: “Has a doctor ever told you that you had asthma/allergic hay fever?” IgE sensitization to inhalant allergens was defined as a positive result of the binary assay output.

The Allergy90-study

The Allergy90-study, was a cross-sectional survey conducted in 1990. A questionnaire was mailed to a random sample of 15–69-year old individuals living in the western part of Copenhagen and 6,998 individuals responded (87.5%). A random group of 793 individuals and a symptom group with reported respiratory symptoms of 788 individuals were selected among the respondents and invited to a health examination, 599 (75.5%) and 635 (80.6%) were examined, respectively (122 individuals were in both groups). Thus, 1,112 individuals (77.5%) were examined in total from February 1990 until January 1991.^{6,7} The Phazet® system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) was used for the skin prick test and the panel comprised birch, grass (timothy), mugwort, horse, cat, dog, two species of house-dust mites (*D. pteronyssinus* and *D. farina*), and two molds (*Cladosporium* and *Alternaria*). A negative control and a positive control (10 mg/mL histamine) were also included. A

positive skin prick test was defined as a mean wheal diameter ≥ 3 mm after subtraction of the negative control. Serum samples were analyzed for specific IgE to birch, grass (timothy), mugwort, dog and cat dander, house dust mites (*D. pteronyssinus* and *D. farina*) and latex by the ADVIA[®] Centaur Specific IgE assay system (Bayer Corporation). The analyses were judged positive if excess of 0.35 kU/L. Total IgE was measured in 1991 using the Pharmacia CAP System (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). IgE sensitization was defined as one or more positive test for specific IgE against the tested allergens and/or one or more positive skin prick test. The methods for allergy testing in Allergy90 have also been described elsewhere.^{6,7}

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