

Association Between IgA Deficiency & Other Autoimmune Conditions: A Population-Based Matched Cohort Study

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Abstract

Purpose To examine autoimmune disorders in patients with IgA deficiency compared with the general population.

Methods Nationwide prospective population-based cohort study. Through six university hospitals in Sweden we identified 2100 individuals with IgA deficiency (IgA levels < .07 g/L) diagnosed between 1980 and 2011. Each patient with IgA deficiency was matched on age, sex, place of residence, and year of diagnosis with up to 10 general population controls ($n=18,653$). Data on nine autoimmune disorders were retrieved from the Swedish National Patient Register (including inpatient and non-primary outpatient care). Autoimmune disorders were defined as having at least two visits listing the relevant international classification of disease (ICD) code as main diagnosis. Prevalences and prevalence ratios (PRs) were calculated.

Results Individuals with IgA deficiency more often had celiac disease (6.7 % vs. 0.19 % in controls) and type 1 diabetes (5.9 % vs. 0.57 %) corresponding to a 35-fold higher PR for celiac disease and 10-fold higher for type 1 diabetes. Also for

the other autoimmune diseases did we see statistically significantly elevated prevalences and PRs (juvenile idiopathic arthritis (0.76 % vs. 0.09 % in controls, PR = 8.9), systemic lupus erythematosus (0.57 % vs. 0.06 %; PR = 8.9), inflammatory bowel disease (3.9 % vs. 0.81 %; PR = 5.0; specifically Crohn's disease (2.4 % vs. 0.42 %; PR = 5.7) and ulcerative colitis (1.7 % vs. 0.46 %; PR = 3.9)), hypothyreosis (0.76 % vs. 0.16 %; PR = 4.6), rheumatoid arthritis (2.2 % vs. 0.50 %; PR = 4.5), and hyperthyreosis (1.7 % vs. 0.43 %; PR = 3.9), but not with myasthenia gravis (0.05 % vs. 0.02 %; PR = 3.0).

Conclusions Individuals with IgA deficiency have a higher prevalence of several other autoimmune disorders.

Keywords Autoimmune · IgA deficiency · immunoglobulin

Abbreviations

PR Prevalence ratio

Introduction

Selective IgA deficiency occurs in an estimated 1:600 individuals in the Western world [1]. Most patients are asymptomatic but some suffer from infections in the gastrointestinal and respiratory tracts, especially when there is a concomitant lack of selected IgG subclasses [2]. We have recently shown that individuals with IgA deficiency suffer an excess mortality in the first 10–15 years after diagnosis [3], but mortality data rarely consider underlying processes and contributing causes such as autoimmune diseases.

IgA deficiency has been linked to a number of autoimmune diseases [4] including Grave's disease [5], systemic

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lupus erythematosus [6, 4], type 1 diabetes [7], celiac disease [8, 9], and rheumatoid arthritis [4]. A number of case-reports of individuals with both inflammatory bowel disease and IgA deficiency have also been published (e.g. [10]). However, with the exception of the studies by Page et al. [7] and Wang et al. [4], studies have been small in size (typically <200 patients), and even the two larger studies failed to identify more than e.g. four [7] and 13 [4] patients respectively with both type 1 diabetes and IgA deficiency.

In this population-based cohort study we examined the risk of nine autoimmune disorders linking data on measured IgA from six university hospitals with the Swedish National Patient Register, and compared patients with IgA deficiency with matched general population controls.

Methods

Through the unique personal identity number [11] assigned to each Swedish resident, we performed a register linkage of patients with IgA deficiency, as well as matched general population controls, to data on visits in inpatient and non-primary outpatient care from the Swedish National Patient Register. Participants were required to be alive and in Sweden on December 31, 2010, as assessed via the Causes of Death Register and emigration/immigration data from Statistics Sweden. IgA patients were required to have been diagnosed prior to December 31, 2010.

Study Participants

Individuals with IgA deficiency were identified from laboratory data between 1980 and 2010 at six university hospitals in Sweden (Karolinska University Hospital in Stockholm, Sahlgrenska University Hospital in Gothenburg, the University hospital in Lund, the University hospital in Linköping, the University hospital in Umeå and the Academic Hospital in Uppsala). These university hospitals handle patients from both urban and rural areas.

IgA Deficiency

We defined IgA deficiency as having a low IgA value < .07 g/L, with normal IgM and IgG levels, in individuals ≥ 4 years of age in accordance with the recommendations of the *International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies* [12]. As selected individuals may still normalize their IgA levels later in childhood [1], we also required that all study participants had a low IgA value

recorded after the age of 10 years. In Sweden, nephelometry is used to measure IgA levels.

Controls

Through the government agency Statistics Sweden, each patient with IgA deficiency was matched on age, sex, place of residence, and year of diagnosis with up to 10 controls from the general population. We did not have data on IgA levels in controls.

Outcome

Data on visits in inpatient and non-primary outpatient care between 2001 and 2010, including dates and diagnoses, were retrieved from the Swedish National Patient Register. We began our study period in 2001 since the National Patient Register includes non-primary outpatient data from this year [13]. Specifically, we investigated presence of at least two separate visits with a main diagnosis of rheumatoid arthritis (ICD-10 M05, M06, M12.3), juvenile idiopathic arthritis (M08), inflammatory bowel disease (Crohn's disease, K50, or ulcerative colitis, K51), type 1 diabetes (E10), systemic lupus erythematosus (SLE; M32), myasthenia gravis (G70), hypothyreosis (E03), hyperthyreosis (E05), and celiac disease (K90).

Statistics

We calculated prevalence, prevalence differences and prevalence ratios (PRs) of the specified autoimmune diseases, comparing the IgA deficiency cohort with the matched general population cohort.

Statistics were calculated using SAS (version 9.4). P -values < .05 were considered statistically significant.

Results

We identified 2533 individuals who were diagnosed with IgA deficiency in 1980–2012 at any of the participating units. We then excluded 10 individuals due to incorrect personal identity numbers. Due to other potential data irregularities, Statistics Sweden (responsible government agency) excluded another seven individuals. An additional six had re-used or changed their personal identity numbers, and three had unclear dates of diagnosis which left us with 2508 IgA deficiency patients. Of these, 13 lacked matched controls leaving 2495 individuals of whom 75 were diagnosed after December 31, 2010, and 320 of the remaining were either dead or had emigrated prior to the same date.

After these exclusions, 2100 IgA deficiency patients remained and 18,653 matched controls (Fig. 1).

Patient Characteristics

Fifty-seven percent of the IgA deficiency patients were women, and the mean age at identification was 35 years while the mean attained age at end of follow-up in 2010 was 44 years (Table I).

Autoimmune Diseases

Statistically significant associations between IgA deficiency and all the selected autoimmune diseases were observed, except for myasthenia gravis (Fig. 2; Table II). In absolute terms, celiac disease, type 1 diabetes, and inflammatory bowel disease were the three most common of the selected autoimmune diseases among patients with IgA deficiency. Register-identified celiac disease was observed in 6.7 % of patients with IgA deficiency compared to 0.19 % in the general population. For type 1 diabetes the prevalence was 5.9 % in patients with IgA deficiency and 0.57 % in the general

population. Corresponding percentages for inflammatory bowel disease were 3.9 % versus 0.81 % (including patients with Crohn's disease, ulcerative colitis, and patients with a mix of these two diagnoses [14]).

Prevalence differences between patients with IgA deficiency and matched general population controls are shown for the selected register-identified autoimmune diseases in Fig. 3, sorted from the largest absolute difference (celiac disease) to the smallest (myasthenia gravis, no statistically significant difference).

Corresponding PRs are shown in Fig. 4, showing that the relative difference was also largest for celiac disease and second largest for type 1 diabetes. Thereafter, juvenile idiopathic arthritis and systemic lupus erythematosus displayed the third largest relative difference PR (Fig. 4).

Discussion

In this population-based cohort study of 2100 individuals with IgA deficiency we found a higher prevalence of eight of the nine investigated autoimmune disorders.

Fig. 1 Flow chart describing the identification of patients with IgA deficiency for this study

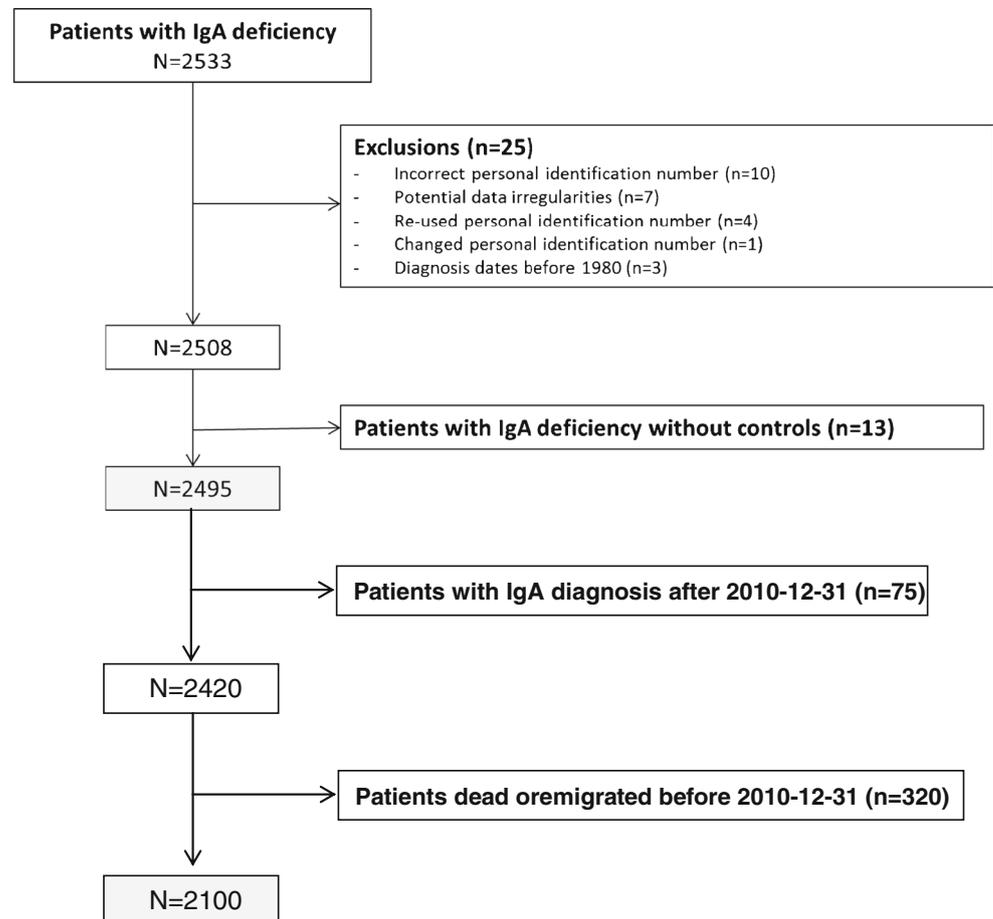


Table I Participant characteristics

	IgA patients n=2100	Matched controls n=18,653
Women, n (%)	1199 (57 %)	10,643 (56 %)
Age at identification, ^a years		
Mean (SD)	35 (19)	35 (18)
Median (25th–75th percentile)	34 (19–49)	33 (18–48)
Age in 2010, mean (SD)	44 (19)	43 (19)
n (%)		
10–39 years	894 (43 %)	8757 (42 %)
40–59 years	673 (32 %)	6591 (31 %)
≥60 years	533 (25 %)	5696 (27 %)
Period of identification		
1980–2004	1254 (60 %)	12,658 (60 %)
2005–2010	846 (40 %)	8386 (40 %)

^a Minimum age by definition: 10 years

Previous Research

Earlier literature has suggested that IgA deficiency is associated with a variety of disorders, especially autoimmune diseases [4]. The highest PR found in this study was seen for celiac disease, consistent with earlier data showing a prevalence of IgG-related celiac antibodies in 5–10 % of patients with IgA deficiency [8, 9]. Almost all celiac individuals are HLA DQ2 positive [15] and HLA typing is in fact used to rule

out celiac disease due to its high negative predictive value [16, 17]. Although the current study did not have access to genetic information, there is evidence [4] that shared genetics contribute to the association with celiac disease. However, detection bias is also likely to explain part of the increased risk as the vast majority of IgA cases are detected as part of an investigation for suspected celiac disease.

Individuals with IgA deficiency had a 10-fold higher prevalence of type 1 diabetes. This is consistent with our recent paper demonstrating IgA deficiency in 1:114 Swedish individuals with type 1 diabetes [4]. In addition, the largest study to date [7] reported a prevalence of IgA deficiency (1:223), markedly exceeding the general population average in England [18] (as did the third largest study [19]). Type 1 diabetes has a markedly high concordance rate in monozygotic twins (around 50 %) indicating that genetic factors play an important role in the disease pathogenesis. Of 11 Swedish individuals with type 1 diabetes in our previous study [4], ten were positive for the HLA-B8, DR3, DQ2 haplotype. Another explanation for the strong association with type 1 diabetes, is that most pediatric departments in Sweden screen their patients with newly onset type 1 diabetes for celiac disease and thereby detecting IgA deficiency [20]. Similar explanations probably underlie the increased risk of Crohn’s disease and ulcerative colitis seen in this study.

We found a 4–5-fold higher prevalence of rheumatoid arthritis in patients with IgA deficiency. This is consistent with the high prevalence of IgA deficiency in rheumatoid arthritis reported by Wang et al. (1:77) [4]. In the current study we

Fig. 2 Prevalence of selected autoimmune disorders in patients with IgA deficiency and matched general population controls. *IBD* inflammatory bowel disease; *RA* Rheumatoid arthritis; *JIA* Juvenile idiopathic arthritis; *SLE* systemic lupus erythematosus; *MG* Myasthenia gravis. The combined percentages for Crohn’s disease and ulcerative colitis exceed that of inflammatory bowel disease since patients may have had both a diagnosis of Crohn’s disease and of ulcerative colitis

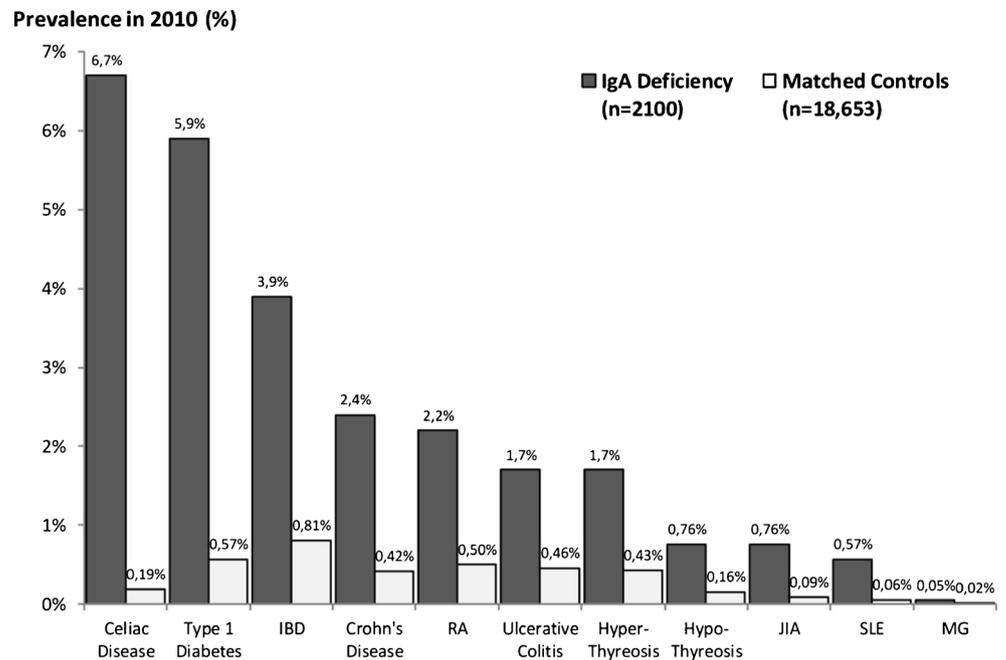
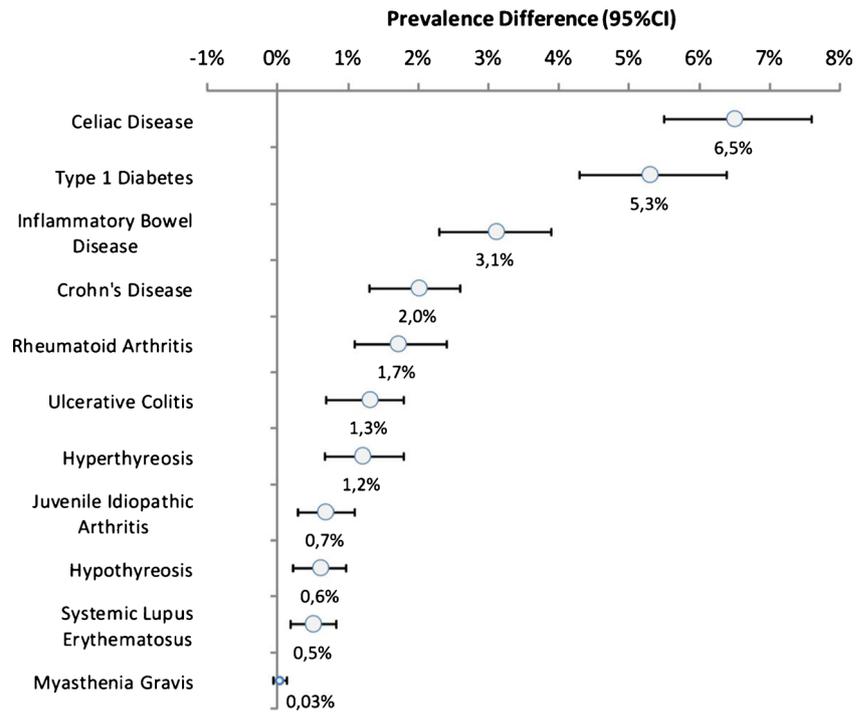


Fig. 3 Forest plot illustrating prevalence differences for selected autoimmune diseases in IgA deficient patients compared to matched general population controls (reference). For instance the difference in celiac disease prevalence (6.5 %) corresponds to a celiac prevalence of 6.7 % in individuals with IgA deficiency vs. 0.19 % in the general population (see Fig. 2)

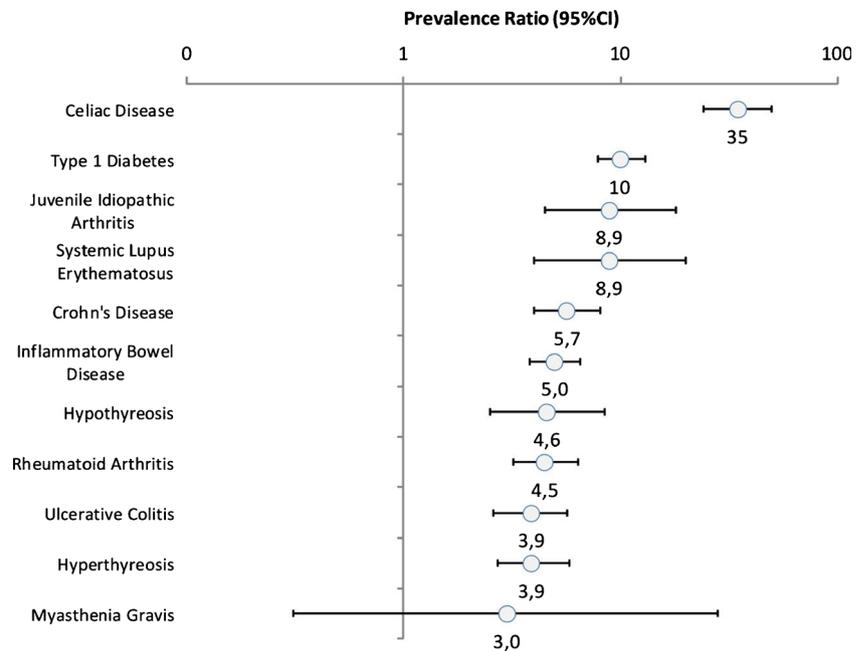


divided rheumatoid arthritis into traditional adult-onset rheumatoid arthritis and juvenile idiopathic arthritis. Also with juvenile idiopathic arthritis did we find a positive association. While rheumatoid arthritis has been especially linked to the HLA-DR4 allele [21], DR3 may be more frequent in subsets

of patients such as those who are anticyclic citrullinated peptide antibody-negative [22].

The increased risk of systemic lupus erythematosus confirms earlier reports of a positive association with IgA deficiency [6, 4]. In a recent Swedish study, all six systemic lupus

Fig. 4 Forest plot illustrating prevalence ratios for selected autoimmune diseases in IgA deficient patients compared to matched general population controls (reference)



erythematosus patients with IgA deficiency carried the HLA-B8, DR3, DQ2 haplotype in a heterozygous form. [4] Of note, Wang et al. described a strong association between systemic lupus erythematosus and IgA deficiency also in the Chinese population, suggesting that this association occurs also in non-Caucasians [4].

Among the autoimmune thyroid disease spectrum, Grave's disease, (characterised by thyrotropin-receptor autoantibodies resulting in hyperthyroidism) is common. Interestingly, of five Swedish patients with IgA deficiency and Grave's disease and available DNA in our previous study, four (80 %) were positive for DR3-DQ2 [5] highlighting that the association between the two diseases may be genetic.

We failed to detect a positive association between IgA deficiency and myasthenia gravis. Myasthenia gravis is characterised by autoantibodies to the acetylcholine receptor. Earlier screening studies have reported contradicting data on myasthenia gravis and IgA deficiency (e.g. Liblau et al. [23] and Wang et al. [4]), and we were unable to support either view. The current study cannot rule out an excess risk due to insufficient statistical power.

We suggest that the association between IgA deficiency and the autoimmune diseases examined in the current study are due to shared genetics, but also other mechanisms such as detection bias is likely to have contributed. Thus, caution should be exercised when interpreting the PRs for celiac disease and type 1 diabetes where a majority is likely to have undergone testing for IgA.

Even though we required an IgA level $< .07$ g/L after the age of 10 years as a prerequisite for the diagnosis of IgA deficiency, most individuals with IgA deficiency will have had the disease since birth. During early years of life, respiratory tract infections are common [24] with substantial comorbidity. Exposure to infections in childhood have been implicated in several of our outcomes [25] (although not attaining statistical significance, infections at time of gluten introduction was associated with a 1.8-fold increased risk of celiac disease in a recent study [26]; and a number of viruses have been linked to type 1 diabetes [27, 28]).

Strengths and Limitations

This paper has several strengths. First we measured actual IgA levels to identify individuals with IgA deficiency. Second the number of patients in our study greatly exceeds that of earlier studies. The greater statistical power in our study is important because it allows us to calculate more precise risk estimates. Still, even our study was of insufficient size to demonstrate a statistically significantly increased risk of myasthenia gravis. Third, we had virtually complete data on both inpatient and non-primary outpatient care over a 10-year period. This was

possible through register linkage using the unique personal identity number [11]. Through this number, most residents can be followed over long periods of time. We ascertained status regarding comorbid autoimmune conditions via the National Patient Register. This register started in 1964, and covers non-primary outpatient data since 2001 [13].

Among the limitations is that IgA levels are often measured as part of a clinical work-up for celiac disease (and indirectly for type 1 diabetes since these patients are routinely screened for celiac disease), or due to signs and symptoms suggestive of immunodeficiencies. Given that celiac disease has been linked to a number of autoimmune conditions (e.g. thyroid disease [29] and type 1 diabetes [30]), it is likely that this comorbidity may have influenced also the risk estimates in IgA deficiency.

Finally some controls may suffer from undiagnosed IgA deficiency, since Sweden has no general screening for IgA deficiency. This is however unlikely to influence our risk estimates more than marginally since IgA deficiency occurs in $<1:200$ individuals in Sweden.

Conclusion

In conclusion this nationwide population-based study found a higher prevalence of several autoimmune disorders in patients with IgA deficiency.

Acknowledgments

Conflict of Interest The authors (JFL, MN, LH) declare that they have no conflicts of interest relevant to the contents of this manuscript.

Details of Contributors Dr Ludvigsson and Dr Neovius had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ludvigsson

Acquisition of data: Hammarström

Drafting of the manuscript: Ludvigsson, Neovius

Critical revision of the manuscript for important intellectual content: Hammarström, Ludvigsson, Neovius

Statistical analysis: Ludvigsson, Neovius

Obtained funding: Hammarström

Study supervision: Ludvigsson, Hammarström

Ethical Approval This project (2011/69-31/3) was approved by the Regional Ethical Review Board in Stockholm on Feb 23, 2011. This was a register-based study and therefore all data were anonymised prior to analysis, and we were not allowed to contact the patients.

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Appendix

Table II Prevalence of autoimmune diseases in patients with diagnosed IgA deficiency and matched general population controls

Outcome	Cases, n (%)		IgA deficiency versus matched controls	
	IgA deficiency (n=2100)	Matched controls (n=18,653)	Prevalence difference (95 % CI)	Prevalence ratio (95 % CI)
Rheumatoid Arthritis (M05, M06, M12.3)	47 (2.2 %)	94 (0.50 %)	1.7 % (1.1–2.4)	4.5 (3.2–6.4)
Juvenile Idiopathic Arthritis (M08)	16 (0.76 %)	16 (0.09 %)	0.68 % (0.30–1.1)	8.9 (4.5–18)
Inflammatory bowel disease (K50, K51)	82 (3.9 %)	151 (0.81 %)	3.1 % (2.3–3.9)	5.0 (3.8–6.5)
Crohn's disease (K50)	50 (2.4 %)	78 (0.42 %)	2.0 % (1.3–2.6)	5.7 (4.0–8.0)
Ulcerative colitis (K51)	36 (1.7 %)	85 (0.46 %)	1.3 % (0.70–1.8)	3.9 (2.6–5.7)
SLE (M32)	12 (0.57 %)	11 (0.06 %)	0.51 % (0.19–0.84)	8.9 (4.0–20)
Myasthenia Gravis (G70)	1 (0.05 %)	3 (0.02 %)	0.03 % (–0.06–0.13)	3.0 (0.31–28)
Hypothyreosis (E03)	16 (0.76 %)	29 (0.16 %)	0.61 % (0.23–0.98)	4.6 (2.5–8.4)
Hyperthyreosis (E05)	35 (1.7 %)	80 (0.43 %)	1.2 % (0.68–1.8)	3.9 (2.7–5.8)
Celiac disease (K90)	141 (6.7 %)	35 (0.19 %)	6.5 % (5.5–7.6)	35 (24–50)
Type 1 Diabetes (E10)	124 (5.9 %)	107 (0.57 %)	5.3 % (4.3–6.4)	10 (7.9–13)

Identified from visits between 2001 and 2010 in inpatient and non-primary outpatient care registered in the National Patient Register. Two visits with the respective diagnoses as main diagnosis was required

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