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ORIGINAL RESEARCH

IgA Deficiency and Risk of Cancer: A Population-Based Matched Cohort Study

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Abstract
Purpose To investigate the risk of cancer in individuals with IgA deficiency compared with the general population.
Methods Prospective nationwide population-based cohort study. We identified 2320 individuals with IgA deficiency (IgA levels < 0.07 g/L) diagnosed between 1980 and 2010 in six Swedish university hospitals. Individuals with IgA deficiency were then matched on age, sex, place of residence, and year of diagnosis with up to 10 general population controls (n=23,130). Through linkage with the Swedish Cancer Register we calculated conditional hazard ratios (HRs) for cancer diagnosed after IgA deficiency diagnosis in patients without a previous cancer diagnosis.
Results During follow-up, 125 individuals with IgA deficiency (61/10,000 person-years) and 984 controls (47/10,000 person-years) developed cancer (HR 1.31; 95%CI = 1.09–1.58). In cause-specific analyses, we found an increased risk of any gastrointestinal cancer (HR = 1.64; 95%CI = 1.07–2.50), but not for lymphoproliferative malignancy (HR 1.68; 95%CI = 0.89–3.19). Relative risk estimates for overall cancer were very high in the first year of follow-up (overall: HR = 2.80; 95%CI = 1.74–4.49), but failed to reach statistical significance thereafter. IgA deficiency diagnosed in childhood (n=487) was not associated with overall cancer (HR = 3.26; 0.88–12.03).
Conclusions Individuals with IgA deficiency are at a moderately increased risk of cancer, with excess risks of gastrointestinal cancer. This excess risk is highest just after diagnosis suggesting a degree of surveillance bias. Children with IgA deficiency were at no increased risk of cancer but the statistical power was limited in subanalyses.

Keywords IgA deficiency · cancer · immunoglobulin · lymphoma · malignancy · tumour

Abbreviations

CD	Celiac disease
GI	Gastrointestinal
HR	Hazard ratio
LPM	Lymphoproliferative malignancy

Introduction

Selective IgA deficiency is the most common immunodeficiency in the Western world and occurs in about 1:600 individuals [1]. In a recent paper we found that individuals with IgA deficiency were at increased risk of death (Hazard ratio [HR] = 1.8; 95 % confidence interval [CI] = 1.6–2.1), with cancer being the most common cause of death in IgA deficiency patients [2].

Earlier research has suggested that patients with IgA deficiency are at an increased risk of especially lymphoma and gastric cancer [3]. Mellemkjaer et al. examined 386 patients with IgA deficiency in Sweden or Denmark and found a 5.4-fold increased relative risk of gastric cancer (95%CI = 0.7–19.5), but no excess risk of overall cancer [3]. However due to

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few cases with cancer, the 95%CI for any cancer ranged from 0.5 to 1.7 and therefore does not rule out even a 70 % increased risk of cancer in IgA deficiency [3].

Furthermore the data by Mellemkjaer et al. suggested a two-fold increased risk of lymphoma (Standardized incidence ratio [SIR] = 2.1), but due to limited power, the excess risk did not attain statistical significance ($p>0.05$). Given the strong association between IgA deficiency and other autoimmune disease [4], and earlier evidence of a link with lymphoma or lymphoproliferative malignancy (LPM) in both rheumatoid arthritis [5] and celiac disease (CD) [6], we hypothesized that IgA deficient individuals may be at an increased risk of any cancer, particularly LPM. Similarly an increased risk of gastrointestinal cancer has been found in CD, albeit only seen in the first year of follow-up [7].

For the reasons above, we found it motivated to carry out a large-scale population based study on cancer in IgA deficient patients. Through the unique personal identity number [8] we were able to link IgA deficiency data in more than 2000 patients to nationwide cancer data from the Swedish Cancer Register [9].

Methods

Study Participants

We identified individuals with IgA deficiency using data between 1980 and 2010 from the laboratories of six Swedish university hospitals (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). The catchment area of these university hospitals includes both cities and rural areas.

IgA Deficiency

IgA deficiency was defined as having a low IgA value <0.07 g/L, with normal IgM and IgG levels, in individuals at least 4 years old. This definition is consistent with recommendations from *the International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies* [10]. Since subsets of individuals may normalize their IgA levels later in childhood, the definition of IgA deficiency in this study was conditional on having a low IgA value recorded at 10 years of age or later. Nephelometry was used to measure IgA levels.

Preliminary data suggest that >95 % of individuals with IgA deficiency in this cohort were diagnosed due to recurrent infections or gastrointestinal symptoms, while a small proportion were diagnosed due to being blood donors (<5 %).

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

We obtained data on cancer between years 1958 and 2010 from the Swedish Cancer Register [9]. The Cancer Register began in 1958. Some 99 % of all cancers are verified morphologically [11], and the sensitivity is almost 100 % [11].

Overall cancer was defined as ICD-7: 140–209; while for LPM (200–204) and gastrointestinal cancer (140–157) which included cancers in the oro-pharynx, oesophagus, stomach, small intestine, large intestine, rectum and anus, liver, and pancreas. In a sensitivity analysis, gastrointestinal cancer was defined as ICD-7 150–157, excluding oral and pharyngeal cancer.

Follow-Up

Follow-up started with first IgA deficiency diagnosis (corresponding date in matched controls), or in case the IgA measurement occurred in early childhood, at the age of 10 years since the diagnosis was conditional on having an IgA value <0.07 g/L after that age for inclusion in this study. Follow-up ended with first cancer, death, emigration, or Dec 31, 2010, whichever occurred first.

Study participants with a diagnosis of cancer at or before the IgA deficiency diagnosis date ($n=97$) (or corresponding date in controls ($n=646$)) were excluded from all analyses. Since follow-up began at the age of 10 years, this means that anyone with a cancer diagnosis by that age was excluded from the study.

Covariates

We obtained data on education from the government agency Statistics Sweden. Education data were categorized (a priori) into three groups: ≤9, 10–12, and >12 years. Through the Swedish National Patient Register [12] we identified individuals with a diagnosis of CD. CD was classified according to relevant international classification of disease codes (ICD-8: 269.0; ICD-9: 579; ICD-10: K90) since this disease is strongly linked to IgA deficiency [4], but also to our cancer outcome measures [6, 7].

Statistics

We first calculated absolute cancer rates in patients with IgA deficiency and their general population controls. This included incidence rates (cancer outcomes per 10,000 person-years) and Kaplan-Meier curves. Through Cox regression we estimated conditional HRs for overall cancer, and specifically for LPM and gastrointestinal cancer since these subtypes of cancer have been implicated in IgA deficiency before. In the stratified Cox regression, each individual with IgA deficiency was only compared with his/her matched controls (stratum-wise comparison). This allowed us to eliminate the influence of matching factors (sex, age, calendar year, and county).

We examined the proportional hazards assumption through introducing an interaction term between follow-up time and IgA deficiency. Finding that the proportional hazard assumption was violated (P=0.014) we present both overall HRs and HRs according to follow up time since IgA deficiency diagnosis (or since the age of 10 years if IgA deficiency was diagnosed before that age) (0–0.9, 1–4.9, and ≥5 years).

Finally we examined overall cancer according to age at IgA deficiency diagnosis (10–39, 40–59, and ≥60 years), calendar year of diagnosis (1980–2004 versus 2005–2010) and sex. We also specifically examined overall cancer risk in individuals diagnosed with IgA deficiency in childhood (10 to <18 years).

Interaction with sex, age and calendar period was tested using interaction terms.

All statistical analyses were performed using SAS (version 9.3) and graphs drawn using Stata (version 11). P-values <0.05 were considered statistically significant.

Results

Patient Characteristics

Of the 2320 individuals with IgA deficiency, 1297 (56 %) were women (Table 1). This is comparable with 12,930 (56 %) of the 23,130 matched controls. The median age at IgA deficiency diagnosis was 35 years (interquartile range: 20–51 years). Education level was similar in IgA deficient individuals and general population controls (Table 1). The median follow-up durations in patients and controls were 7 years (Table 2). More than 100 individuals with IgA deficiency were followed for 25 years or more (Fig. 1).

Table 1 Participant characteristics

	IgAD (n=2320)	General population (n=23,130)
Women, n (%)	1297 (56 %)	12,930 (56 %)
Age at identification, years		
Mean (SD)	37 (19)	37 (19)
Median (25th-75th percentile)	35 (20–51)	35 (20–51)
Minimum-Maximum	10–89	10–89
Age categories, n (%)		
10–39 years	1369 (59 %)	13,556 (59 %)
40–59 years	613 (26 %)	6176 (27 %)
≥60 years	338 (15 %)	3398 (15 %)
Education level, n (%)		
≤9 years	531 (23 %)	5510 (24 %)
10–12 years	926 (40 %)	9031 (39 %)
≥12 years	684 (29 %)	6827 (30 %)
missing	179 (8 %)	1762 (8 %)
Calendar period of diagnosis, n (%)		
1980–2002	1111 (48 %)	–
2003–2010	1209 (52 %)	–
Ever diagnosed with coeliac disease, n (%)	231 (10 %)	96 (0.4 %)

Overall Cancer

During follow-up, 125 individuals with IgA deficiency (61/10,000 person-years) and 984 controls (47/10,000 person-years) developed cancer (HR 1.31; 95%CI = 1.09–1.58; P=0.005). Some 22 individuals with IgA deficiency developed cancer in their first year of follow-up. While the HR for cancer was 1.47 in men and 1.18 in women (Table 2; Fig. 2), this difference was not statistically significant (interaction for sex: P=0.26). The absolute risk of cancer was higher in both males and females with IgA deficiency throughout the follow-up until 25 years after diagnosis. The highest relative risk was however seen in the first year after IgA deficiency diagnosis, and we found no statistically significant excess risk thereafter (Table 2). There were no differences in overall cancer risk according to age at first IgA deficiency diagnosis (interaction for age: P=0.41) (Table 2; Fig. 3). Looking specifically at IgA deficiency diagnosed in childhood (n=487) we found a more than 3-fold risk, but only borderline statistically significant (HR = 3.26; 95%CI = 0.88–12.03). Cancer risk did not differ with calendar period (HR for cancer in 2003–2010: 1.36; 95%CI = 0.96–1.93; Table 2).

When we excluded individuals with a lifetime diagnosis of CD, the HR for any cancer in IgA deficiency was 1.39 (95%CI = 1.15–1.67;p<0.001).

LPM, Gastrointestinal Cancer, and Other Cancer

During follow-up, 11 individuals with IgA deficiency developed *LPM* compared with 67 matched controls. This corresponds to a 68 % increased risk of LPM in IgA deficiency but failed to reach statistical significance (P=0.11) (Table 2). Some 25 individuals with IgA deficiency vs. 158 controls had a later diagnosis of *GI cancer* (HR = 1.64, 95%CI =

Table 2 Malignancies and person-years

	IgAD (n=2320)		General population (n=23,130)	
Person-years				
Median	6.9		7.1	
Sum	20,574		210,808	
Cancer cases	125		984	P=0.34
Gastrointestinal[a]	25 (20 %)		158 (16 %)	
LPM[b]	11 (9 %)		67 (7 %)	
Other	89 (71 %)		759 (77 %)	
Events per 10,000 PYR	61		47	
Conditional[c] hazard ratio		1.31 (1.09–1.58)		
		P=0.005		
Excluding patients with coeliac disease (122 vs 978 events)		1.39 (1.15–1.67)		
		P<0.001		
Excluding first year (103 vs 905 events)		1.17 (0.96–1.44)		
		P=0.12		
By follow-up time				
<1 years		2.80 (1.74–4.49)		
22 vs 79 events		P<0.001		
1–4.9 years		1.22 (0.86–1.74)		
35 vs 291 events		P=0.26		
≥5 years		1.15 (0.90–1.48)		
68 vs 614 events		P=0.27		
By Sex				
Women		1.18 (0.91–1.53)		Interaction
64 vs 555 events		P=0.20		P=0.26
Men		1.47 (1.12–1.92)		
61 vs 429 events		P=0.005		
By age				
Age 10–39 years		1.75 (1.16–2.63)		Interaction
27 vs 156 cases		P=0.01		P=0.41
Age 40–59 years		1.23 (0.91–1.66)		
47 vs 409 cases		P=0.18		
Age ≥60 years		1.36 (1.01–1.81)		
51 vs 419 cases		P=0.04		
By period				
1980–2002		1.32 (1.06–1.63)		Interaction
95 vs 747		P=0.01		P=0.14
2003–2010		1.28 (0.88–1.87)		
30 vs 237		P=0.20		
By cause of cancer				
Gastrointestinal[d]		1.64 (1.07–2.50)		
25 vs 158 events		P=0.02		
Gastrointestinal[e]		1.61 (1.02–2.51)		
22 vs 142		P=0.04		
LPM[f]		1.68 (0.89–3.19)		
11 vs 67 events		P=0.11		
Other		1.21 (0.97–1.50)		
89 vs 759 events		P=0.10		

[a] ICD7 140–157

[b] ICD7 200–204

[c] Cox regressions conditioned on the matching set (consisting of 1 patient with IgAD and up to 10 controls matched by age, sex, place of residence and calendar year of diagnosis)

[d] ICD7 140–157

[e] ICD7 150–157

[f] ICD7 200–204

1.07–2.50) (Table 2). Restricting our outcome GI cancer to the codes 150–157 (GI cancer not including mouth and pharynx), the risk increase remained statistically significant (HR = 1.61; 95%CI = 1.02–2.51; P=0.04).

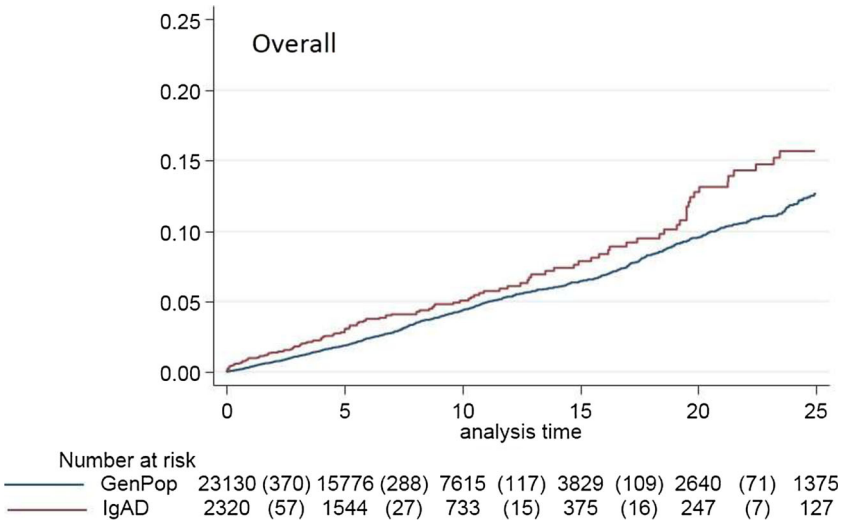

Fig. 1 Malignancies in IgAD (IgA deficiency) patients and matched general population comparators over 25 years of follow-up

The HR for other cancer in IgA deficiency was 1.21 (95%CI = 0.97–1.50) (Table 2).

Consistent with the non-significant HR for overall cancer after the first year of follow-up, so did also specific cancer HRs fail to attain statistical significance when we excluded the first year of follow-up (GI cancer: HR = 1.29, 95%CI = 0.79–2.10, P=0.31; LPM: HR = 0.68, 95%CI = 0.25–1.86, P=0.45; other cancer: HR = 1.19, 95%CI = 0.95–1.50, P=0.13).

Excluding individuals with CD, the risk of GI cancer was still increased (HR = 1.57, 95%CI = 1.00–2.45, P=0.048) while the risk of LPM was not, despite a nearly 2-fold relative risk (HR = 1.82, 95%CI = 0.97–3.46, P=0.064).

Discussion

In this nationwide population-based cohort study, based on more than 2000 individuals with IgA deficiency (<0.07 g/L), we found an increased risk of cancer. This excess risk is highest just after diagnosis and we cannot rule out that surveillance bias contributed to our increased HRs. Children with IgA deficiency were at no increased risk of cancer.

Until now, the largest study examining cancer in IgA deficiency is that by Mellemkjaer et al. [3] who found no increased risk of overall cancer, but did identify excess risks of both LPM and gastric cancer (although none of the two sub-outcome measures attained statistical significance). One explanation for their lack of positive association was the limited statistical power (Mellemkjaer et al. identified <400 patients with IgA deficiency) [3].

This study was six times larger than the Mellemkjaer study [3] and during the more than 20,000 years of follow-up 125 IgA deficient individuals developed cancer. Of note, the 95 % CI was wide in the earlier Swedish-Danish study (95%CI = 0.5–1.7) [3] and did not actually rule out an excess risk of cancer. In fact, the risk estimate (1.31) in the current study is well within the 95 % CI of the earlier Swedish-Danish study.

Although we found a 31 % increased relative risk of cancer in IgA deficiency, this figure should be put in perspective and

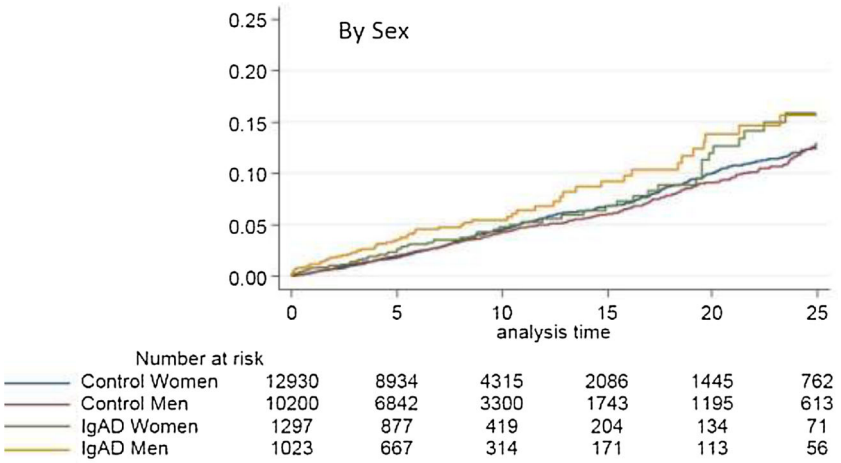

Fig. 2 Malignancies in IgAD (IgA deficiency) patients and matched general population comparators over 25 years of follow-up (by sex)

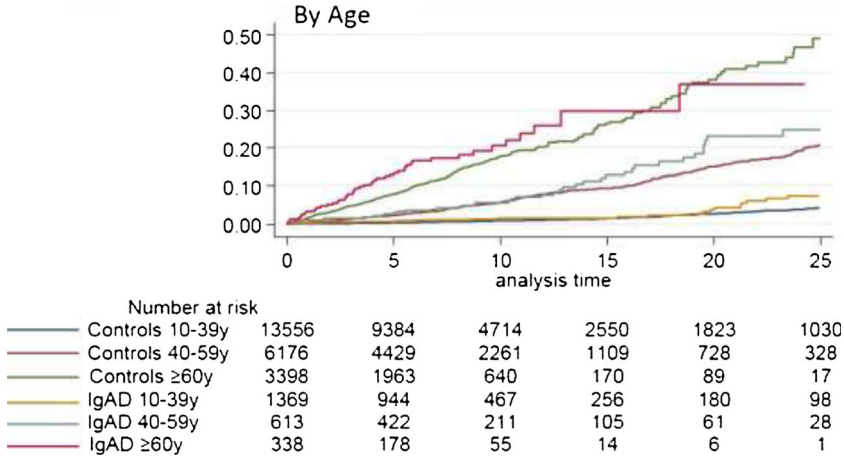

Fig. 3 Malignancies in IgAD (IgA deficiency) patients and matched general population comparators over 25 years of follow-up (by age)

we want to stress that the absolute excess risk of cancer was small. There was one extra case of cancer in the IgA deficiency cohort for every 700 years of follow-up.

While we did not calculate the exact relative risk of any cancer in CD in our earlier paper on biopsy-verified CD [6] (we presented separated HRs for LPM (2.82) and solid cancer (1.11), it can be estimated from the data that the overall cancer risk was around 1.20 in that study [6] (non-LPM is much more common than LPM and therefore influences the overall HR more). Data from the current study suggest that the risk of cancer is similar in IgA deficiency and CD. Many patients with CD undergo investigation for IgA deficiency and we have earlier shown that the two diagnoses are strongly linked [4]. However it is important to note that underlying CD does not explain our findings. Excluding individuals with a lifetime diagnosis of CD did not influence our risk estimate.

We found an increased risk of GI cancer. This is expected given the high excess risk of this kind of cancer in CD. Earlier data from our group have shown that the excess risk of GI cancer in CD is very high in the first year, and then drop drastically to a neutral relative risk at 1 year after celiac diagnosis [7], and we cannot rule out that part of the early risk increase was due to surveillance bias. However it is also possible that decreased levels of HP-specific IgA levels have contributed to the excess risk of GI cancer [13]. Data from Sweden otherwise suggest that the incidence of adenocarcinoma distal to the gastric cardia has decreased while the incidence of cardia cancer seems stable [14].

Although the term selective IgA deficiency should be reserved for individuals with IgA deficiency and no other immunoglobulin deficiency [15], common variable immune deficiency (CVID) may develop over time and may have a common genetic basis [16]. CVID has been linked to both lymphoproliferative [17] and gastric cancer [18, 19]. Hence we cannot rule out that an increased prevalence of CVID among patients with IgA deficiency in our cohort has contributed to the excess risk of cancer.

Strengths/Limitations

This study has some strengths and limitations. For an IgA deficiency diagnosis we requested an IgA level <0.07 g/L after the age of 10 years. In young children, IgA levels may vary and a diagnosis cannot be made before the age of 4 years according to international consensus [10]. We chose to use more stringent diagnostic criteria to increase specificity even further.

The population-based cohort of individuals with IgA deficiency originated from six Swedish university hospitals, and the more than 2300 patients were followed for a median of 7 years. The resulting high statistical power allowed us to examine follow-up specific HRs, showing that the excess risks were highest just after IgA deficiency diagnosis.

The large number of IgA deficient individuals also enabled us to estimate the relative risk of cancer in subgroup. Still we acknowledge the limited power in subanalyses. The 68 % excess risk of LPM was not statistically significant and we cannot rule out that childhood IgA deficiency is also associated with an overall increased cancer risk.

This study took advantage of nationwide Swedish registries. Through the unique personal identity number [8], individuals can be tracked with virtually no loss of follow-up. We used the Swedish national Cancer Register [9] and the Cause of Death Register [20] to ascertain cancer. Both these registers have coverage rates close to 100 %. Through another register (Swedish Education Register) we had access to data on education. This is important since socioeconomic status may influence health care seeking pattern. Education levels were similar in individuals with IgA deficiency and in controls.

IgA deficiency has been linked to a number of immune-mediated diseases, perhaps most prominently with CD [4] which has already been linked to LPM [6] and gastrointestinal cancer [7]. To rule out that the excess risk of these cancer subtypes were due to concomitant CD we carried out stratified analyses excluding all individuals with a lifetime diagnosis of CD. Also in these analyses we did see a positive association

between IgA deficiency, and any cancer, GI cancer and LPM although the HR for LPM was not statistically significant due to insufficient power in that analysis (HR = 1.82).

Nor can we rule out that a number of individuals with undiagnosed IgA deficiency were misclassified as controls. Sweden has no nationwide IgA screening in asymptomatic individuals and hence false-negative cases may occur. This is unlikely to influence the risk estimate as the number of healthy controls vastly outnumbers false-negative IgA deficient individuals.

Conclusion

In conclusion this population-based study found an excess risk of cancer among individuals with IgA deficiency.

Conflict of Interest The authors (JFL, MN, LH, WY) 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, Ye, Hammarström
Critical revision of the manuscript for important intellectual content: Hammarström, Ludvigsson, Neovius, Ye
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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