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The association between asthma and type 1 diabetes - a peadiatric case-cohort study in Finland, years 1981-2009

Johanna Metsälä[a,b*] (ORCID 0000-0003-3806-1020), Annamari Lundqvist[a], Lauri J. Virta[c] (ORCID 0000-0001-6909-3178), Minna Kaila[d] (ORCID 0000-0002-9645-4925), Mika Gissler[e, f] (ORCID 0000-0001-8254-7525), Suvi M. Virtanen[a,b,g,h], Jaakko Nevalainen[b] (ORCID 0000-0001-6295-0245)

[a] Department of Public Health Solutions, National Institute for Health and Welfare, Helsinki, Finland

[b] Health Sciences, Faculty of Social Sciences, University of Tampere, Tampere, Finland

[c] Research Department, Social Insurance Institution, Turku, Finland

[d] Department of Public Health, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[e] Department of Information Services, National Institute for Health and Welfare, Helsinki, Finland

[f] Department of Neurobiology, Care and Society, Division of Family Medicine, Karolinska Institute, Stockholm, Sweden

[g] Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital, Tampere, Finland

[h] The Science Center of Pirkanmaa Hospital District, Tampere, Finland

Corresponding author: Johanna Metsälä

National Institute for Health and Welfare

Department of Public Health Solutions, Nutrition Unit

P.O. Box 30, FI-00271 Helsinki

email: johanna.metsala@thl.fi, tel: +358 40 507 8868, fax: +358 29 524 6981

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Abstract

Background: The association between asthma and type 1 diabetes, two chronic, immune-mediated diseases, has been of longstanding interest, but the evidence is still conflicting. We examined this association in a large, nationwide case-cohort study among Finnish children using a novel statistical approach.

Methods: Among the initial cohort of all children born between 1.1.1981–31.12.2008, those who were diagnosed with asthma (*n* = 81 473) or type 1 diabetes (*n* = 9541) up to age 16 years by the end of 2009 were identified from the Central Drug Register maintained by the Social Insurance Institution of Finland. A 10% random sample from each initial birth year cohort was selected as a reference cohort (*n* = 171 138). The association between asthma and type 1 diabetes was studied using a multistate modeling approach to estimate transition rates between healthy and disease states since birth. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to represent the change in the transition rate between the disease states.

Results: After adjusting for sex and birth decade, prior diagnosis of asthma increased the risk of subsequent type 1 diabetes by 41% (95% CI: 1.28, 1.54), while prior diagnosis of type 1 diabetes decreased the risk of subsequent asthma by 18% (95% CI: 0.69, 0.98).

Conclusions: The findings of the present study imply that the association between the diseases is more complex than previously thought, and its direction depends on the sequential appearance of the diseases.

Key words: asthma, type 1 diabetes, children, coexistence, cohort, registers

MeSH terms: Asthma; Diabetes Mellitus, Type 1; Child; Association; Cohort Studies; Registries

Key messages:

- This study used nationwide registers to design the case-cohort setting and a multistate modelling approach to analyze the association between asthma and type 1 diabetes in childhood and adolescence.
- Children with prior diagnosed asthma were at increased risk of subsequent type 1 diabetes.
- Children with prior diagnosed type 1 diabetes were at decreased risk of subsequent asthma.
- These findings were not explained by age at diagnosis, birth decade, sex, maternal asthma/diabetes or birth-related factors
- The findings imply that the association between asthma and type 1 diabetes is complex, and the direction of the association may depend on which disease appears first.

Asthma is among the leading chronic diseases in children in many developed countries, and incidence of childhood type 1 diabetes has increased in several parts of the world. (1, 2) The pathogenesis of type 1 diabetes has been related to T-cell-mediated, primarily T helper type 1 (Th1), autoimmune responses, whereas Th2-type responses are considered to play a major role in the pathogenesis of asthma and allergic diseases. The paradigm of reciprocal counter-regulation of Th1 and Th2 cells predicts that asthma and type 1 diabetes would occur in mutually exclusive populations of individuals, and several studies have investigated an inverse association between asthma and type 1 diabetes.

Pooled results from a meta-analysis published in 2003 supports the inverse association (OR= 0.82; 95% CI: 0.68, 0.99) (3), although findings from individual studies included in the meta-analysis and published thereafter are inconsistent; inverse, direct and null associations have all been reported. (3, 4) These inconsistencies imply that the early version of the so-called Th1/Th2 paradigm may be an oversimplification (4), but also methodological issues may have contributed to the contradictory findings. Thus, the association between asthma and type 1 diabetes needs clarification with methods allowing assessment of the potential complexity of the association.

The aim of the present study was to clarify the association between asthma and type 1 diabetes in childhood and adolescence in a large, nationwide case-cohort study using a novel approach. With multistate modeling, we estimated transition rates between healthy and disease states, asthma and type 1 diabetes, since birth.

METHODS

Data sources

Data for the present case-cohort study were obtained from nationwide Finnish health registers, which were merged by deterministic linkage with unique personal identity codes. (5,

6) Information on asthma, type 1 diabetes, and the reference cohort as well as anti-asthmatic drug and insulin purchases was obtained from the Central Drug Register maintained by the Social Insurance Institution (SII). Since 1964, patients with certain severe and chronic diseases, such as asthma or type 1 diabetes, have been entitled to special reimbursements for the cost of drugs needed in the treatment of the disease, regardless of their socioeconomic status, residence or place of treatment. To be eligible for this special reimbursement, the diagnosis has to be verified by a specialist in pediatrics and/or a respective field, and a certificate of the diagnosis is required. Further, in the case of childhood asthma, a long-lasting drug treatment is required. For example, the use of antiasthmatic drugs during a few months in the pollen season does not fulfill this requirement. Finally, a clinical specialist at the SII reviews all special reimbursement applications and certificates. The administrative process for decision-making by the SII takes only a couple of weeks. Thus, the date of the entitlement decision obtained from the Central Drug Register's Special Reimbursement database was used as a proxy for the date of diagnosis.

To further verify the case definitions, we used information on antiasthmatic drug and insulin purchases obtained from the Central Drug Register's Purchase database. In Finland, all these drugs are prescription-only medicines, and since 1994 they have been reimbursed by the National Health Insurance scheme, and recoded to the Central Drug Register. However, drugs used in hospital settings are not recoded to this register. Information included in the study was the date of purchase and the Anatomical Therapeutic Chemical (ATC) code of the drug.

Information on potential confounding factors, like maternal age at delivery, socioeconomic status (based on occupation or the highest education level if the occupation was missing, and categorized as "upper white-collar workers", "lower white-collar workers", "blue-collar workers" and "others" including farmers, entrepreneurs, retired, unemployed, students and housewives), smoking during pregnancy (no/yes), number of previous deliveries (0, 1, ≥2)

and mode of delivery (vaginal delivery/caesarean section) was derived from the Finnish Medical Birth Register, which has been collected since 1987 and is currently maintained by the National Institute for Health and Welfare. Information on maternal socioeconomic status has been available since 1991. Information on maternal asthma and diabetes was based on special reimbursements granted from the Central Drug Register. Information on the child's sex and year of birth, further categorized as birth decade (1980s, 1990s, 2000s), was available in both registers.

Study population

From the initial cohort of all children born between January 1, 1981, to December 31, 2008, we identified all those who had received a special reimbursement for the costs of insulin or antiasthmatic drug purchases before age 16 years by the end of year 2009 as type 1 diabetes (n = 9541) and asthma cases (n = 81 473), respectively. A 10% random sample from each initial birth year cohort (1981–2008) was selected as a reference cohort (n = 171 138).

As the above definitions could be open to false positive cases, we also conducted a sensitivity analysis applying a stricter case definition. In type 1 diabetes, cases who had no insulin (ATC code A10A) purchases after the diagnosis were excluded (n = 64, 0.7%). For a strict asthma definition, cases who had a short duration of the special reimbursement (less than 6 months) and/or no antiasthmatic drug purchases (inhaled corticosteroids, ATC code R03BA; a fixed combination containing inhaled corticosteroids and either salmeterol or formoterol, codes R03AK06 and R03AK06; and montelukast, code R03DC03) after the diagnosis were excluded (n = 5197, 6.4%).

Statistical analysis

The data were analyzed with a multistate modeling approach with transition times based on the dates of diagnosis obtained from the Central Drug Register. The states were defined as "healthy" (i.e. no type 1 diabetes or asthma), "asthma only", "type 1 diabetes only" and "both asthma and type 1 diabetes". We modeled the transition rates between the states by a piecewise exponential model for each transition with knots placed at 4, 8 and 12 years of age allowing heterogeneity in the incidence of asthma and diabetes at different ages. The results were not sensitive to the particular choice of knot positions. The piecewise exponential model was chosen because the assumption of constant transition rates for such a long follow-up period was considered unrealistic, and it is a conventional and incorporated feature in available multistate models software. (7) Birth was taken as the time of origin without time reset at a transition. The time scale was from birth up to age 16 years, death, or December 31, 2009, whichever came first.

Four transitions between states were therefore possible over the follow-up time for each child. Our initial model included no covariates, and we estimated four piecewise transition rates (rate 0–3.9, 4–7.9, 8–11.9 and 12–16 years) for the four transitions. Based on the raw transition rates, we noted that the rates for a disease were modified similarly at different ages by the appearance of the other disease, and we estimated a single hazard ratio to represent that average change. Another hazard ratio parameter was estimated to represent the change in the reverse time-order of the diseases. After this simplification of the model, we investigated the effect of potential confounders known to be associated with the incidences of asthma and type 1 diabetes (maternal age, socioeconomic status, smoking, previous deliveries, mode of delivery, asthma and diabetes, as well as the child's sex and birth decade). Among them, sex and birth decade appeared to be the most important confounders. Thus, they were included in the final model as main effects, assuming proportionality of rates, as we did not detect

evidence of second-order interactions between age group, sex and birth decade. The final multistate model is illustrated in Figure 1. The transition rates of the final model were converted into transition-, sex- and birth decade-specific incidences to aid their interpretation and to allow comparisons with previous evidence.

The model was fitted with maximum likelihood, and the standard errors of the parameter estimates were derived from the observed information matrix. The case-cohort setting of the data was taken into account by acknowledging the sampling probabilities in the derivation of the likelihood expression via Bayesian inversion, as in the approach of Chen et al. (8) The model was fitted with the NLMIXED procedure in SAS, version 9.4 (SAS Institute, Cary, NC).

We conducted a series of analyses to examine sensitivity 1) to the case definition criteria by using a strict definition; 2) to different approaches of handling missing values in the confounding factors: missing values treated as a category of their own, excluding children with missing values in at least one of the confounding variables, and multiple imputation; and 3) of associations and the effect of the order and age at diagnosis of the diseases using more conventional but crude methods of analysis (9). As the results using a strict case definition did not change substantially, only the results using the main case definition are presented.

Ethics committee approval

This study was approved by the National Data Protection Authority, the institutions keeping the registers and the Institutional Review Board of the National Institute for Health and Welfare.

RESULTS

We identified 80 871 children with only asthma and 8939 children with only type 1 diabetes and 602 with both diseases. Median follow-up time was 15.5 years, and 90% of the children were followed-up for at least 3.8 years. Of the children with both diseases, 75.7% had asthma diagnosed before type 1 diabetes, 20.9% had type 1 diabetes diagnosed before asthma, and 3.3% had both diseases diagnosed within the same month. Median age at diagnosis was 4.6 years (interquartile range, IQR 5.9) in asthma and 7.5 years (IQR 6.7) in type 1 diabetes. The proportion of boys was 61.9% in children with only asthma, 54.4% in children with only type 1 diabetes and 62.5% in children with both asthma and type 1 diabetes, as well as 51.2% in the reference cohort (Table 1). Maternal diabetes and asthma were more common in cases of both diseases compared to the reference cohort. The frequency of children with asthma and type 1 diabetes increased with age and from the 1980s, although in asthma the striking increase seems to level off in children born in the 2000s (Figure 2). Annual, multistate model-based and sex-, age group- and birth decade-specific incidences of type 1 diabetes and asthma are presented in Supplementary Tables 1 and 2, available as Supplementary data at *IJE* online.

The observed transitions from healthy state (no asthma or type 1 diabetes) to disease state (asthma or type 1 diabetes) and between disease states (from asthma to type 1 diabetes and vice versa) presented in Table 2 show that type 1 diabetes developed more frequently in children with asthma (0.6%) than in healthy children (0.4%), and asthma developed less frequently in children with type 1 diabetes (1.7%) than in healthy children (2.7%). This phenomenon remained similar when children with diseases diagnosed before age 4 years were excluded: type 1 diabetes developed more frequently between ages 8 to 16 years in children with asthma diagnosed between ages 4 to 7.9 years (0.4%) than in children with good health for up to 8 years (0.3%). Further, asthma developed less frequently between ages 8 to 16

years in children with type 1 diabetes diagnosed between ages 4 to 7.9 years (1.0%) than in with good health for up to 8 years (1.3%).

The multistate model gave similar results: children with asthma were at increased risk of subsequent type 1 diabetes (unadjusted HR= 1.45, 95% CI: 1.32, 1.60), while children with type 1 diabetes were at decreased risk of subsequent asthma (unadjusted HR= 0.70, 95% CI: 0.59, 0.84) compared with children without asthma or type 1 diabetes, respectively. Results from the final multistate model are presented in Figure 3. Adjustment for sex and birth decade diminished the crude estimates slightly, but further adjustment for other potential confounding factors did not change the estimates substantially (data not shown). Boys had a higher risk of both asthma and type 1 diabetes compared with girls, and children born in the 1990s and 2000s had a higher risk of both asthma and type 1 diabetes compared with children born in the 1980s (Figure 3).

The results were not sensitive to the particular missing data approach used (Supplementary Table 3). In addition, the results from the sensitivity analyses underline the importance of careful recognition of the sequential ordering and the age on the association between asthma and type 1 diabetes, as the multistate model does (Supplementary Table 4).

DISCUSSION

In the present study, children with asthma had an increased risk of subsequent type 1 diabetes, but children with type 1 diabetes had a decreased risk of subsequent asthma after adjustment for putative confounding factors. Thus, the presence of asthma or type 1 diabetes modified the incidence of type 1 diabetes and asthma respectively, compared with the incidence in children without these diseases.

Previous studies assessing the association between asthma and type 1 diabetes have reported conflicting findings. While a meta-analysis summarizing studies published in March

2003 reported a slight inverse association between asthma and type 1 diabetes, (3) both direct and null associations have been reported as well. (4, 10–12) Many of these previous studies were of case-control design with relatively small sample sizes, and type 1 diabetes was mainly used as the index disease. Further, whether an asthma diagnosis or symptoms were present during the time before type 1 diabetes diagnosis was not clear in all studies. Only a few studies have investigated an association between asthma and type 1 diabetes in a prospective cohort design with inconsistent findings. (11–14)

Our finding that type 1 diabetes develops more often in asthmatic children compared with non-asthmatic children is in line with two other cohort studies, (11, 14) and a birth cohort study where early life wheezing (associated with asthma development) increased the risk of appearance of autoantibodies (associated with type 1 diabetes development). (10) However, our finding that asthma develops less often in type 1 diabetic children compared with healthy children is in contrast to the findings by Hsiao et al. (12) and Kero et al. (13) This discrepancy may be due to methodological differences between the studies. Kero et al. (13) did not distinguish the sequential appearance of the diseases, and they followed up the children only until 7 years of age. Findings from the study by Hsiao et al. (12) may be subject to surveillance bias, which may occur when regular contacts or screenings after the diagnosis of a chronic disease increase the likelihood of subsequent detection of another disease. In the study by Hsiao et al. (12) the risk of asthma was increased in those type 1 diabetics who were more than two times hospitalized or visited the emergency room because of type 1 diabetes, while no association was observed in those type 1 diabetics with two or less hospitalizations or emergency room visits compared with control children. As far as we know, no previous studies exploring the sequential appearance of these diseases similarly to the present study have been published.

Major strengths of the present study were the size of the study, the particularly large number of cases and prospectively collected information. The latter allowed us to establish the temporal relationship of the diagnoses and minimize recall bias. However, we were not able to verify the initial starting point of the disease process, which in both asthma and type 1 diabetes may be several months before the actual date of diagnosis. Further, challenges in the diagnosis of asthma in small children increase the possibility that transient early wheezers were included as asthma cases in the present study. (15) However, as the results did not change substantially when analysis was restricted to children receiving the asthma diagnosis after 4 years of age, or when a more strict case definition was applied, this misclassification is probably not a major source of bias in our study. Further, as information on the exact diagnosis codes was not complete for the whole study period, we cannot exclude the possibility that some cases of type 2 diabetes may have been falsely classified as type 1 diabetics in our data. Although we were able to take into account several confounders, information on some important environmental factors affecting the development of both asthma and type 1 diabetes, like infections and nutritional factors, (16, 17) was not available. Thus, residual confounding cannot be excluded. Our observation of an increased incidence of type 1 diabetes after asthma diagnosis may be subject to surveillance bias, but as an opposite was observed when the diseases occurred vice versa, we believe that the surveillance bias does not fully explain our results. Further, the higher incidence of type 1 diabetes and lower asthma prevalence in Finland compared to many other countries, and the fact that the study includes asthmatics needing long-lasting drug treatment limits the generalizability of our results.

The results of the present study support the view that the Th1/Th2 paradigm is likely an oversimplification. In fact, far more complex immunological mechanisms, which explain that asthma and type 1 diabetes may coexist, have been described: Th1-inflammation may

suppress the development of atopy, and atopy may suppress the severity but not necessarily the onset of autoimmunity (4) However, our findings do not fully support this immunological model. This inconsistency may be due to the fact that asthma is not a single disease, but a heterogeneous syndrome with different endotypes that do not all have Th2-dominant mechanisms. (18)

The medication used in the treatment of asthma, mainly inhaled corticosteroids, may potentially underpin the observed association. Although, the use of systemic corticosteroids is known to induce insulin resistance and hyperglycemia, the role of inhaled corticosteroids in glucose metabolism is still debated. (19) Thus, the role of corticosteroids in the development of type 1 diabetes is potential, but uncertain. As far as we know, no human studies linking insulin used in the treatment of type 1 diabetes and the development of asthma have been published. Another explanation for the fewer asthma diagnoses after type 1 diabetes could be that parents may not recognize their child's asthma-like symptoms or that the symptoms are considered less relevant due to the burden of caring for a child with type 1 diabetes.

The present findings indicate that the association between type 1 diabetes and asthma is complex, and further studies that also take into account the sequential appearance of the diseases in prospective study settings and in different study populations are needed to confirm or refute the findings. Further, the role of antiasthmatic drugs, particularly corticosteroids, in the development of type 1 diabetes should be explored. In addition, studies assessing other allergic diseases, biomarkers of atopy and Th-balance may further elucidate the coexistence of allergic diseases and type 1 diabetes.

In conclusion, we observed that children with asthma had an increased risk of subsequent type 1 diabetes, but children with type 1 diabetes had a decreased risk of subsequent asthma. Before any clinical implications can be drawn from these findings, further studies in different populations and on potential biological mechanisms are warranted.

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Conflict of interest: All authors declare no competing interests.

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Table 1. Characteristics in children with asthma, type 1 diabetes, and the reference cohort children

Characteristic	Children with only asthma	Children with only type 1 diabetes	Children with both asthma and type 1 diabetes	Reference cohort
N of subjects	80 871	8 939	602	171 138
Male sex (%)	61.9	53.9	62.5	51.2
Child's birth decade (%)				
1980s	30.3	38.9	27.7	33.3
1990s	50.2	47.1	61.3	36.5
2000s	19.6	14.1	11.0	30.3
Maternal diabetes (%)	2.2	4.9	4.2	1.8
Maternal asthma (%)	14.4	6.0	15.0	5.4
Maternal age at delivery[a] (mean, years)	28.9	29.3	29.3	29.3
Maternal socioeconomic status at delivery (%)				
Upper white-collar worker	9.7	9.0	11.3	12.0

Lower white-collar worker	29.6	25.9	34.7	35.1
Blue-collar worker	10.7	9.3	9.6	12.2
Others	11.3	8.9	10.3	12.0
Missing information	38.8	47.0	34.1	28.7

Table 1 continues...

Characteristic	Children with only asthma	Children with only type 1 diabetes	Children with both asthma and type 1 diabetes	Reference cohort
Maternal smoking during pregnancy (%)				
No	67.5	66.0	72.4	65.8
Yes	11.4	6.7	8.5	9.2
Missing information	21.1	27.3	19.1	25.0
Number of maternal previous deliveries (%)				
0	33.2	30.6	31.4	31.3
1	27.4	26.1	31.9	26.0
≥2	20.0	17.7	18.9	19.3
Missing information	19.5	25.6	17.8	23.4
Mode of delivery (%)				
Vaginal delivery	65.3	61.7	64.0	64.5
Caesarean section	15.5	12.9	18.1	12.3
Missing information	19.3	25.5	17.9	23.2

[a] The Medical Birth Register data including maternal age at delivery, smoking during pregnancy, number of previous deliveries, and mode of delivery is from 1987 onwards (maternal socioeconomic status from 1991 onwards)

Table 2. Observed transitions from disease/healthy states by 4 years of age to disease state at the age of 4 to 16 years.

Prior disease state by age 4 years	Subsequent disease state at age 4 to 16 years		
	Disease state	*n*	(%)
Asthma (*n* = 36 162)	Type 1 diabetes	219	(0.6)
	No change	35 943	(99.4)
Healthy (*n* = 1 672 974[a])	Type 1 diabetes	6807	(0.4)
	Asthma	44 928	(2.7)
	Asthma and type 1 diabetes	271	(<0.1)
	No change	1 620 968	(96.9)
Type 1 diabetes (*n* = 2168)	Asthma	36	(1.7)
	No change	2132	(98.3)
Both asthma and type 1 diabetes (*n* = 76)	No change	76	(100.0)

[a] As the size of the initial cohort was not available, but the subcohort sampling fraction was 10%, the denominator in status "Healthy" was estimated by multiplying the subcohort size by 10.

Supplementary Table 1. Age-, birth decade- and sex-specific, multistate model-based annual incidences of type 1 diabetes according to prior asthma diagnosis

Age Group, Birth Decade	Annual Incidence per 100 000 children (95% CI)							
	Boys				Girls			
	No Prior Asthma		Prior Asthma		No Prior Asthma		Prior Asthma	
0–3.9 years								
1980s	29.7	(28.0–31.4)	41.7	(37.2–46.3)	26.	(24.6–27.7)	36.8	(32.6–40.9)
1990s	38.6	(36.5–40.6)	54.2	(48.5–59.9)	34.	(32.1–35.8)	47.7	(42.6–52.9)
2000s	40.8	(38.2–43.4)	57.3	(51.0–63.7)	35.	(33.6–38.2)	50.5	(44.8–56.2)
4–7.9 years								
1980s	44.8	(42.5–47.1)	62.9	(56.4–69.5)	39.	(37.4–41.6)	55.5	(49.5–61.4)
1990s	58.1	(55.4–60.9)	81.7	(73.6–89.8)	51.	(48.7–53.7)	72.0	(64.6–79.3)
2000s	61.5	(57.5–65.6)	86.4	(77.0–95.9)	54.	(50.6–57.8)	76.2	(67.6–84.7)
8–11.9								
1980s	51.3	(48.7–53.8)	72.0	(64.7–79.4)	45.	(42.8–47.5)	63.5	(56.8–70.1)
1990s	66.5	(63.4–69.7)	93.5	(84.4–102.6)	58.	(55.8–61.5)	82.4	(74.1–90.6)
2000s	- [a]	-	-	-	-	-	-	-
12–16								
1980s	42.4	(40.1–44.8)	59.6	(53.4–65.8)	37.	(35.2–39.6)	52.6	(46.9–58.2)
1990s	55.1	(51.9–58.3)	77.4	(69.5–85.3)	48.	(45.7–51.4)	68.2	(61.1–75.3)
2000s	- [a]	-	-	-	-	-	-	-

[a] Annual incidences for age groups 8–11.9 and 12 –16 years for children born in 2000s could not be estimated due to the end of follow-up by December 31, 2009.

Supplementary Table 2. Age-, birth decade- and sex-specific, multistate model-based annual incidences of asthma according to prior type 1 diabetes diagnosis

	Annual Incidence per 100 000 children (95% CI)							
	Boys				Girls			
Age Group,	No Prior Type 1 Diabetes		Prior Type 1 Diabetes		No Prior Type 1 Diabetes		Prior Type 1 Diabetes	
0–3.9 years								
1980s	485.	(476.3–494.5)	397.	(326.7–468.0)	306.	(300.6–312.9)	251.	(206.5–295.6)
1990s	808.	(794.6–821.4)	661.	(544.4–778.9)	510.	(501.8–520.1)	418.	(344.3–492.2)
2000s	749.	(734.6–764.0)	613.	(504.5–722.5)	473.	(463.7–483.8)	387.	(319.0–456.6)
4–7.9 years								
1980s	390.	(382.3–397.6)	319.	(262.5–375.9)	246.	(241.2–251.6)	201.	(165.9–237.4)
1990s	649.	(637.9–660.8)	531.	(437.5–625.8)	410.	(402.7–418.2)	336.	(276.6–395.4)
2000s	602.	(588.5–615.7)	492.	(405.3–580.6)	380.	(371.5–389.6)	311.	(256.2–366.8)
8–11.9								
1980s	297.	(290.7–303.6)	243.	(200.0–286.5)	187.	(183.4–192.0)	153.	(126.4–180.9)
1990s	494.	(485.0–504.9)	405.	(333.3–477.0)	312.	(306.1–319.4)	256.	(210.7–301.3)
2000s	- [a]	-	-	-	-	-	-	-
12–16 years								
1980s	171.	(166.2–175.9)	140.	(115.0–165.0)	108.	(104.9–111.2)	88.4	(72.7–104.2)
1990s	285.	(277.0–293.1)	233.	(191.7–274.9)	180.	(174.9–185.3)	147.	(121.2–173.6)
2000s	- [a]	-	-	-	-	-	-	-

[a] Annual incidences for age groups 8–11.9 and 12 –16 years for children born in 2000s could not be estimated due to the end of follow-up by December 31, 2009.

Supplementary Table 3. Results from sensitivity analyses using different approaches in handling missing data in the confounding variables

Outcome disease (Exposure disease)	**Primary model reported in the paper**	**Models that account for maternal sociodemographic and perinatal confounders** [a]		
		Missing values as an own category	Children with missing data excluded	Multiple imputation[b]
	HR	HR	HR	HR
Type 1 diabetes (Asthma)	1.41	1.37	1.45	1.37
Asthma (Type 1 diabetes)	0.82	0.86	0.90	0.82

[a] variables obtained from the Medical Birth Register

[b] an analysis that was based on a multiple imputation scheme of fully conditional specification including all relevant variables, and implemented in SAS PROC MI and MIANALYZE

Supplementary Table 4. The associations between asthma and type 1 diabetes - comparison of unadjusted hazard ratios from the multistate and the crude case-cohort Cox proportional hazards regression models

Outcome disease	**Model**[a]				
(Exposure disease)	**Multistate**[b]	**Cox 3**[c]	**Cox 2**[d]	**Cox 1**[e]	**Cox 0**[f]
	unadjusted HR (95% CI)	unadjusted HR (95% CI)	unadjusted HR (95% CI)	unadjusted HR (95% CI)	unadjusted HR (95% CI)
Type 1 diabetes (Asthma)	1.45 (1.32-1.60)	1.50 (1.29-1.74)	1.33 (1.16-1.52)	0.87 (0.79-0.95)	1.16 (1.07-1.27)
Asthma (Type 1 diabetes)	0.70 (0.59-0.84)	0.72 (0.57-0.92)	0.81 (0.72-0.92)	0.24 (0.20-0.28)	1.11 (1.00-1.23)

[a] The most appropriate models to the left, crudeness increases to the right

[b] Unadjusted multistate model reported in the paper. The follow-up from birth up to 31 Dec 2008 is decomposed into distinct time intervals carefully defined by the observed state transitions, and age is incorporated by the piecewise exponential model.

[c] A Cox model where both the order of the diagnoses and age were crudely taken into account as well as the case-cohort design and the stratified subcohort sampling (Cox 3: follow-up time starting from age of 3 years, exposure disease occurring before age of 3 years no vs. yes). We used the SAS macros written by and described in Langholz and Jiao. Computational methods for case-cohort studies. Comput Stat & Data Anal 2007;51:3737-48.

[d] A Cox model where both the order of the diagnoses and age were crudely taken into account using different cut off point than in Cox 3 (Cox 2: follow-up time starting from age of 6 years, exposure disease occurring before age of 6 years no vs. yes).

[e] A Cox model where the sequential order of the diagnoses was taken crudely into account, but not the age (Cox 1: follow-up time since birth, exposure disease no vs. yes occurring prior to the index disease)

[f] A Cox model where neither the sequential order of the disease diagnoses nor the age were taken into account in any way (Cox 0: follow-up time since birth, exposure disease no vs. yes (occurring at any time).

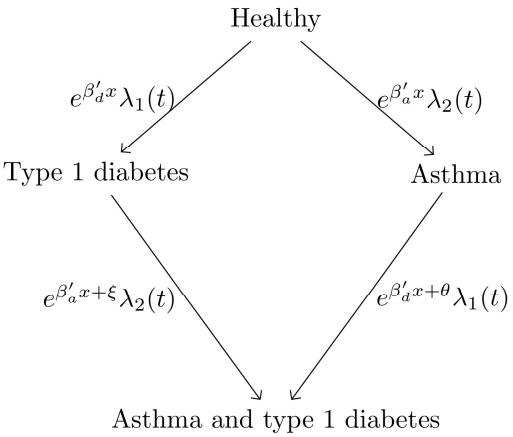

Figure 1. The final multistate transition model, where $\lambda_1(t)$ and $\lambda_2(t)$ are the piecewise constant baseline transition rates, β_d and β_a consist of the log hazard ratios for factors sex and birth decade contained in x, both for type 1 diabetes and asthma, respectively. Parameters ξ and θ represent the change in the transition rate (log hazard ratios) due to prior appearance of the other disease.

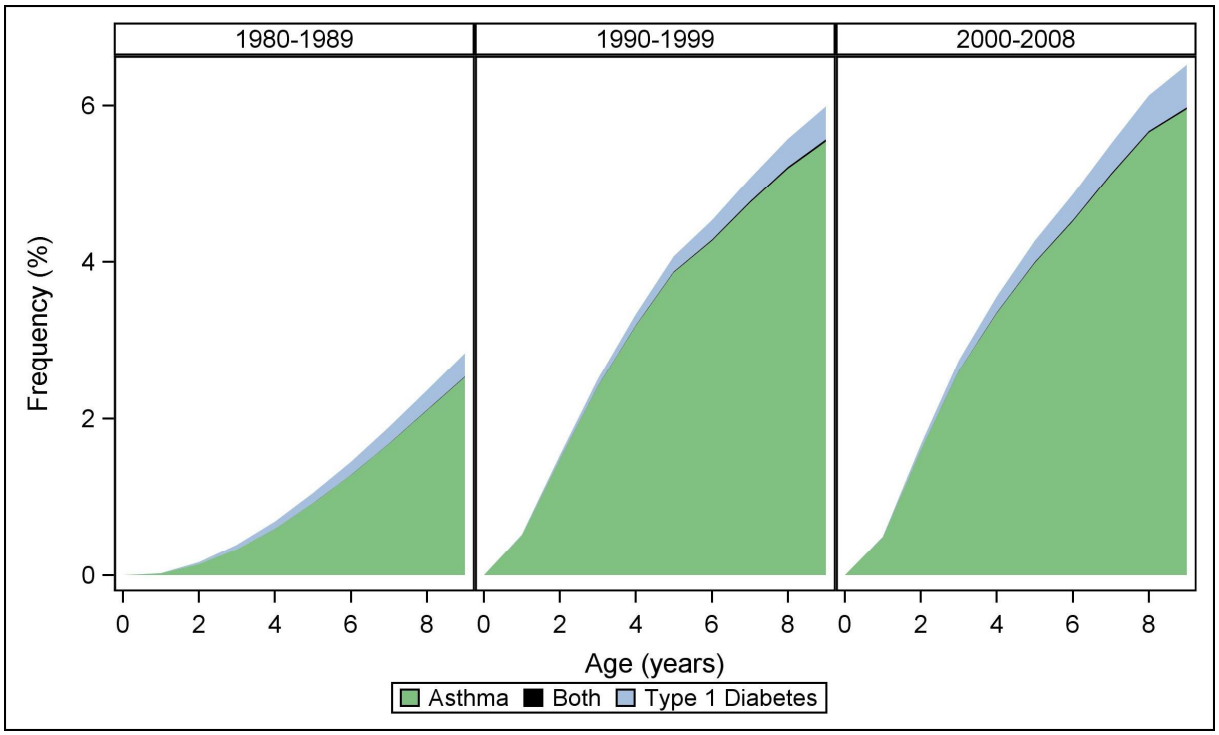

Figure 2. Frequency of children with only asthma (green), only type 1 diabetes (blue), and both asthma and type 1 diabetes (black) by age and birth decade.

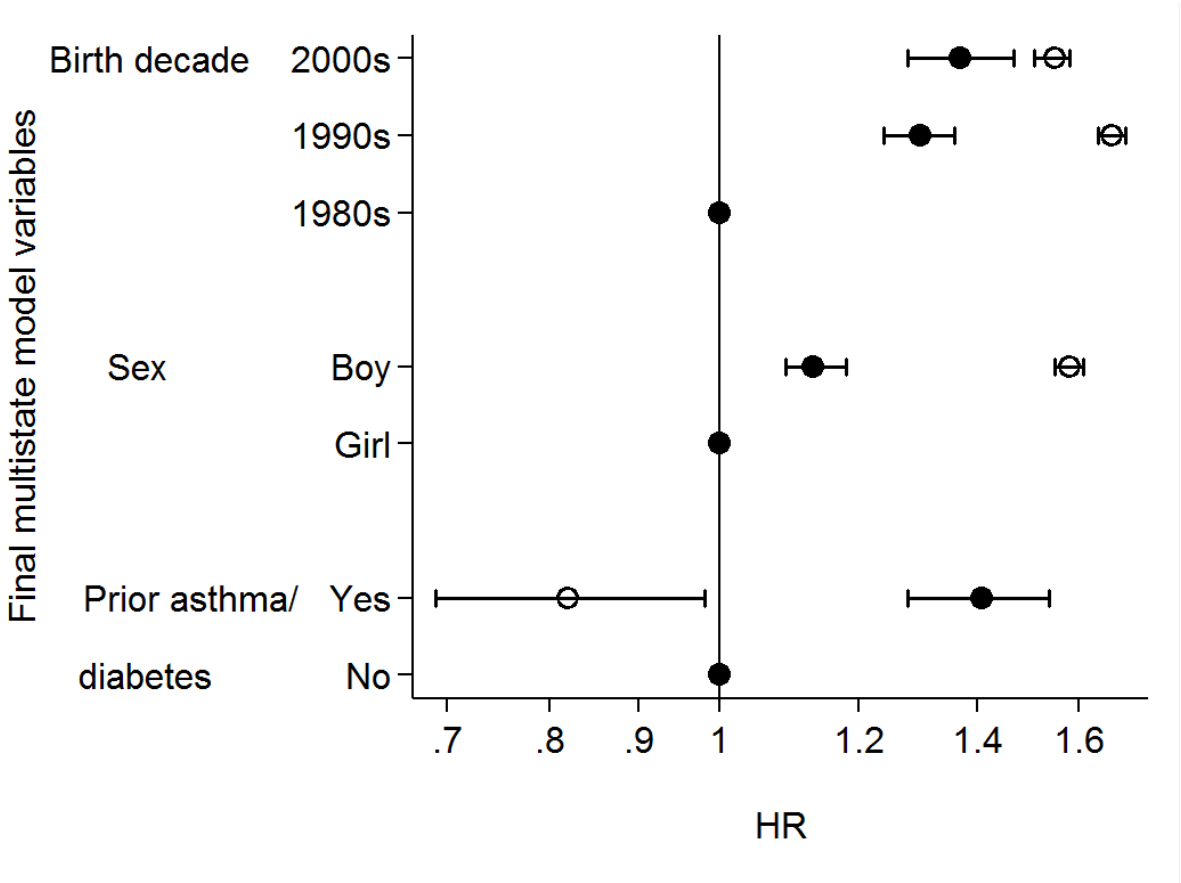

Figure 3. The association of prior asthma/type 1 diabetes, sex and birth decade with type 1 diabetes (black dots) and asthma (white dots). Data points are hazard ratios (HR) with 95% confidence intervals (bars) converted from the final multistate model, no prior asthma/type 1 diabetes, female sex and birth decade 1980s as the reference categories.