



Diabetes

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

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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 January 1981 and 31 December 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 modelling 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, previous diagnosis of asthma increased the risk of subsequent type 1 diabetes by 41% (95% CI: 1.28, 1.54), whereas previous 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

Key Messages

- This study used nationwide registers to design the case-cohort setting, and a multistate modelling approach to analyse the association between asthma and type 1 diabetes in childhood and adolescence.
- Children with previously diagnosed asthma were at increased risk of subsequent type 1 diabetes.
- Children with previously 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.

Introduction

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 support the inverse association [odds ratio (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 modelling, we

estimated transition rates between healthy and disease states, asthma and type 1 diabetes, from 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 paediatrics and/or a associated field, and a certificate of the diagnosis is required. Further, in the case of childhood asthma, long-lasting drug treatment is required. For example, the use of anti-asthmatic 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 anti-asthmatic 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 1 January 1981 and 31 December 2008, we identified all those who had received a special reimbursement for the costs of insulin or anti-asthmatic 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, children who had no insulin (ATC code A10A) purchases after the diagnosis were excluded ($n = 64$, 0.7%). For a strict asthma definition, children who had a short duration of the special reimbursement (less than 6 months) and/or no anti-asthmatic drug purchases (inhaled corticosteroids, ATC code R03BA; a fixed combination containing inhaled corticosteroids and either salmeterol or formoterol, codes R03AK06 and R03AK06; or montelukast, code R03DC03) after the diagnosis were excluded ($n = 5197$, 6.4%).

Statistical analysis

The data were analysed with a multistate modelling 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 modelled 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 31 December 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

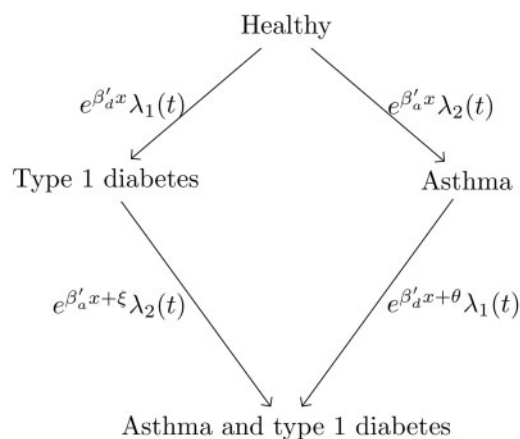


Figure 1. The final multistate transition model, where $\lambda_1(t)$ and $\lambda_2(t)$ are the piecewise constant baseline transition rates, β_d and β_a consist of the log hazard ratios for factors sex and birth decade contained in x , both for type 1 diabetes and asthma, respectively. Parameters ξ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

NLMIXED procedure in SAS, version 9.4 (SAS Institute, Cary, NC).

We conducted a series of analyses to examine sensitivity: (i) to the case definition criteria by using a strict definition; (ii) 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 (iii) 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, 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 with the reference cohort. The proportion 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 up to age 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 those with good health up to age 8 years (1.3%).

The multistate model gave similar results: children with asthma were at increased risk of subsequent type 1 diabetes [unadjusted hazard ratio (HR)=1.45, 95% confidence interval (CI): 1.32, 1.60], whereas 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, available as Supplementary data at *IJE* online). In addition, the results from the sensitivity analyses underline the importance of

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	80871	8939	602	171138
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
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

^aThe Medical Birth Register data including maternal age at delivery, smoking during pregnancy, number of previous deliveries and mode of delivery are from 1987 onwards (maternal socioeconomic status from 1991 onwards).

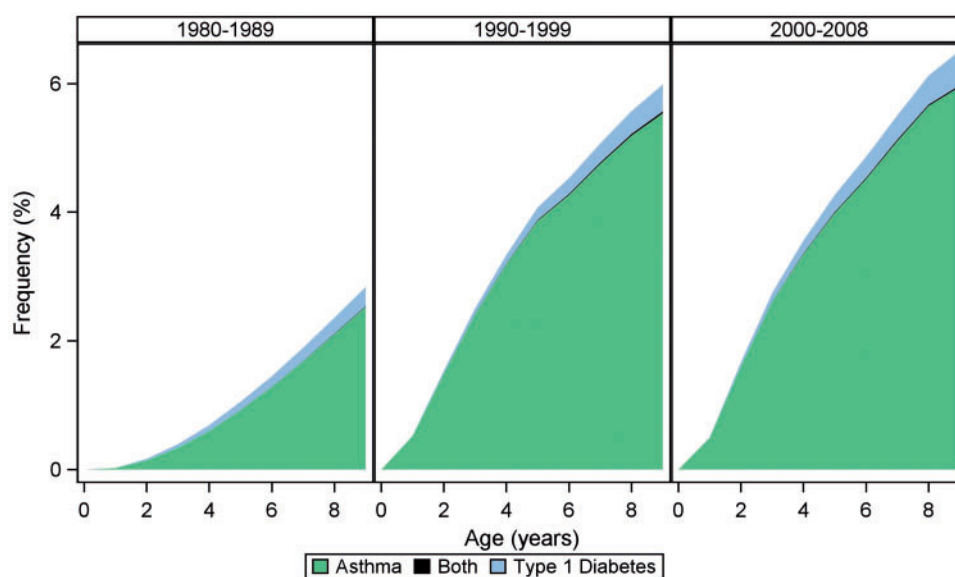
**Figure 2.** Frequency of children with only asthma, only type 1 diabetes or both asthma and type 1 diabetes by age and birth decade.

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	<i>n</i>	(%)
Asthma (<i>n</i> = 36 162)	Type 1 diabetes	219	(0.6)
	No change	35943	(99.4)
Healthy (<i>n</i> = 1 672 974 ^a)	Type 1 diabetes	6807	(0.4)
	Asthma	44928	(2.7)
	Asthma and type 1 diabetes	271	(< 0.1)
	No change	1620968	(96.9)
Type 1 diabetes (<i>n</i> = 2168)	Asthma	36	(1.7)
	No change	2132	(98.3)
Both asthma and type 1 diabetes (<i>n</i> = 76)	No change	76	(100.0)

^aAs 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.

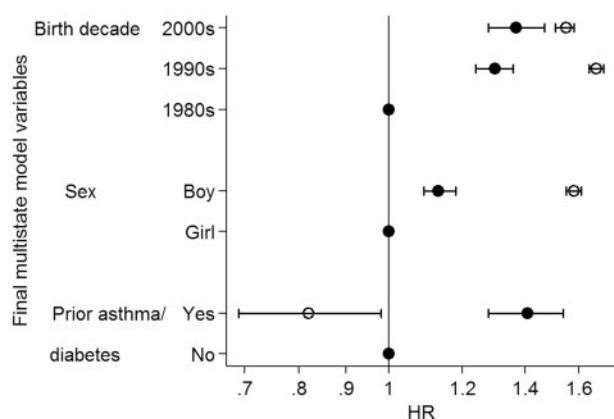


Figure 3. The association of prior asthma/type 1 diabetes, sex and birth decade with type 1 diabetes (black dots) and asthma (white dots). Data points are hazard ratios (HR) with 95% confidence intervals (bars) converted from the final multistate model, no prior asthma/type 1 diabetes, female sex and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

careful recognition of sequential ordering and age on the association between asthma and type 1 diabetes, as the multistate model does (Supplementary Table 4, available as Supplementary data at *IJE* online).

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. A meta-analysis summarizing studies published in March 2003 reported a slight inverse association between

asthma and type 1 diabetes,³ but 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 twice hospitalized or visited the emergency room because of type 1 diabetes, whereas 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, such as 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 the 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 with many other countries, and the fact that the study includes asthmatics needing long-lasting drug treatment, limit 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 hyperglycaemia, 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 anti-asthmatic 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.

Supplementary Data

Supplementary data are available at *IJE* online.

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