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# Asthma Related Medication Use and Exacerbations in Children and Adolescents With Type 1 Diabetes

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**Summary.** Objectives: To investigate the use of asthma medication and occurrence of asthma exacerbations up to 5 years before and after the onset of type 1 diabetes mellitus (T1DM) in children and adolescents. Methods: Children and adolescents younger than 19 years with at least 2 insulin prescriptions between 1999 and 2009 classified as T1DM cohort (n = 915) and a 4 times larger reference cohort (n = 3,590) with the same age and gender were identified from the Dutch PHARMO Record Linkage System. The date of first insulin dispensing was selected as the index date. Results: The 5-year prevalence rate of asthma medication use in the T1DM cohort (23.2%) was significantly higher than the reference cohort (18.3%) after the onset of diabetes. No statistically significant difference between the two cohorts was observed in the use of specific types of asthma medication except for short acting muscarinic antagonists that were significantly more used in the T1DM cohort (5.5%) compared with the reference cohort (0.62%) after the onset of diabetes. The incidence rate of asthma medication use declined over time with a peak in the T1DM cohort the 1st year after the onset of diabetes. Furthermore, 1 year after the index date there was a peak in incidence rate of asthma exacerbations in both T1DM (7.8 per 1,000 person year) and reference (6.8 per 1,000 person year) cohorts. Conclusions: T1DM is associated with statistically significantly higher asthma medication use after the onset of T1DM, especially in the 1st year after the onset of diabetes. **Pediatr Pulmonol. 2016;51:1113–1121.** 

**Key words: asthma medication prevalence rate; asthma medication incidence rate; childhood respiratory symptoms; Netherlands.**

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## INTRODUCTION

The association of type 1 diabetes (T1DM) and asthma in children has been studied with controversial results. Some studies have reported a significant reduction in the prevalence of asthma in children with T1DM,[1,2] while other studies have shown a higher risk of asthma in this population.[3–6] Tosca et al.[7] also showed no difference in the frequency of asthma between T1DM patients and control group.

It has also been reported that children with T1DM have an abnormal lung function in which forced vital capacity (FVC), forced expiratory volume in 1 sec ($FEV_1$) and transfer factor for carbon monoxide (TLCO) were reported to be significantly lower compared with children in the general population.[8–10] Previous studies investigating the association between lung function and glucose regulation showed that dysregulated glucose was related with impaired lung function.[3,11]

So far, no study has quantified asthma medication use in children and adolescents with T1DM before and after the onset of diabetes. Quantification of asthma medication use in children and adolescents before and after the onset of T1DM might provide further insight into the relation between T1DM and impaired lung function or asthma. Therefore, we conducted a population-based cohort study by using community pharmacy prescription records

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Conflict of interest: None.

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linked to hospital diagnoses to calculate the prevalence and incidence rates of asthma medication use and incidence rates of asthma exacerbations in children and adolescents with T1DM and we compared these rates with a group of age- and sex-matched diabetes-free children and adolescents in the Netherlands.

## METHODS

### Setting

A population-based cohort study was conducted using the Dutch PHARMO Record Linkage System (RLS) (http://www.pharmo.nl) that comprises community pharmacy dispensing records linked to hospital admissions. Nowadays data from more than 4 million residents (both rural and urban areas) of the Netherlands (approximately 24% of the Dutch population) are collected in PHARMO RLS.[12,13] The drug dispensing records consist of data on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, and the written dose instructions. Dates of hospital admissions and discharges, together with primary and secondary diagnoses are documented in the hospital records. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (http://icd9cm.chrisendres.com), whereas the drugs are coded according to the Anatomical Therapeutic Chemical codes (ATC codes) (http://www.whocc.no/atc_ddd_index). Information is recorded since 1986 and has been used in many pharmacoepidemiologic studies.[12,13] Hospital diagnoses and drug exposures retrieved from the prescription records in the PHARMO RLS have been validated in several studies.[14–16]

### Study Population

In this study, the T1DM cohort was defined as a cohort including children and adolescents (<19 years old) with at least 2 insulin prescriptions between 1999 and 2009. The date of first insulin prescription or first hospital admission for T1DM was selected as the entry date (index date). For each patient in the T1DM cohort, up to 4 diabetes-free children and adolescents (without any prescription of glucose lowering medications (ATC code: A10) or hospitalization for diabetes (ICD-9-CM code: 250) during the study period with the same gender, age, and calendar time distribution were randomly sampled from the PHARMO RLS (reference cohort). Patients in both cohorts were included in the study if they had at least 12 months of drug history before and at least 12 months follow up after the index date. Exclusion criteria for the T1DM cohort were having a glucagon (ATC code H04AA01) prescription prior to the index date (glucagon is usually prescribed in patients with diabetes for the management of hypoglycemia, therefore in patients who had prescriptions of glucagon before the insulin prescriptions, the index date was not clear) and ever use of oral anti-diabetic agents (in order to exclude potential patients with type 2 diabetes, ATC code A10B). Also patients in both cohorts with a history of cystic fibrosis (CF) (ICD-9-CM code: 277) were excluded from the study in order to exclude CF-related diabetes and respiratory problems. Both cohorts were followed from a maximum of 5 years before until a maximum of 5 years after the index date.

ABBREVIATIONS:

| | |
|---|---|
| ATC codes | Anatomical Therapeutic Chemical codes |
| CF | Cystic fibrosis |
| ICD-9-CM | International Classification of Disease, 9th edition, Clinical Modification |
| PHARMO RLS | PHARMO Record Linkage System |
| T1DM | Type 1 diabetes |

### Asthma Medication Use and Exacerbations

For both cohorts, exposure to asthma medication was defined as a dispensing for any asthma medication categorized as ATC code R03 (drugs for obstructive airway disease) (Table S1 in Appendix). Asthma exacerbations in both cohorts was defined as discharge diagnoses of asthma (ICD-9 code 493) and/or short courses of oral corticosteroids (OCSs) (ATC code: H02AB), for a period $<=14$ days that were dispensed in children using asthma (R03) medication.

### Statistical Analysis

To summarize the characteristics of both cohorts we used descriptive statistics. Five-year prevalence rates of asthma medication use in general and for specific subgroups in the period before and after the index date were calculated by dividing the total number of patients receiving prescriptions to treat asthma symptoms by the average number of children and adolescents studied 5 years before and after the index date. Annual prevalence rates of asthma medication use were also calculated. The 5-year prevalence rate and annual prevalence rate of asthma medication were stratified by different age categories (using age bands 0–4, 5–9, 10–14, and 15–18 years) and gender which was compared by an ordinal chi square test. To assess patterns over time, the 5-year prevalence rate of asthma medication use and the 5-year number of asthma prescriptions per child were calculated from 5 years prior to the index date up to 5 years after the index date in both cohorts and further stratified by age. Annual incidence rates of asthma medication use and asthma exacerbations in both cohorts were defined as the number of incident medication users and incident cases with asthma exacerbations during a

given time period divided by the person time at risk. For calculating annual incidence rates, to exclude prevalent cases in each year, subjects were required to have at least 12 months prior history (either a drug prescription or the occurrence of asthma exacerbations) in the database. Time to events (asthma medication consumption and exacerbations) in the two cohorts was compared using the Kaplan–Meier method followed by log-rank test. Two-tailed *P*-values were considered significant at 0.05. Data analyses in this study were performed using SPSS version 23.0 (SPSS, Chicago, IL).

## RESULTS

We identified 915 children and adolescents with at least 2 insulin prescriptions (T1DM cohort) from the PHARMO RLS and compared them with a group of 3,590 age- and sex-matched diabetes-free individuals (reference cohort). At the index date, boys comprised just over half of the population in both T1DM (50.9%) and the reference (50.6%) cohorts and the median age was 10 years (interquartile range (IQR) 7–14 years) (Table 1).

### Prevalence Rates of Asthma Medication Use

Before the index date there was no difference between the 5-year prevalence rate of asthma medication use in the T1DM cohort (28.3%, 95%CI: 25.2–31.7) compared to the reference cohort (27.6%, 95%CI: 26.0–29.2), while after the index date the 5-year prevalence rate was statistically significantly higher in the T1DM cohort (23.2%, 95%CI: 20.4–26.3 vs. 18.3%, 95%CI: 16.9–19.7). As shown in Figure 1, the prevalence rate of asthma medication use in the T1DM cohort slightly dropped from 28.3% (n = 206 asthma medication users) during 5 years before the index date to 23.2% (n = 182 asthma medication users) in the years after diagnosing T1DM. After the index date there were 100 prevalent users who also used asthma medication before the onset of diabetes and the percentage of incident asthma medication users was 45.0% (n = 82). In the reference cohort the

**TABLE 1— Baseline Characteristics of Patients With T1DM Compared With Diabetes-Free Subjects**

| | T1DM cohort (n = 915) | Reference cohort (n = 3,590) |
|---|---|---|
| Gender, n (%) | | |
| Male | 466 (50.9) | 1,817 (50.6) |
| Female | 450 (49.2) | 1,773 (49.4) |
| Age at diagnosis (index date), n (%) | | |
| 0–4 y | 132 (14.3) | 537 (15.0) |
| 5–9 y | 269 (29.1) | 1,042 (29.0) |
| 10–14 y | 333 (36.4) | 1,295 (36.1) |
| 15–18 y | 181 (19.8) | 716 (19.9) |
| Age (median, IQR), y | 10 (7–14) | 10 (7–14) |
| Follow-up before the index date (median, IQR), y | 2.8 (1.8–3.8) | 2.9 (1.9–3.9) |
| Follow-up after the index date (median, IQR), y | 3.1 (2.0–4.1) | 3.1 (2.0–4.1) |
| Number of participants in each year of the study period | | |
| 5 y before the index date | 480 | 1,911 |
| 4 y before the index date | 600 | 2,378 |
| 3 y before the index date | 731 | 2,908 |
| 2 y before the index date | 914 | 3,582 |
| 1 y before the index date | 915 | 3,590 |
| 1st y of follow up | 915 | 3,590 |
| 2nd y of follow up | 913 | 3,578 |
| 3rd y of follow up | 800 | 3,130 |
| 4th y of follow up | 698 | 2,725 |
| 5th y of follow up | 595 | 2,314 |
| Average number of participants during 5 years of the study period | | |
| Before the index date | 728 | 2,874 |
| After the index date | 784 | 3,067 |
| Number of prescriptions per child before the index date, n (%) | | |
| One prescription | 54 (26.2) | 211 (26.6) |
| Two prescriptions | 49 (23.8) | 144 (18.2) |
| ≥3 prescriptions | 103 (50.0) | 437 (55.2) |
| Number of prescriptions per child after the index date, n (%) | | |
| One prescription | 57 (31.3) | 161 (28.8) |
| Two prescriptions | 28 (15.4) | 88 (15.7) |
| ≥3 prescriptions | 97 (53.3) | 311 (55.6) |

IQR, interquartile range; T1DM, type 1 diabetes mellitus; Y, years.

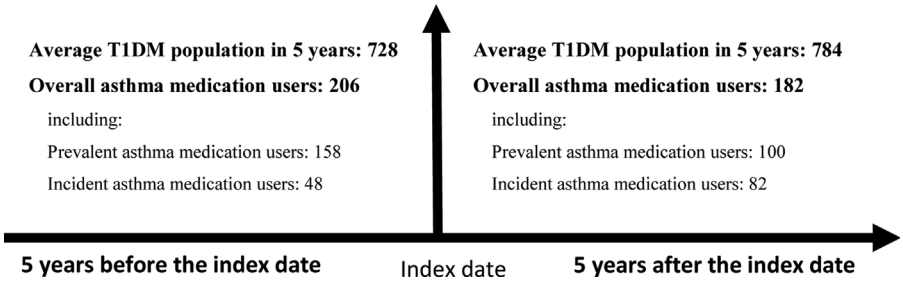


**Fig. 1. Five-year prevalence rate of asthma medication use, comparing T1DM cohort before and after the onset of diabetes. Index date is the date of first insulin dispensing.**

percentage of incident users was 23.0% in the period after the index date.

The higher prevalence rate of the use of asthma medication in the T1DM cohort compared with the reference cohort was most pronounced in the 1st year after the index date ($P < 0.001$) and disappeared afterwards ($P = 0.47$ in the 5 years after the index date) (Fig. 2A).

As shown in Figure 3, children aged 4 years and younger in both cohorts, had considerably higher prevalence rates of asthma medication use over the 5 year period before and after the index date (14.7% and 17.4% in the T1DM cohort and 15.3% and 11.4% in the reference cohort, respectively) compared with those in the other age categories (rates below 12%). Furthermore, substantially higher prevalence rates of asthma medication use in the T1DM cohort compared with the reference group in the year after the index date was observed only in children aged 0–4 ($P < 0.001$) and 10–14 ($P = 0.02$) years old (Fig. 4).

Asthma medication was more frequently used by boys in the T1DM cohort (32.7%) compared with girls (23.8%) before the index date ($P = 0.02$). The same pattern was observed in the reference cohort (30.8% vs. 24.3%, respectively; $P < 0.001$). After the index date, there was no statistically significant difference between girls and boys in both T1DM ($P = 0.29$) and reference ($P = 0.07$) cohorts.

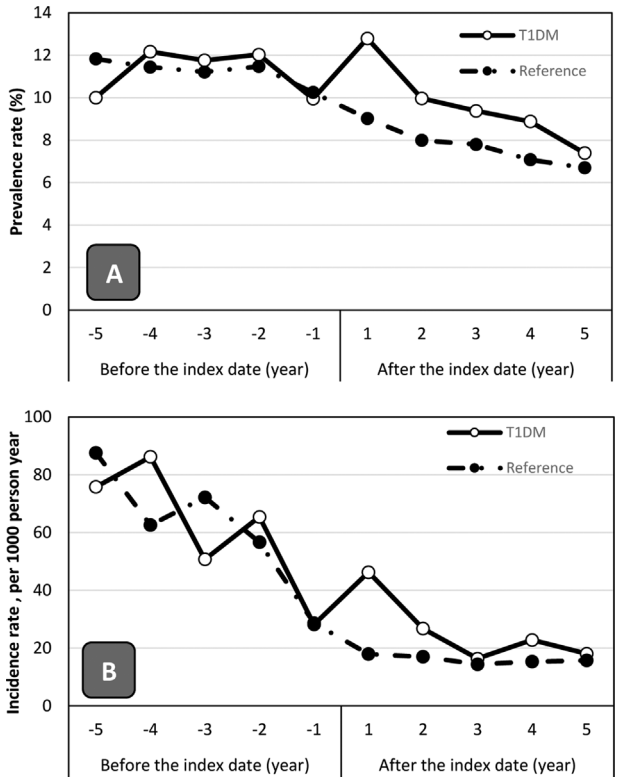


**Fig. 2. A: Annual prevalence rate of asthma medication use, comparing T1DM and reference cohorts before and after the index date. B: Annual incidence rate of asthma medication use, comparing T1DM and reference cohorts before and after the index date. In both figures index date is the date of first insulin dispensing.**

## Asthma Medication Utilization Pattern

When investigating subgroups of medication, short acting beta agonists (SABAs) and inhaled corticosteroids (ICSs) were used most frequently in both cohorts. The 5-year prevalence rate of short acting muscarinic antagonists (SAMAs) was significantly higher in the T1DM cohort compared with the reference cohort (5.5% vs. 0.6%, $P < 0.001$) after the onset of diabetes (Table S2 in Appendix). Forty-three out of 182 patients (almost 24%) who used asthma medications after the index date in

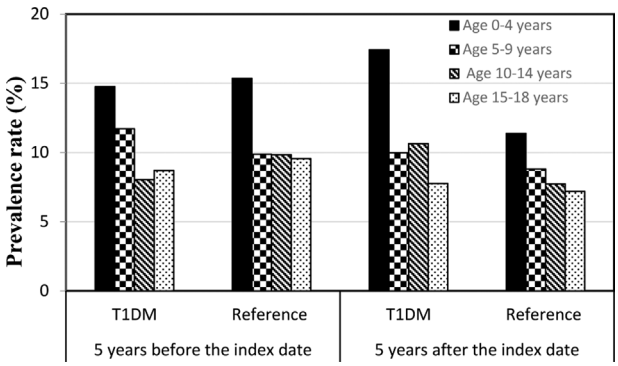


**Fig. 3. Five-year prevalence rate of asthma medication use, comparing T1DM and reference cohorts before and after the index date stratified by age. Index date is the date of first insulin dispensing.**

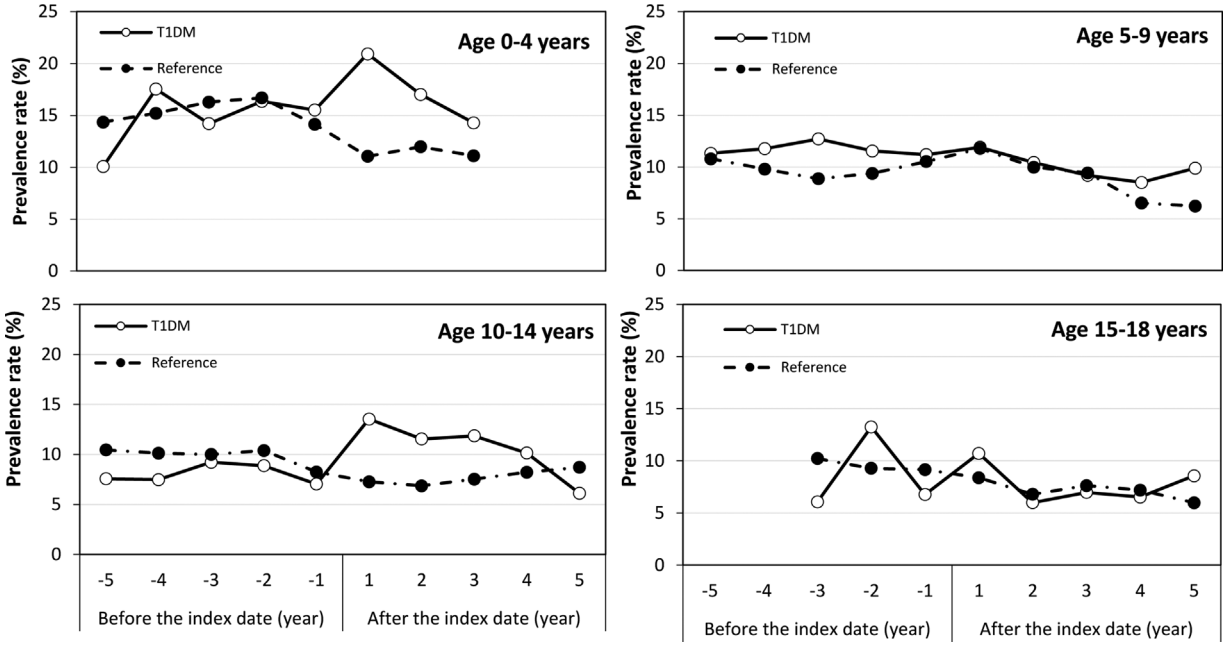


**Fig. 4. Annual prevalence rate of asthma medication use, comparing T1DM and reference cohorts before and after the index date stratified by age. Index date is the date of first insulin dispensing.**

the T1DM cohort received SAMAs. Many of these patients were treated with SAMAs only or had a medication history of only using SABAs and ICSs before and after the index date.

After the index date, children aged 4 years and younger were more likely to use SABAs and ICSs compared to the other age categories in both the T1DM cohort (36.2% and 14.9%, respectively; $P = 0.02$) and reference cohort (8.9% and 7.3% respectively; $P < 0.001$). A higher consumption of long acting beta agonists (LABAs) and SAMAs was found in 10–14 years old adolescents compared to the other age categories in T1DM cohort (Fig. S1 in Appendix).

A majority of children among asthma medication users in the T1DM cohort (51.2%) and in the reference cohort (55%) received at least three asthma prescriptions while the percentage of children who received only one prescription was 28.8% and 27.7%, respectively during the complete follow up. Children aged 4 years and younger received more frequently at least three prescriptions for asthma compared to only one prescription. SABAs and SAMAs were more often prescribed only once while the number of prescribed ICSs per child was higher; for these drugs children received at least three prescriptions.

## Incidence Rate of Asthma Medication Use

Annual incidence rate of asthma medication use during the 5 years before and 5 years after the index date are presented in Figure 2B. The results show that the highest incidence rate of asthma medication use was observed in the period 4–5 year before the index date and further declined through follow up in both cohorts with a peak in the T1DM cohort the 1st year after the onset of disease; 46.3 per 1,000 person year (PY) (95% CI: 33.0–64.6) in the T1DM cohort compared to 17.9 per 1,000 PY (95%CI: 13.6–23.6) in the reference group. The decreasing pattern in the T1DM cohort further continued until the end of follow up (18.1 per 1,000 PY). In the reference cohort, the incidence rate of asthma medication use shows a decrease during the years before and after the index date. The results of the Kaplan–Meier analyses showed a statistically significant difference for the incidence rate of asthma medication use between the two cohorts after the index date ($P = 0.001$) (Fig. 5).

## Incidence Rate of Asthma Exacerbations

There was a peak in asthma exacerbations in the 1st year after the index date in both the T1DM (7.8 per 1,000 PY) and the reference (6.8 per 1,000 PY) cohorts. Although, the decreasing pattern after the index date was more pronounced in the T1DM cohort; at the end of follow-up both cohorts had almost the same incidence rates of exacerbations (5.2 per 1,000 PY in the T1DM cohort and 5.4 per 1,000 PY in the reference cohort) (Fig. 6).

Kaplan–Meier analyses and log rank tests showed no statistically significant difference in time to exacerbations between the two cohorts after the index date ($P = 0.49$) (Fig. 7).

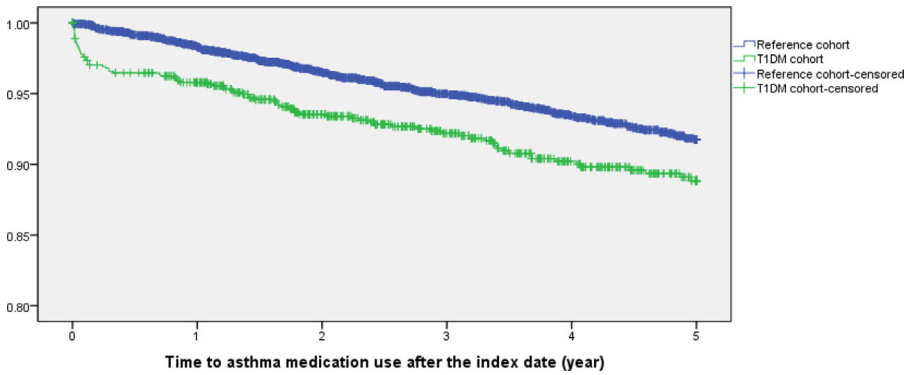


**Fig. 5. Kaplan–Meier analysis comparing time to asthma medication use in the T1DM and the reference cohorts after the index date (*P*-value = 0.001).**

## DISCUSSION

In this study, significantly more children and adolescents with new onset T1DM used asthma medication in the period after the onset of diabetes than diabetes-free individuals while no statistically significant difference in the 5-year prevalence rate of asthma medication use was observed before the index date. The number of children and adolescents using asthma medication decreased in both cohorts during follow up time. Remarkably, in the T1DM cohort there was a peak in both the annual prevalence and incidence rates of asthma medication in the 1st year after the onset of diabetes; however, the incidence rate of asthma exacerbations was comparable to the reference group.

Asthma is a chronic inflammatory airway disease with symptoms of cough, wheeze and shortness of breath usually related to some triggering events, which are not specific and many other conditions can cause similar symptoms in children, especially preschool children. This makes the diagnosis of asthma difficult.

In our study we found that children aged 4 years and younger in both cohorts were more likely to have asthma medication prescriptions compared to the other age groups. Moreover, our results show that the higher prevalence rate of asthma prescriptions in recent onset diabetic patients compared to the reference group in the year after the index date was more pronounced in children aged 0–4 and 10–14 years old. Firstly, our finding strongly reflects the higher burden of respiratory complaints in younger age groups,[17,18] not only in those with T1DM. Prevalence rate of asthma-like symptoms was shown to be 32.0% in the 1st years of life (children younger than 5 years) in a Danish population[19] and also higher in children aged 0–4 years (12.5%) than those in age of 5–7 (10.4%) in the Dutch population.[20] This could be explained by the smaller airways of young children (and more specific boys, premature and low for gestational age children) that are more prone to a relevant airway obstruction (and wheezing) during viral colds and after exposure to irritants. Therefore, the rise in asthma medication prevalence after T1DM onset might be partly related to a potential increase of asthmatic symptoms by the diabetes itself, but might also be related to a higher concern and awareness of parents and physicians to treat respiratory symptoms properly after the T1DM diagnosis was established.

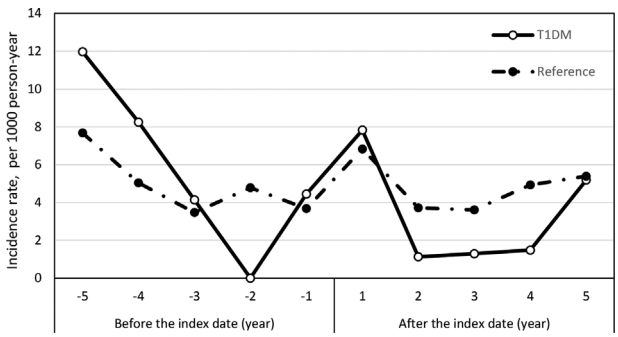


**Fig. 6. Annual incidence rate of asthma exacerbations, comparing T1DM and reference cohorts before and after the index date.**

The statistically significant higher prevalence rate of asthma medication use in boys confirms previous findings that boys are more often diagnosed and treated with asthma medication.[20–22] Lowered microbial exposure in early life might also contribute to the increasing prevalence of asthma.[23] When specifically considering a possible correlation of airway patency and glucose metabolism within this above mentioned pathophysiologic concept, an association between low body weight in the 1st years of life and impaired glycemic tolerance and decreased lung function can be considered.[24–29] Secondly, diabetes control might be influenced by hormonal changes in puberty in which puberty in diabetic adolescents (10–14 years) is associated with declined insulin sensitivity.[30,31] However, another explanation could be the increased therapy adherence triggered by the T1DM diagnosis in adolescents where treatment adherence is generally lower in this age group.

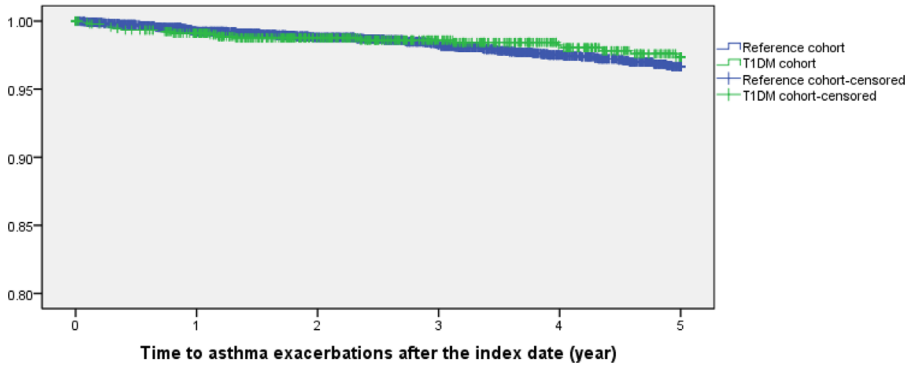


**Fig. 7. Kaplan–Meier analysis comparing time to asthma exacerbations in the T1DM and the reference cohorts after the index date (*P*-value = 0.49).**

The annual prevalence and incidence rates showed a peak in the 1st year after the onset of diabetes followed by a gradual decline in asthma medication use during the follow up time. The peak might be a result of regular contact with the physician after the diagnosis of T1DM which increases the probability of diagnosing and prescribing medications for respiratory symptoms (detection bias). The disappearance of the peak 1 year after the index date could be explained in two ways. Basically, part of the observed effect can be probably explained by increasing age. Besides, it might be because of the link between glucose regulation and lung function as mentioned above.[3,11,32,33] When diabetes is well regulated the asthma-like complaints disappear in these children. Therefore, we suggest physicians to pay more attention to control and treat diabetic children before starting medication for respiratory symptoms.

Our study showed no statistically significant difference between the two cohorts for the subgroups of asthma medication that were used except for SAMAs, that were statistically significantly more prescribed in the diabetic adolescents after the index date compared with the reference cohort.

Given the low numbers of SAMAs prevalence rate in general, it is not clear whether the difference in use is of clinical relevance. However, one possible explanation might be that it is a marker for the severity of respiratory problems in this cohort. In pediatric asthma exacerbations, use of SAMAs in combination with SABAs improves pulmonary function to a greater extent than the use of SABAs alone.[34,35] Although, most diabetic patients in our study were treated with SAMAs alone and the pattern of exacerbations in the reference cohort was almost the same.

To the best of our knowledge, this is the first population-based cohort study to investigate the prevalence and incidence rates of asthma medication use and exacerbations in children and adolescents with T1DM compared with diabetes-free subjects in the period both before and after the onset of this disease. An important strength of our study is the use of the PHARMO RLS database which is a large, population-based data set providing accurate data on medications dispensing and hospital admissions. Probability for occurrence of information bias and recall bias is therefore low. Another strength of this study is the low probability of T1DM misclassification. We used insulin prescription as a proxy for T1DM since hyperglycemia is the only indication for insulin and it has been validated in several studies.[36–39] Furthermore, children with CF were excluded at baseline from the study population and other types of diabetes in which insulin is indicated, for example, mitochondrial diabetes have reported low prevalence rates compared with T1DM.[40,41] An important limitation in this study is misclassification of asthma since the definition of asthma is based on the drug prescription information. Another limitation is the reference cohort which was randomly captured from the PHARMO database and it only includes children that filled prescriptions in the community pharmacies. Therefore, the difference between asthma medication use in patients with T1DM and the general population might be larger than observed in our study. Another important limitation in this study is that there were no additional descriptive characteristics such as race/ethnicity, body mass index (BMI), or family history of asthma available in the database.

In conclusion, our study shows that children and adolescents with T1DM use more asthma medication than age- and gender-matched diabetes-free controls in the 1st year after the onset of diabetes. However, this difference disappears after the 1st year of diabetes diagnosis. As respiratory symptoms could be decreased by glycemic control, it might be worthwhile to re-evaluate asthma medication once glycemic control has been established.

## REFERENCES

1. Cardwell CR, Shields MD, Carson DJ, Patterson CC. A meta-analysis of the association between childhood type 1 diabetes and atopic disease. Diabetes CareSep 2003;26:2568–2574.
2. Decreased prevalence of atopic diseases in children with diabetes. the EURODIAB substudy 2 study group. J Pediatr 2000;137:470–474.

3. Black MH, Anderson A, Bell RA, Dabelea D, Pihoker C, Saydah S, Seid M, Standiford DA, Waitzfelder B, Marcovina SM, et al. Prevalence of asthma and its association with glycemic control among youth with diabetes. Pediatrics 2011;128:e839–e847.
4. Stene LC, Nafstad P. Relation between occurrence of type 1 diabetes and asthma. Lancet 2001;357:607–608.
5. Villa-Nova H, Spinola-Castro AM, Garcia FE, Sole D. Prevalence of allergic diseases and/or allergic sensitisation in children and adolescents with type 1 diabetes mellitus. Allergol Immunopathol (Madr) 2015;43:157–161.
6. Hsiao YT, Cheng WC, Liao WC, Lin CL, Shen TC, Chen WC, Chen CH, Kao CH. Type 1 diabetes and increased risk of subsequent asthma: A nationwide population-based cohort study. Medicine (Baltimore) 2015;94:e1466.
7. Tosca MA, Villa E, Silvestri M, D'Annunzio G, Pistorio A, Aicardi M, Minicucci L, Lorini R, Rossi GA. Discrepancy between sensitization to inhaled allergens and respiratory symptoms in pediatric patients with type 1 diabetes mellitus. Pediatr Allergy Immunol 2009;20:385–391.
8. Martin-Frias M, Lamas A, Lara E, Alonso M, Ros P, Barrio R. Pulmonary function in children with type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2015;28:163–169.
9. Cazzato S, Bernardi F, Salardi S, Tassinari D, Corsini I, Ragni L, Cicognani A, Cacciari E. Lung function in children with diabetes mellitus. Pediatr Pulmonol 2004;37:17–23.
10. Van Gent R, Brackel HJL, De Vroede M, Van Der ent CK. Lung function abnormalities in children with type 1 diabetes. Respir Med 2002;96:976–978.
11. McKeever TM, Weston PJ, Hubbard R, Fogarty A. Lung function and glucose metabolism: An analysis of data from the third national health and nutrition examination survey. Am J Epidemiol 2005;161:546–556.
12. Houweling LM, Bezemer ID, Penning-van Beest FJ, Meijer WM, van Lingen RA, Herings RM. First year of life medication use and hospital admission rates: Premature compared with term infants. J Pediatr 2013;163:61, 6.e1.
13. Overbeek JA, Penning-van Beest FJ, Heintjes EM, Gerber RA, Cappelleri JC, Hovius SE, Herings RM. Dupuytren's contracture: A retrospective database analysis to determine hospitalizations in the netherlands. BMC Res Notes 2011;4:402, 0500-4-402.
14. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50:619–625.
15. De Bruin ML, van Hemel NM, Leufkens HG, Hoes AW. Hospital discharge diagnoses of ventricular arrhythmias and cardiac arrest were useful for epidemiologic research. J Clin Epidemiol 2005;58:1325–1329.
16. Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F, Stergachis A. Current use of thiazide diuretics and prevention of femur fractures. J Clin Epidemiol 1996;49:115–119.
17. Goldstein E, Greene SK, Olson DR, Hanage WP, Lipsitch M. Estimating the hospitalization burden associated with influenza and respiratory syncytial virus in new york city, 2003–2011. Influenza Other Respir Viruses 2015;9:225–233.
18. Gresh L, Kuan G, Sanchez N, Azziz-Baumgartner E, Ojeda S, Melendez M, Lopez R, Martin ET, Widdowson MA, Bresee J, et al. Burden of influenza and influenza-associated pneumonia in the first year of life in a prospective cohort study in managua, nicaragua. Pediatr Infect Dis J 2016;35:152–156.
19. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. Pediatr Pulmonol 2007;42:723–728.
20. Zuidgeest MG, Koster ES, Maitland-van der Zee AH, Smit HA, Brunekreef B, Leufkens HG, Koppelman GH, Postma DS, de Jongste JC, Hoekstra MO, et al. Asthma therapy during the first 8 years of life: A PIAMA cohort study. J Asthma 2010;47:209–213.
21. Almqvist C, Worm M, Leynaert B. Working group of GA2LEN WP 2.5 Gender. Impact of gender on asthma in childhood and adolescence: A GA2LEN review. Allergy 2008;63:47–57.
22. Zuidgeest MG, van Dijk L, Smit HA, van der Wouden JC, Brunekreef B, Leufkens HG, Bracke M. Prescription of respiratory medication without an asthma diagnosis in children: A population based study. BMC Health Serv Res 2008;8:16, 6963-8-16.
23. Tedeschi A, Airaghi L. Common risk factors in type 1 diabetes and asthma. Lancet 2001;357:1622.
24. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fand infant growth and impaired glucose tolerance at age 64. BMJ 1991;303:1019–1022.
25. Phipps K, Barker DJ, Hales CN, Fall CH, Osmond C, Clark PM. Fetal growth and impaired glucose tolerance in men and women. Diabetologia 1993;36:225–228.
26. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ 1991;303:671–675.
27. Cazzato S, Ridolfi L, Bernardi F, Faldella G, Bertelli L. Lung function outcome at school age in very low birth weight children. Pediatr Pulmonol 2013;48:830–837.
28. Saarenpaa HK, Tikanmaki M, Sipola-Leppanen M, Hovi P, Wehkalampi K, Siltanen M, Vaarasmaki M, Jarvenpaa AL, Eriksson JG, Andersson S, et al. Lung function in very low birth weight adults. Pediatrics 2015;136:642–650.
29. Darlow BA, Horwood LJ, Mogridge N. Very low birthweight and asthma by age seven years in a national cohort. Pediatr Pulmonol 2000;30:291–296.
30. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med 1986;315:215–219.
31. Trast J. CE: Diabetes and puberty: A glycemic challenge. Am J Nurs 2014;114:26–35; quiz 36, 48.
32. Davis WA, Knuiman M, Kendall P, Grange V, Davis TM, Fremantle Diabetes Study. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: The fremantle diabetes study. Diabetes Care 2004;27:752–757.
33. Wheatley CM, Baldi JC, Cassuto NA, Foxx-Lupo WT, Snyder EM. Glycemic control influences lung membrane diffusion and oxygen saturation in exercise-trained subjects with type 1 diabetes: Alveolar-capillary membrane conductance in type 1 diabetes. Eur J Appl Physiol 2011;111:567–578.
34. Acute Asthma Guideline, Cincinnati Children's Hospital Medical Center: Evidence-based care guideline for management of acute asthma exacerbation in children. Management of acute exacerbation of ASTHMA in children. September 16, 2010; Guideline 4:1–35.
35. Aaron SD. The use of ipratropium bromide for the management of acute asthma exacerbation in adults and children: A systematic review. J Asthma 2001;38:521–530.
36. Rawshani A, Landin-Olsson M, Svensson AM, Nystrom L, Arnqvist HJ, Bolinder J, Gudbjornsdottir S. The incidence of diabetes among 0–34 year olds in sweden: New data and better methods. Diabetologia 2014;57:1375–1381.
37. Hsia Y, Neubert AC, Rani F, Viner RM, Hindmarsh PC, Wong IC. An increase in the prevalence of type 1 and 2 diabetes in children and adolescents: Results from prescription data from a UK general practice database. Br J Clin Pharmacol 2009;67:242–249.
38. Herings RM, de Boer A, Stricker BH, Bakker A, Sturmans F. A rapid method to estimate the incidence rate and prevalence of insulin-dependent diabetes mellitus in children 0–19 years of age. Pharm World Sci 1995;17:17–19.

39. Ahmadizar F, Fazeli Farsani S, Souverein PC, van der Vorst MM, de Boer A, Maitland-van der Zee AH. Cardiovascular medication use and cardiovascular disease in children and adolescents with type 1 diabetes: A population-based cohort study. Pediatr Diabetes 2015;1–8.
40. Guglielmi C, Palermo A, Pozzilli P. Latent autoimmune diabetes in the adults (LADA) in asia: From pathogenesis and epidemiology to therapy. Diabetes Metab Res Rev 2012;28: 40–46.
41. Martikainen MH, Ronnemaa T, Majamaa K. Prevalence of mitochondrial diabetes in southwestern finland: A molecular epidemiological study. Acta Diabetol 2013;50:737–741.

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