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Original Article

Increasing trends in the incidence and prevalence rates of type 1 diabetes among children and adolescents in the Netherlands

Fazeli Farsani S, Souverein PC, van der Vorst MMJ, Knibbe CAJ, Herings RMC, de Boer A, Mantel-Teeuwisse AK. Increasing trends in the incidence and prevalence rates of type 1 diabetes among children and adolescents in the Netherlands.
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Objective: To assess the trends in the incidence and prevalence rates of type 1 diabetes (T1D) among children and adolescents in the Netherlands.
Methods: A population-based cohort study was conducted in the Dutch PHARMO record linkage system (1998–2011). All children and adolescents aged ≤19 yr with at least one insulin dispensing (as a proxy for T1D) were identified and the numbers of incident and prevalent cases (numerators) were calculated. Overall age-adjusted (0–19 yr) incidence and prevalence rates together with age- and sex-specific rates of T1D and their 95% confidence intervals (CI) were calculated using data from the Dutch Central Bureau of Statistics as denominator. Trends over time were assessed using Joinpoint regression software (National Cancer Institute, Bethesda, MD, USA).
Results: In 2011, the overall age-adjusted incidence and prevalence rates of T1D were 25.2/100 000 (95% CI, 23.7–26.8) person-years (PY) and 174.4/100 000 (95% CI, 170.2–178.5) children, respectively. The average annual percentage change (AAPC) in the overall age-adjusted incidence and prevalence rate was 3.7% (95% CI, 1.8–5.7) and 3.8% (95% CI, 2.4–5.2), respectively. While during the study period the largest increases in the incidence and prevalence rates of T1D were observed for the oldest age groups (10–14 and 15–19 yr), a decreasing trend was detected for the 0- to 4-yr-old category (with AAPCs of −1.8 (95% CI, −9.9 to 7.1) and −6.9% (95% CI, −11.5 to −2.1) for incidence and prevalence, respectively).
Conclusion: Age-adjusted incidence (1999–2011) and prevalence rates (1998–2011) of T1D in Dutch children (aged 0–19 yr) continued to increase and a shift was observed to a later onset of the disease.

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Key words: adolescents – children – incidence rate – prevalence rate – time trends – type 1 diabetes

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Introduction

In 2013, an estimated 500 000 children aged 0–14 yr had type 1 diabetes worldwide. The global number of children developing type 1 diabetes is increasing and it is estimated that the incidence of type 1 diabetes among children under 14 yr of age has increased by 3% annually since 1980s (1–5). There is a substantial variation in the incidence of type 1 diabetes among different countries and the trends are not necessarily uniform (3). Even within a country, different trends in the incidence and prevalence of diabetes were reported for children of different age categories (6, 7). Fluctuations in the incidence rate of type 1 diabetes have been reported numerous times, but it is not known whether these fluctuations are due to real changes in the incidence or changes in the level of ascertainment of the registers (8). Although overall increasing trends were reported in many studies (2–4), recently several studies from European countries (Finland, Sweden, Norway, and the Czech Republic) reported a plateau in the incidence of type 1 diabetes among children younger than 15 yr after an accelerated increase (7, 9–11). It has been hypothesized that these observations might be the result of changes in the environmental risk factors of type 1 diabetes (7, 12, 13). Because of the absence of older children in these studies, it is difficult to determine whether these observations reflect a real plateau in the incidence of type 1 diabetes or only a shift to older ages of disease onset (7, 12). As recommended by Harjutsalo and colleagues, further studies from different countries with longer follow-up and different age categories (including older children) are required (7).

The Netherlands has been categorized as a country with high incidence of type 1 diabetes in children under 14 yr of age (8). Several previous studies have provided estimates of type 1 diabetes among Dutch children (14–17), but there is no data on the epidemiology and trends of type 1 diabetes in recent years and older-age categories (4). Therefore, in this study, we aimed to investigate current trends in the incidence and prevalence rates of type 1 disease among children and adolescents aged 0–19 yr in the Netherlands between 1998 and 2011.

Methods

The PHARMO Record Linkage System (PHARMO RLS) is a large patient-oriented data network designed to be used for pharmacoepidemiology and outcome studies (18). Longitudinal data in the PHARMO RLS consist of, among other data, drug dispensing records from community (outpatient) pharmacies. Data from more than 4 million inhabitants (almost 24% of the Dutch population) of both rural and urban areas can be found in this database which has been shown to be representative of the Dutch population (19, 20). In the Netherlands, most patients (about 90%) always visit the same pharmacy (21). 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. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification (22).

For this population-based cohort study, we used a subset of PHARMO RLS that scatters throughout the whole country, but covers several well-defined areas and therefore a well-defined population (9.4–11.9% of all Dutch children aged 0–19 yr). For this subset, the denominator population of the catchment area was calculated using data from the Dutch Central Bureau of Statistics (CBS) (23). This allowed us to calculate population-based estimates including children who are not registered at any pharmacy in the catchment areas. Clustering of all pharmacies within this subset results in drug-dispensing histories that contain more than 95% of all prescriptions dispensed to a particular patient (17, 24). Additionally, the fact that in the Netherlands, most patients (about 90%) always visit the same pharmacy leads to virtually complete patient medication records (21).

We used insulin as a proxy to identify cases of type 1 diabetes (5, 17, 25–27). According to the Dutch law patients who are treated with insulin only need 1 insulin prescription at the start of treatment, but not for follow-up dispensings (28). Insulin is normally dispensed for 3 months and refills are always registered in the pharmacy records. Unfortunately, in-hospital pharmacy data were not available for our subset. However, in the Netherlands, patients cannot obtain their out-patient medication from in-hospital pharmacies. Therefore, we may have only missed start of insulin therapy at diagnosis in the hospital.

All children and adolescents aged 0–19 yr with at least one insulin dispensing between January 1998 and December 2011 were selected as type 1 diabetes patients. The date of the first insulin dispensing was defined as the cohort entry date (or index date). In order to exclude probable cases of type 2 diabetes, patients who started oral anti-diabetic medications before the start of insulin or at the same date as insulin was started were excluded from the study. Prevalent insulin users were patients with at least one insulin dispensing in a particular year. New insulin users were patients who had insulin dispensing for the first time while they did not have any dispensing record for anti-diabetic medications (ATC code: A10) within 365 days prior to the start of insulin therapy. Therefore, all incident insulin users were required to have at least 1 yr valid history in the PHARMO RLS subset before the cohort entry date. Prevalence

of type 1 diabetes in each year was calculated by dividing the number of prevalent insulin users by the total number of children and adolescents in the PHARMO RLS catchment area according to CBS data at the midyear of that particular year (including children and adolescents who are not registered in a pharmacy because they do not use medicines). Incidence of type 1 diabetes was calculated by dividing the number of new insulin users by the follow-up time of all children and adolescents in the PHARMO RLS catchment area at midyear of that particular year. For both prevalence and incidence rates, 95% confidence intervals (95% CI) were calculated. The mean age at the initiation of insulin therapy (disease onset) was calculated for each year during the study period. Annual crude incidence and prevalence rates were calculated for different sexes and age categories (using the following age bands: 0–4, 5–9, 10–14, and 15–19 yr). Age-adjusted incidence and prevalence rates for the 0- to 19-yr-old children and adolescents were calculated using data from CBS (23) taking into account differences in the composition of the 0–19 population between the catchment area and the whole country. Furthermore, to compare our results with the observed trends in the mentioned European countries (7, 9–11), we performed a secondary analysis restricting the calculation of the incidence rate of type 1 diabetes to 0- to 14-yr-old children.

Trends in the incidence and prevalence rates over time were assessed using Joinpoint Regression software (National Cancer Institute, Bethesda, MD, USA). This method starts with a straight line, or zero joinpoints, to describe a trend over time and tests if the addition of one or more joinpoints identifies a significant change in the trend. A maximum of four joinpoints was allowed for each estimation, and trends were described by an annual percent change (APC) and the corresponding 95% CI for each segment and an average APC (AAPC) and the corresponding 95% CI for the whole study period. Joinpoint regression uses permutation tests to identify points where linear trends change significantly. A p-value less than 0.05 was used to determine if the APC and AAPC differed significantly from zero (29, 30).

Analyses were carried out using spss version 19.0 (SPSS Inc., Chicago, IL, USA), Microsoft Office Excel 2010, and Joinpoint Regression Program Version 4.1.0 (31).

Results

A total of 1213 new cases of type 1 diabetes (aged 0–19 yr, 50.0% boys) were identified from this subset of PHARMO RLS during the 13-yr period (January 1999–December 2011). As shown in Fig. 1A, the age-adjusted incidence rate of type 1 diabetes in 1999 was 19.5 (95% CI, 18.1–20.9) per 100 000 PY which increased to 25.3 (95% CI, 23.7–26.9) per 100 000 PY in 2011 [no joinpoint was detected; AAPC 3.71% (95% CI, 1.8–5.7)]. The trends were similar for boys and girls with significant AAPCs of 3.7% (95% CI, 0.7–6.7) and 3.8% (95% CI, 1.6–6.0), respectively (Fig. 2B). Figure 1C shows age-specific incidence rates of type 1 diabetes. At the start of this study (1999), children aged 0–4 yr had the lowest incidence rate of type 1 diabetes and children aged 5–9 yr had the highest rate with 7.5 (95% CI, 2.0–13.0) and 26.0 (95% CI, 15.6–36.4) per 100 000 PY, respectively (Fig. 1C). From 1999 to 2007, the incidence of type 1 diabetes among 0- to 4-yr-old children increased with a significant APC of 9.2% (95% CI, 0.3–18.9), while after 2007 the trend was decreasing with a non-significant APC of −20.5% (95% CI, −38.2 to 2.4). For the whole study period, a non-significant AAPC of −1.8 (95% CI, −9.9 to 7.1) was observed for the incidence of type 1 diabetes in this age category. For the 5- to 9- and 10- to 14-yr-old children, no joinpoint was detected and the overall trends were increasing with non-significant AAPCs of 2.9% (95% CI, −0.5 to 6.3) and 2.3% (95% CI, −0.6 to 5.4), respectively. From 1999 to 2011, an increasing trend with a significant AAPC of 7.8% (95% CI, 2.3–13.6) was observed for the oldest age group (15–19 yr, no joinpoint was detected).

After the exclusion of 15- to 19-yr-old adolescents, the age-adjusted incidence rate of type 1 diabetes was calculated for 0- to 14-yr-old children. In 1999, the incidence rate was 18.1 (95% CI, 16.6–19.6) per 100 000 PY which increased to 24.9 (95% CI, 23.1–26.7) per 100 000 PY in 2011 with a significant AAPC of 2.4% (95% CI, 0.6–4.1) (Fig. 2).

The mean age at the onset of type 1 diabetes remained relatively constant between 1999 and 2006. There was a gradual increase after 2006 with an unexpected high average age in 2010 (Fig. 3). No difference was observed between girls and boys in the mean age at onset of type 1 diabetes during the study period (data not shown).

There was a significant increase in the age-adjusted prevalence rate of type 1 diabetes among 0- to 19-yr-old children and adolescents with a significant AAPC of 3.8% (95% CI, 2.4–5.2) from 1998 to 2011 (Fig. 4A). A similar increasing pattern for the age-adjusted prevalence rates of type 1 diabetes was observed for boys and girls with significant AAPCs of 3.6% (95% CI, 2.2–5.0) and 4.9% (95% CI, 3.4–6.4), respectively. Figure 4C shows the trends in the prevalence rates of type 1 diabetes among different age categories. Between 1998 and 2011, the prevalence rate of type 1 diabetes decreased significantly in the 0- to 4-yr-old children with a significant AAPC of −6.9% (95% CI, −11.5 to −2.1). In contrast, for the other age groups a significant increase was observed with AAPCs of 1.7% (95% CI,

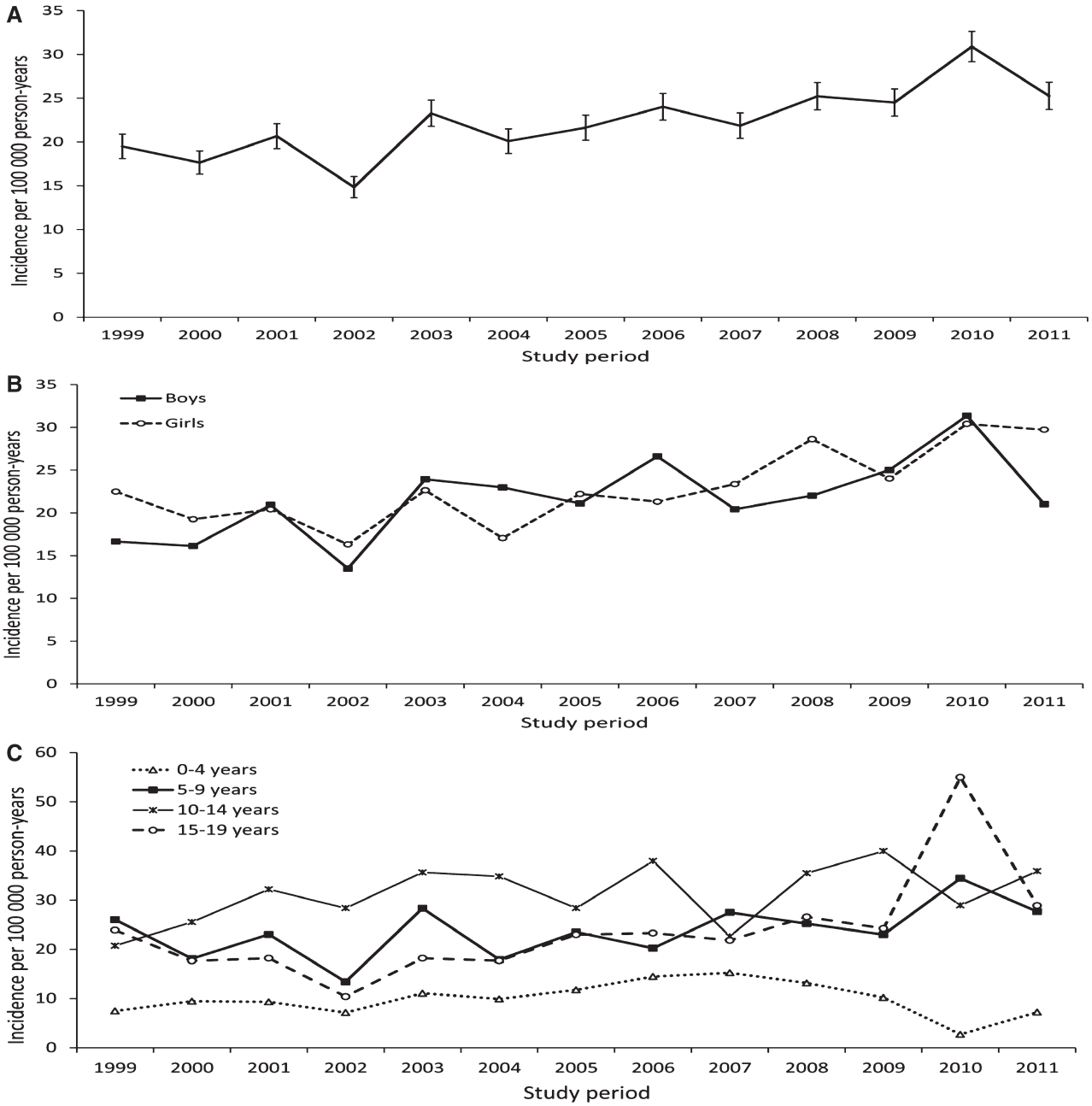

Fig. 1. Trends in the (A) age-adjusted incidence rates of type 1 diabetes in 0- to 19-yr-old children and adolescents; (B) age-adjusted incidence rates of type 1 diabetes in 0- to 19-yr-old boys and girls; and (C) age-specific incidence rates of type 1 diabetes (using age bands: 0–4, 5–9, 10–14, and 15–19 yr).

0.7–2.8) for 5–9 yr, 5.3% (95% CI, 3.5–7.1) for 10–14 yr, and 6.3% (95% CI, 4.8–7.7) for 15–19 yr (Fig. 4C).

Discussion

During the study period, the age-adjusted incidence (1999–2011) and prevalence rates (1998–2011) of type 1 diabetes in 0- to 19-yr-old Dutch children and adolescents continued to increase annually by an average of 3.7 and 3.8%, respectively. Restricting this study population to 0- to 14-yr-old children and adolescents showed a significant but lower annual increase 2.4%. The increase in the incidence and prevalence rates of type 1 diabetes was particularly large in the older age categories (10–14, and 15–19 yr). A decrease in the incidence and prevalence rates of type 1 diabetes was observed in the youngest (0–4 yr) age category in the most recent years after an increase until 2007. These trends resulted in a gradual increase in the age at disease onset (from 10.9 yr in 1999 to 11.7 yr in 2011).

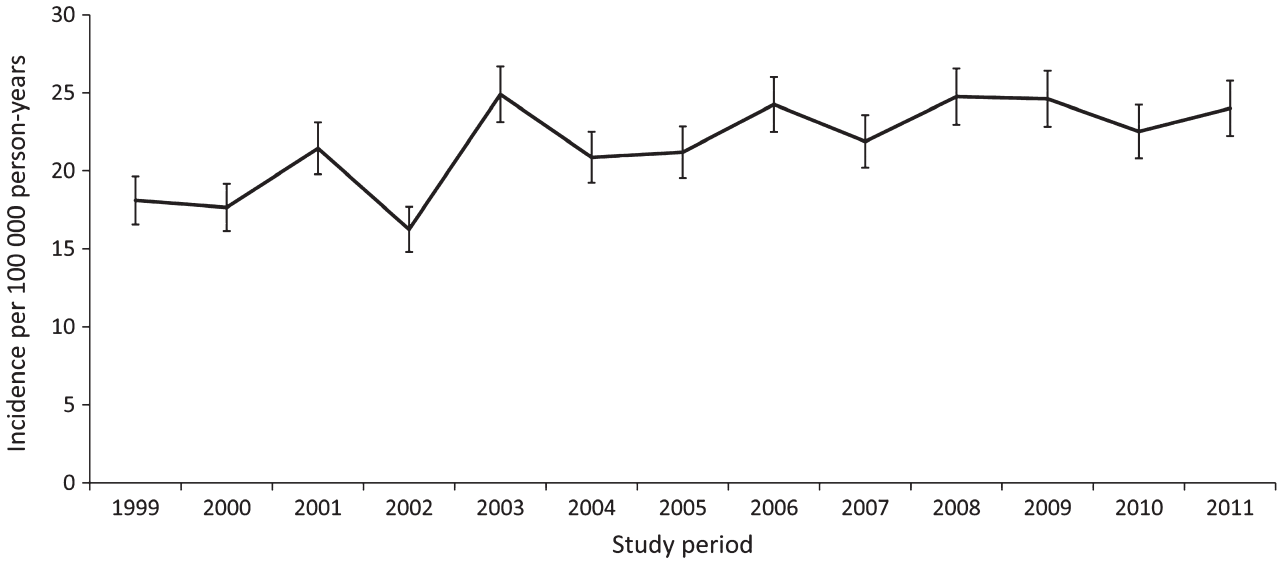

Fig. 2. Trends in the age-adjusted incidence rates of type 1 diabetes in the 0- to 14-yr-old children and adolescents.

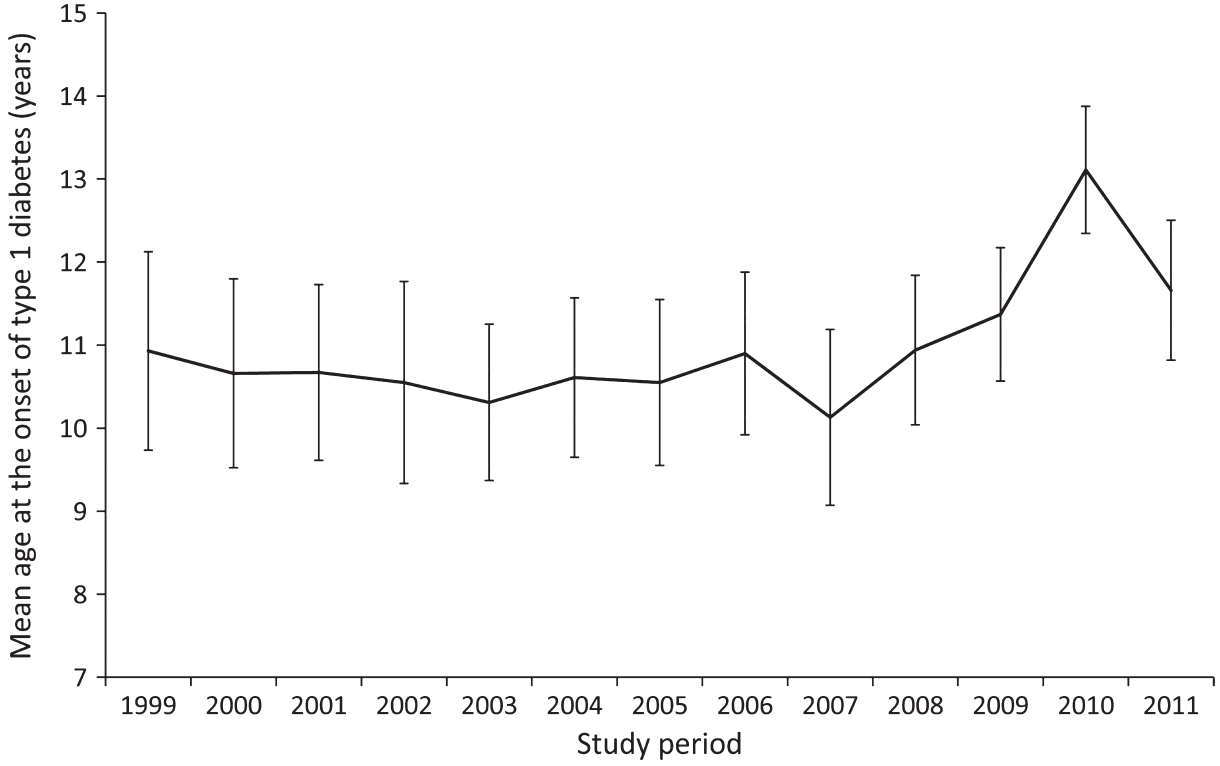

Fig. 3. Mean age at the onset of type 1 diabetes during the study period.

This study is the most recent population-based study on the epidemiology of type 1 diabetes among children and adolescents aged 0–19 yr in the Netherlands. In previous studies, Herings et al. estimated a prevalence of 11.0 per 100 000 children for type 1 diabetes among 0–19 yr children between 1989 and 1990 and van Wouve et al. reported an incidence of 18.6/100 000 (95% CI 17.7–19.4) per year for 0- to 14-yr-old children during 1996–1999 (16, 17). We observed decreasing trends in the incidence and prevalence rate of type 1 diabetes among 0- to 4-yr-old children which is in contrast with the findings of van Wouve et al. who reported the highest increase in rate per year for this age category (4.8% increase per year and 90.0% increase over 18.5 yr) (16).

Recently a number of European studies reported that incidence of type 1 diabetes in children younger than 15 yr stopped to increase (7, 9–11). Although after

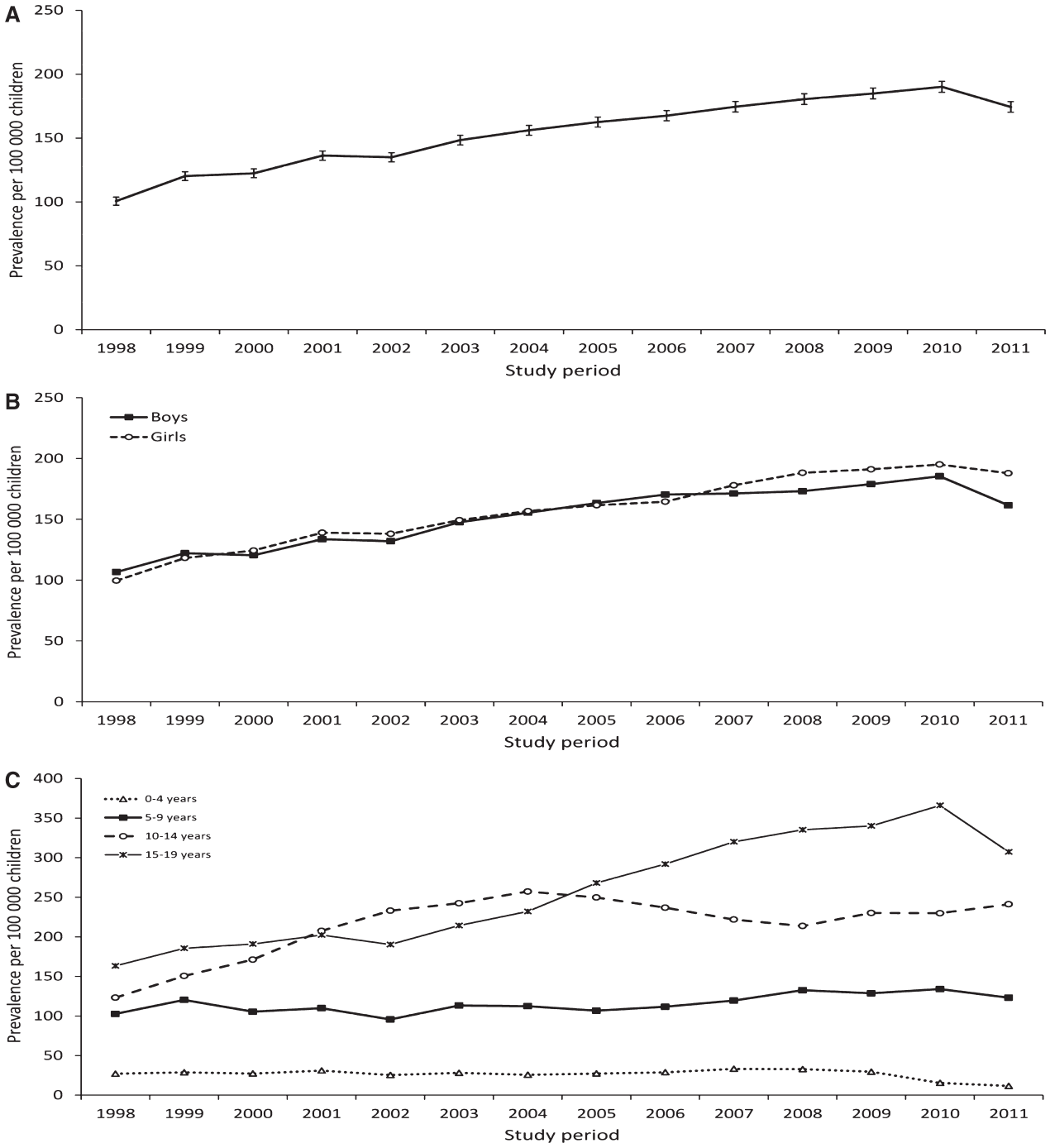

Fig. 4. Trends in the (A) age-adjusted prevalence rates of type 1 diabetes in 0- to 19-yr-old children and adolescents; (B) age-adjusted prevalence rates of type 1 diabetes in 0- to 19-yr-old boys and girls; and (C) age-specific prevalence rates of type 1 diabetes (using age bands: 0–4, 5–9, 10–14, and 15–19 yr).

2003, the age-adjusted incidence rate of type 1 diabetes in children aged 0–14 yr showed some fluctuations around 24.0 per 100 000 PY, the overall incidence rate in this age group continued to rise in this study with a significant AAPC of 2.4% (95% CI, 0.6–4.1). The highest AAPC for the incidence and prevalence rates was observed for the 15- to 19-yr-old adolescents which led to a right shift in the age at the onset of type 1 diabetes. Therefore, it is possible that what these studies observed was just a shift to disease onset at older ages which remained unnoticed due to the exclusion of the oldest age group (7, 9–11). Only a few studies have looked at time trends in the incidence of type 1 diabetes in those aged over 15 yr; therefore, more studies are needed in this age group to confirm the findings for this age group (4).

Although the decline in the incidence rate of type 1 diabetes in the youngest age group is encouraging, the overall increasing number of children and adolescents with type 1 diabetes should be taken seriously because the numbers of new patients with severe complications such as diabetic nephropathy and cardiovascular disorders at younger ages is likely to increase considerably (6). It is very important to investigate the potential factors that caused this shift toward older age at the onset of type 1 diabetes (4). As the environmental risk factors of type 1 diabetes are not completely known, implementing effective prevention programs is not possible yet. Therefore, health policy makers in countries with high numbers of young patients with type 1 diabetes need to provide appropriate facilities, high-quality care resources, and maintenance of good metabolic control for the increased numbers of children who will be diagnosed with diabetes in future years to delay these adverse chronic complications (2). To design appropriate prevention programs, further studies such as the 'Trial to Reduce IDDM in the Genetically at Risk (TRIGR)' study are required to provide better insight into the environmental risk factors and identify the most effective factors against type 1 diabetes (32, 33). Moreover, other studies are required to detect factors which can delay developing chronic complications at early ages.

This is the most recent population-based study in the Netherlands measuring the incidence and prevalence rates of type 1 diabetes in children and adolescents (4). One of the main strengths of this study is the inclusion of adolescents aged 15–19 yr and our long observational period (14 yr). Our population-based design by using the PHARMO RLS database which has been shown to be representative of the Dutch population is another important strength (19). Routinely collected detailed data on medication use in the PHARMO RLS reduced the probability of information bias and provides a better estimation on the number of cases compared with studies which used questionnaires or in which cases were identified through surveillance systems (they might underestimate the number of cases because of incomplete ascertainment rates or information bias) (15, 16, 34). This study consists of a cohort of 357–463 thousands children (including adolescents aged 15–19 yr), allowing us to provide a valid estimate of the incidence and prevalence rates of treated type 1 diabetes in the Netherlands in a long observational period of almost 14 yr. Finally, the rates were adjusted for the age- and sex-distribution of the Dutch children and adolescent population (using CBS data) which reduced bias in calculating incidence and prevalence rates (34).

The main limitation of this study is potential misclassification of patients with other types of diabetes. However, because of the low prevalence of other types of diabetes compared with type 1 diabetes, misclassification is probably a minor problem (35–40). Furthermore, by excluding patients who started oral glucose lowering medications before the start of insulin therapy (or at the same day) we aimed to exclude patients with type 2 diabetes. In a recent study, Rawshani et al. validated the use of insulin as a proxy for identifying cases of type 1 diabetes. They showed that using a case definition of receiving at least one insulin prescription for men and at least three insulin prescriptions for women if they had never been given oral glucose-lowering drugs for age 18–34 yr resulted in identifying 91% of cases who were classified as type 1 diabetes in the National Diabetes Register (NDR) (5). We used a slightly different definition. Because of our focus on children and adolescents aged 0–19 yr we did not expect gestational diabetes to occur and therefore used the same proxy for boys and girls. In addition, we know that in the Netherlands oral glucose lowering medications (e.g., metformin) are prescribed in children and adolescents with type 1 diabetes in order to decrease insulin resistance and the insulin dosage (41–43). Therefore, we decided to keep all the patients who started oral glucose lowering medications after starting insulin (or at the same) in our study population (n = 69). One remarkable finding was the high incidence rate of type 1 diabetes among 15–19 yr old adolescents in 2010 (Fig. 1C) for which we do not have any explanation. The last limitation of this study is related to outpatient pharmacies located inside the hospitals. Starting in 2004, a very low number of outpatient pharmacies inside the hospitals started to work which are located inside the hospitals. The number of these pharmacies gradually increased with a peak in 2010. Our database does not cover these pharmacies; therefore we might have missed a few cases of type 1 diabetes patients who always obtain their prescriptions from these outpatient pharmacies within the hospitals.

In conclusion, the incidence and prevalence rates of type 1 diabetes among children and adolescents aged 0–19 yr continued to increase in the Netherlands. An increase in incidence and prevalence rate was found in older age categories (10–14 and 15–19 yr), while in the youngest age group (0–4 yr) a decreasing trend was seen in the incidence and prevalence rate of type 1 diabetes. The increase in the number of new cases and older age at the onset of disease warrants further research to identify environmental triggering factors. Furthermore, providing appropriate health care facilities and maintenance of good metabolic control is highly recommended to protect young patients with type 1 diabetes from complicated comorbidities at young ages.

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Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

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