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Long term trends in oral antidiabetic drug use among children and adolescents in the Netherlands

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Global prevalence of type 2 diabetes mellitus is increasing rapidly, including in children and adolescents.
- There are limited data available on the incidence and prevalence of paediatric oral antidiabetic drug (OAD) use despite its importance in the treatment of paediatric type 2 diabetes.

WHAT THIS STUDY ADDS

- The incidence rates of OAD use among children and adolescents in the Netherlands increased from 1998 to 2011 by an average of 19% per year.
- OADs were not only used for type 2 diabetes, but also for other diseases such as type 1 diabetes and obesity.
- The increase in the number of new OAD users and use of OADs by younger children warrants further research to identify the indications for which these medications were prescribed and to find optimal treatment in children and adolescents with obesity and diabetes.

AIM

The aim of the study was to document long term trends in oral antidiabetic drug (OAD) use among children and adolescents in the Netherlands.

METHODS

A population-based cohort study was conducted using the Dutch PHARMO Database Network. All patients younger than 20 years old with at least one OAD dispensing were identified. Age-adjusted and age-specific incidence (1999–2011) and prevalence (1998–2011) rates of OAD use were calculated. Trends over time were assessed using joinpoint regression software. A subset of PHARMO Database Network (including community pharmacy dispensing records linked to general practitioner data (OPD-GP database)) was used to assess indications for OADs.

RESULTS

In 2011, the overall age-adjusted incidence and prevalence rates of OAD use were 20.7/100 000 (95% CI 19.2, 22.1) person-years (PY) and 53.8/100 000 (95% CI 51.5, 56.1) persons, respectively. The average annual percentage change (AAPC) in the overall age-adjusted incidence rates from 1999 to 2011 was 18.9% (95% CI 4.5, 35.2). The incidence and prevalence rates of OAD use were higher among females and older age categories. The increases in rates of OAD use were mainly driven by metformin. For only 50% of the 98 patients in the OPD-GP database, indications for OAD prescriptions were reported with type 1 diabetes (n = 20), type 2 diabetes (n = 16), and overweight/obesity (n = 10).

CONCLUSIONS

Incidence and prevalence rates of OAD use in children and adolescents substantially increased in the Netherlands, especially among older age categories (10–14 and 15–19 years) and females. The main indications for use of OADs were type 1 and 2 diabetes and overweight/obesity.

Introduction

Global prevalence of paediatric type 1 and type 2 diabetes mellitus is increasing rapidly [1–5]. Therefore the treatment and management of diabetes is a major burden for health care systems worldwide [4–6]. Although the main type of diabetes in children and adolescents is still type 1 diabetes, the prevalence of type 2 diabetes in children

and adolescents is increasing in many countries because of rising rates of obesity due to sedentary lifestyle [2, 4, 7, 8]. The increasing prevalence of obesity and type 1 and 2 diabetes among younger people and consequently the increased risk of micro- and macro-vascular complications at earlier ages, makes it necessary to use effective strategies to manage obesity, diabetes and their complications [9–11].

There are limited data available on the incidence and prevalence of paediatric oral antidiabetic drug (OAD) use despite its importance in the treatment of children and adolescents with type 2 and, to a lesser extent, type 1 diabetes where it can be used to improve body mass index (BMI) as well as insulin sensitivity [12–18]. Although insulin and metformin (in children aged 10 years and older) are the only antidiabetic agents currently approved for use in children and adolescents, other antidiabetic medicines (e.g. sulfonylureas, thiazolidinediones and incretins) are occasionally used in adolescents younger than 18 years [19]. Furthermore, although obesity is not an approved indication for using metformin, its use in obese children and adolescents has proceeded faster than the evidence of its benefits [20]. Having knowledge on the epidemiology and patterns of paediatric OAD use is important because it can give insight in the epidemiology of type 2 diabetes and/or the size of off-label use of OADs in children and adolescents. The aim of this study was to describe long term trends in the incidence and prevalence rates of OAD use including indications in children and adolescents in the Netherlands from 1998 to 2011.

Methods

Data for this study were obtained from the PHARMO Database Network which links drug dispensing records to hospital discharge records and other data sources such as general practitioner (GP) data using probabilistic linkage (www.pharmo.nl). 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 (www.pharmo.nl). 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 (http://www.whocc.no/atc_ddd_index).

For this population-based cohort study we used two different subsets of PHARMO Database Network. The first subset scatters throughout the whole country and covers several well-defined areas and therefore a well-defined population (n = 350 000–460 000 which is 9.4% to 11.9% of all children and adolescents aged 0–19 years in the Netherlands between 1998 and 2011). For this subset, the denominator population of the catchment area was obtained from the Dutch Central Bureau of Statistics (CBS) (http://www.cbs.nl). This allowed us to calculate population-based estimates including children and adolescents who are not registered at any pharmacy in the catchment area because they do not use medicines. 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 [21, 22]. Additionally, the fact that in the Netherlands most patients (about 90%) visit the same pharmacy leads to virtually complete patient medication records [23].

All children and adolescents aged 0–19 years with at least one dispensing for an OAD (based on the ATC codes for OAD preparations (A10B), listed in Supporting Information Table S1) between January 1998 and December 2011 were selected from this first subset and the date of the first OAD dispensing was defined as the cohort entry date (or index date). Prevalent OAD users were patients with at least one OAD dispensing in a particular year. New OAD users were patients who had an OAD dispensing for the first time while they did not have any OAD dispensing within 365 days prior to the cohort entry date. Therefore, all incident OAD users (older than 1 year old) were required to have at least 1 year valid history in the PHARMO Database Network before the cohort entry date. Prevalence rates of OAD use in each year were calculated by dividing the number of prevalent OAD users by the total number of children and adolescents living in the catchment area of the first subset of the PHARMO Database Network at the midyear of that particular year according to the Dutch CBS (http://www.cbs.nl). Annual incidence rates of OAD use were calculated by dividing the number of new OAD users by the follow-up time of all children and adolescents living in the catchment area of the first subset of the PHARMO Database Network at the midyear of that particular year (based on CBS data (http://www.cbs.nl)). Overall age-adjusted incidence and prevalence rates for 0–19 year old children and adolescents were calculated (http://seer.cancer.gov/seerstat/tutorials/aarates/definition.html) and stratified by gender. Annual crude incidence and prevalence rates were also calculated for different age categories (using the following age bands: 0–4 years, 5–9 years, 10–14 years and 15–19 years). For all incidence and prevalence rates 95% confidence intervals (95% CI) were calculated. The mean age at the initiation of OAD therapy was calculated for each year during the study period and stratified by gender.

To study further the patterns of OAD use, annual prevalence rates of use of different OAD classes together with rates of metformin monotherapy, sulfonylurea monotherapy, and a combination of metformin and a sulfonylurea were calculated during the study period.

Metformin monotherapy was defined as only metformin being dispensed with no other OADs in a particular year, whereas metformin combination therapy was defined as a dispensing for metformin with at least one additional dispensing for sulfonylurea. Furthermore, the prevalence rate of children and adolescents who had a combination of an OAD and insulin was calculated.

Trends in incidence rates over time were assessed using Joinpoint regression software (National Cancer Institute, USA). This method starts with a straight line, or 0 joinpoints, to describe a trend over time and tests if the addition of one or more joinpoints identifies a significant change in the trend. Joinpoint regression uses permutation tests to identify points where linear trends change significantly. A maximum of three joinpoints was allowed for each estimation, and trends were described by an average annual percent change (AAPC) and the corresponding 95% CI for the whole study period. A *P* value less than 0.05 was used to determine if the AAPC differed significantly from zero [24].

In order to investigate the indications for OADs we used a second, distinct subset of patients for whom their PHARMO community pharmacy dispensing records (outpatient database (OPD)) were linked to a general practitioner (GP) database (GP-OPD database). All children and adolescents aged 0–19 years with a valid history both in the community pharmacy and GP database and at least one OAD dispensing between 2002 and 2011 were selected from this second subset. The indication of the first OAD was retrieved from the GP files using International Classification of Primary Care (ICPC) codes (Supporting Information Table S1) (http://www.who.int/classifications/icd/adaptations/icpc2/en/). When the indication of the first OAD prescription was not available in the database, we tried to find the indication by checking further prescriptions of the same patient by looking at subsequent prescriptions for the same patient.

All analyses were carried out using SPSS version 19.0 (SPSS Inc. Chicago, Illinois, USA), Microsoft Office Excel 2010 and Joinpoint Regression Program Version 4.1.0 (National Cancer Institute, Bethesda, Maryland, USA).

Results

Incidence and prevalence rates

A total of 513 incident OAD users (mean age 13.3 [SD 4.6] years, 53.6% females) were identified from the first subset of the PHARMO Database Network during the period January 1999 to December 2011. The overall age-adjusted incidence rate of OAD use in children and adolescents aged 0–19 years was 10.7 (95% CI 9.6, 11.7) per 100 000 person-years (PY) at the beginning of our study period (1999) which decreased to 1.3 (95% CI 1.0, 1.7) per 100 000 PY in year 2000 (Figure 1A). From 2000 onwards a gradual increase with an unexpected peak in 2010 was observed in the incidence rate of OAD use. Joinpoint analysis of the overall age-adjusted incidence rates showed a significant increase during the whole period with an AAPC of 18.9% (95% CI 4.5, 35.2) (no joinpoint detected). This trend was similar for males and females with a statistically non-significant AAPC of 15.3% (95% CI –0.1, 33.0) for males and a statistically significant AAPC of 21.5% (95% CI 8.5, 36.0) for females (Figure 1B). During the whole study period, adolescents aged 15–19 years had the highest incidence rate of OAD use and the youngest age category (0–4 years) had the lowest incidence rate (Figure 1C). From 1999 to 2011, an increasing trend with statistically significant AAPCs of 21.3% (95% CI 3.0, 42.9) and 24.2% (95% CI 9.6, 40.8) were observed for 10–14 and 15–19 year old adolescents, respectively.

Apart from year 1999 when the mean age was 9.1 years, the mean age at onset of OAD therapy fluctuated between 12.4 and 16.4 years over the period 2000–2011. In 1999, females started OAD therapy at older ages than males, but at the end of the study (2011) the mean age at the initiation of OAD therapy was the same for both genders (Supporting Information Table S2).

There was an increasing trend in the age-adjusted prevalence rate of OAD use among 0–19 year old children and adolescents from 1998 to 2011 (Figure 2A). A similar increasing pattern for the prevalence rates of OAD use was observed for males and females (Figure 2B). Figure 2C shows the trends in the prevalence rates of OAD use among different age categories. The highest prevalence rate for OAD use was observed for the oldest age group (15–19 years) and the youngest age group (0–4 years) had the lowest prevalence rates (Figure 2C).

Patterns of OAD use

From 1998 to 2011, a total of 4650 OAD dispensings in (350 000–460 000) children and adolescents aged 0–19 years took place. While in 1998 a total of 53 OAD dispensings were issued to 0–19 year old children and adolescents, this number increased by 40.3-fold to 2137 in 2011 and the average number of OAD dispensings ranged from 14.8 in 1998 to 461.0 per 100 000 children and adolescents in 2011. During the whole study period, metformin was most frequently dispensed with 3148 dispensings (67.7%), followed by sulfonylureas (including glimepiride (10.7%), tolbutamide (8.1%) and gliclazide (6.9%)) (Table 1). Figure 3A shows the annual prevalence rates of OAD dispensings stratified by different classes. While in 1998 sulfonylureas had the highest prevalence rate among dispensed OADs, from 2002 onwards the highest annual prevalence rate of OAD dispensings was related to metformin (Figure 3A). There were no dispensings of dipeptidyl peptidase 4 (DPP-4)

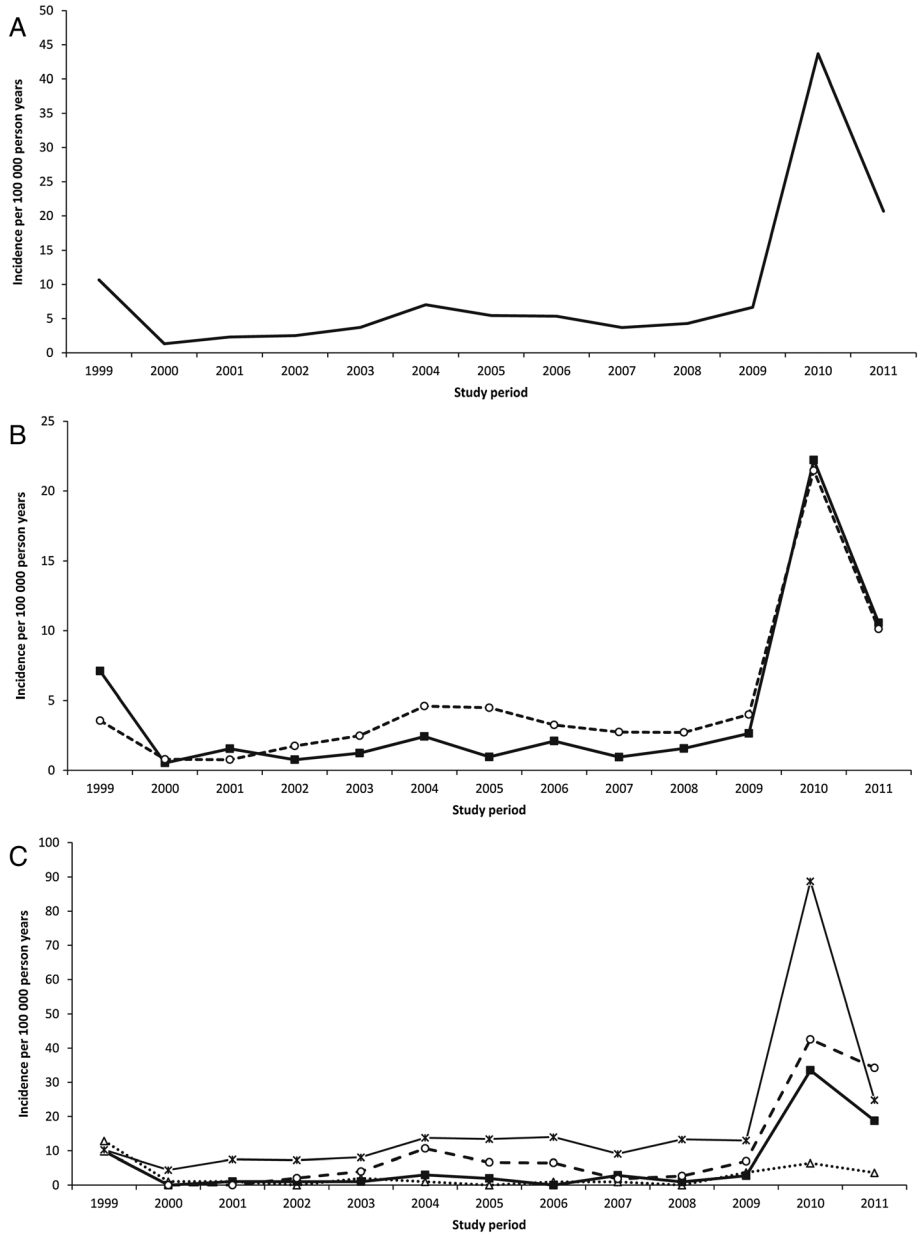

Figure 1

Trends in the (A) age-adjusted incidence rates of oral antidiabetic drug (OAD) use in 0–19 year old children and adolescents, (B) age-adjusted incidence rates of OAD use in 0–19 year old males (—■—) and females (- -○- -) and (C) age-specific incidence rates of OAD use (using age bands: 0–4 years (···△··), 5–9 years (—■—), 10–14 years (- -○- -) and 15–19 years (—×—))

inhibitors before 2009. The prevalence rate of this class of OADs was 0.2 per 100 000 children in 2009 which increased seven-fold to 1.5 per 100 000 children in 2011. For the thiazolidinediones the prevalence rate was 0.5 per 100 000 children in 2002 which increased to 1.1 per 100 000 persons at the end of study period. Assessment of the treatment regimens of metformin and sulfonylureas showed different patterns. The prevalence of metformin monotherapy increased from 2 per 100 000 persons in 1998 to 32.8 per 100 000 persons in 2011. The prevalence of sulfonylurea monotherapy had a decreasing trend while the combination of metformin and a sulfonylurea steadily increased from 0.3 per 100 000 persons in 1998 to 14.2 per 100 000 persons in 2011. As shown in Figure 2A the prevalence rate of OAD use in combination with insulin also increased during the study period (ranging from 1.7 per 100 000 persons in 1998 to 11.9 per 100 000 persons in 2011).

Figure 3B shows the prevalence rates of metformin dispensings in different age categories. As can be observed from this figure, older age categories (10–14 and 15–19 years) had the highest prevalence rates and metformin was dispensed to children younger than 10 years as well (off-label use). In 2010–11 a sharp increase was

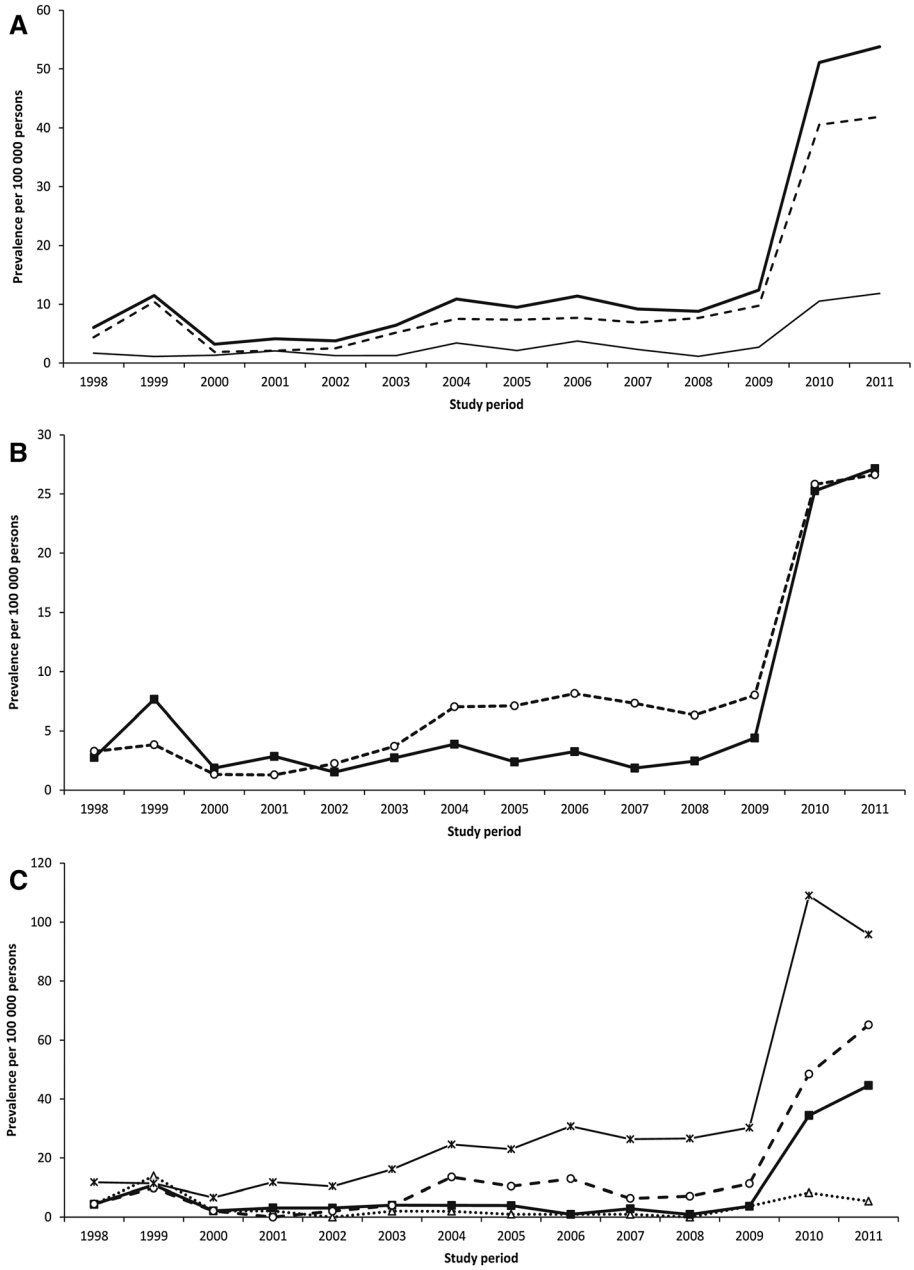

Figure 2

Trends in the (A) age-adjusted prevalence rates of oral antidiabetic drug (OAD) use in 0–19 year old children and adolescents (with and without insulin use); ——, OAD; ——, OAD + insulin; - - -, OAD only; (B) age-adjusted prevalence rates of OAD use in 0–19 year old males (—■—) and females (-○-) and (C) age-specific prevalence rates of OAD use in different age categories (using the following age bands: 0–4 (···△···), 5–9 (—■—), 10–14 (-○-), and 15–19 (—×—) years.

observed in the prevalence rates of metformin dispensing in all age categories. A similar pattern was observed for sulfonylurea with a peak in 2010 and 2011 (Figure 3C).

Figure 3D shows the annual prevalence rates of sulfonylureas during the study period. In 1998, a total of 33 sulfonylurea dispensings were obtained by our study population (18 dispensings were for gliclazide). The number of sulfonylurea dispensings increased by 16.8-fold to 556 in 2011. The prevalence rate of sulfonylurea dispensings increased by 4.7-fold (from 4.2 per 100 000 persons in 1998 to 19.6 per 100 000 persons in 2011). During the whole study period, glimepiride and tolbutamide had the highest prevalence rates among the sulfonylureas.

Indications for OAD prescriptions

In the GP-OPD database a total of 98 children and adolescents aged 0–19 years (65.3% females, mean age 13.5

Table 1

Number and percentage of different OAD dispensings from 1998 to 2011 in children and adolescents aged 0–19 years in the first subset of the PHARMO Database Network (population ranged from 357 051 children and adolescents aged 0–19 years in 1998 to 463 585 in 2011)

Drug name	Number of prescriptions Females	Males	Total
Biguanides	1780 (73.7%)	1368 (61.2%)	3148 (67.7%)
Metformin	1780 (73.7%)	1368 (61.2%)	3148 (67.7%)
Sulfonamides, urea derivatives	529 (21.9%)	721 (32.3%)	1250 (26.9%)
Glibenclamide	10 (0.4%)	42 (1.9%)	52 (1.1%)
Tolbutamide	137 (5.7%)	240 (10.7%)	377 (8.1%)
Glipizide	0 (0%)	1 (0.04%)	1 (0.02%)
Gliclazide	185 (7.7%)	136 (6.1%)	321 (6.9%)
Glimepiride	197 (8.2%)	302 (13.5%)	499 (10.7%)
Sulfonamides (heterocyclic)	0 (0%)	0 (0%)	0 (0%)
Combinations of oral blood glucose lowering drugs	3 (0.1%)	0 (0%)	3 (0.06%)
α-glucosidase inhibitors	14 (0.6%)	1 (0.04%)	15 (0.3%)
Thiazolidinediones	26 (1.1%)	27 (1.2%)	53 (1.1%)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	39 (1.6%)	84 (3.8%)	123 (2.6%)
Other blood glucose lowering drugs, excluding insulins*	24 (1.0%)	34 (1.5%)	58 (1.2%)
Total	2415 (100%)	2235 (100%)	4650 (100%)

*These include repaglinide, exenatide, liraglutide, etc.

[SD 4.8] years) had at least one OAD prescription. Information related to the main indications of OAD prescriptions was available in the GP-OAD subset for only 49 children and adolescents (50%). The majority of patients were prescribed OAD medication for type 1 diabetes (n = 20, 41%), followed by type 2 diabetes (n = 16, 33%) and overweight/obesity (n = 10, 20%). Out of 49 children and adolescents 22 used a combination of insulin and an OAD (17 had type 1 diabetes and five had type 2) (Supporting Information Table S3).

Discussion

From 1999 to 2011, the age-adjusted incidence rates of OAD use in 0–19 year old children and adolescents increased significantly by an average of 18.9% per year. The increase in the incidence and prevalence rates of OAD use was particularly large in females and older age categories (10–14 and 15–19 years). Metformin was the most frequently dispensed OAD (67.7%), followed by glimepiride, tolbutamide and gliclazide. In our second subset of the PHARMO Database Network it appeared that the majority of patients were prescribed OADs for type 1 diabetes, followed by type 2 diabetes and overweight/obesity.

There are few studies on prescription patterns and epidemiology of OAD use in children and adolescents [12–15,17]. Neubert *et al*. compared the prevalence of anti-diabetic medication use in children and adolescents aged 0–18 years across seven European countries in 2008 and they reported that this prevalence ranged from 8.0 in Sweden and Germany to 21.0 per 100 000 persons in the UK [17]. For the Netherlands they obtained data from the InterAction (IADB.nl) database which is a database of community pharmacies in the northern part of the country covering approximately 123 000 children and adolescents aged 0–18 years in 2008 [25]. According to Neubert *et al*., the prevalence of OAD use among Dutch children and adolescents was 12.0 (95% CI 6.0, 19.0) per 100 000 persons, and in our study the age-adjusted prevalence of OAD use was 8.8 (95% CI 7.8, 9.7) per 100 000 persons. In the study by Neubert *et al*., the highest prevalence of OAD use was found in the 6–11 year old children but in our study the highest prevalence of OAD use was observed in 15–19 year old adolescents [17]. A possible explanation for the observed differences may lie in regional differences since Neubert *et al*. used a database from the northern part of the country. In addition, the population in the study of Neubert *et al*. was relatively small and our 95% CIs were well within the 95% CI range of their study. Therefore, we think that the different point estimates may also have occurred by chance.

In another study by Liberman *et al*., trends in the use of antidiabetic, antihypertension and dyslipidaemia medications in children and adolescents aged 6–18 years in the US between 2004 and 2007 were documented [15]. They reported that the prevalence rate of OAD use in 2007 was 50 per 100 000 persons (23% increase since 2004) which is considerably higher

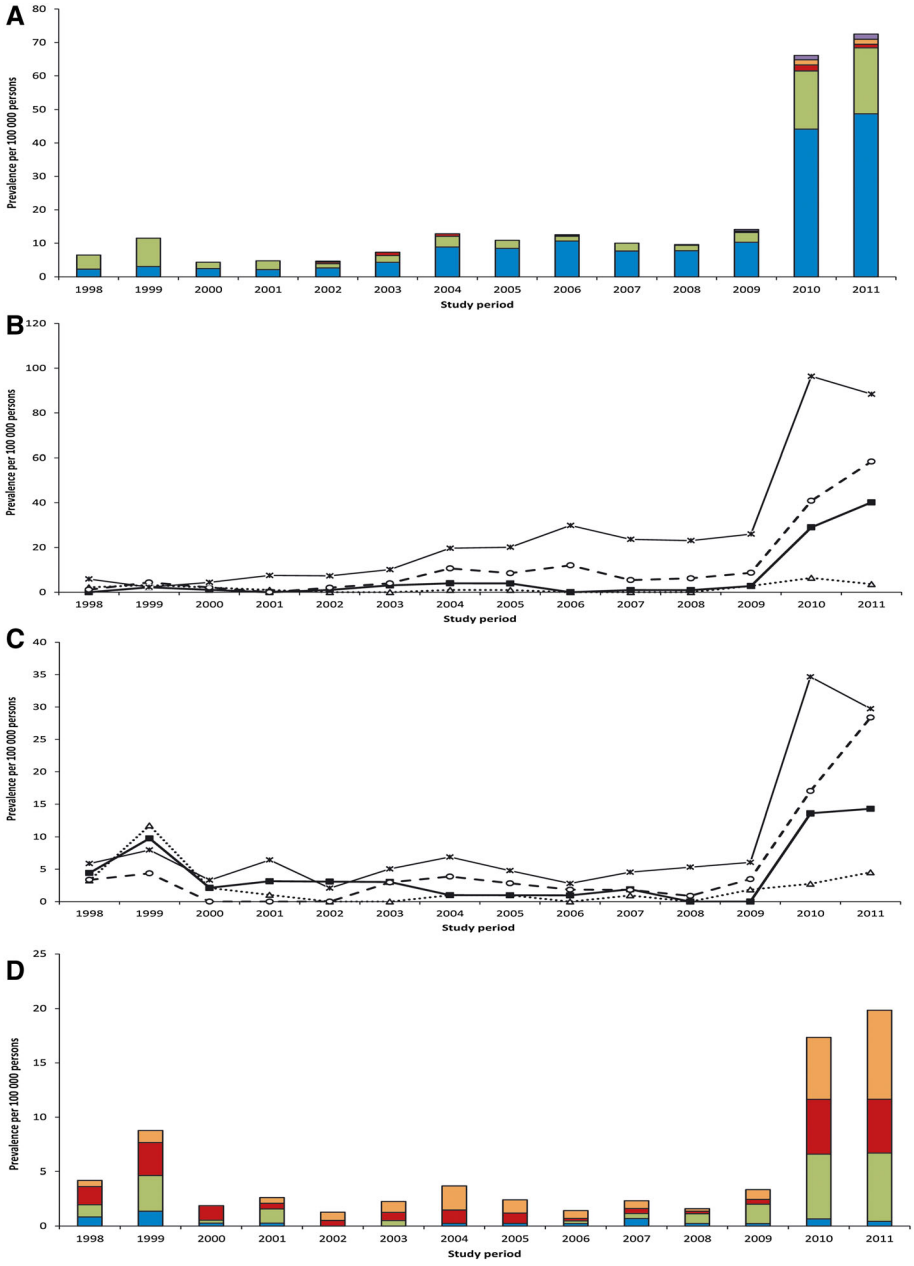

Figure 3

Annual prevalence rates of (A) oral antidiabetic drug (OAD) dispensings in children and adolescents aged 0–19 years stratified by different OAD classes, (▭) others (A10BX), (▭) DPP-4 inhibitors (A10BH), (▭) thiazolidinediones (A10BG), (▭) sulfonylureas (A10BB), (▭) biguanides (A10BA), (B) metformin in \different age categories, (•••△••) 0–4, (—■—) 5–9, (— o—) 10–14, (—x—) 15–19 years, (C) sulfonylurea dispensings in different age categories, (•••△••) 0–4, (—■—) 5–9, (— o—) 10–14, (—x—) 15–19 years and (D) sulfonylurea dispensings in different classes, (▭) glimepiride (A10BB12), (▭) gliclazide (A10BB09), (▭) tolbutamide (A10B03), (▭) glibenclamide (A10BB01)

than what we observed for Dutch children at the same time which may be explained by the higher prevalence of overweight, obesity and type 2 diabetes in US children [2, 15].

Surprisingly, we found a sharp increase in the prevalence rate of OAD use in 2010 (51.1 per 100 000 persons) which continued to rise in 2011 (53.8 per 100 000 persons) and was mainly caused by an increase in the number of metformin dispensings. This increase is in line with recent estimates of the Dutch central bureau of statistics (CBS) which shows more people were reported to have diabetes in the Netherlands and there is a peak in the percentage of patients with diabetes between 2010 and 2012 (http://www.cbs.nl/en-GB/menu/themas/gezondheid-welzijn/publicaties/artikelen/archief/2014/2014-4173-wm.htm). Although these data refer to the whole population and not to children and adolescents specifically, the similarity between these data and our findings is

noteworthy. However, we do not think the increase we observed only represents an increase in the prevalence of type 2 diabetes (the only formal indication for use of metformin [26]) in children and adolescents in the Netherlands. An explanation for this increase might be related to the effect of media and social awareness about the increasing trends in paediatric overweight/obesity and type 2 diabetes and the role of OADs in weight loss. Furthermore, there are a few recent publications which highlight the potential benefits of combination therapy (insulin and metformin) in type 1 diabetes [16, 27, 28]. Indeed, type 1 diabetes was the main indication reported for OAD use in our data and these patients used a combination of insulin and metformin.

At the beginning of our study (1998–2001), sulfonylureas were the most frequently dispensed OADs. From 2002 onwards, metformin was the dominant OAD medication dispensed to children and adolescents in the Netherlands. Up to now, metformin is the only oral hypoglycaemic agent approved for youths with type 2 diabetes from the age of 10 years onwards [26]. The prevalence rate of metformin use among children under 10 years was very low until 2009. We observed an increase in the prevalence rate of metformin use in children under 10 years of age in 2010 which continued to rise in 2011 suggesting that off-label use of metformin increased in the later years. In the study by Liberman *et al*., metformin had the highest frequency (approximately 73% of all medications) and the prevalence rate of metformin use increased by 24.9% from 2004 to 2007 [15]. In another study, Hsia *et al*. reported a substantial increase in metformin prescriptions in children and adolescents in the past decade. This increase was considerably higher among teenage females receiving metformin for the treatment of polycystic ovary syndrome (PCOs) in general practice which is also an off-label indication [13]. In our study we only found one case of PCOs as an indication for OAD use in the medical files.

Sulfonylureas are often prescribed in patients with permanent neonatal diabetes mellitus (PNDM) and maturity onset diabetes of the young (MODY) [29, 30]. The underlying problem in these types of diabetes is failure of insulin secretion and action and therefore they respond very well to sulfonylureas. The incidence and prevalence of sulfonylurea use in children and adolescents may reflect the number of PNDM and MODY cases. However because of the low prevalences of these types of diabetes and incomplete indication data (for OAD use) we cannot draw a certain conclusion on the epidemiology of PNDM and MODY in the Netherlands.

In another study, Kostev *et al*. used IMS Disease Analyzer data from Germany and France (2000–2010) to document the unlicensed use of metformin in children and adolescents aged 1–18 years. The main indication for metformin in their study was diabetes mellitus, with the majority of patients having a diagnosis of type 2 diabetes. The share of diabetes as a prescription indication is rather different in Germany and France from what Hsia *et al*. reported for the UK, where PCOs was the most common indication for metformin prescriptions in females [13, 14]. In our database the majority of patients with OAD dispensings did not have any recorded indication and for those with recorded indications, the most frequently recorded indication was type 1 diabetes, followed by type 2 diabetes and overweight/obesity.

Under-diagnosis and under-treatment of paediatric type 2 diabetes will lead to significant increases in micro- and macro-vascular complications and subsequently increased usage of health care facilities and health care costs [15]. Therefore, enhancing efforts to educate health care professionals (mainly public health physicians) regarding optimal screening of children and adolescents at risk for type 2 diabetes and referring them to lifestyle and behavioural management programmes are necessary. Moreover, proper pharmacotherapy should be commenced in children and adolescents who are diagnosed with type 2 diabetes at an appropriate point in time. Despite the lack of enough randomized clinical trials on efficacy and safety of OADs (particularly long term treatment), increasing trends in overweight and obesity in children and adolescents have resulted in increased off-label use of OAD medications (especially metformin). In our study the indications for OAD prescriptions were not completely recorded which makes it difficult to draw firm conclusions on the magnitude of off-label use of OADs in children and adolescents and further studies are required.

Our study is the most recent population-based study in the Netherlands measuring the incidence and prevalence rates of OAD use in children and adolescents. One of the main strengths of this study is our long observational period (14 years). Our population-based design, by using the PHARMO Database Network which has been shown to be representative of the Dutch population, is another important strength (www.pharmo.nl) [31]. Routinely collected detailed data on medication use in the PHARMO Database Network reduces the probability of information bias and provides a valid estimation of the number of dispensings. This study consists of a large cohort of approximately 350 000–460 000 children and adolescents aged 0–19 years living in a well-defined catchment area, allowing us to provide valid estimates of the incidence and prevalence rates of OAD use. Rates were further adjusted for the age and gender distribution of the children and adolescent population (using CBS data) in order to be representative for the population of children and adolescents in the Netherlands [32]. Identifying the indications for OAD prescriptions was another strength of our study. However, the subset of PHARMO which we used to identify the indications of OAD medications was relatively small and did not have complete records on the indications. Another limitation of our

study is related to outpatient pharmacies located inside the hospitals. From 2004 onwards, outpatient pharmacies were initiated inside the hospitals, of which the numbers increased gradually over the years. Our database does not cover these pharmacies. Therefore we might have missed a small number of OAD dispensings to patients who always obtain their prescriptions from these outpatient pharmacies within the hospitals.

In conclusion, we observed that incidence and prevalence rates of OAD use among children and adolescents aged 0–19 years increased from 1998 to 2011 in the Netherlands. The highest increase in the incidence and prevalence rates was found among females and older age categories (10–14 and 15–19 years). Metformin was the most frequently dispensed OAD for our study population (68%) with the highest increase in incidence and prevalence rates, and was also used for off-label indications such as prescribing for patients with obesity, type 1 diabetes and children younger than 10 years of age. The increase in the number of new OAD users and use of OADs by younger children warrants further research to identify the indications for which these medications were prescribed and to find optimal treatment in children and adolescents with obesity and diabetes.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Contributors

S.F. contributed to the study design, analyzed the data and wrote the manuscript. P.S., J.O., M.V., C.K., R.H., A.B. and A.M. contributed to the study design, the discussion and edited the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1
List of codes used to identify different oral antidiabetic (OAD) medications (ATC codes) and their indications (ICPC codes)

Table S2
Mean age at the onset of oral antidiabetic drug (OAD) therapy during the study period

Table S3
Indications for oral antidiabetic (OAD) prescriptions in children and adolescents aged 0–19 years