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## Use of non-insulin antidiabetic drugs in children and young adults – a Scandinavian drug utilization study from 2010-2019

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**What is already known about this subject:**

- The prevalence of type 2 diabetes mellitus is rising among children, adolescents and young adults.
- There are limited data on the prevalence of non-insulin antidiabetic drug use in children and young adults, and no European studies report data beyond 2011.

**What this study adds:**

- This study provides updated prevalence proportions of non-insulin antidiabetic drug use in Scandinavian children and young adults.
- Use of non-insulin antidiabetic drugs increased 37% from 2010 to 2019, reaching 0.59 per 1000 individuals in 2019, which is substantially higher than the presumed prevalence of type 2 diabetes at this age.
- Metformin was by far the most widely used drug, but there was a marked uptake in the use of GLP-1 analogues.

## **Abstract**

Knowledge on utilization patterns of non-insulin antidiabetic drugs in childhood and youth is limited. Therefore, we conducted a population-based drug utilization study using publicly available aggregate data on use of non-insulin antidiabetics from 2010-2019 in Scandinavia (Denmark, Norway, and Sweden) in individuals aged up to 24 years. For each non-insulin antidiabetic drug, we calculated the annual prevalence proportion of users, overall and for specific age groups.

From 2010 to 2019, the prevalence of non-insulin antidiabetic users in Scandinavia increased 37% from 0.43 to 0.59/1000 individuals. The prevalence proportions were highest among female adolescents and young adults, but the largest relative increase in use was seen among 10-14-year-olds (78%). Metformin was by far the most widely used non-insulin antidiabetic drug with a prevalence proportion of 0.51/1000 in 2019, followed by glucagon-like peptide-1 (GLP-1) analogues, which, however, showed an 8-fold relative increase during the study period.

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## Introduction

The prevalence of type 2 diabetes mellitus (T2DM) in childhood and youth has been increasing in recent decades (1,2), although prevalence rates varies widely depending on age, sex, ethnicity and geographical region in a range of 0 to 5,300 per 100,000 population (3). Generally, there is little evidence regarding the optimal strategies for the treatment of young-onset T2DM (4). Lifestyle changes are recommended along with initiation of metformin as first line therapy except in cases of severe hyperglycemia or ketosis where insulin is preferred (5,6). Metformin is approved for children over the age of 10 with type 2 diabetes in most countries (5). Only recently, the first glucagon-like peptide-1 (GLP-1) analogue liraglutide was approved for use in pediatric patients (7,8). Use of other non-insulin antidiabetic agents known to be effective in adults with T2DM, such as dipeptidyl peptidase-4 (DPP4) inhibitors and sodium-glucose co-transporter-2 (SGLT2) inhibitors, may also be beneficial in children and young adults with T2DM, but there are limited studies specifically regarding their use and safety in young adults, and they are generally not approved for patients < 18 years of age (5).

Knowledge on utilization of non-insulin antidiabetics for children, adolescents and young adults are needed to support rational use of these therapies as well as to identify evidence gaps. We therefore aimed to describe trends in the use of non-insulin antidiabetic drugs among Scandinavian individuals aged 0-24 years.

## Methods

### Study design and population

This study was a population-based drug utilization study on use of non-insulin antidiabetics among individuals aged 0-24 years in the Scandinavian countries (Denmark, Norway, and Sweden) in the period from 1 January 2010 to 31 December 2019. The size of the study population increased slightly during the study period and consisted of 6,039,632 individuals in 2010 and 6,278,992 individuals in 2019.

## **Data sources**

The study used publicly available prescription data from Scandinavian national health data authorities; Danish online drug use statistics ([www.medstat.dk](http://www.medstat.dk)) (9), the Norwegian Prescription Database ([www.norpd.no](http://www.norpd.no)) (10) and the Swedish Prescribed Drug Register ([https://sdb.socialstyrelsen.se/if\\_lak/val.aspx](https://sdb.socialstyrelsen.se/if_lak/val.aspx)) (11). All three databases are nationwide and provide aggregate drug use statistics based on individual-level patient data on prescriptions filled at community pharmacies. As it is mandatory to report drug sales electronically in Scandinavia, and as all antidiabetic drugs require prescription from a medical provider, data are virtually complete and the databases thus represent valid information on the annual prevalence of a given drug (12).

We identified non-insulin antidiabetic drug use by WHO Anatomical Therapeutic Chemical (ATC) codes and included data on overall use of non-insulin antidiabetics (ATC code A10B) and on use of specific antidiabetic drug groups; biguanides (A10BA), sulfonylureas (A10BB), DDP-4 inhibitors (A10BH), GLP-1 analogues (A10BJ), SGLT2 inhibitors (A10BK) and combinations of oral glucose lowering drugs (A10BD).

## **Analyses**

We calculated the annual prevalence proportion of users as the annual number of individuals aged 0-24 years per 1000 individuals in the population who had filled at least one prescription for non-insulin antidiabetics in Scandinavia. We calculated the annual prevalence proportion of users overall, and by drug group, sex, age specific categories (0-9, 10-14, 15-19, 20-24 years) and country. All statistical analyses and plots were generated using Stata software version 16.0 (StataCorp, Tx, USA).

## **Ethics**

Data were publicly available in all three countries and therefore approvals from data protection agencies or ethical committees were not required.

## Results

During 2010, we identified 2,572 individuals 0-24 years of age who had filled one or more prescriptions for a non-insulin antidiabetic drug in Scandinavia, equivalent to a prevalence of 0.43 users per 1000 individuals (Figure 1A). This number increased to 3,682 users in 2019, corresponding to a prevalence of 0.59/1000 (Figure 1A).

The majority of users were female who had a prevalence of 0.90/1000 in 2019 compared to 0.30/1000 in males (Figure 1B). With respect to age, use of non-insulin antidiabetics was highest in young adults aged 20-24 years, where the prevalence increased 35% from 1.43/1000 in 2010 to 1.93 /1000 in 2019 (Figure 1C). Increase in the use of non-insulin antidiabetics was also seen among adolescents aged 15-19 years where the prevalence increased 47% from 0.51 to 0.75/1000 during the study period. In children aged 10-14 years the prevalence nearly doubled from 0.09 to 0.16/1000, whereas there were very few users under 10 years of age (Figure 1C). Compared to Norway and Sweden, Denmark had more prevalent use of non-insulin antidiabetics, but the difference in prevalence diminished over time and was similar by 2019 (Figure 2).

Metformin was by far the most commonly used non-insulin antidiabetic drug in Scandinavia during the entire study period. During 2010-2019, the use increased by 37% reaching a prevalence of 0.51/1000 individuals in 2019 (Figure 3). In 2010, the second most used non-insulin antidiabetic were sulfonylureas, but these were surpassed by GLP-1 analogues from 2013 and onwards and by SGLT-2 inhibitors in 2018. During the study period, we observed an 8-fold increase in the use of GLP-1 analogues reaching a prevalence of 0.08/1000 by 2019 (Figure 3). This increase was driven by an increased prevalence among the 15-24 year-olds, whereas use of GLP-1 analogues in children under 15 years of age was extremely rare. Among Scandinavian children under 15 years of age,

there were <5 users of SGLT-2 inhibitors, DPP-4 inhibitors or combinations of glucose lowering drugs and only very few users in the 15-19 year age group. However, among young adults aged 20-24 years, we observed a marked relative increase in the use of DPP-4-inhibitors and SGLT-2 inhibitors during the study period, although the total number of users was still low.

In a *post hoc* analysis to identify the potential impact from metformin prescribed for polycystic ovarian syndrome, we repeated the analysis specified by sex restricted to 0-19 year olds, finding a slightly attenuated ratio of female to male prescribing (Supplementary Figure S1)

## Discussion

In this Scandinavian study of nationwide prescription data, we found increasing prevalence of non-insulin antidiabetic drug use in children, adolescents and young adults from 2010 to 2019. In line with previous studies (13–16), use was most prevalent among females and young adults and adolescents had the highest prevalence with metformin being the most commonly prescribed drug. Use of GLP-1 analogues increased markedly during the study period, whereas use of DPP-4 inhibitors and SGLT-2 inhibitors were extremely rare in children aged 0-19 years.

There exists only few studies on prescription patterns of non-insulin antidiabetic drugs in children and adolescents (13–18) and comparison between these is hindered by varying age cutoffs and variation in the drug classes included in the studies. The most recent study, conducted in US claims data of commercially-insured children and adolescents aged 10-18 years, showed increasing prevalences of non-insulin antidiabetic drug use from 2004 to 2019 reaching 1.62 per 1,000 in 2019 (16). This is markedly higher than the prevalence among 10-19 year-olds observed in our study (0.45/1000 in 2019). This difference may be explained by ethnic disparities and by the higher prevalence of overweight, obesity and type 2 diabetes in US children (3). No European studies report data beyond 2011 (13,18) and

only one is population-based (18). The latter, a study of Dutch children and adolescents under 20 years of age, found a prevalence of non-insulin antidiabetic use of 0.54/1000 in 2011 (18), compared to only 0.17/1000 in 2011 in our study. Another study investigated the prevalence of oral antidiabetic drug use in 2008 in children aged 0-18 years across seven European countries and found wide variations in the use of antidiabetics with prevalences ranging from 0.08 to 0.21/1000 (19). All studies, however, show increasing use of non-insulin antidiabetic drugs (14,16,18), which might be due to an increasing prevalence of T2DM. Unfortunately, there are only limited data available on the prevalence of T2DM in Scandinavian children. One cross-sectional study from 2014 reported a prevalence of T2DM in Danish children and adolescents of 0.006/1000 (age 0-18 years) (20). Studies from other European countries found prevalence rates of 0.02/1000 in German children under 20 years of age in 2016 (21) and 0.01/1000 in Irish children below 16 years in 2015 (22). In both Germany and Denmark, prevalence rates remained unchanged compared to data from the beginning of the 2000's (20,21). All prevalence estimates, however, stems from cross sectional surveys where patients were only identified at specialized diabetes care institutions. The reported prevalence numbers are substantially lower than the observed prevalence of antidiabetic drug use in this study, which, assuming comparable prevalences of T2DM across Scandinavia, indicates either increased pharmacological treatment of existing patients with T2DM and/or significant off-label use.

Off-label use for other indications than diabetes is primarily an issue when reporting on metformin and GLP-1 analogue prescription rates, as these may be used off-label for e.g. prediabetes, obesity and polycystic ovarian syndrome (PCOS). Previous studies have reported conflicting results on the proportion of off-label metformin use in children and adolescents aged 0-18 years and use seemingly varies considerably between countries. In the UK and US, studies have reported that 50-65% of metformin prescriptions among children and adolescents are made for other indications than diabetes (15,23), and that PCOS is listed as the indication on 30-40% of prescriptions (16,23). In Germany and France, however, only 8-20% of metformin prescriptions among children are not made for T2DM (24)



Across sexes, use of non-insulin antidiabetic drugs were 2-3 times higher among females than among males. This finding is in line with previous studies that have shown a female preponderance in young-onset type 2 diabetes with a female:male ratio of ~2:1 (2,4). This sex difference is not explained by overweight and obesity, as rates of overweight and obesity is slightly higher in Scandinavian boys than girls; the estimated prevalence of obesity in 2013 being 4.3-8.7% in boys<20 years and 4.0-5.9% in girls<20 years (25).

The major strength of our study is the inclusion of nationwide prescription data from three neighboring countries, eliminating selection and recall bias and resulting in a large sample size. Furthermore, the Scandinavian prescription registries have high validity (12) with >99% of antidiabetic drugs being identifiable on an individual level. However, the study also has limitations. Due to the use of aggregate-level data, we were not able to describe utilization trends on an individual level, e.g. incidence of use and duration of treatment, and we did not have information on indications for use of antidiabetic drugs to clarify the extent of off-label use.

## **Conclusions**

Use of non-insulin antidiabetic drugs is increasing steadily among children and young adults and more than the presumed prevalence of T2DM in this group. Further studies are required to investigate the extent and safety of off-label use as well as utilization trends on an individual level.

## **Conflicts of interest statement**

All authors except CEC are involved in a regulator mandated phase IV safety study on use of semaglutide funded by Novo Nordisk with funding paid to the institution where the authors are employed and with no relation to the present study.

## **Funding**

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## **Data availability statement**

The data that support the findings of this study are publicly available. Data can be retrieved from the Danish online drug use statistics ([www.medstat.dk](http://www.medstat.dk)) (9), the Norwegian Prescription Database ([www.norpd.no](http://www.norpd.no)) (10) and the Swedish Prescribed Drug Register ([www.socialstyrelsen.se](http://www.socialstyrelsen.se)) (11).

## **Author contributions:**

HKJ, LR and AP conceived and designed the study, analyzed and interpreted the data, and HKJ wrote the manuscript. KF, ØK, ML and CEC contributed to the design of the study and assisted with the interpretation of the data and writing of the manuscript. All authors have approved the final version of the manuscript.

## **Ethics approval statement**

Data were publicly available in all three countries and therefore approvals from data protection agencies or ethical committees were not required.

## **Nomenclature Statement**

Key ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>.

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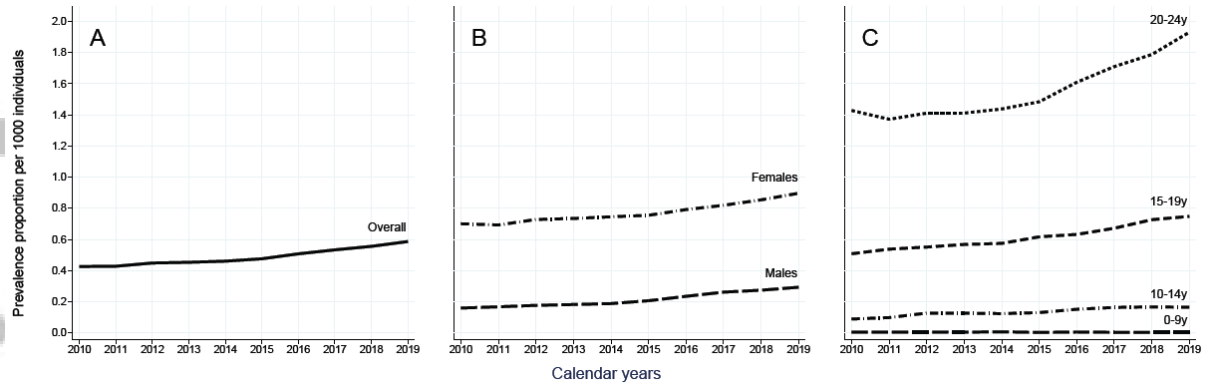
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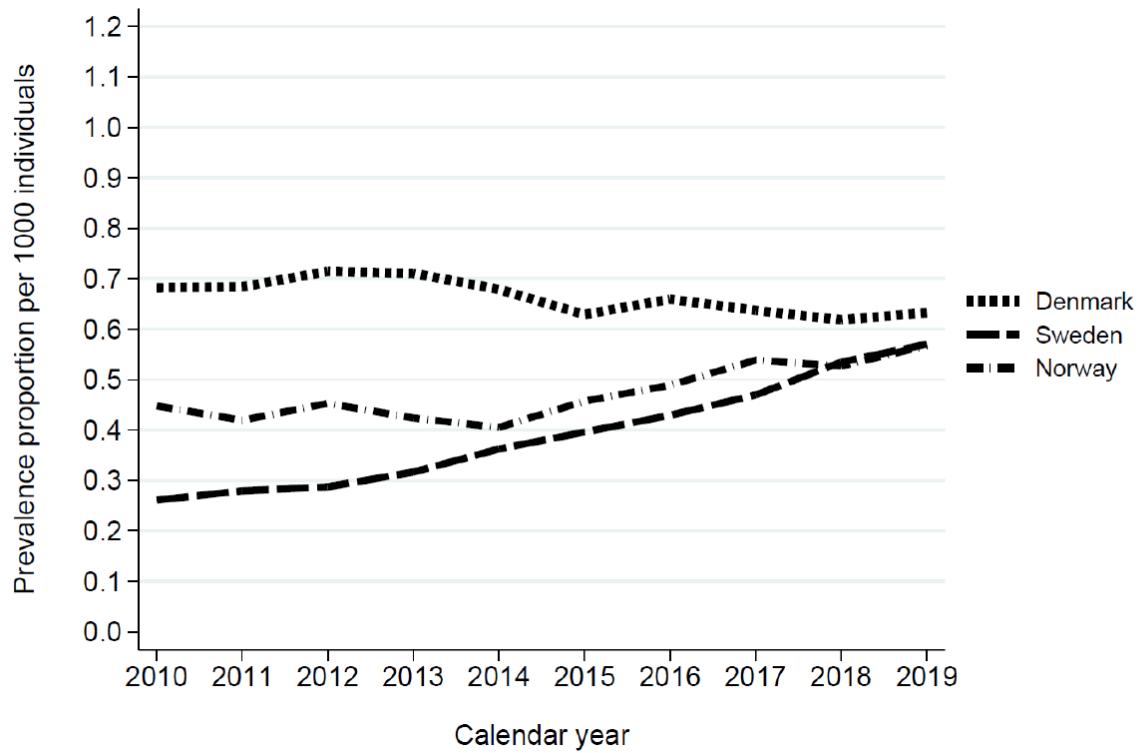
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**Figure 1**

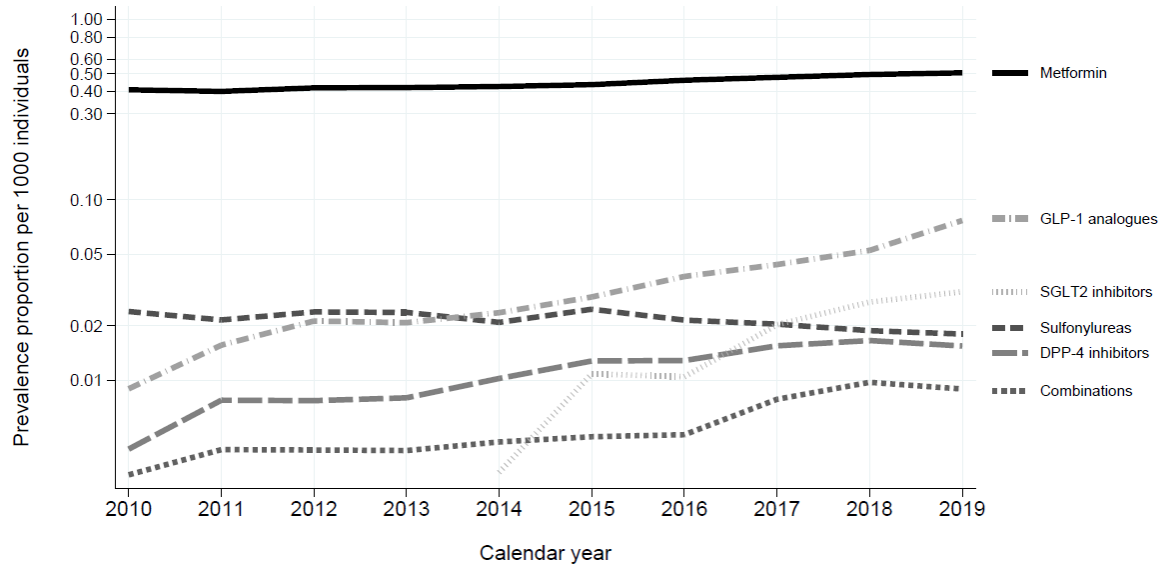
Prevalence of non-insulin antidiabetic drug use among children and young adults age 0-24 during 2010-2019, (A) overall, (B) stratified by sex and (C) stratified by age groups.



**Figure 2**

Prevalence of non-insulin antidiabetic drug use among children and young adults age 0-24 during 2010-2019, stratified by country

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**Figure 3**

Prevalence of non-insulin antidiabetic drug use among children and young adults age 0-24 during 2010-2019, stratified by drug group. Note the logarithmic y-axis.

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