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ORIGINAL ARTICLE

Geographical variation in the use of glucose-lowering drugs in type-2 diabetes in Denmark: A nationwide drug utilization study

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Aims: To analyse geographical variation in use of glucose-lowering drugs (GLDs) for type-2 diabetes (T2DM) in Denmark.

Methods: We included all adults who filled a prescription for a non-insulin GLD indicated for T2DM from 2010 to 2023 in Denmark. Stratified by each of the five regions, we calculated the annual incidence rate, the annual prevalence proportion and the total volume of dispensed GLDs from 2010 to 2023. We calculated the proportion of incident prescriptions for GLDs that were issued by different prescriber types and characterized non-insulin GLD users in each region in 2023. Finally, we analysed variation at the municipal level.

Results: Totally, data from 478 118 adults were included. The user characteristics were comparable across the regions with no differences in the median age (range 66–67 years) or in the sex distribution (range 56–58% males). In all regions, general practitioners were the main prescribers of GLDs. There were minor regional differences in the use of GLDs, with a predominant and increasing use of metformin, accelerating use of SGLT-2is and GLP-1RAs, and declining use of SUs over time. In Q4 2023 the ranges of prevalence per 1000 inhabitants were 31 to 44 for metformin, 16 to 23 for SGLT2is, 14 to 23 for GLP-1RAs and 1.37 to 1.58 for SUs. There were some differences in characteristics of GLD users across regions, with a slightly higher prevalence of diabetes-related complications and larger involvement of hospital physicians in the Capital Region compared to the other regions. We identified four municipality clusters that differed marginally in the prescribing pattern of non-insulin GLD.

Conclusion: The minor differences in the use of GLDs indicate equal access to GLDs across Denmark. Differences at the municipal level call for future studies to investigate if these reflect differences in clinical practice or differences in T2DM populations.

KEYWORDS
anti-diabetics, diabetes 2, pharmacoepidemiology, prescribing pattern

1 | INTRODUCTION

The prevalence of type-2 diabetes (T2DM) is increasing globally.[1] From 1996 to 2017, the prevalence of T2DM in Denmark increased from 1.2% to 4.5%.[2] The expected lifetime risk of T2DM was 26% for Danish men and 21% for Danish women in 2017, corresponding to an increase of 51% and 36% over barely 20 years.[3] Despite improvements in the disease burden and mortality at the individual level,[2] the increasing number of patients contributes to a significant loss of life to T2DM in the population.[3]

The diabetes epidemic has led to both the development of new non-insulin glucose-lowering drugs (non-insulin GLD), modification of treatment strategies,[4,5] and rapid revisions of guidelines. The most recent consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) downplays the role of metformin as first-line glucose-lowering therapy and advocates a highly individualized and patient-centred approach to the management of T2DM.[6] This has fueled dramatic changes in the prescribing of non-insulin GLD in Denmark with a decreasing use of sulphonyl urea analogues (SUs) and an increasing use of the newer agents, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2is).[7]

Denmark has a tax-financed health care system that provides free access to treatment based on needs rather than financial capacity, social status or membership in any insurance scheme.[8] All residents have free and direct access to general practitioners (GPs) and selected specialists. The GPs are the gatekeepers who control further patient access to the secondary health care system,[9] and most prescriptions are issued by GPs.[10] As all other Danish doctors, GPs are expected to provide due care and adherence to prescribing guidelines is a matter of professional accountability rather than a legal requirement. Prescription drugs can only be obtained from pharmacies, and patients have access to prescription and over-the-counter drugs with a progressive reimbursement scheme for prescribed medicines.[11] Anyone who buys a dipeptidyl-peptidase-4 inhibitor (DPP-4i) or a SGLT-2i receives reimbursement at the pharmacy (general reimbursement) but to be eligible for reimbursement for a GLP-1RA, a patient should have T2DM (conditional reimbursement).

Still, patients with lower socioeconomic status experience more severe complications of diabetes and die earlier[12] and the likelihood of referral to municipal rehabilitation is highest among patients affiliated with GPs with the least deprived patient populations.[13] Moreover, the use of out-patient services, rehabilitation and specialists in primary care shows different utilization patterns according to socioeconomic status among patients with diabetes.[12] Especially, patients living in the countryside use less resources than patients in the cities.

Compared to older agents such as DPP-4is and SUs, GLP-1RAs and SGLT-2is represent a therapeutic advantage in terms of e.g., reduced cardiovascular risk[14] and progression of diabetic renal disease.[15] Although transforming diabetes outcomes where they are available, access to newer GLDs remains highly unequal worldwide. A large variety of socioeconomic and cultural barriers in access to diabetes medicines have been identified including high pricing and affordability, availability and supply chain issues, access to trained healthcare professionals, long distances to clinics, inadequate insurance and reimbursement structures and the degree to which patient groups accept the medicines.[16] Several studies have reported regional variation in prescribing of newer GLDs.[17–21] One study found considerable variation in use of GLP-1RAs and SGLT-2is across different states in the US[19] while another study found wide variation in use of second-line GLDs in England.[18] and a third Australian study revealed lower SGLT2i use in more disadvantaged areas and localized areas of high GLP-1RA use.[21] Likewise, a Danish study revealed distinct differences in the prevalence of GLP-1RA use in Denmark in 2012.[17] There is wide variation in the cost of GLDs,[22] and geographical variation may indicate unequal access to newer and more expensive non-insulin GLDs.

Therefore, the aim of the present study was to analyse geographical variation in the use of GLD for T2DM in Denmark from 2010 to 2023, and to characterize users of non-insulin GLDs in Denmark in 2023 across regions.

What is already known about this subject

- The use of GLDs in Denmark has changed dramatically over time, with increasing use of glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors.
- Geographical variation in the use of GLDs indicates inequity in access to newer and more expensive GLDs among patients with type-2 diabetes.

What this study adds

- General practitioners make the most initial and subsequent prescriptions for GLDs, but hospital physicians play a greater role in maintenance treatment in the Capital Region compared to other regions.
- The regional differences in use of old and newer GLDs and in comorbidities among GLD users are minor and indicate equal access to treatment in Denmark.
- At the municipal level, there are smaller differences in use of GLDs, which may reflect differences in type-2 diabetes populations or in the uptake of newer GLDs.

2 | MATERIALS AND METHODS

We conducted a repeated cross-sectional drug utilization study including all adult users of non-insulin GLDs from January 1st, 2010,

to December 31st, 2023. For this cohort, we described the use of GLDs from 2010 to 2023 across different geographical areas in Denmark and characterized users in 2023 across regions.

2.1 | Data sources

We used the Danish National Prescription Registry,[23] the Danish National Patient Registry[24] and laboratory values from 2015 up to and including 2023.[25] The Prescription Registry holds information on all prescriptions redeemed at Danish community pharmacies since 1995. For each prescription, the registry includes information on the dispensing date, the dispensed volume in defined daily doses (DDD), the anatomical therapeutic chemical (ATC) classification code and a prescriber identifier. We had no information on the indication for the prescription. The patient registry holds information on all in- and out-patient contacts and given diagnoses at Danish hospitals since 1977. We used the Danish Civil Registry System[26] to obtain information on vital status, migrations and residence both on the level of regions and municipalities. Data were linked via the unique personal identification number given to all residents at birth or migration.

2.2 | Study population

The study population included all adults ≥18 years living in Denmark who redeemed at least one prescription of a non-insulin GLD (ATC: A10B* [Table S1]) from January 1st, 2010, to December 31st, 2023. Non-insulin GLDs included metformin, SU, DPP-4i, GLP-1RA, SGLT-2i and others (glinides, thiazolidinediones and acarbose). We only included drugs which were indicated for the treatment of T2DM and therefore excluded GLP-1RA indicated specifically for weight management (Saxenda® and Wegovy®). In all analyses, combination products were split into their individual components. We excluded patients with a diagnosis of PCOS (ICD-10: E28.2).

2.3 | Analysis

Denmark has five regions: the Capital Region of Denmark ("Capital"), Region Zealand ("Zealand"), Region of Southern Denmark ("South"), the North Denmark Region ("North") and the Central Denmark Region ("Central"). Unless mentioned, all analyses were stratified according to the region of an individual's residence on January 1st each year.

2.3.1 | Regional variation in GLD use from 2010 to 2023 in Denmark

We calculated the quarterly incidence rate of non-insulin GLD from January 1st, 2010, to December 31st, 2023, using the follow-up time in the total adult population per region in the denominator and the quarterly number of incident drug users per region in the numerator. Incident drug use was defined as no use of any non-insulin GLD during the previous 10 years to ensure identification of actual incident medication use. We required that each individual had no migration history 10 years prior to initiating non-insulin GLD to ensure long and complete follow-up in the health care registries.

We calculated the quarterly prevalence proportion of GLDs, including insulins (ATC: A10A*), using the total adult population per region in the denominator and the number of adults who redeemed at least one GLD prescription in a given quarter of the year per region in the numerator. We ensured that individuals included in the prevalence analyses were registered with a Danish address per 1st of January for each calendar year. The incidence and prevalence were computed overall and by age group (18–39, 40–59, 60–79 and ≥ 80 years).

To describe the age-distribution among the overall population of non-insulin GLD users, we calculated the median age and interquartile range (IQR) of users of non-insulin GLDs by region during the study period from 2010 to 2023 (using the age on January 1st that given year).

We calculated the total amount of GLDs prescribed in DDDs specified by type of GLD from 2010 to 2023 (and the proportional distribution in 2023 only).

2.3.2 | Regional variation in 2023 in prescribers of GLDs and skewness in prescribing of GLDs

We calculated the proportion of all prescriptions for GLDs per region in 2023 that were issued by GPs, hospital specialists or private practicing specialists. We did this overall and specified by whether the prescription marked treatment initiation or continued treatment (all other prescriptions).

To assess skewness in the prescribing of GLDs among GPs in 2023, i.e., whether a few GPs are responsible for a high proportion of the total dispensed drug volume, we calculated the number of prescribed DDDs of GLDs in 2023 that accounted for by each prescriber from general practice. We then plotted the percentile of the total DDD prescribed by GPs ranked from practices that prescribed the greatest amount to practices that prescribed the least amount (Lorenz curves). We did this for GLDs overall and for each type of GLD, separately.

2.3.3 | Regional variation in characeteristics of T2DM populations in 2023

To investigate regional variation in T2DM populations, we characterized users (prevalent) who redeemed a prescription for non-insulin GLD from January 1st to December 31st, 2023. Users were characterized on January 1st, 2023, regarding the presence of diabetes-related complications, comorbidities including hospital diagnoses related to cardiovascular- and chronic kidney disease, use of selected prescription drugs, lifestyle risk factors and laboratory results. The time window for identifying diabetes-related complications and comorbidities was from January 1st, 2013, to December 31st, 2022, and the time window for

assessing prescription drug use was from January 1st, 2022, to December 31st, 2022. The time windows used thus allowed for a 10-year look-back period for diagnoses and a 1-year look-back period for prescription drug use. We calculated the number of hospital contacts as well as the number of contacts to GPs from January 1st, 2022, to December 31st, 2022. We also assessed relevant biochemical measures using the most recent results in each patient. Relevant codes and definitions of diabetes-related complications, comorbidities and prescription drug use can be found in Table S3.

2.3.4 | Potential clinical impact of regional variation in GLD use

To estimate the potential clinical impact of regional variation in GLD use, we performed a Kaplan–Meier survival analysis to depict the cumulative mortality and incidence of diabetes-related complications (Table S3) during the first 5 years after initiating treatment with non-insulin GLDs. In this analysis, we only included users who initiated treatment from January 1st, 2010, to December 31st, 2018, to allow for at least 5 years follow-up. Follow-up began at the first date of redeeming a prescription of a non-insulin GLD and ended at death, emigration or end of the study period (December 31st, 2023). In a supplementary analysis, we depicted the cumulative mortality and the incidence of diabetes-related complications during the first 5 years in users who initiated treatment from January 1st, 2010, to December 31st, 2018.

2.3.5 | Variations in use of GLDs at municipality level in 2023

We investigated variations in the use of GLD use between the 98 Danish municipalities by calculating the proportion of users of non-insulin GLDs in each municipality who filled a prescription for each type of GLD in 2023. For data privacy reasons, we excluded municipalities with less than 500 users of GLDs. Additionally, we used K-means cluster analysis to group municipalities based on similarity of GLD patterns characterized by the proportion of users of the four different non-insulin GLDs (excluding the "other" category). Proportions were centered and scaled before clustering, and we used the majority vote from 30 different diagnostic indexes to determine the optimal number of clusters.

2.4 | Ethical approvals

This is an original pharmacoepidemiologic study. No interventions were performed with human subjects/patients and or substances administered, and as such, there was no principal investigator for this paper who had direct clinical responsibility for patients.

In terms of data protection, the study was registered at the repository of the University of Southern Denmark. Research & Innovation Organization (Registration no. 10.940). Ethical approval is not required for register-based studies in Denmark, not including human biological material[27]

3 | RESULTS

A total of 478 118 adults filled at least one prescription of a non-insulin GLD from January 1st, 2010, to December 31st, 2023.

3.1 | Regional variation in GLD use from 2010 to 2023 in Denmark

The incidence rate of non-insulin GLD use did not vary between regions and followed patterns with an increasing incidence rate over time among all age groups (Figure S1).

The prevalence of GLD use varied between the regions but followed similar patterns over time with a predominant and increasing use of metformin, an accelerating use of GLP-1RAs and SGLT-2is from 2019 onwards, and declining use of SUs and DPP-4is (Figure 1). In Q4 2023 the ranges of prevalence per 1000 inhabitants were 31 to 44 for metformin, 16 to 23 for SGLT2is, 14 to 23 for GLP-1RAs and 1.37 to 1.58 for SUs. In all regions, the prevalence proportion increased over time in all four age groups (Figure S2).

The median age of users was similar in all regions, ranging from a median of 66–67 years in 2023 with no changes during the study period (data not shown). Totally, there were 56–58% males.

From 2010 to 2023, a profound increase in total GLD use occurred in all regions (Figure S3). The proportional distribution of the total dispensed DDDs of GLDs in 2023 varied slightly between the regions for insulin and GLP-1RA (Figure 2). Insulin accounted for 13% in the Capital Region compared to 18% in Region North and in the Central Region. GLP-1RAs accounted for a slightly greater proportion of the total DDDs in Region Zealand (21%) and the Capital Region (20%) compared to Region North (14%). DPP-4is accounted for a slightly larger proportion in Region North (8.0%) compared to Region South (5.7%).

3.2 | Regional variation in 2023 in prescribers of GLDs and skewness in prescribing of GLDs

In all regions, 70–79% of the initial and 83–93% of the subsequent prescriptions for GLDs in 2023 were issued by GPs. Yet, hospital physicians initiated a slightly smaller proportion of prescriptions in Region North (20%) and South (21%) compared to the other regions (range 25–29%). In the Capital Region, hospital physicians played a greater role in maintenance treatment (17%) compared to the other regions (range: 6.8–11%) (Figure 3). Although most prescriptions were issued by GPs, there was a skewness in the distribution of DDDs between GPs in all regions since 50% of GPs accounted for approximately 80% of the total amount of dispensed DDDs (Figure S4). In all regions, this skewness in prescribing was observed for all types of GLDs (data not shown).

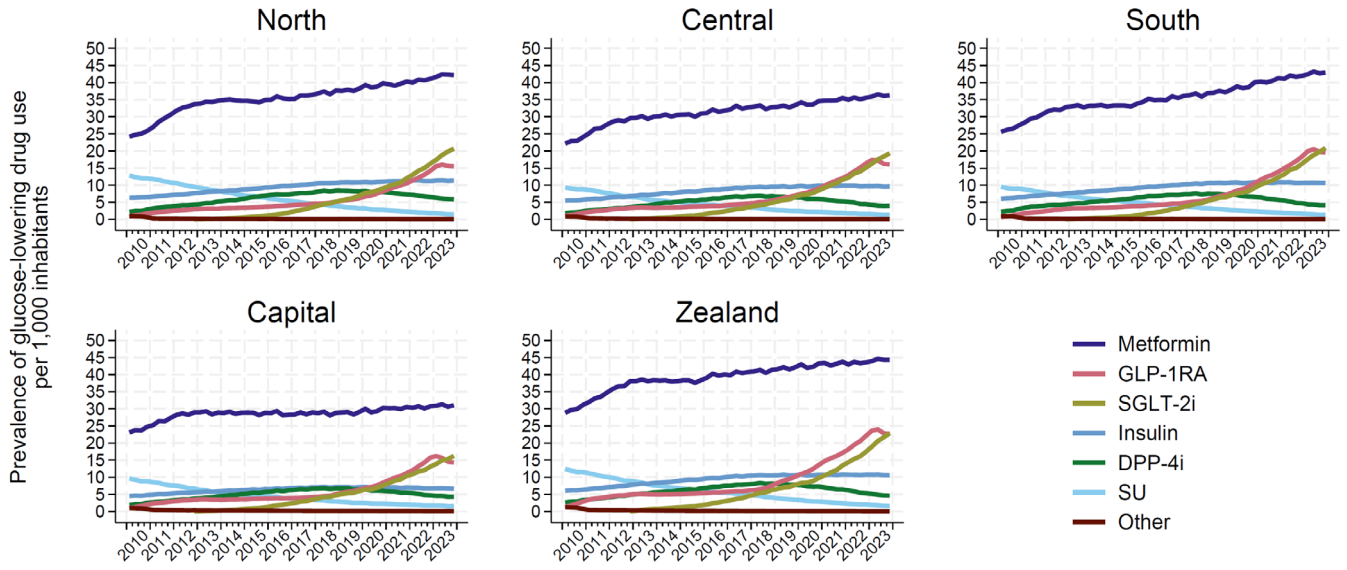

FIGURE 1 Prevalence of glucose-lowering drug use per 1000 inhabitants from 2010 to 2023 in the five Danish regions. DPP-4i = dipeptidyl-peptidase-4 inhibitors; GLP-1RA = glucagon-like peptide-1 receptor agonists; SGLT-2i = sodium-glucose co-transporter-2 inhibitors; SU = sulphonyl urea analogs.

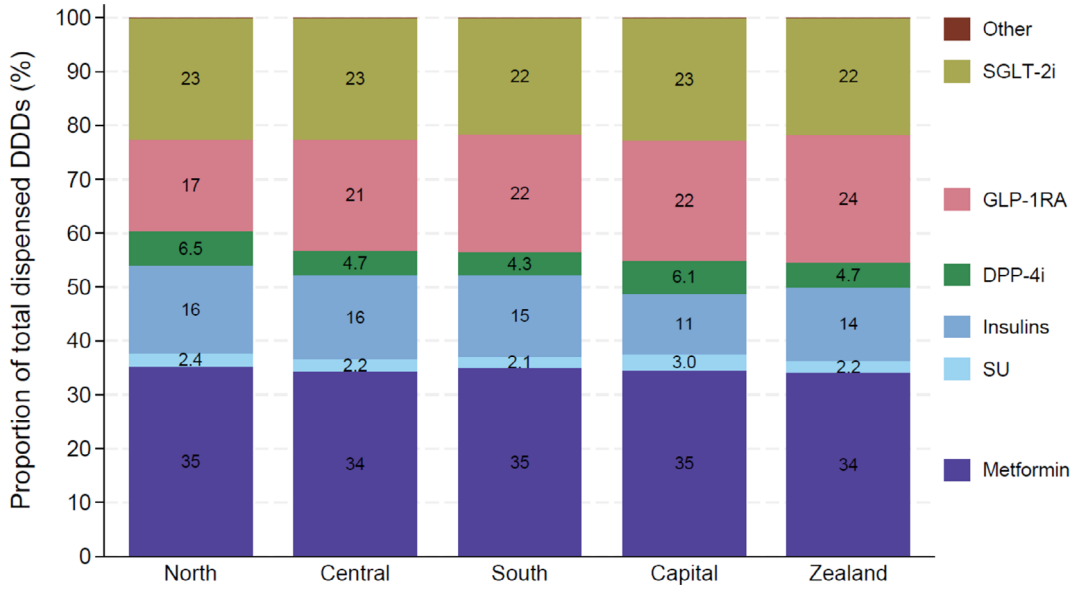

FIGURE 2 The proportional distribution (%) of the total DDD of dispensed glucose-lowering drugs in 2023 in the five Danish regions. DPP-4i = dipeptidyl-peptidase-4 inhibitors; GLP-1RA = glucagon-like peptide-1 receptor agonists; SGLT-2i = sodium-glucose co-transporter-2 inhibitors; SU = sulphonyl urea analogs.

3.3 | Regional variation in characeteristics of T2DM populations in 2023

Table 1 displays characteristics of users of non-insulin GLDs in 2023. Despite minor differences in the prevalence of diabetes complications, hospital-diagnosed obesity and heart failure, the user characteristics were comparable across the regions, and there were no differences in the median age (range 66–67 years) or in the sex distribution (range 56–58% males) (Table 1). However, a higher proportion of non-insulin GLD users in the Capital Region had diabetes-related nephropathy (5.0%), retinopathy (3.3%), neuropathy (6.0%) and other diabetes-related complications (13%) compared to the other regions.

3.4 | Potential clinical impact of regional variation in GLD use

There were minor regional differences in the cumulative incidence of diabetes-related complications during the first 5 years after treatment

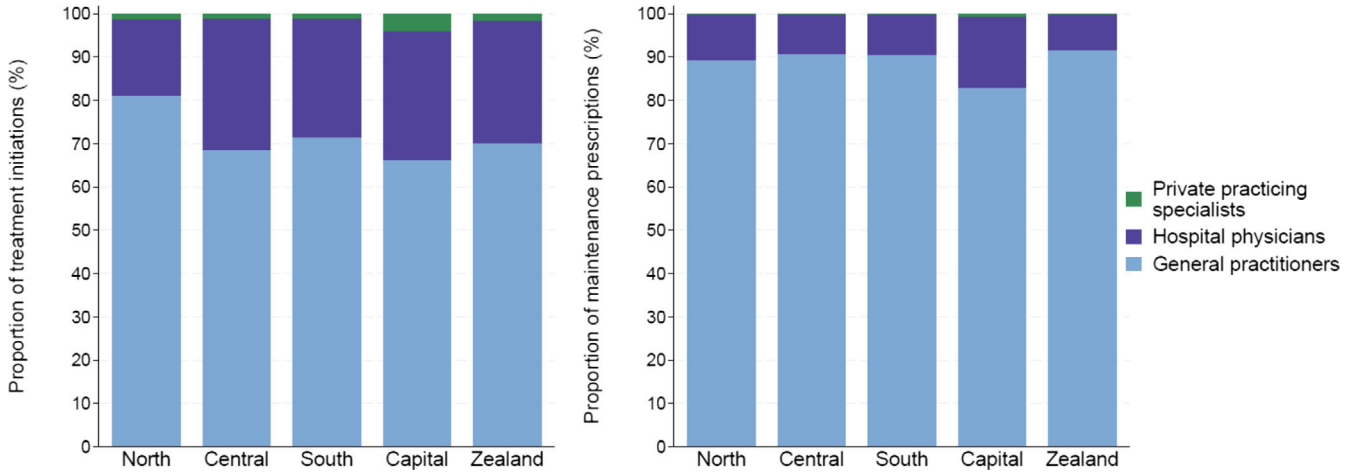

FIGURE 3 Distribution of prescriber types (%) in first prescriptions (treatment initiation) and subsequent prescriptions (maintenance treatment) in 2023 in the five Danish regions.

initiation (Figure S5), while there were no regional differences in the cumulative mortality (Figure S6). No regional differences were seen during the first 2 years of treatment (data not shown).

3.5 | Variations in use of GLDs at municipality level in 2023

The prevalence of use differed between the individual municipalities (Table S1). Although the proportion of users who filled at least one prescription for metformin was high in all municipalities, it varied mostly for the municipalities in the Capital Region (range: 62–84%) and in Region Zealand (range: 69–80%). Likewise, there was a variation between the municipalities for GLP-1RAs and SGLT-2is. For GLP-1RAs, the lowest proportion was in Region North (Frederikshavn municipality [26%]) and the highest proportion was in Region Zealand (Faxe and Solrød municipalities [48% and 45%]) and in Capital Region (Gentofte municipality [44%]). For SGLT-2is, the lowest proportion was in Region Central, Capital and Zealand (Odder, Bornholm and Stevns, respectively [33%]), and the highest proportion was in Central Region (Skive municipality [47%]).

The cluster analysis revealed four clusters of municipalities that differed in the pattern of non-insulin GLD use in 2023 (Figure 4). None of the clusters were explicitly rural or urbanized, but cluster 2 comprised primarily rural municipalities (Figure 4A). Cluster 1 was characterized by lower use of metformin, DPP-4i and SGLT-2is combined with higher use of GLP-1RAs. Cluster 2 was characterized by lower use of metformin and DPP-4i combined with higher use of SGLT-2is and GLP-1RAs. Cluster 3 showed higher use of metformin, DPP-4i, SGLT-2is and GLP-1RAs. Cluster 4 showed higher use of metformin and DPP-4i combined with lower use of SGLT-2is and GLP-1RAs (Figure 4B).

4 | DISCUSSION

This study reveals that from 2010 to 2023, the use of GLDs in Denmark changed significantly with an increasing use of metformin, declining use of SUs and DPP-4is and over the latest years, an accelerating use of SGLT-2is and GLP-1RAs. Only minor regional differences, however, in the use of GLDs were documented. Still, there were some differences in comorbidities among GLD users and in the involvement of hospital physicians across regions. Furthermore, we found minor differences in the use of non-insulin GLDs at the municipality level.

The changing use of GLDs over time reflected utilization patterns previously observed in Denmark from 2005 to 2021[7] and in other countries.[18,28,29] Our finding of only smaller regional differences in use of GLDs in Denmark indicates the patients may have equal access to the newer and more expensive classes of GLDs. Our results are thus in contrast to studies documenting a wide geographical variation in use of second-line GLDs in England,[18] Ireland,[30] Australia,[21] and in the US.[19]

The users of GLDs were comparable across the five Danish regions. differences in sociodemographic parameters[31] or in the access to specialists might contribute to the minor differences in GLD use found between the Danish regions. In 2018, the Capital Region had more GPs and specialists per inhabitant compared to the other regions.[32] Other studies have reported an increasing involvement of cardiologists and nephrologists in the prescribing of e.g. SGLT-2is.[33]

The geographic variation was not reflected in mortality. However, we found some differences in comorbidities among non-insulin GLD users across regions with users in the Capital Region having a slightly higher prevalence of diabetes-related complications compared to the other regions. These differences may have multiple explanations and might be due to differences in registration or coding practices across the regions, and different involvement of hospital physicians in the treatment of T2DM. The increased involvement of hospital physicians in the Capital Region indicates that T2DM patients in this region are more often treated in the hospital setting and they are thus also more likely to receive a hospital diagnosis compared to patients who are primarily treated in general practice. Given their expanded indication for heart failure and chronic kidney disease irrespective of diabetes, the increased involvement of cardiologists and nephrologists in

TABLE 1 Characteristics of prevalent users of non-insulin glucose-lowering drugs in 2023 in the five Danish regions.

	Zealand	Capital	South	Central	North
Total number of users	(n = 51 524)	(n = 84 004)	(n = 68 500)	(n = 65 320)	(n = 31 964)
Number of new users, n (%)	6504 (13%)	10 957 (13%)	8656 (13%)	8344 (13%)	3926 (12%)
Age, years on 1st January 2023, median (IQR)	67 (57–75)	66 (56–75)	67 (57–76)	66 (56–75)	67 (57–76)
Men, n (%)	29 782 (58%)	46 976 (56%)	39 318 (57%)	37 587 (58%)	18 379 (57%)
Median number of contacts with general practitioner (IQR)	12 (7–20)	12 (7–18)	13 (8–20)	13 (8–20)	13 (8–19)
Median number of hospital admissions (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Median number of hospital outpatient contacts (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)
Diabetes-related complications, n (%)					
Diabetic nephropathy	1580 (3.1%)	4177 (5.0%)	2501 (3.7%)	1306 (2.0%)	585 (1.8%)
Diabetic retinopathy	911 (1.8%)	2775 (3.3%)	1278 (1.9%)	360 (0.55%)	219 (0.69%)
Diabetic neuropathy	1341 (2.6%)	5032 (6.0%)	1822 (2.7%)	843 (1.3%)	455 (1.4%)
Peripheral diabetes-related complications	1677 (3.3%)	2246 (2.7%)	2140 (3.1%)	1749 (2.7%)	832 (2.6%)
Amputations of lower extremities	473 (0.92%)	594 (0.71%)	539 (0.79%)	450 (0.69%)	259 (0.81%)
Other diabetes-related complications	4586 (8.9%)	10 602 (13%)	6300 (9.2%)	4549 (7.0%)	3749 (12%)
Comorbidities, n (%)					
Hypertension	39 473 (77%)	60 361 (72%)	53 149 (78%)	49 897 (76%)	25 195 (79%)
Atherosclerotic cardiovascular disease	12 035 (23%)	18 502 (22%)	15 264 (22%)	14 101 (22%)	6822 (21%)
Myocardial infarction	3014 (5.8%)	4513 (5.4%)	3141 (4.6%)	3207 (4.9%)	1345 (4.2%)
Ischaemic stroke	3460 (6.7%)	5555 (6.6%)	4250 (6.2%)	3358 (5.1%)	1774 (5.5%)
Hemorrhagic stroke	284 (0.55%)	403 (0.48%)	296 (0.43%)	314 (0.48%)	142 (0.44%)
Renal disease	19 789 (38%)	30 657 (36%)	25 995 (38%)	23 445 (36%)	12 053 (38%)
Eye disease	3280 (6.4%)	4628 (5.5%)	4111 (6.0%)	4130 (6.3%)	1487 (4.7%)
Neurological disease	1059 (2.1%)	1708 (2.0%)	3502 (5.1%)	2331 (3.6%)	831 (2.6%)
Hospital-diagnosed obesity	6286 (12%)	9251 (11%)	11 174 (16%)	7892 (12%)	3993 (12%)
Heart failure	5241 (10%)	7696 (9.2%)	5523 (8.1%)	5437 (8.3%)	2011 (6.3%)
Chronic lung disease	7822 (15%)	13 553 (16%)	10 999 (16%)	9714 (15%)	4852 (15%)
Atrial fibrillation	6313 (12%)	8999 (11%)	7467 (11%)	7097 (11%)	3486 (11%)
Acute pancreatitis	560 (1.1%)	889 (1.1%)	793 (1.2%)	714 (1.1%)	368 (1.2%)
Cancer	5657 (11%)	8715 (10%)	7387 (11%)	7361 (11%)	3257 (10%)
Prescriptions, n (%)					
Loop diuretics	8295 (16%)	11 440 (14%)	11 057 (16%)	10 308 (16%)	4914 (15%)
Lipid-modifying agents*	35 196 (68%)	55 196 (66%)	48 978 (72%)	46 613 (71%)	22 958 (72%)
Beta blocking agents	16 023 (31%)	22 602 (27%)	21 030 (31%)	20 408 (31%)	10 248 (32%)
Agents acting on the renin-angiotensin system	33 173 (64%)	50 244 (60%)	44 040 (64%)	43 138 (66%)	21 715 (68%)
Calcium channel blockers	16 490 (32%)	25 190 (30%)	23 641 (35%)	22 994 (35%)	11 308 (35%)
NSAIDs	10 164 (20%)	14 424 (17%)	11 601 (17%)	10 191 (16%)	5794 (18%)
Glucocorticoids	3138 (6.1%)	3798 (4.5%)	4184 (6.1%)	4554 (7.0%)	2177 (6.8%)
Low-dose aspirin	10 335 (20%)	16 681 (20%)	14 167 (21%)	15 869 (24%)	6910 (22%)
Platelet aggregation inhibitors	5243 (10%)	7761 (9.2%)	6853 (10%)	4943 (7.6%)	2998 (9.4%)
Warfarin	1247 (2.4%)	1468 (1.7%)	1813 (2.6%)	1753 (2.7%)	818 (2.6%)
Direct oral anticoagulants	6175 (12%)	9125 (11%)	7101 (10%)	7162 (11%)	3559 (11%)
Antipsychotics	2222 (4.3%)	3417 (4.1%)	3759 (5.5%)	3110 (4.8%)	1531 (4.8%)
Antiretroviral therapy	1217 (2.4%)	2385 (2.8%)	1516 (2.2%)	1496 (2.3%)	716 (2.2%)
Lifestyle, n (%)					
Markers of smoking	4232 (8.2%)	6710 (8.0%)	5594 (8.2%)	3551 (5.4%)	2294 (7.2%)
Markers of alcohol overuse	1516 (2.9%)	2496 (3.0%)	2162 (3.2%)	1583 (2.4%)	910 (2.8%)

(Continues)

TABLE 1 (Continued)

	Zealand	Capital	South	Central	North
Biochemistry					
HbA1c, median (IQR)	49 (44–56)	49 (44–57)	49 (45–56)	49 (44–56)	50 (45–57)
LDL cholesterol, median (IQR)	1.80 (1.30–2.40)	2.10 (1.60–2.90)	2.10 (1.60–2.70)	1.80 (1.40–2.40)	1.90 (1.50–2.40)
Albuminuria, n (%)					
Unknown	23 646 (46%)	41 674 (50%)	24 840 (36%)	21 803 (33%)	13 917 (44%)
No/stage A1 (UACR < 30 mg/g)	16 856 (33%)	27 503 (33%)	31 368 (46%)	32 050 (49%)	12 185 (38%)
Stage A2 (UACR 30–300 mg/g)	8948 (17%)	12 170 (14%)	10 236 (15%)	9274 (14%)	4725 (15%)
Stage A3 (UACR > 300 mg/g)	2074 (4.0%)	2657 (3.2%)	2056 (3.0%)	2193 (3.4%)	1137 (3.6%)
eGFR, median (IQR); ml/min/1.73m^2	85 (67–96)	84 (66–96)	82 (64–95)	85 (67–97)	83 (64–95)
- < 15	119 (0.23%)	181 (0.22%)	125 (0.18%)	117 (0.18%)	61 (0.19%)
15–29	783 (1.5%)	1440 (1.7%)	963 (1.4%)	1027 (1.6%)	469 (1.5%)
30–44	2394 (4.6%)	4182 (5.0%)	3723 (5.4%)	3243 (5.0%)	1737 (5.4%)
45–59	4758 (9.2%)	7928 (9.4%)	7668 (11%)	6213 (9.5%)	3529 (11%)
≥ 60	38 242 (74%)	60 005 (71%)	50 576 (74%)	48 667 (75%)	23 786 (74%)
Missing, (%)					
HbA1c	12%	16%	9%	11%	9%
LDL cholesterol	21%	96%	61%	20%	16%
Albuminuria	46%	50%	36%	33%	44%
eGFR categories	10%	12%	8%	9%	7%

prescribing is particularly evident for SGLT2i.[34] This is not the case with other non-insulin GLDs.

Studies have suggested that rurality is associated with delayed decline in use of SUs[35] and a slower uptake of DPP-4is.[36] We revealed some differences in the use of GLDs between the individual Danish municipalities. The use of metformin was high, and the use of SUs was low in all municipalities, and we found no clear indication that municipalities in rural areas of Denmark differ from more urban municipalities in their prescribing patterns. Previous research has found variation in sociodemographic variables, such as educational level and income level, in T2DM populations between individual municipalities in Region Zealand[37] and in Region South.[38] Differences in sociodemographic variables between T2DM populations or differences in clinical practice may explain the minor variation in GLD use between the municipalities. However, as we did not have access to sociodemographic data, future studies should investigate this further.

The profound changes in GLD prescribing patterns over time across all regions, with an increase in use of newer and more expensive GLDs, have a sizeable impact on drug budgets[39,40] and call for continuous monitoring of GLD use patterns. The newer GLDs represent a significant financial burden, both for patients and for the health system. Affordability and lack of adequate reimbursement and health insurance to cover the cost are well-known barriers to access to diabetes medicines.[16] The present study was conducted in a small high-income country with a high degree of public reimbursement, reducing patients' out-of-pocket expenditure, which may explain the high degree of usage. If not associated with a significant reduction in diabetes-related complications, such as the very expensive end-stage renal disease, coverage of the newer GLDs is a magnificent challenge to the health system, even in high-income countries. Compared to SU, DPP-4is, GLP-1RAs and SGLT-2is seem more effective in delaying cardiovascular events and death when used in second-line treatment of T2DM after metformin monotherapy failure.[41] Although potentially cost-effective in second-line treatment,[41] the question of which GLD is cost-effective in which patients is still unanswered.[42] To achieve cost-effectiveness in low- and middle-income countries, both SGLT-2i and particular GLP-1RA would need to have a significant price reduction.[43] This is probably also the case in most high-income countries. The situation may, however, soon change if generic competitors come in the market when the SGLT-2i dapagliflozin, as the first newer GLD, soon goes off patent.

The main strength of this study was the use of nationwide data on filled prescriptions with high validity and completeness and no risk of selection or recall bias. The limitations include the potential use of GLDs for other indications than T2DM, as we could not control for the use of GLDs in non-diabetic patients with established cardiovascular or kidney disease or the use of GLP-1RA for cosmetic weight loss in the present study. This is especially relevant in the most recent study years, where GLP-1RAs and SGLT-2is (with demonstrated cardiovascular and renal benefit) are increasingly used in non-diabetic patients with cardiovascular and chronic kidney disease. Despite not being approved for weight loss in people without T2DM, a recent study revealed that 12% of all

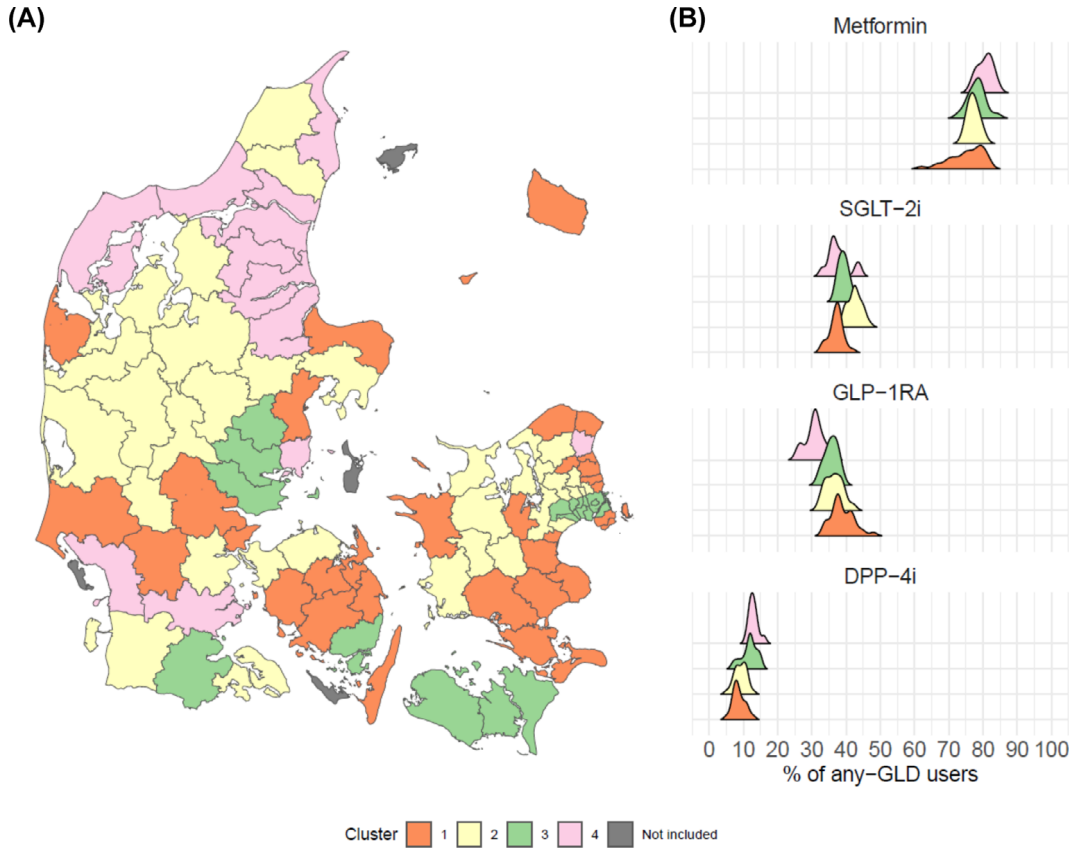

FIGURE 4 (A) Danish municipalities coloured according to cluster membership. (B) Distribution of the proportion of users for each GLD type in the municipalities, grouped by cluster membership. GLP-1RA = glucagon-like peptide-1 receptor agonists; SGLT-2i = sodium-glucose co-transporter-2 inhibitors; DPP-4i = dipeptidyl-peptidase-4 inhibitors. The data are from 2023.

prevalent users and 13% of new users of semaglutide (Ozempic®) in 2023 did not have T2DM.[44] Another limitation is the use of filled prescriptions as a proxy for drug use and the inclusion of hospital-based diagnoses only. The definition of diabetes-related complications was restricted to ICD-10 codes that specifically denote a complication as such. This may have resulted in underestimations of the true prevalence of these complications in our study. As mentioned above, we did not have access to sociodemographic variables such as educational level and income, which have been shown to be associated with the incidence of T2DM,[45] and health in general.[46] Finally, our study was cross-sectional by design, and the data presented do not allow us to draw conclusions on possible associations.

5 | CONCLUSION

We document profound changes in the prescribing of GLDs with an increasing use of newer and expensive GLDs. The regional differences in usage patterns and characteristics of non-insulin GLD users in Denmark were only minor, indicating equal access to older and newer GLDs. The small regional differences are likely due to differences in the registration of comorbidities and differences in the involvement of hospital physicians. The differences found on the municipality level call for future studies to investigate if these reflect true differences in clinical practice or in the T2DM populations.

AUTHOR CONTRIBUTIONS

Stig Ejdrup Andersen, Anton Pottegård and Lotte Rasmussen conceived the initial study idea. Jacob Harbo Andersen and Peter Bjødstrup Jensen programmed the analyses. Stig Ejdrup Andersen, Anton Pottegård, Lotte Rasmussen, Gesche Jürgens, Allan Kofoed-Enevoldsen, Gitte Krogh Madsen and Jacob Harbo Andersen contributed to the design, analysis and interpretation of the results. Stig Ejdrup Andersen and Lotte Rasmussen wrote the first draft of the manuscript. All authors contributed to the final draft of the manuscript and approved the final version submitted for publication.

CONFLICT OF INTEREST STATEMENT

LR and JHA report participation in a regulator-mandated phase IV-study funded by Novo Nordisk with funds paid to the institution where they are employed (no personal fees) and with no relation to the present study. AP reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma (all regulator-mandated phase IV-studies), and an unrestricted research grant from Novo Nordisk, all with funds paid to the institution where he was employed

(no personal fees) and with no relation to the work reported in this paper. PBJ report participation in a regulator-mandated phase IV-study funded by Leo Pharma with funds paid to the institution where they are employed (no personal fees) and with no relation to the present study. SEA, GJ, AK-E and GKM have no conflicts of interests.

DATA AVAILABILITY STATEMENT

Data are not publicly available. The data for this study are population-wide registers, placed at our disposal on the servers of the Danish Health Authority. They are barred from the release to the public on the grounds of confidentiality.

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