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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Use of prescription drugs in the older adult population—a nationwide pharmacoepidemiological study

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Abstract

Purpose Multi-morbidity and polypharmacy are common among older people. It is essential to provide a better understanding of the complexity of prescription drug use among older adults to optimise rational pharmacotherapy. Population-based utilisation data in this age group is limited. Using the Danish nationwide health registries, we aimed to characterise drug use among Danish individuals ≥ 60 years.

Methods This is a descriptive population-based study assessing drug prescription patterns in 2015 in the full Danish population aged ≥ 60 years. The use of specific therapeutic subgroups and chemical subgroups and its dependence on age were described using descriptive statistics. Profiles of drug combination patterns were evaluated using latent class analysis.

Results We included 1,424,775 residents (median age 70 years, 53% women). Of all the older adults, 89% filled at least one prescription during 2015. The median number of drug groups used was five per person. The most used single drug groups were paracetamol and analogues (34%), statins (33%) and platelet aggregation inhibitors (24%). Eighteen drug profiles with different drug combination patterns were identified. One drug profile with expected use of zero drugs and 11 drug profiles expected to receive more than five different therapeutic subgroup drugs were identified.

Conclusion The use of drugs is extensive both at the population level and increasing with age at an individual level. Separating the population into different homogenous groups related to drug use resulted in 18 different drug profiles, of which 11 drug profiles received on average more than five different therapeutic subgroup drugs.

Keywords Pharmacoepidemiology · Drug utilisation · Drug profiles · Older adults · Prescription drugs

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Introduction

The use of prescription drugs is widespread in older people [1, 2], and the number of drugs used is increasing with age [3–6]. This is prompted by an increasing prevalence of multimorbidity and hospitalisations by age supplemented by a higher number of specialists who treat single disease [7–9]. Strict adherence to guidelines for each of the chronic conditions may complicate older persons' pharmacotherapy and may be associated with adverse drug events [10]. Furthermore, the use of many drugs simultaneously increases the risk of adverse drug events and drug–drug interactions [11, 12]. Due to age-related changes in pharmacokinetics and pharmacodynamics, older people are at very high risk of such complications [1, 5, 11, 13]. To this end, up to 30% of hospital admissions in older patients are related to adverse drug events [14–16]. Thus, pharmacotherapy in the older adults is very complicated, and the vast variety of drugs and drug combination effect on the pharmacokinetics and pharmacodynamics make it a difficult phenomenon to analyse.

A better and updated understanding of the real-life utilisation of prescription drugs is needed, and further research is required to deepen our understanding of how drugs tend to compound and interact. In addition, identifying common drug profiles, i.e. which drugs are used together, to identify long-term risk drug profiles may enable health care policies, clinicians and research fellows to optimise a rational pharmacotherapy, prescribing and deprescribing patterns among older adults. However, the population-based utilisation data in this age group is limited, and data are rather old. Therefore, we aimed to provide a detailed study of drug use and how it changes with age to identify different homogeneous drug profiles among older adults aged 60 years and older.

Methods

We performed a nationwide cross-sectional drug utilisation study in the older adult Danish population.

Data sources

Denmark has a public tax-financed health care system, which provides free and equal access to primary medical care, hospitals and home care services for all people. Patient copayments are required for prescription drugs. A central authority (the Reimbursement Committee) decides whether a particular drug is reimbursable. Some prescription drugs, e.g. benzodiazepines, are not reimbursed [17]. Virtually, all medical care in Denmark is furnished by the public health authorities, whereby the data resources allow accurate population-based studies, covering all inhabitants of Denmark.

We used data from four Danish nationwide registries; the National Prescription Registry, the Registry for Migration, the Danish Registry of Causes of Death and the Civil Registration System. The National Prescription Registry contains full information on all prescription drugs dispensed at Danish community pharmacies, including prescriptions for nursing home residents [17]. Prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC) classification system [18]. Drugs used during hospitalisation are not recorded in the register. The Register for Migration contains the date of both immigration and emigration [19]. The Danish Register of Causes of Death contains data on all deaths among people dying in Denmark [20]. The Civil Registration System contains various information including sex and date of birth [21]. All Danish residents are recorded in the registries with a uniquely personal and permanent identification number that makes it possible to cross-link individual-level data across the different registries.

Study population

We included all Danish residents aged ≥ 60 years on January 1, 2016. Residents who migrated during 2015 were excluded to ensure full follow-up data on all subjects.

Study drugs

We retrieved information on all redeemed prescriptions in 2015. The drugs were categorised according to ATC codes into the anatomical main group (1st level), therapeutic subgroup (2nd level) and chemical subgroup (4th level) [18]. ATC levels 1, 2 and 4 are referred to as the main drug group, therapeutic subgroup drug and drug class, respectively. We defined drug users as individuals who had redeemed at least one prescription of a drug class or main drug group in 2015. In the latent class analysis (LCA), we disregarded the main drug group: anti-infectives for systemic use.

Analyses

First, to investigate simultaneous drug use, we measured the proportion of users of 0, 1–2, 3–4, 5–9 or 10+ different drug classes in 2015 stratified by age groups. Second, we determined the ten most frequently used drug classes stratified by age groups. Third, we reported the number of redeemed drug classes among all residents as mean, median, interquartile range, minimum and maximum, stratified by 1-year age categories. Fourth, we identified the number of residents who filled at least one prescription of a main drug group in 2015. These analyses were stratified by 1-year age categories.

Finally, we identified drug profiles using LCA. LCA is a method designed to identify subgroups of residents who show similar patterns of behaviour, e.g. drug use [22]. LCA is an

explorative method to classify individuals into different latent classes (groups of patients with a similar pattern of drug use) based on their use of drugs. We assumed local independence in the LCA, meaning that given the latent class membership the use of two different drugs is independent of each other. The term "drug profile" is subsequently used instead of drug pattern. To reduce computer running time, we selected five random samples of our population, each with 50,000 residents. For the same reason, we chose drugs at therapeutic subgroup level instead of drug classes. To avoid too few observations, the drugs were identified as the 95% most used drugs in 2015. Thus, the LCA was based on drugs from 28 therapeutic subgroups. Moreover, this made it possible to investigate the consistency of the drug profiles identified in five random samples. The number of drug profiles was estimated in an iterative process starting with a model with a two LCA class solution and continuing up to 20 LCA classes for each of the five datasets. We used the Bayesian Information Criterion (BIC) together with substantive interpretability and clinical judgement to determine the right number of drug profiles for each of the five datasets [23]. Low values at the BIC indicate better model fit [24]. Afterwards, the optimal number of drug profiles and parameter estimates were compared for the five datasets, and the final number of drug profiles was decided. The entropy-based pseudo-R^2 indicates how well one can predict class memberships based on the observed variables (drugs). The closer these values are to 1, the better the predictions. The values 0.36, 0.65 and 0.90 represent low-, medium- and high-separation conditions, respectively [25]. Posterior probabilities for drug profile membership were calculated for all residents in the cohort using the average parameter estimates from the five datasets. All residents were assigned to a specific drug profile based on modal assignment (the drug profile with the highest posterior probability). The distribution of sex and the median for age were performed for each drug profile. To account for local maxima of the likelihood function for LCA, we initially used 450 randomly generated starting values. If the best likelihood were not replicated, then the number of starting values was increased.

Results

Drug use

We identified 1,424,775 residents aged ≥ 60 years in Denmark in 2015. The female proportion was 53%. The median age of the population was 70 years (interquartile range (IQR) 65–77, range 60 to 110) without differences across sex (70 years for men and 71 years for women). The most used single drug classes measured by the number of unique users were paracetamol and analogues (34%), statins (33%), platelet aggregation inhibitors (24%), proton pump inhibitors (21%) and calcium channel blockers (20%) (Table 1).

Of all the older adults, 89% filled at least one prescription during 2015. The median number of unique drug classes filled was five per person (IQR, 2–8), similar for men and women (four drug classes (IQR, 2–8) and five drug classes (IQR, 2–9), respectively). We observed a trend towards an increasing number of prescribed drug classes by age, however with a levelling off around age 90 (Fig. 1).

Cardiovascular drugs were the most used main drug group (1≥ prescription filled by 62% of all residents), followed by drugs related to the nervous system (48%), alimentary tract and metabolism (38%), anti-infectives for systemic use (35%) and blood and blood-forming organs (34%). This was largely consistent across age (Fig. 2), although a tendency towards a slightly increased proportion of drugs related to blood and blood-forming organs was observed whereas the proportion of drugs related to the genitourinary system and sex hormones decreased slowly by age.

Drug profiles

By using the drugs from the 28 covering 95% of all drug groups used in 2015, 19 LCA models were fitted, covering models assuming 2 to 20 classes. Looking at the model fit, the BIC was lowest in the model with 19 drug profiles for four datasets and in the model with 18 drug profiles for one dataset. When comparing the therapeutic subgroup drug probabilities within each drug profile among the five different datasets for the 19–drug profile models, two of the 19 drug profiles were very differently estimated, showing relatively little consistency among the datasets in how to identify the two classes in the 19-class model. However, for the LCA assuming 18-drug different profile, the results for the five datasets were similar (Online Resource 1). Since we experienced two classes with low consistency in the LCA assuming 19 different drug profiles, and with a clinical judgement of the drug profiles, we used the 18–drug profile model as our final model. Moreover, the mean entropy-based pseudo-R^2 measure was in our study 0.67 (range 0.66–0.68), placing the separation of the 18 drug profiles as medium-separation conditions.

Table 2 shows the conditional probabilities of the 28 therapeutic subgroup drugs in the 18 identified drug profiles and the relationship between age and sex for each drug profile. Multiple drug use was in this study defined as high probability of receiving drugs from five or more different therapeutic subgroup drugs. Multiple drug use was observed in 11 drug profiles (drug profiles 1 to 11). Drug profiles 1 and 4 had a considerable overlap. Thus, drug profile 1 consisted of high probabilities for all 28 therapeutic subgroup drugs and was characterised by the highest expected numbers of therapeutic subgroup drugs whereas drug profile 4 had a high probability of receiving all therapeutic subgroup except for mineral

Table 1 Demographic and drug characteristics

Characteristic		Age groups (year)		
	Total No. (%) 1,424,775	60–69 No. (%) 688,623 (48.3)	70–79 No. (%) 490,295 (34.4)	80+ No (%) 245,857 (17.3)
Sociodemographic characteristics				
Female sex	759,255 (53.3)	348,609 (50.6)	258,311 (52.7)	152,335 (62.0)
Medication				
Median number drug classes (IQR)	5 (2–8)	4 (1–7)	5 (3–9)	8 (4–11)
Number of simultaneously used drug classes				
0	155,692 (10.9)	105,130 (15.3)	40,986 (8.4)	9576 (3.9)
1–2	253,138 (17.8)	157,282 (22.8)	76,033 (15.5)	19,823 (8.1)
3–4	264,930 (18.6)	141,372 (20.5)	90,590 (18.5)	32,968 (13.4)
5–9	477,536 (33.5)	201,525 (29.3)	178,395 (36.4)	97,616 (39.7)
10+	273,479 (19.2)	83,314 (12.1)	104,291 (21.3)	85,874 (34.9)
10 most frequent drug classes				
Paracetamol and analogues (N02BE)	483,772 (34.0)	184,981 (26.9)	173,338 (35.4)	125,453 (51.0)
HMG CoA reductase inhibitors (C10AA)	466,062 (32.7)	190,265 (27.6)	189,804 (38.7)	85,993 (35.0)
Platelet aggregation inhibitors excl. heparin (B01AC)	337,985 (23.7)	109,735 (15.9)	134,318 (27.4)	93,932 (38.2)
Proton pump inhibitors (A02BC)	295,668 (20.8)	120,132 (17.4)	108,428 (22.1)	67,108 (27.3)
Dihydropyridine derivatives (C08CA)	285,250 (20.0)	107,662 (15.6)	110,412 (22.5)	67,176 (27.3)
Beta-blocking agents, selective (C07AB)	241,009 (16.9)	82,228 (11.9)	94,658 (19.3)	64,123 (26.1)
Propionic acid derivatives (M01AE)	229,475 (16.1)	120,989 (17.6)	78,864 (16.1)	29,622 (12.0)
ACE inhibitors, plain (C09AA)	206,732 (14.5)	80,935 (11.8)	79,301 (16.2)	46,496 (18.9)
Beta-lactamase sensitive penicillins (J01CE)	199,701 (14.0)	94,581 (13.7)	67,817 (13.8)	37,303 (15.2)
Thiazides and potassium in combination (C03AB)	185,262 (13.0)	65,308 (9.5)	71,188 (14.5)	48,766 (19.8)

IQR, interquartile range

supplements and diuretics. In drug profile 2, the second highest number of expected therapeutic subgroup drugs was observed in combination with the highest median age, and the highest proportion of females. The probability of receiving a drug both for the cardiovascular system, alimentary tract and metabolism and for the blood and blood-forming organs was

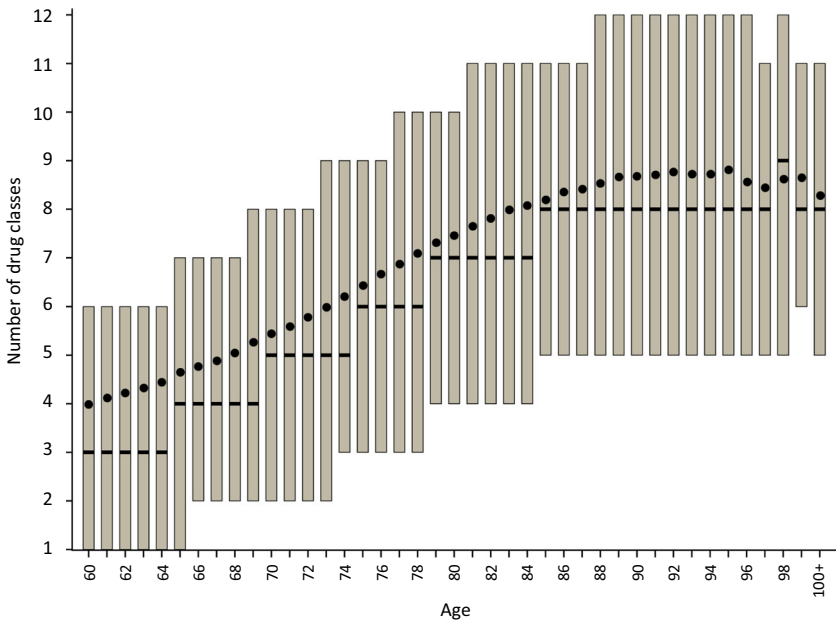

Fig. 1 Mean, median and IQR of the number of unique drug classes per older adult as a function of age. Boxes represent the interquartile range with the median score shown as a horizontal line and the means represented as circles

characterised by drug profiles 1–7. Drug profile 6 and drug profile 8 had an overlap. However, drug profile 8 had a low probability of receiving diuretics, beta-blocking agents, calcium channel blockers, agents acting on the renin–angiotensin system and lipid-modifying agents compared with drug profile 6. Furthermore, drug profile 11 had a high probability of receiving mineral supplement, diuretics, beta-blocking agents and calcium channel blockers. An expected number of different therapeutic subgroup drugs under five were characterised by drug profiles 12–18 (Table 2). The highest proportion of males was found in drug profile 12. Similarly, drug profile 15 was characterised by low probability of receiving drugs except for anti-inflammatory and antirheumatic products and analgesics, drug profile 16 for high probability of receiving hypertensive drugs and drug profile 17 for high probability of receiving drugs for nasal preparations, drugs for obstructive airway diseases, antihistamines for systemic use and ophthalmologicals. Drug profile 18 was the largest. It had a prevalence of 21% and consisted of those with a probability of zero or very close to zero for receiving any drug from the different included therapeutic subgroup drugs. The median age for residents in drug profile 18 was the lowest among the 18 drug profiles at 67 years old, and the sex ratio was also almost 1:1. Thus, the most prevalent drug profiles characterised by expected multiple drug use were drug profiles 1–6 (11.2–7.6 expected therapeutic subgroup drugs) and had a total prevalence of 19%. To characterise the different therapeutic subgroup drugs used in LCA, we have listed the three most frequent drug classes at the 28 different therapeutic subgroup drugs in Online Resource 2.

Discussion

In this cross-sectional nationwide drug utilisation study, we investigated prescribing patterns and drug combination profiles in older adults in Denmark in 2015. Our study showed that extensive drug use among older adults was very common. Older people aged ≥ 60 years redeemed drugs from five (median) different drug classes at the pharmacy each year. The number of redeemed drugs increased by age from a median level at 4 for persons between 60 and 69 years old to a median level at 8 for older people aged ≥ 80 years. However, the distribution of drugs from main groups was almost stable across age groups. Further, we identified 18 different drug profiles; one drug profile with a low probability of receiving any drugs, which included 21% of the population ≥ 60, and 11 drug profiles, which on average received drugs from more than five different therapeutic subgroups.

Our study investigated current drug use among older adults in Denmark and showed that drug consumption is well within the range of previous studies. Previous studies were, however, primarily based on selected populations and fairly old datasets. To our knowledge, no other studies have included the entire Danish population ≥ 60 years. A Swedish study showed that older adults (≥ 65) used an average of 4.6 different drugs (ATC level 5) [26], whereas a Danish study found that the median number of drugs among residents ≥ 60 years was 5 (IQR 2–9) (ATC level 5) [27]. We confirmed the findings from Linjakumpu et al. [3] that the number of drugs increased by age. However, the increase in the number of redeemed drug classes seems larger in our study. One reason for this might be the larger population and the general increase in drug consumption. Similar to our findings, Lagerin et al. [28] reported that the number of drugs at ATC level 3 stabilised at the age of 85–90. This stabilisation of the drug use can be expected because the increased life expectancy in the older population has raised the prevalence of multi-morbidity [29], and the number of drugs was highly correlated with the number of chronic conditions [26]. The impact of evidence-based clinical guidelines for the treatment of the specific disease may also contribute to the observed increase in drug use [30]. This can be explained by the fact that each guideline has several recommended drugs and the majority of older people are multimorbid.

We found that cardiovascular drugs were the most commonly used main drug group, which is in accordance with previous findings. Barat et al. found that the two most

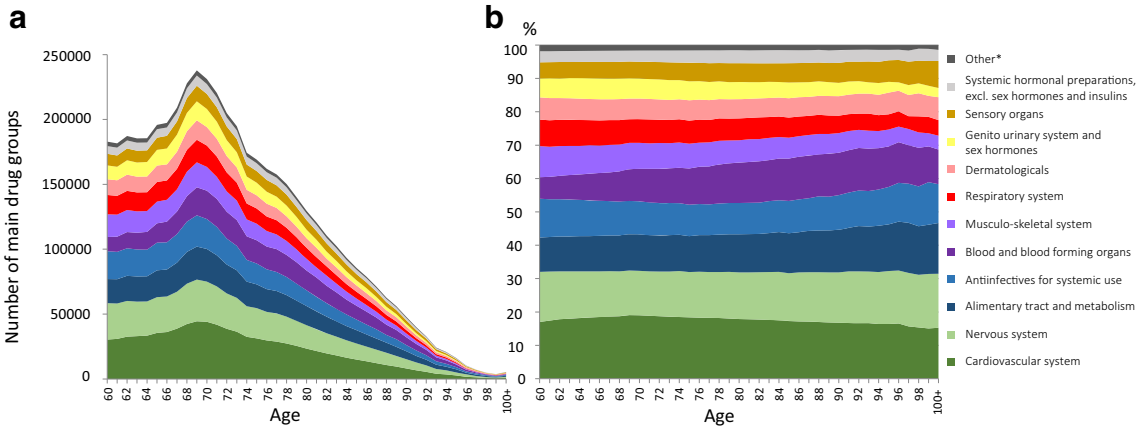

Fig. 2 Overall distribution of drugs used. **a** Number of main drug groups stratified by age. **b** Percentage of main drug groups stratified by age

Table 2 The conditional probabilities of the 28 therapeutic subgroup drugs in the 18 identified drug profiles

Profile	P[a]	1	2	3	4	5	6	7	8
Profile size, No (%)		42,743 (3)	28,496 (2)	56,991 (4)	56,991 (4)	42,743 (3)	42,743 (3)	71,239 (5)	42,743 (3)
Age, median (IQR)	70 (62-77)	78 (71-84)	81 (72-89)	78 (71-84)	75 (69-82)	75 (68-82)	71 (66-77)	72 (68-78)	73 (66-81)
Sex, female (%)	53.3	62.5	72.7	48.7	49.7	61.1	68.6	36.1	74.9
Expected number of therapeutic subgroup drugs		11.2	8.3	8.1	7.6	7.6	7.2	6.7	6.7
Therapeutic subgroup drug									
A02: Drugs for acid related disorders	22%	72%	60%	30%	49%	45%	43%	20%	62%
A06: Drugs for constipation	5%	29%	43%	6%	12%	22%	2%	1%	25%
A10: Drugs used in diabetes	11%	34%	5%	20%	16%	28%	11%	55%	2%
A12: Mineral supplement	10%	63%	74%	59%	0%	16%	8%	18%	2%
B01: Antithrombotic agents	30%	90%	43%	99%	100%	62%	28%	77%	17%
B03: Antianemic preparations	6%	25%	22%	9%	13%	17%	5%	11%	14%
C01: Cardiac Therapy	6%	38%	12%	46%	33%	3%	3%	8%	2%
C03: Diuretics	23%	91%	91%	96%	12%	36%	37%	48%	18%
C07: Beta blocking agents	20%	59%	22%	81%	55%	25%	21%	55%	10%
C08: Calcium channels blockers	21%	41%	24%	33%	33%	39%	32%	62%	12%
C09: Agents acting on the renin-angiotensin system	36%	60%	27%	66%	47%	62%	59%	96%	20%
C10: Lipid modifying agents	33%	76%	15%	64%	73%	73%	45%	91%	16%
D07: Topical dermatological Corticosteroids	13%	26%	22%	15%	21%	16%	35%	13%	23%
G03: Sex hormones and modulators of the genital system	10%	17%	14%	6%	13%	10%	26%	3%	26%
G04: Urologicals	10%	16%	11%	13%	18%	14%	12%	14%	11%
H02: Corticosteroids for system use	6%	27%	19%	8%	12%	0%	19%	2%	17%
H03: Thyroid therapy	6%	14%	12%	10%	8%	11%	10%	5%	11%
M01: Antiinflammatory and antirheumatic products	19%	25%	23%	10%	24%	19%	32%	11%	46%
M05: Drugs for treatment of bone diseases	6%	16%	19%	6%	11%	8%	8%	1%	16%
N02: Analgesics	38%	94%	89%	53%	76%	73%	63%	31%	97%
N03: Antiepileptics	5%	20%	17%	3%	10%	20%	4%	3%	23%
N04: Anti-parkinson drugs	2%	6%	6%	1%	3%	7%	2%	0%	7%
N05: Psycholeptics	15%	45%	42%	16%	30%	46%	28%	6%	55%
N06: Psychoanaleptics	13%	40%	44%	11%	22%	61%	15%	8%	48%
R01: Nasal preparations	6%	11%	5%	4%	9%	2%	41%	3%	13%
R03: Drugs for obstructive airways diseases	13%	41%	29%	19%	22%	13%	43%	7%	25%
R06: Antihistamines for systemic use	6%	17%	12%	4%	11%	6%	43%	3%	19%
S01: Ophthalmologicals	17%	31%	29%	18%	26%	23%	48%	17%	31%

Profile	9	10	11	12	13	14	15	16	17	18
Profile size, N (%)	71239 (5)	28,496 (2)	71,239 (5)	113,982 (8)	56,991 (4)	1,245 (0.1)	128,230 (9)	156,725 (11)	99,734 (7)	299,203 (21)
Age, median (IQR)	71 (66-77)	74 (68-81)	74 (68-82)	72 (68-79)	70 (65-75)	69 (64-75)	68 (64-74)	70 (65-75)	69 (64-74)	67 (63-72)
Sex, female (%)	55.1	69.2	75.3	34.7	39.0	63.8	60.8	50.2	62.7	49.0
Expected number of therapeutic Subgroup drugs	6.4	5.2	5.1	4.3	4.2	3.3	3.0	2.9	2.8	0.5
Therapeutic subgroup drug										
A02: Drugs for acid related disorders	41%	33%	18%	13%	14%	17%	25%	10%	18%	3%
A06: Drugs for constipation	4%	5%	2%	0%	1%	7%	3%	0%	1%	0%
A10: Drugs used in diabetes	18%	4%	7%	3%	56%	2%	1%	3%	1%	1%
A12: Mineral supplement	7%	7%	41%	1%	0%	0%	0%	4%	0%	0%
B01: Antithrombotic agents	35%	30%	24%	97%	34%	10%	3%	7%	4%	1%
B03: Antianemic preparations	6%	16%	6%	3%	8%	7%	4%	2%	4%	1%
C01: Cardiac Therapy	1%	1%	1%	13%	0%	1%	0%	1%	1%	0%
C03: Diuretics	32%	20%	100%	12%	8%	6%	5%	21%	4%	1%
C07: Beta blocking agents	23%	10%	30%	47%	4%	8%	3%	17%	2%	1%
C08: Calcium channels blockers	43%	23%	33%	25%	21%	8%	4%	43%	4%	1%
C09: Agents acting on the renin-angiotensin system	72%	33%	43%	42%	69%	14%	11%	68%	10%	4%
C10: Lipid modifying agents	55%	28%	31%	66%	85%	16%	7%	28%	11%	4%
D07: Topical dermatological Corticosteroids	14%	8%	15%	10%	10%	12%	11%	10%	22%	5%
G03: Sex hormones and modulators of the genital system	12%	11%	14%	4%	4%	15%	13%	7%	19%	5%
G04: Urologicals	14%	7%	4%	14%	14%	7%	9%	10%	10%	4%
H02: Corticosteroids for system use	6%	52%	4%	2%	2%	1%	5%	1%	10%	0%
H03: Thyroid therapy	6%	10%	12%	4%	6%	9%	4%	4%	7%	2%
M01: Antiinflammatory and antirheumatic products	71%	18%	16%	7%	14%	8%	58%	9%	10%	4%
M05: Drugs for treatment of bone diseases	4%	43%	7%	3%	2%	7%	6%	3%	8%	2%
N02: Analgesics	100%	60%	42%	20%	22%	35%	78%	13%	17%	3%
N03: Antiepileptics	7%	3%	2%	2%	1%	11%	3%	1%	1%	0%
N04: Anti-parkinson drugs	2%	2%	1%	1%	1%	5%	1%	0%	0%	0%
N05: Psycholeptics	18%	14%	12%	5%	5%	46%	10%	5%	9%	1%
N06: Psychoanaleptics	9%	15%	8%	5%	7%	45%	5%	4%	5%	1%
R01: Nasal preparations	5%	0%	2%	4%	3%	2%	4%	3%	23%	1%
R03: Drugs for obstructive airways diseases	11%	44%	12%	7%	7%	7%	9%	6%	26%	2%
R06: Antihistamines for systemic use	5%	0%	4%	2%	3%	3%	3%	2%	18%	0%
S01: Ophthalmologicals	16%	19%	18%	13%	14%	16%	12%	12%	30%	7%

[a] Probability of receiving the therapeutic subgroup drug in general

The coloured boxes indicate increase of at least 10 percent points over the overall probability. Different colours represent different main groups

common prescription drugs among 75-year-old community-dwelling residents were cardiovascular drugs (25%) and central nervous system drugs (23%) [31]. In a Swedish study among older adults ≥ 78 years of age, cardiovascular drugs were also the most frequently used drugs followed by nervous system drugs and alimentary tract metabolism drugs [30]. Similar results were found by Wastesson et al. [32]. We further found that the distribution of main drug groups was stable over age, which indicates that the drug patterns do not change significantly with age and suggests that drugs may not be discontinued in late life.

A complex drug burden is potentially harmful to the patients and difficult to manage [10, 33]. The drug burden is often measured by the number of different drugs used but ignoring the complexity of the drug profiles. To our knowledge, LCA has never been performed in a large, national population, and with therapeutic subgroup drugs as outcomes. In previous studies, LCA has been used to define, e.g., subtypes of drug abuse in a Swedish cohort ($n = 192{,}501$) [34], and to identify patterns of drug use associated with lower serum sodium concentration in older hospitalised patients ($n = 101$) [35]. In both studies, the drugs were selected to fit a selected patient group, and the analysis included only a limited number of drugs or drug classes, whereas only three and six different drug profiles were identified. In this study, 18 drug profiles, i.e. clinical recognisable medication patterns, were identified. For example, drug profile 13 is characterised by a high probability of receiving drugs for diabetes, agents acting on the renin–angiotensin system and lipid-modifying agents. In general, the drug profiles demonstrated very complex therapeutic profiles and reflecting the high level of multimorbidity. However, the drug profiles should be explored more thoroughly to fit the clinical practice, e.g. to risk-stratified patients in a hospital or a general practice. When identifying drug profiles, LCA is considered highly suitable because the drug groups differ qualitatively from each other. Also, we found similar drug profiles for the five randomly selected samples which indicates that the 18 drug profiles are very stable. The drug profiles allow us to study drug use and drug combinations in a new way. By using the drug profiles, it is possible to identify in which of the drug profiles a given drug is used and, thereby, restrict studies of adverse effects to individuals with different drug combination profiles. Real-world evidence in different drug profiles makes the result more usable in clinical practice. We believe that the new method is important also when studying drug channelling bias in more sufficient ways and when studying polypharmacy more comprehensively.

Strengths and limitations

Our study is the first study investigating drug profiles in a large population using LCA. The use of LCA in an unselected population enables a nuanced identification and description of drug profiles. More in-depth knowledge of the drug patterns is desired, e.g. studying drug profiles at drug class level instead of at therapeutic subgroup level. This was, however, not possible in this study due to the lack of computer power. This study is exploratory and initialises the groundwork for future research. Drug profiles have the potential to be evaluated on drug class level, to achieve knowledge on among other drug safety, interactions, adverse drug events, maybe by investigating individuals with a specific drug profile. Another strength of this study is that data were obtained from nationwide registers containing high-quality data. This ensures complete coverage and eliminates the risk of selection bias. This study has not investigated the differences in prescribing patterns among different regions in Denmark, as this is a subject in itself. However, Denmark is a small country with 5.7 million citizens in 2016. We do not believe that regional factors influence prescribing patterns, as most drugs are prescribed by GPs [1], which are organised in single or very small practices. Also, a study by Henriksen et al. [36] found homogeneity between all of the five Danish regions with regard to sociodemographic and health-related characteristics.

A limitation of this study is that certain drugs can be purchased over the counter in Denmark and drug consumption, therefore, can be slightly underestimated. Olesen et al. [37] found that 28% of the patients aged 65 years or more used non-prescription drugs. Indeed, the majority are prescription drugs, especially with respect to the most potent drugs and those with the greatest potential of interactions. An additional limitation is that drugs used during hospitalisation are not recorded in the register, including drugs administered at the hospital for outpatient treatment. Another potential limitation is that we had no information on drug adherence among older adults. Though we know the older adults have filled the prescription, we do not know whether the older adults have taken the drug. At the same time, we eliminate primary non-adherence, which is a strength. We required at least one prescription for all drugs in the analyses, though we did not know if the older adults were compliant to the given drug. Due to the excessive computer running time, we were further compelled to reduce the population to five random samples of 50,000 individuals each. We assume a sample of 50,000 individuals as a large population and that the results would not be different compared with the final population.

In conclusion, we found that the use of drugs is extensive both at the population level and at the individual level and that it is increasing with age. Cardiovascular drugs, analgesics and psychotropic drugs were the most prevalent drug classes. Eighteen different drug profiles were identified, with 11 drug profiles reflecting probable drug combination profiles among users of multiple drug use. The identified drug profiles described clinical recognisable medication patterns. The drug profiles have the potential to be used in future studies

investigating high-risk prescription patterns. Studies of the older adult population with diverging drug profiles may provide useful information to prevent drug-related problems and optimise drug treatment. For instance, with more research into risk patterns, we can produce risk profiles that will provide a better understanding of which patients benefit most from medication review. Furthermore, these risk profiles may also benefit the patients when a new medication is added to the treatment for a more rational drug prescribing.

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Compliance with ethical standards

The study was approved by the Scientific Board of Statistics Denmark and the Danish Data Protection Agency (Ref. 00003115). An approval from an ethics committee is not required for registry-based studies in Denmark. No identifiable patient data could be retrieved. The study was conducted by following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [38].

Conflict of interest The authors declare that they have no conflicts of interest.

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