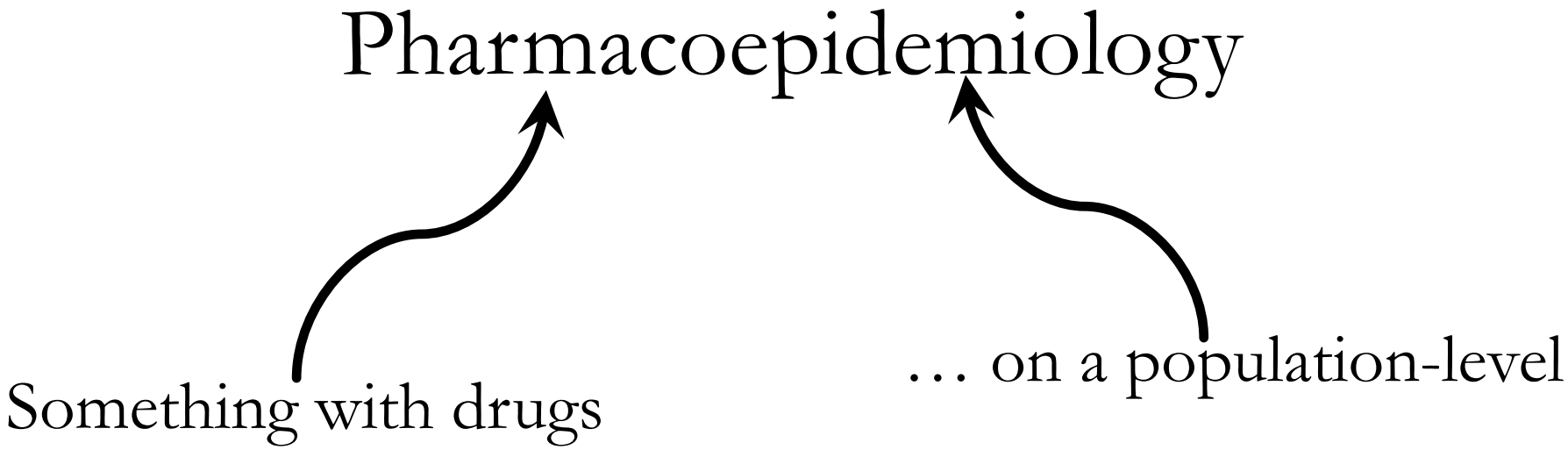
Drug utilization


Pharmacoepidemiology
Something with drugs
… on a population-level

”The study of use and effects of medications on a population basis”

Strom’s Pharmacoepidemiology

”The study of effects of medications on a population basis”

Clinical Epidemiology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

A cohort study on the risk of lymphoma and skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids (Joint European Longitudinal Lymphoma and Skin Cancer Evaluation – JOELLE study)

This article was published in the following Dove Press journal:
Clinical Epidemiology

Jordi Castellsague,[1] Josephina G Kuiper,[2] Anton Pottegård,[3] Ingegärd Anveden Berglind,[4] Daniel Dedman,[5] Lia Gutierrez,[1] Brian Calingaert,[6] Myrthe PP van Herk-Sukel,[2] Jesper Hallas,[3] Anders Sundström,[4] Arlene M Gallagher,[5] James A Kaye,[7] Carolina Pardo,[8] Kenneth J Rothman,[7] Susana Perez-Gutthann[1]

[1]Department of Epidemiology, RTI Health Solutions, Barcelona, Spain; [2]Department Research, PHARMO Institute for Drug Outcomes Research, Utrecht, the Netherlands; [3]Clinical Pharmacology and Pharmacy, Department

Background: There is a concern that topical tacrolimus and pimecrolimus, indicated for second-line treatment of atopic dermatitis, may increase the risk of lymphoma and skin cancer, particularly in children.

Objective: The aim of this study was to compare incidence rates (IRs) of lymphoma and skin cancer between new users of topical tacrolimus or pimecrolimus and users of moderate- to high-potency topical corticosteroids (TCSs) and untreated subjects.

Methods: This is a multicenter cohort study with frequency matching by strata of propensity scores in population databases in the Netherlands, Denmark, Sweden, and the UK. IR ratios (IRRs) were estimated using Mantel–Haenszel methods for stratified analysis.

Results: We included 19,948 children and 66,127 adults initiating tacrolimus, 23,840 children and 37,417 adults initiating pimecrolimus, 584,121 users of TCSs, and 257,074 untreated subjects. IRs of lymphoma per 100,000 person-years were 10.4 events in children and 41.0 events in adults using tacrolimus and 3.0 events in children and 27.0 events in adults using pimecrolimus. The IRR (95% confidence interval [CI]) for lymphoma, tacrolimus versus TCSs, was 3.74 (1.00–14.06) in children and 1.27 (0.94–1.71) in adults. By lymphoma type, the highest IRR was 3.17 (0.58–17.23) for Hodgkin lymphoma in children and 1.76 (95% CI, 0.81–3.79)

Drug utilization-studies

Incidence rates

Prevalence proportions

Use of single substances

Persistence ('drug survival')

Co-medication

Daily dose (≈)

Prescriber type

Regional differences

Skewness in use

Drug utilization-studies

Incidence rates

Prevalence proportions

Use of single substances

Persistence ('drug survival')

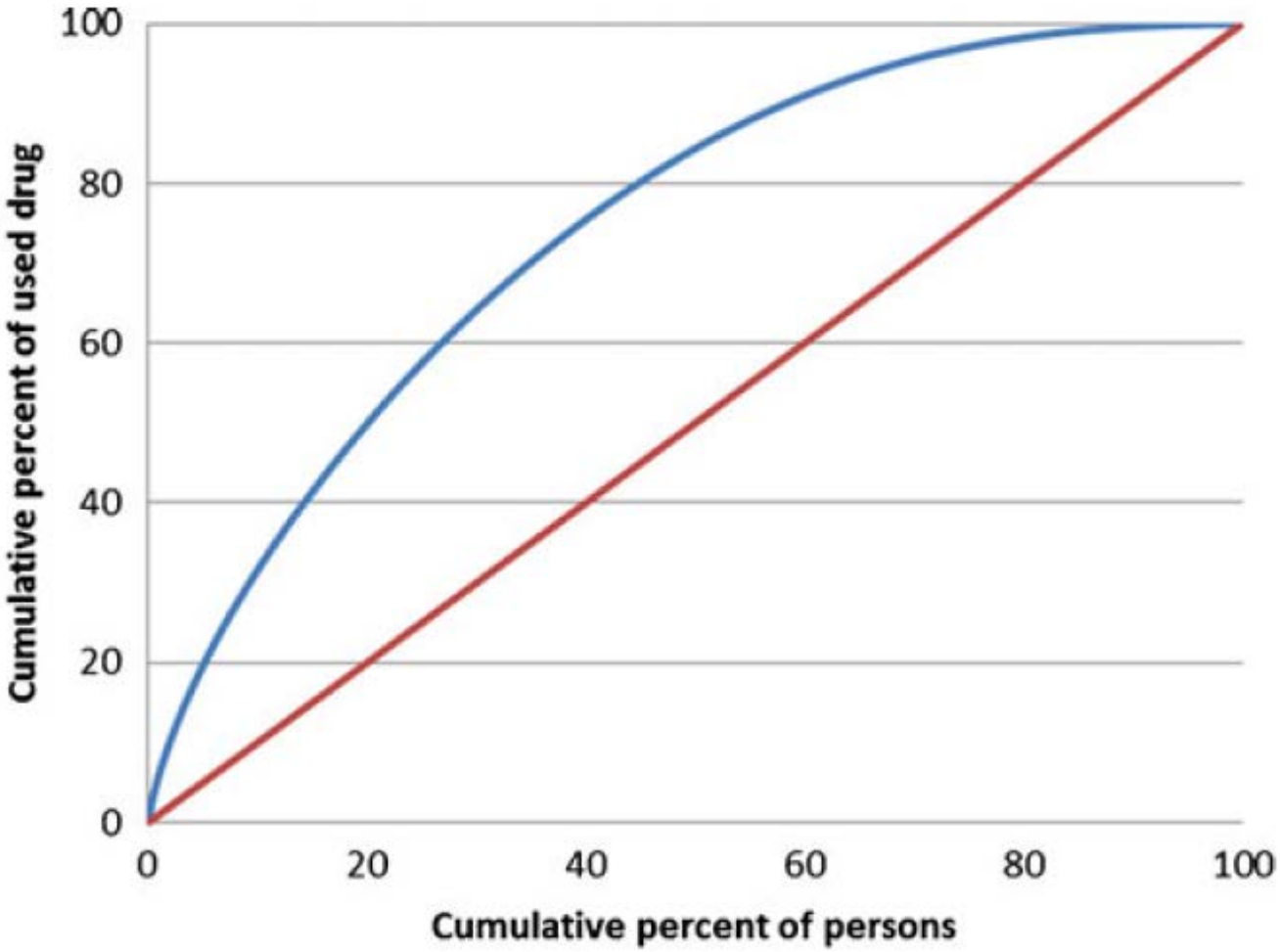
Co-medication

Daily dose (≈)

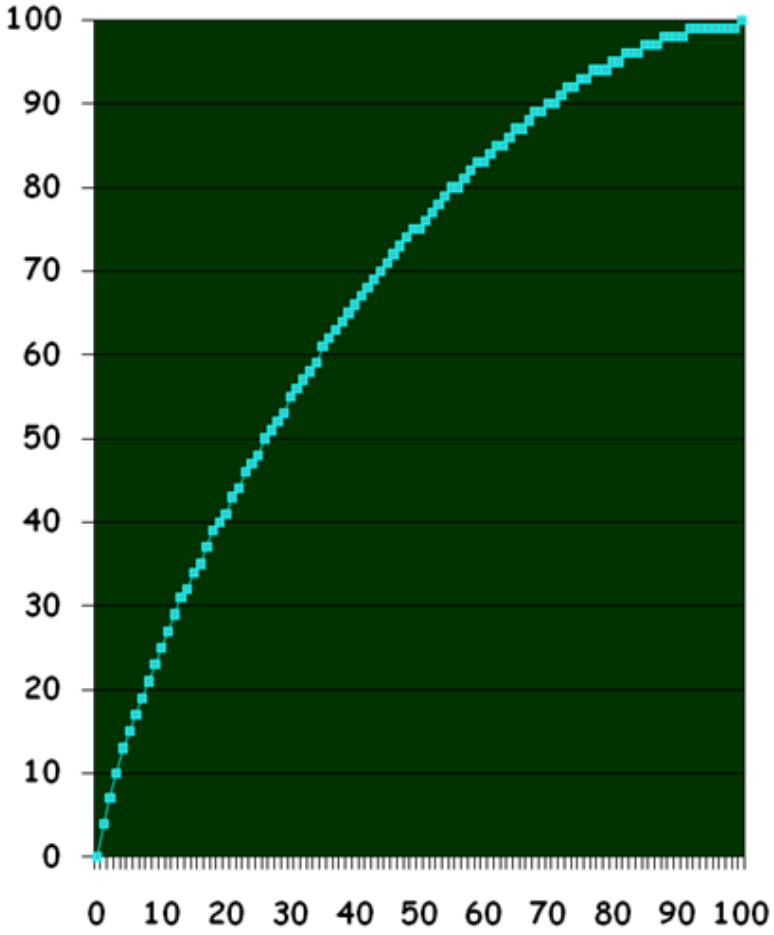
Prescriber type

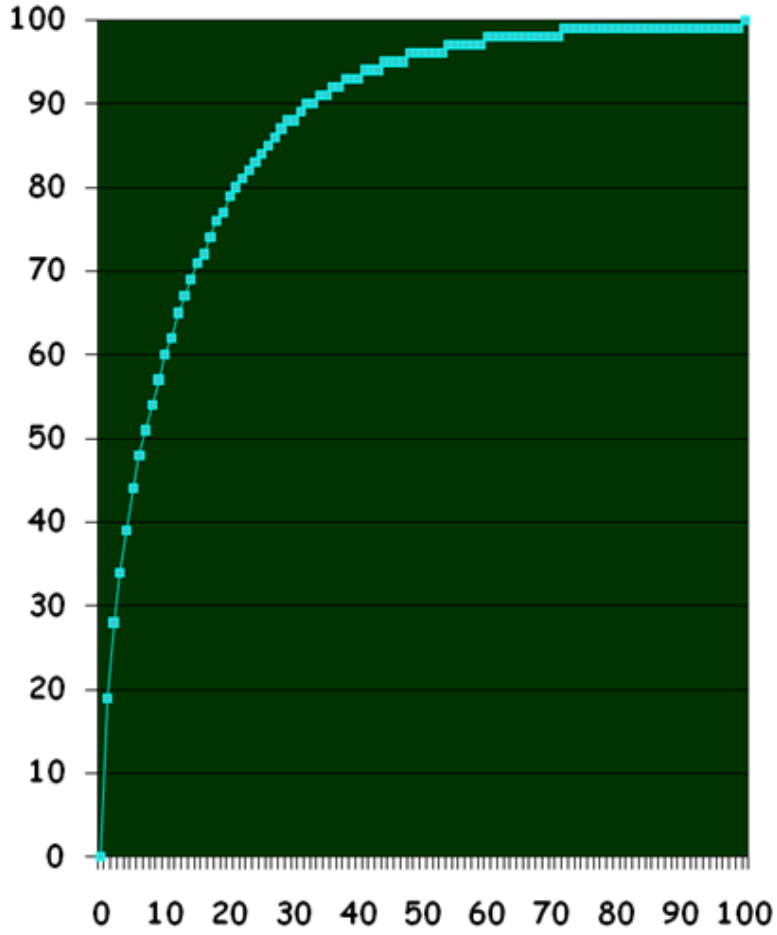
Regional differences

Skewness in use


100
80
60
40
20
0
Cumulative percent of used drug
0
20
40
60
80
100
Cumulative percent of persons

Lorenz curves
Insulin and opioids (Funen 2003)





1. Inappropriate use of sumatriptan: population based register and interview study.
Gaist D, Tsiropoulos I, Sindrup SH, **Hallas** J, Rasmussen BK, Kragstrup J, Gram LF.
BMJ. 1998 May 2;316(7141):1352-3. No abstract available.
PMID: 9563984 **Free PMC Article**
Similar articles

2. Use of sumatriptan in Denmark in 1994-5: an epidemiological analysis of nationwide prescription data.
Gaist D, Andersen M, Aarup AL, **Hallas** J, Gram LF.
Br J Clin Pharmacol. 1997 Apr;43(4):429-33.
PMID: 9146856 **Free PMC Article**
Similar articles

3. Is overuse of sumatriptan a problem? A population-based study.
Gaist D, **Hallas** J, Sindrup SH, Gram LF.
Eur J Clin Pharmacol. 1996;50(3):161-5. Erratum in: Eur J Clin Pharmacol 1996;50(5):431.
PMID: 8737753
Similar articles

4. Misuse of sumatriptan.
Gaist D, Sindrup S, **Hallas** J, Gram LF.
Lancet. 1994 Oct 15;344(8929):1090. No abstract available.
PMID: 7934471
Similar articles

Drug utilization-studier

Incidence rates

Prevalence proportions

Use of single substances

Persistence ('drug survival')

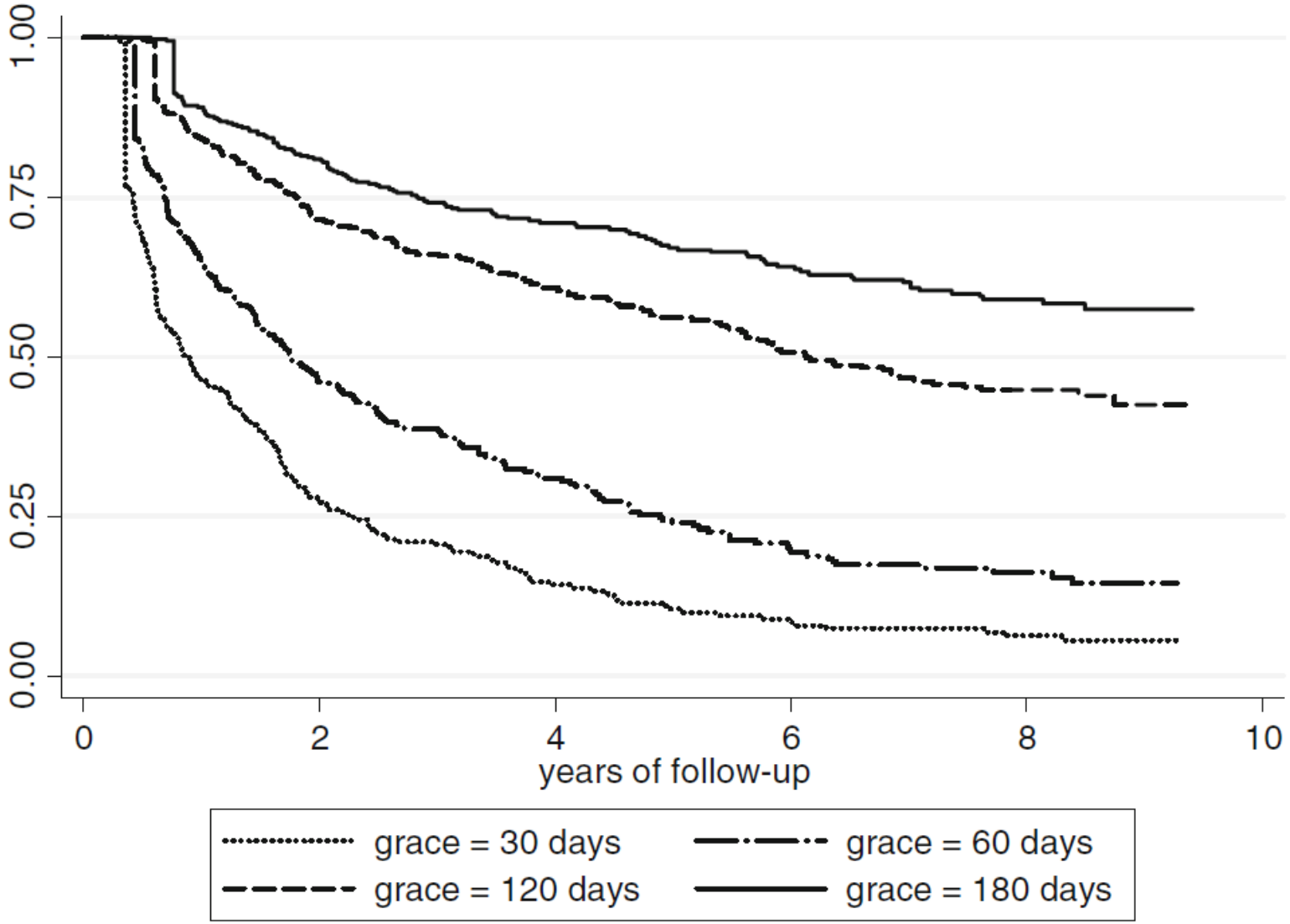
Co-medication

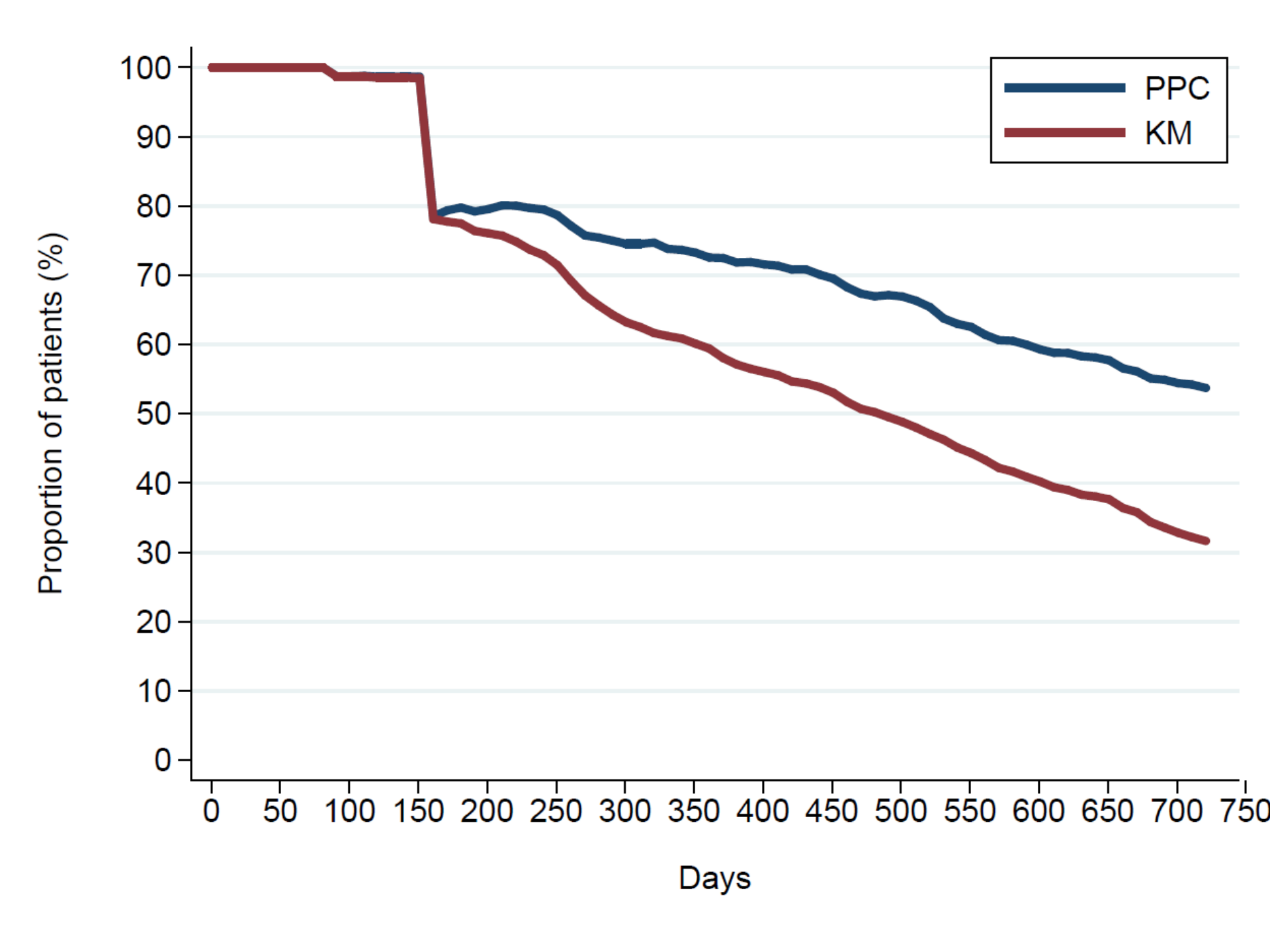
Daily dose (≈)

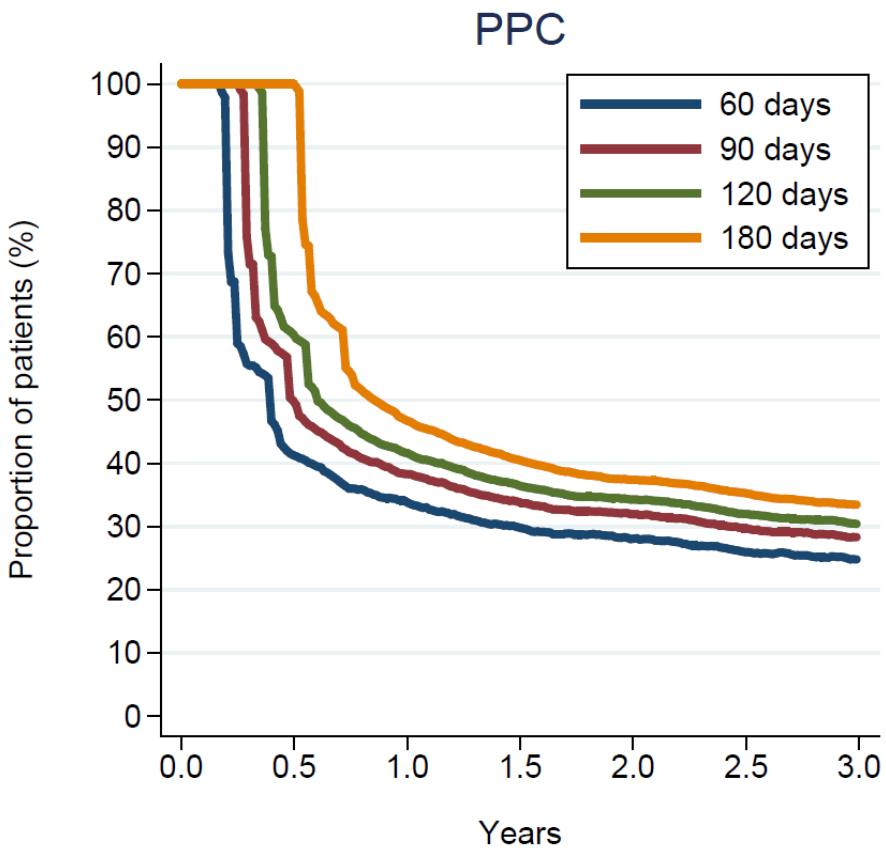
Prescriber type

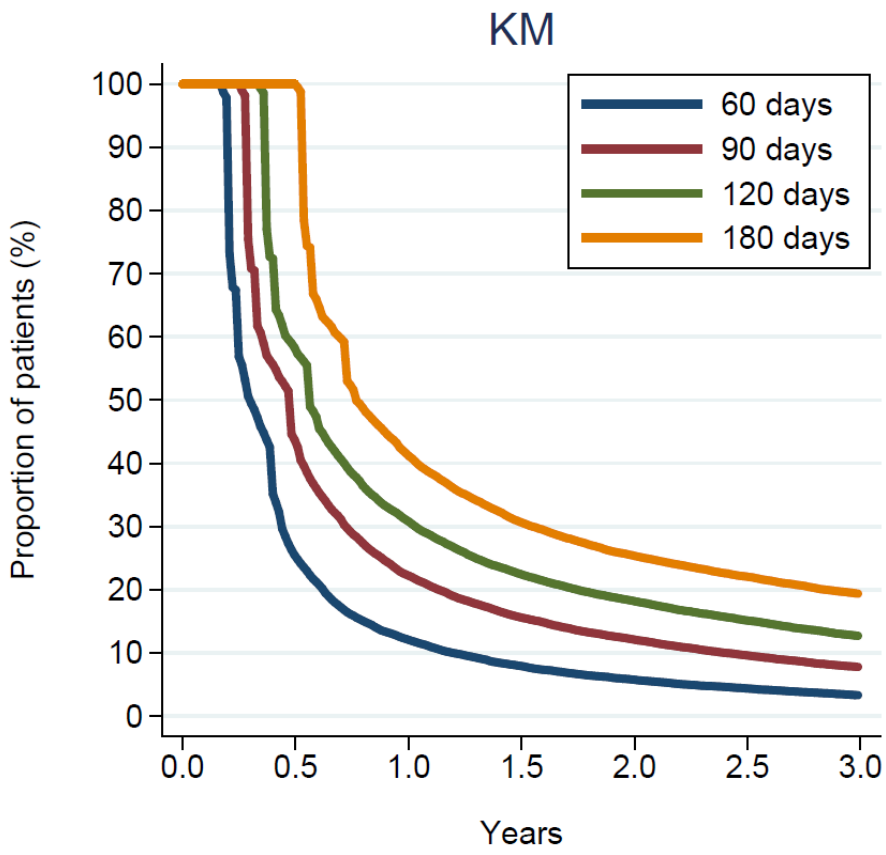
Regional differences

Skewness in use


1.00
0.75
0.50
0.25
0.00
0
2
4
6
8
10
years of follow-up
grace = 30 days
grace = 60 days
grace = 120 days
grace = 180 days


PPC
KM
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
Days


PPC
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Years
60 days
90 days
120 days
180 days


KM
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Years
60 days
90 days
120 days
180 days

Received: 13 November 2017 | Revised: 16 May 2018 | Accepted: 28 May 2018

DOI: 10.1002/pds.4582

ORIGINAL REPORT

WILEY

Using the "proportion of patients covered" and the Kaplan-Meier survival analysis to describe treatment persistence

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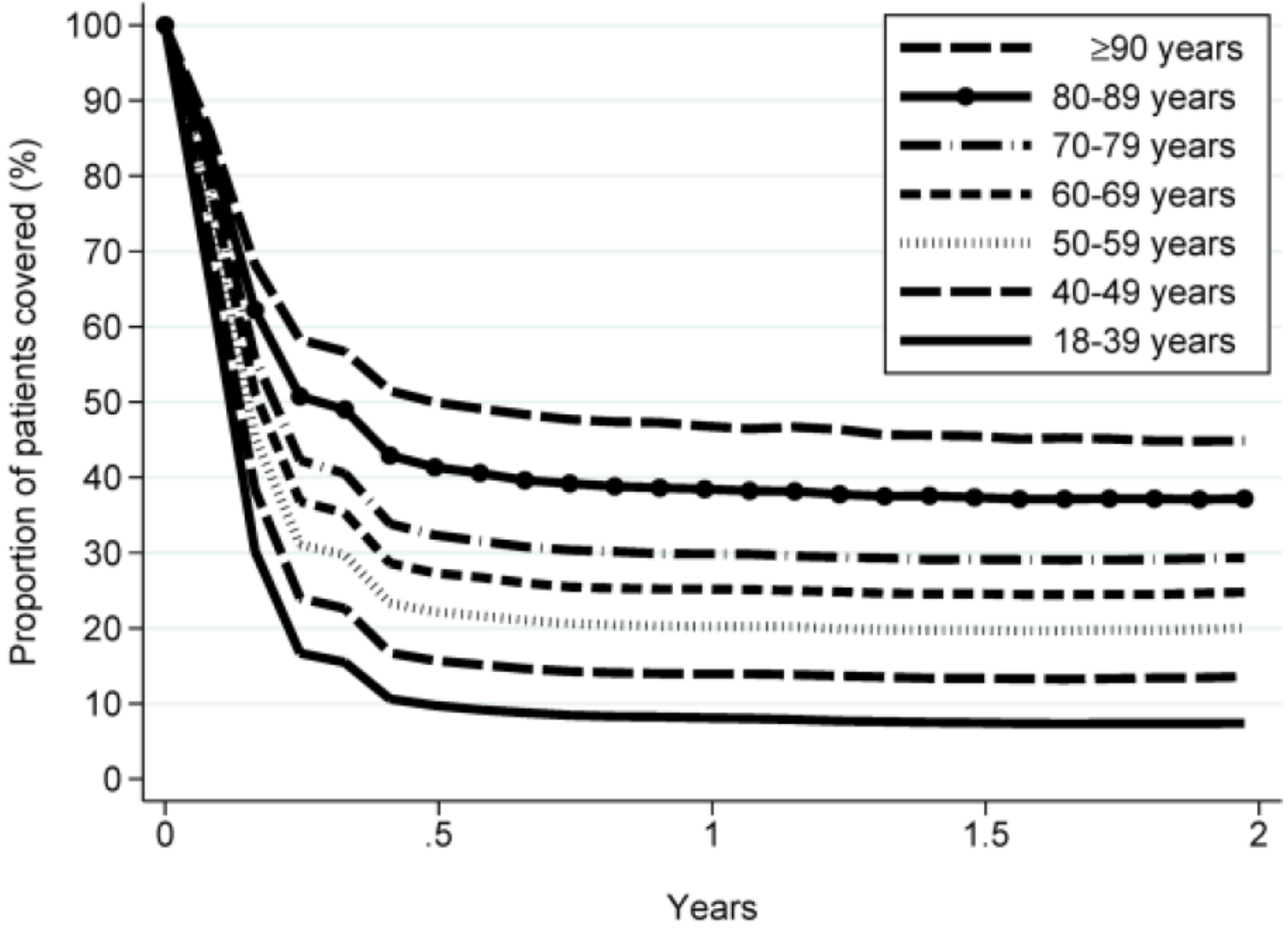
Email: lorasmussen@health.sdu.dk

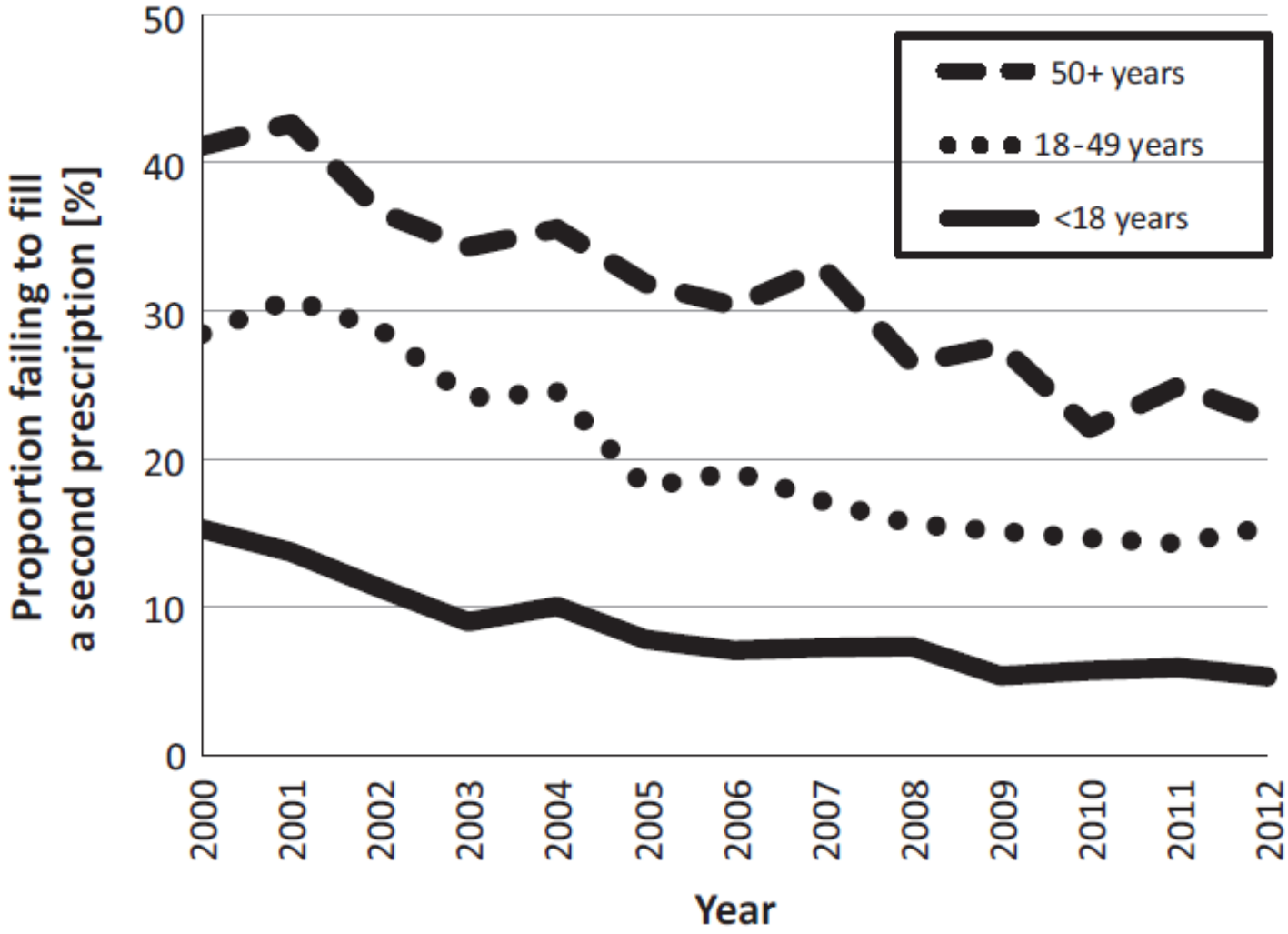
Abstract

Purpose: Standard Kaplan-Meier (KM) survival analysis is often used to study treatment persistence estimating the proportion of patients who have not yet experienced a treatment break by a given day after treatment initiation. This method only allows patients to be studied until their first treatment break. The "proportion of patients covered" (PPC) method is another approach to study treatment persistence. It measures the proportion of live patients currently covered by treatment. We aimed to describe the PPC method, show how the KM survival analysis and the PPC method can describe treatment persistence, and discuss the interpretation/application of the methods.

Methods: We identified new users of statins, selective serotonin reuptake inhibitors, hormone replacement therapy, and ibuprofen. We used KM estimates and the PPC to describe persistence in the 3 years post treatment initiation, using a grace period of 90 days to define a treatment break.

Results: Three years after statin initiation, approximately 40% of patients were still in continuous treatment (KM survival) and 60% of patients still alive were in current treatment (PPC). Corresponding numbers were 12% and 25% for selective serotonin reuptake inhibitors and 9% and 29% for hormone replacement therapy. At 1 year, numbers were 5% and 10% for ibuprofen. The PPC showed markedly less variability than the KM survival analysis with different choices of grace periods.


Proportion of patients covered (%)
100
90
80
70
60
50
40
30
20
10
0
0
.5
1
1.5
2
Years
≥90 years
80-89 years
70-79 years
60-69 years
50-59 years
40-49 years
18-39 years


50
40
30
20
10
0
Proportion failing to fill a second prescription [%]
50+ years
18-49 years
<18 years
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Year

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2006; **15**: 565–574
Published online 2 March 2006 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.1230

ORIGINAL REPORT

Methods for evaluation of medication adherence and persistence using automated databases†

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[1]*Meyers Primary Care Institute, University of Massachusetts Medical School, Fallon Foundation, Fallon Community Health Plan, Worcester, MA, USA*
[2]*Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA*
[3]*Harvard School of Public Health, Boston, MA, USA*

SUMMARY

Purpose Our aim was to perform a systematic review of the methods currently being used to assess adherence and persistence in pharmacoepidemiological and pharmacoeconomic studies using automated databases.

Methods A MEDLINE search of English language literature was performed to identify studies published between January 1, 1980 and March 31, 2004 that evaluated adherence, compliance, persistence, switching, or discontinuations of medications using automated dispensing data (pharmacy records). Two study investigators independently reviewed the abstracts and articles to determine relevant studies according to specified criteria.

Results A total of 136 articles met the criteria for evaluation. The types of measures of adherence and persistence commonly reported include the medication possession ratio and related measures of medication availability (77 studies), discontinuation/continuation (58 studies), switching (34 studies), medication gaps (13 studies), refill compliance (7 studies), and retentiveness/turbulence (4 studies). Specific issues considered include the assessment of exposed time to drug therapy and specification of the follow-up period.

Conclusions The terminology, definitions, and methods to determine adherence and persistence differ greatly in the published literature. The appropriateness and choice of the specific measure employed should be determined by the overall goals of the study, as well as the relative advantages and limitations of the measures.

KEY WORDS — medication compliance; adherence; persistence; automated data; administrative data

INTRODUCTION

Adherence to prescribed medications is a key factor according to schedule, while persistence generally indicates whether a patient stays on therapy or the time from initiation to discontinuation of therapy.[3,11] How-

Drug utilization-studier

Incidence rates

Prevalence proportions

Use of single substances

Persistence ('drug survival')

Co-medication

Daily dose (≈)

Prescriber type

Regional differences

Skewness in use

Table 2 Percent distribution of prescriptions between different prescriber types [general practitioner (GP), specialist (SP), hospital doctor (HP)] specified by patient age category, drug, and incident and nonincident prescriptions. Study period: 1 October 2008–30 September 2011

Drug	Patient age category					
	2–5 years	6–12 years	13–17 years	18–24 years	25–49 years	50+ years
Incident prescriptions: percent distribution: GP/SP/HP						
Methylphenidate (*n*)	6/28/66 (539)	7/27/66 (6,338)	10/30/59 (4,231)	18/44/38 (5,243)	20/49/31 (9,767)	22/24/53 (2,864)
Atomoxetine (*n*)	<10	5/27/68 (228)	8/32/60 (371)	15/28/55 (632)	14/35/48 (875)	17/32/50 (96)
Modafinil (*n*)[a]	<10	<10	<10	<10	19/59/22 (27)	42/21/32 (19)
Nonincident prescriptions, weighed by DDD: percent distribution: GP/SP/HP						
Methylphenidate (*n*)	18/25/57 (9,451)	23/24/53 (157,135)	29/24/47 (95,082)	39/33/27 (78,283)	43/38/18 (203,690)	58/23/19 (3,126)
Atomoxetine (*n*)	18/32/51 (565)	10/34/56 (22,985)	13/35/52 (18,211)	21/38/40 (14,520)	22/47/29 (24,007)	24/55/21 (2,201)
Modafinil (*n*)[a]	<10	26/44/27 (75)	27/49/24 (391)	34/50/16 (1,571)	38/50/13 (5,094)	49/35/15 (2,692)

[a] Only persons previously using either methylphenidate or atomoxetine

	6–12 years	25–49 years
MPH	GP/SP/HP 7/27/66 (6,338)	GP/SP/HP 20/49/31 (9,767)

BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology Doi: 10.1111/bcpt.12610

Validity of the Prescriber Information in the Danish National Prescription Registry

Lotte Rasmussen[1], Julie Valentin[1], Katarina Margareta Gesser[2], Jesper Hallas[1] and Anton Pottegård[1]

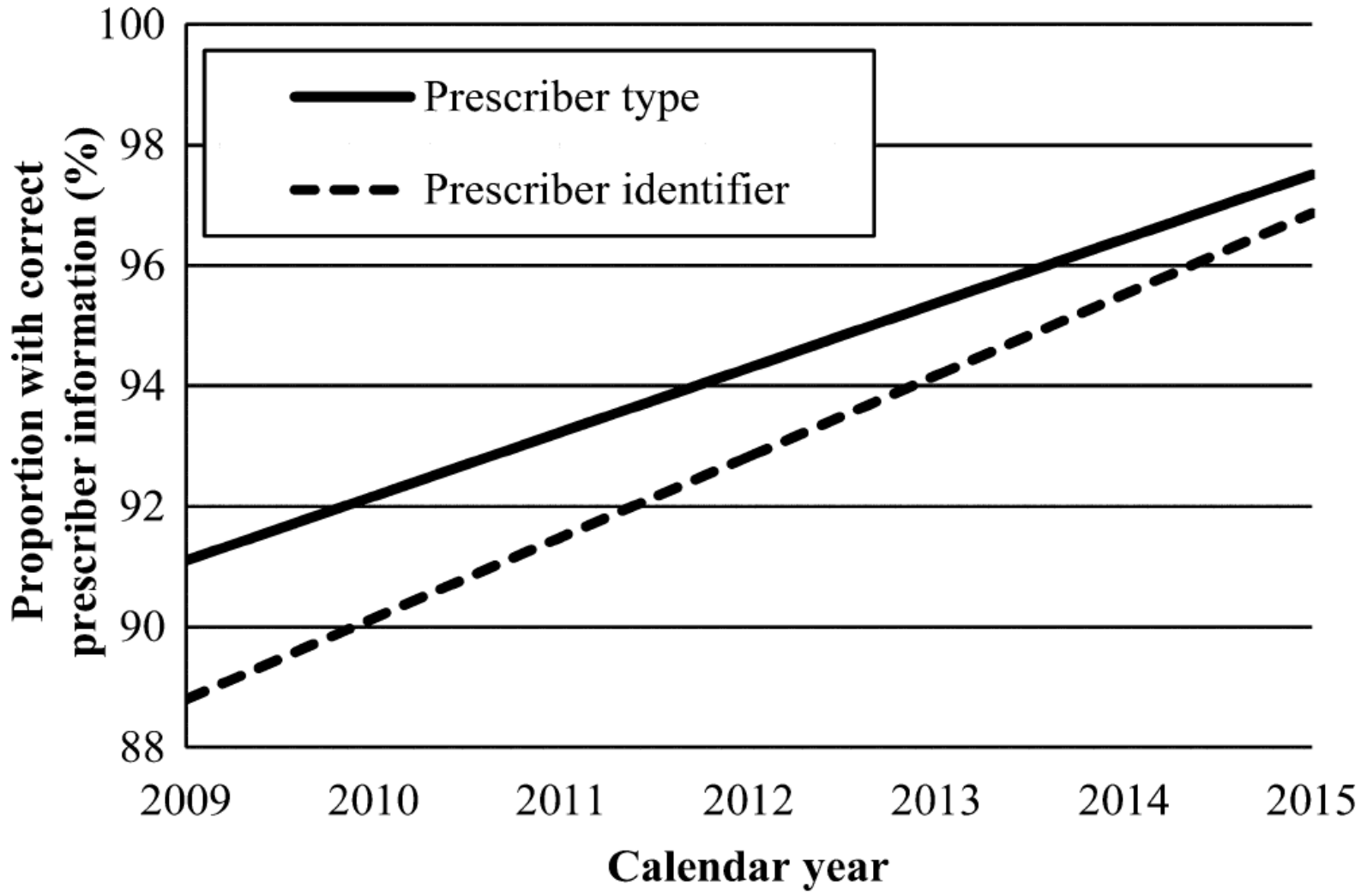
[1]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark and [2]Department of Data Delivery & Medicinal Product Statistics, The Danish Health Data Authority, Copenhagen, Denmark

(Received 23 December 2015; Accepted 5 April 2016)

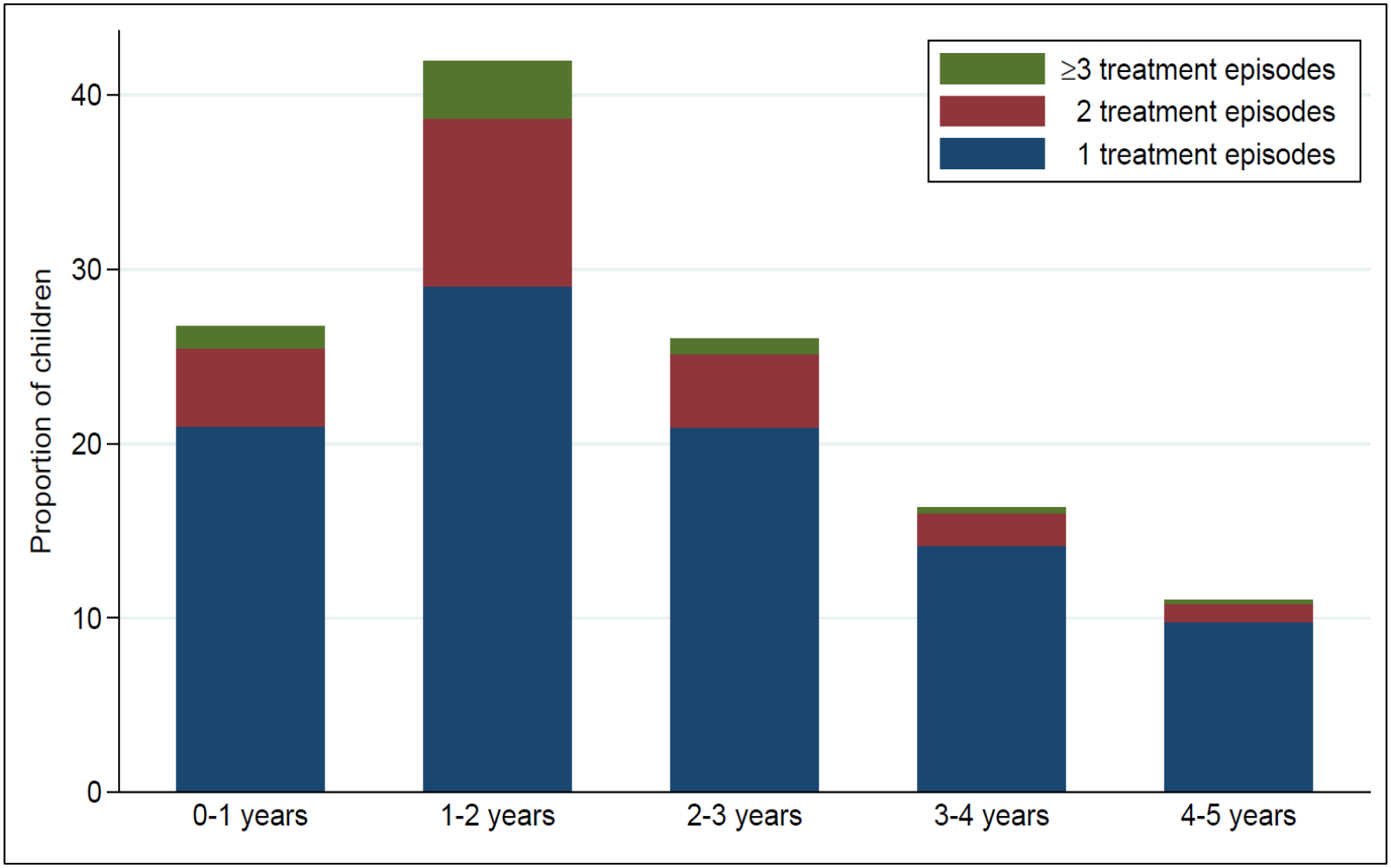
Abstract: The aim of this study was to measure the validity of the prescriber information recorded in the Danish National Prescription Registry (DNPR). The prescriber information recorded in the pharmacies' electronic dispensing system was considered to represent the prescriber information recorded in the DNPR. Further, the problem of validity of the prescriber information pertains only to non-electronic prescriptions, as these are manually entered into the dispensing system. The recorded prescriber information was thus validated against information from a total of 2000 non-electronic prescriptions at five Danish community pharmacies. The validity of the recorded prescriber information was measured at the level of the individual prescriber and the prescriber type, respectively. The proportion of non-electronic prescriptions with incorrect registrations was 22.4% (95% confidence interval (CI): 20.6–24.3) when considering individual prescriber identifiers and 17.8% (95% CI: 16.1–19.5) when considering prescriber type. When excluding prescriptions specifically registered as 'missing prescriber identifier', the proportions decreased to 9.5% (95% CI: 8.2–11.0) and 4.1% (95% CI: 3.2–5.1), respectively. The positive predictive values for the classification of prescriber types were in the range of 94.0–99.2%, while the sensitivity ranged between 64.6% and 91.8%. With a maximum of 14% non-electronic prescriptions of all prescriptions in the DNPR in 2015, this corresponds to correct classification of prescriber types in the DNPR of at least 97.5%. In conclusion, the prescriber information in the DNPR was found to be valid, especially in recent years. Researchers should be aware of the low sensitivity towards prescriptions from private practicing specialists.

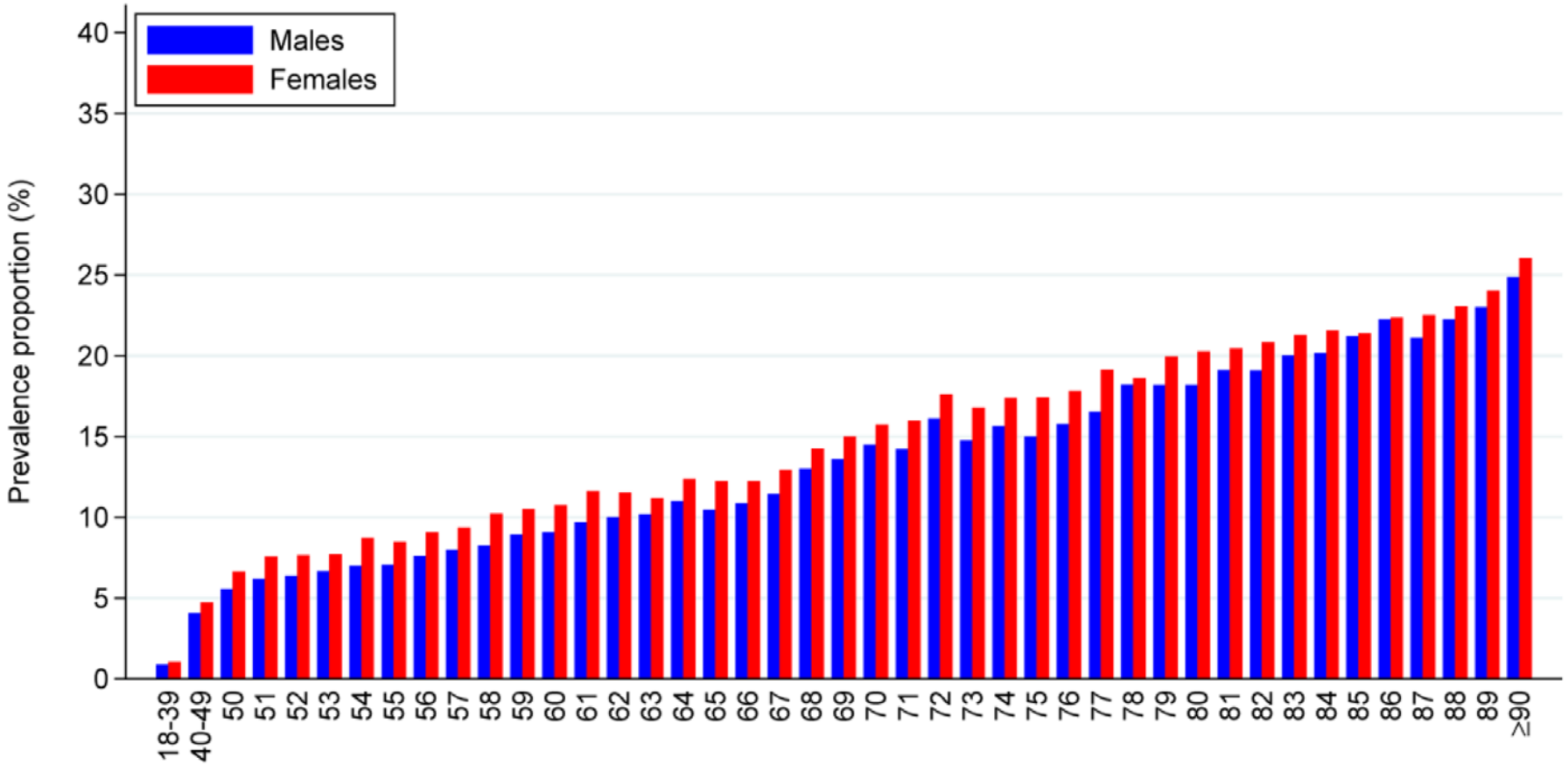
The Danish National Prescription Registry (DNPR) constitutes a unique data source that has been widely used in Danish pharmacoepidemiological research ever since it was made accessible to researchers in 2003 [1]. The DNPR contains several variables describing the single drug purchase since 1995, the prescriber variable was incorrectly recorded in 11% of non-electronic prescriptions [2].

We undertook this study to validate the prescriber information recorded in the DNPR.


Prescriber type
Prescriber identifier
Proportion with correct prescriber information (%)
100
98
96
94
92
90
88
2009
2010
2011
2012
2013
2014
2015
Calendar year

Visualization


≥3 treatment episodes
2 treatment episodes
1 treatment episodes
Proportion of children
0
10
20
30
40
0-1 years
1-2 years
2-3 years
3-4 years
4-5 years


Males
Females
Prevalence proportion (%)
0
5
10
15
20
25
30
35
40
18-39
40-49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
≥90

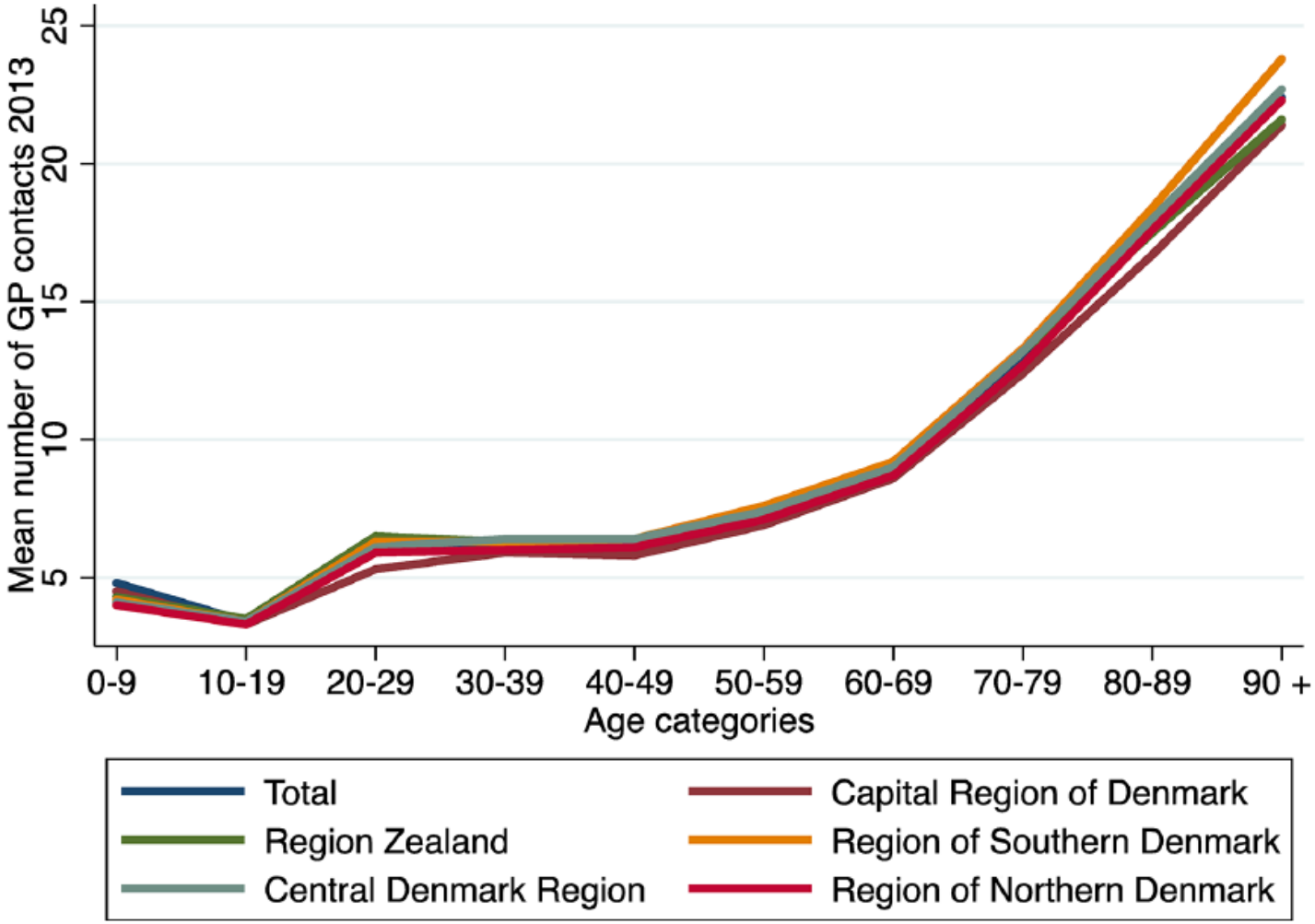
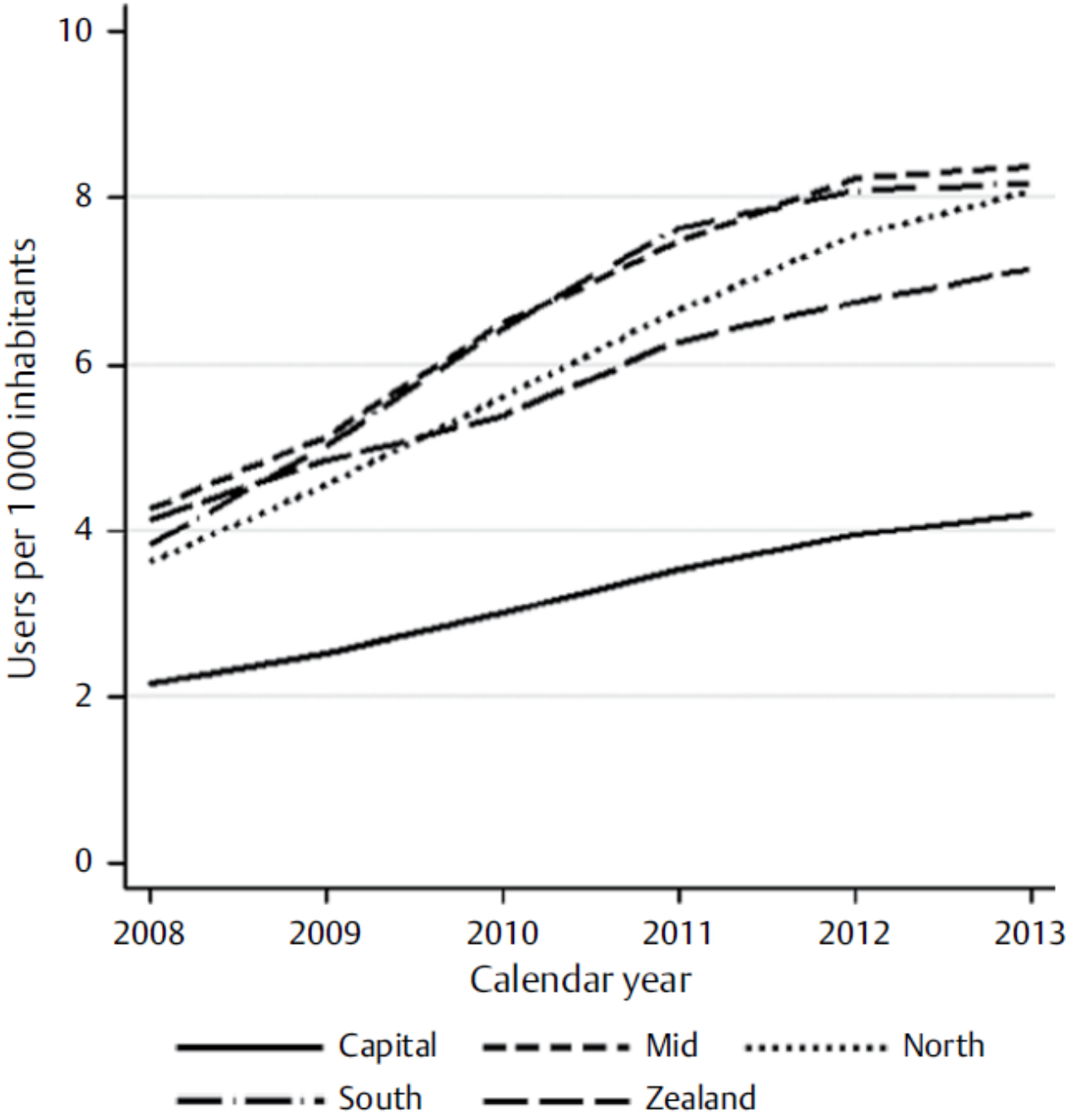
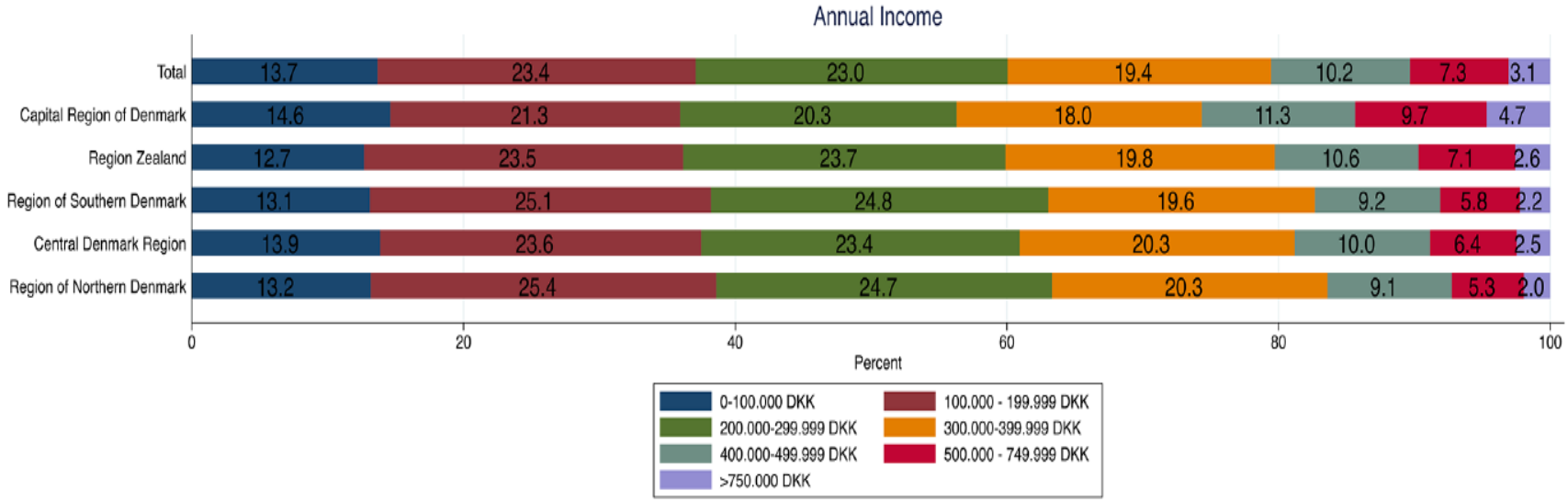


Fig 4. Mean number of contacts per resident to the general practitioners divided into 10-year age categories in 2013.


10
8
6
4
2
0
Users per 1 000 inhabitants
2008
2009
2010
2011
2012
2013
Calendar year
Capital
Mid
North
South
Zealand

2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
5917
13,835
3308
3760
10,078
2657
3139
9335
2227
2670
8572
1969
2279
7722
1713
1898
7092
1550
1673
6292
1346
1476
5708
1174
1370
5143
1041
1195
4668


Annual Income
Total
Capital Region of Denmark
Region Zealand
Region of Southern Denmark
Central Denmark Region
Region of Northern Denmark
13.7
23.4
23.0
19.4
10.2
7.3
3.1
14.6
21.3
20.3
18.0
11.3
9.7
4.7
12.7
23.5
23.7
19.8
10.6
7.1
2.6
13.1
25.1
24.8
19.6
9.2
5.8
2.2
13.9
23.6
23.4
20.3
10.0
6.4
2.5
13.2
25.4
24.7
20.3
9.1
5.3
2.0
0
20
40
60
80
100
Percent
0-100.000 DKK
100.000 - 199.999 DKK
200.000-299.999 DKK
300.000-399.999 DKK
400.000-499.999 DKK
500.000 - 749.999 DKK
>750.000 DKK

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Drug utilization

Examples

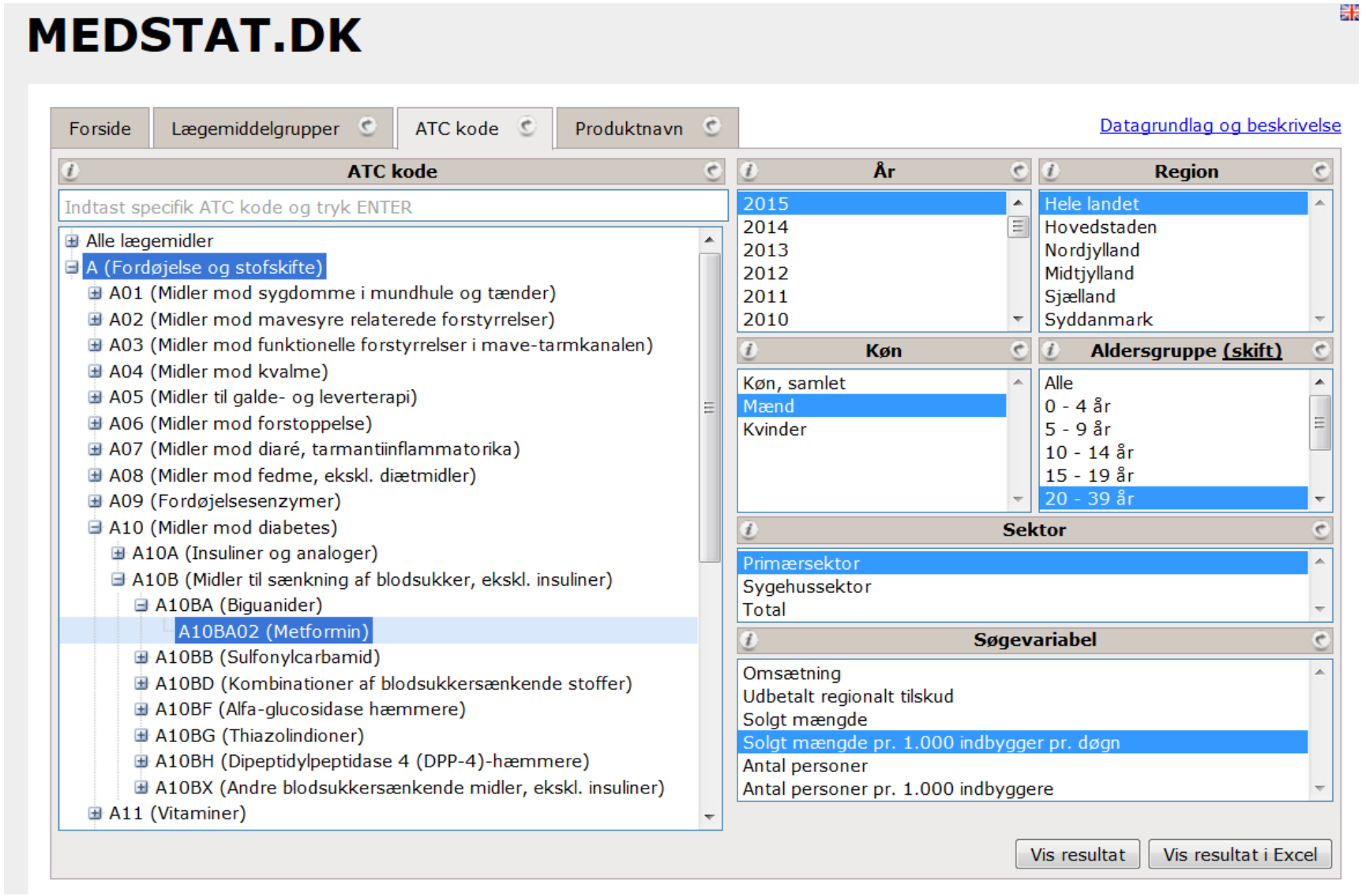
Aggregated Danish

Aggregated Nordic

Individual-level Nordic

Individual-level Danish

Combination


MEDSTAT.DK
Forside
Lægemiddelgrupper
ATC kode
Produktnavn
Datagrundlag og beskrivelse
ATC kode
Indtast specifik ATC kode og tryk ENTER
Alle lægemidler
A (Fordøjelse og stofskifte)
A01 (Midler mod sygdomme i mundhule og tænder)
A02 (Midler mod mavesyre relaterede forstyrrelser)
A03 (Midler mod funktionelle forstyrrelser i mave-tarmkanalen)
A04 (Midler mod kvalme)
A05 (Midler til galde- og leverterapi)
A06 (Midler mod forstoppelse)
A07 (Midler mod diaré, tarmantiinflammatorika)
A08 (Midler mod fedme, ekskl. diætmidler)
A09 (Fordøjelsesenzymer)
A10 (Midler mod diabetes)
A10A (Insuliner og analoger)
A10B (Midler til sænkning af blodsukker, ekskl. insuliner)
A10BA (Biguanider)
A10BA02 (Metformin)
A10BB (Sulfonylcarbamid)
A10BD (Kombinationer af blodsukkersænkende stoffer)
A10BF (Alfa-glucosidase hæmmere)
A10BG (Thiazolindioner)
A10BH (Dipeptidylpeptidase 4 (DPP-4)-hæmmere)
A10BX (Andre blodsukkersænkende midler, ekskl. insuliner)
A11 (Vitaminer)
År
2015
2014
2013
2012
2011
2010
Region
Hele landet
Hovedstaden
Nordjylland
Midtjylland
Sjælland
Syddanmark
Køn
Køn, samlet
Mænd
Kvinder
Aldersgruppe (skift)
Alle
0 - 4 år
5 - 9 år
10 - 14 år
15 - 19 år
20 - 39 år
Sektor
Primærsektor
Sygehussektor
Total
Søgevariabel
Omsætning
Udbetalt regionalt tilskud
Solgt mængde
Solgt mængde pr. 1.000 indbygger pr. døgn
Antal personer
Antal personer pr. 1.000 indbyggere
Vis resultat
Vis resultat i Excel

ORIGINAL ARTICLE

Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies

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ABSTRACT

Objective Antithrombotic drugs are widely used in the prevention and treatment of cardiovascular diseases; yet, nationwide long-term usage trends remain unexplored. We examined long-term trends in the use of antithrombotic drugs in Denmark.

Methods Using nationwide prescription data, we obtained information on primary care use of antiplatelet drugs, vitamin K antagonists (VKA), non-vitamin K antagonist oral anticoagulants (NOAC), heparins and fondaparinux during 1999–2014.

Results During the 16-year period, the use of antithrombotic drugs per 1000 inhabitants/day increased from 64 to 96 defined daily doses (DDD), and the prevalence proportion of users doubled from 5.1% to 9.6% of the Danish population. From 1999 to 2014, there was an increased use of both antiplatelet drugs (from 60 to 79 DDD per 1000 inhabitants/day) and VKA (from 4 to 9 DDD per 1000 inhabitants/day). NOAC was marketed in 2008 and had an abrupt rise in use to 8 DDD per 1000 inhabitants/day in 2014. The use of heparins and fondaparinux increased slightly during the study period (from 0 to 0.6 DDD per 1000 inhabitants/day). Hospital use of antithrombotic drugs also increased during the study period, but constituted a minor part of the total use (4 DDD per 1000 inhabitants/day in 2014).

Conclusions Considerable changes have occurred in the use of antithrombotic drugs during the past 16 years, including the introduction of several new and

affected by expert recommendations in international clinical guidelines from large organisations such as the European Society of Cardiology, American Heart Association and the American College of Cardiology.[3] It is unknown to what extent changes in scientific evidence on antithrombotic drugs are being implemented in clinical practice.

Despite the importance of understanding the patterns in use of antithrombotic drugs, no previous studies have examined these trends in a nationwide setting. We examined 16-year trends in antithrombotic drug use in Denmark.

METHODS

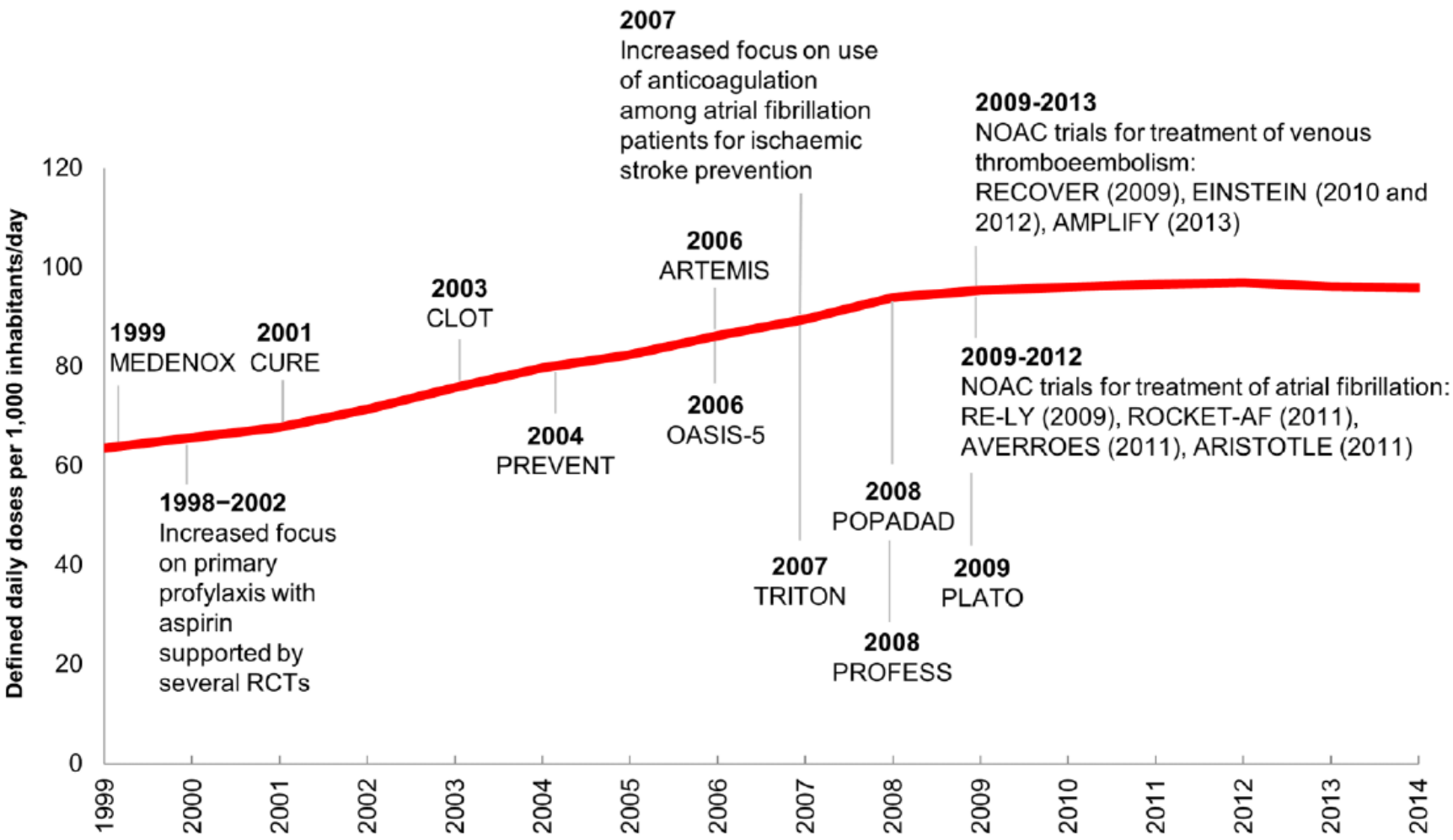
Setting

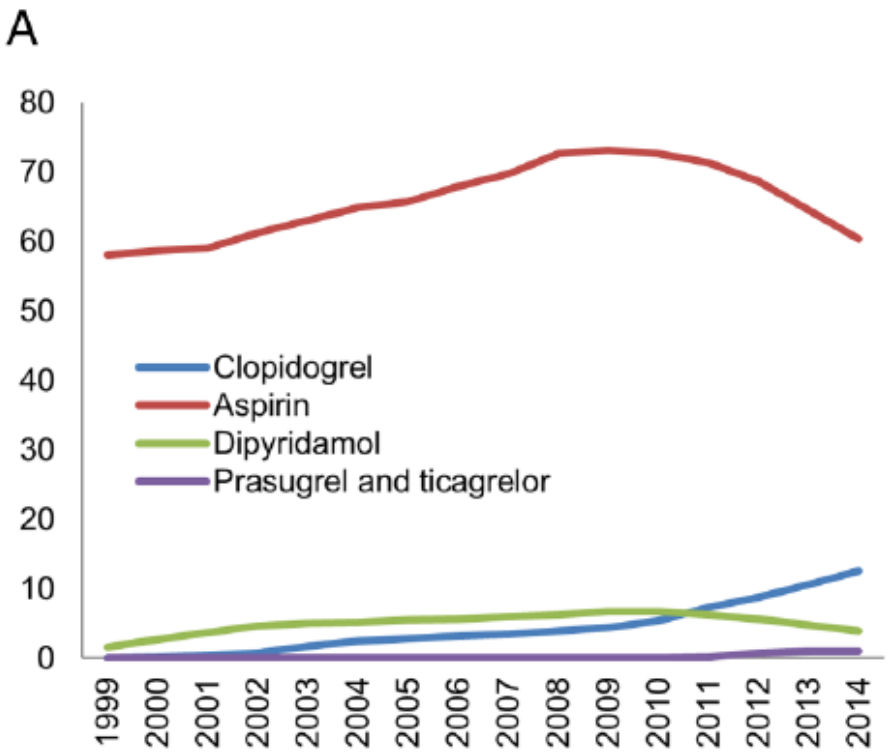
We conducted this study in Denmark from 1 January 1999 to 31 December 2014. Denmark has a population of approximately 5.6 million inhabitants, and all inhabitants have equal and free access to universal tax-supported healthcare, including services at general practitioners, hospitals and partial reimbursement for prescribed medications, including antithrombotic drugs. Antithrombotic drug sales in the primary healthcare sector comprise purchases of prescription drugs and pharmacy-only over-the-counter sale of aspirin. Of note, the vast majority of low-dose aspirin is obtained by prescription due to coprescribing with other drugs and cost reduction by reimbursement.[4] Drugs prescribed by physicians

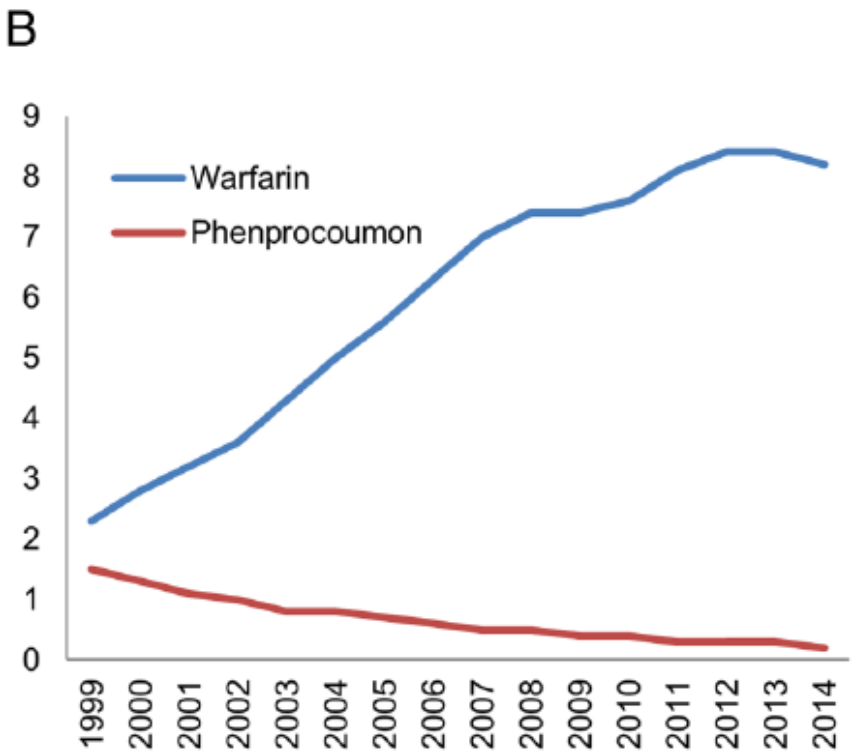
Table 1 Antithrombotic drug use in the primary healthcare sector during 1999–2014 in Denmark

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Overall																
DDD*	63.5	65.6	67.7	71.3	75.7	79.7	82.3	86.2	89.5	93.9	95.3	96.0	96.5	96.9	96.1	95.9
Users†	50.6	53.5	59.3	65.5	71.1	76.3	80.2	84.5	88.2	91.4	92.5	93.9	95.3	96.0	95.7	95.5
Antiplatelet drugs																
DDD*	59.7	61.6	63.2	66.7	70.5	73.9	75.9	79.1	81.7	85.7	86.9	87.5	87.3	85.7	82.4	79.0
Users†	44.6	47.0	52.5	58.4	63.6	68.1	71.3	75.0	78.1	81.1	81.9	82.6	83.1	82.1	79.4	76.9
VKA																
DDD*	3.8	4.0	4.4	4.6	5.1	5.7	6.3	6.9	7.5	7.9	7.8	8.0	8.4	8.7	8.7	8.5
Users†	7.4	8.0	8.7	9.4	10.3	11.4	12.5	13.5	14.3	14.7	14.9	15.3	16.1	16.2	16.3	16.0
NOAC																
DDD*	–	–	–	–	–	–	–	–	–	0	0	0	0.2	1.9	4.5	7.9
Users†	–	–	–	–	–	–	–	–	–	0.04	0.43	0.79	1.8	3.6	6.1	8.5
Heparins and fondaparinux																
DDD*	0	0	0.10	0.10	0.10	0.10	0.10	0.20	0.30	0.40	0.50	0.50	0.50	0.60	0.60	0.60
Users†	0.12	0.15	0.18	0.20	0.24	0.31	0.36	0.49	0.70	0.85	0.89	1.1	1.2	1.4	1.4	1.3

*DDD per 1000 inhabitants/day.
†Number of users per 1000 inhabitants.
DDD, defined daily doses; NOAC, non-vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonists.


Defined daily doses per 1,000 inhabitants/day
120
100
80
60
40
20
0
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
1999
MEDENOX
2001
CURE
1998–2002
Increased focus on primary profylaxis with aspirin supported by several RCTs
2003
CLOT
2004
PREVENT
2006
ARTEMIS
2006
OASIS-5
2007
Increased focus on use of anticoagulation among atrial fibrillation patients for ischaemic stroke prevention
2007
TRITON
2008
POPADAD
2008
PROFESS
2009
PLATO
2009-2013
NOAC trials for treatment of venous thromboembolism:
RECOVER (2009), EINSTEIN (2010 and 2012), AMPLIFY (2013)
2009-2012
NOAC trials for treatment of atrial fibrillation:
RE-LY (2009), ROCKET-AF (2011), AVERROES (2011), ARISTOTLE (2011)


A
80
70
60
50
40
30
20
10
0
Clopidogrel
Aspirin
Dipyridamol
Prasugrel and ticagrelor
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014


B
9
8
7
6
5
4
3
2
1
0
Warfarin
Phenprocoumon
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014

Doi: 10.1111/bcpt.13003

Trends in Use of Paracetamol in the Nordic Countries

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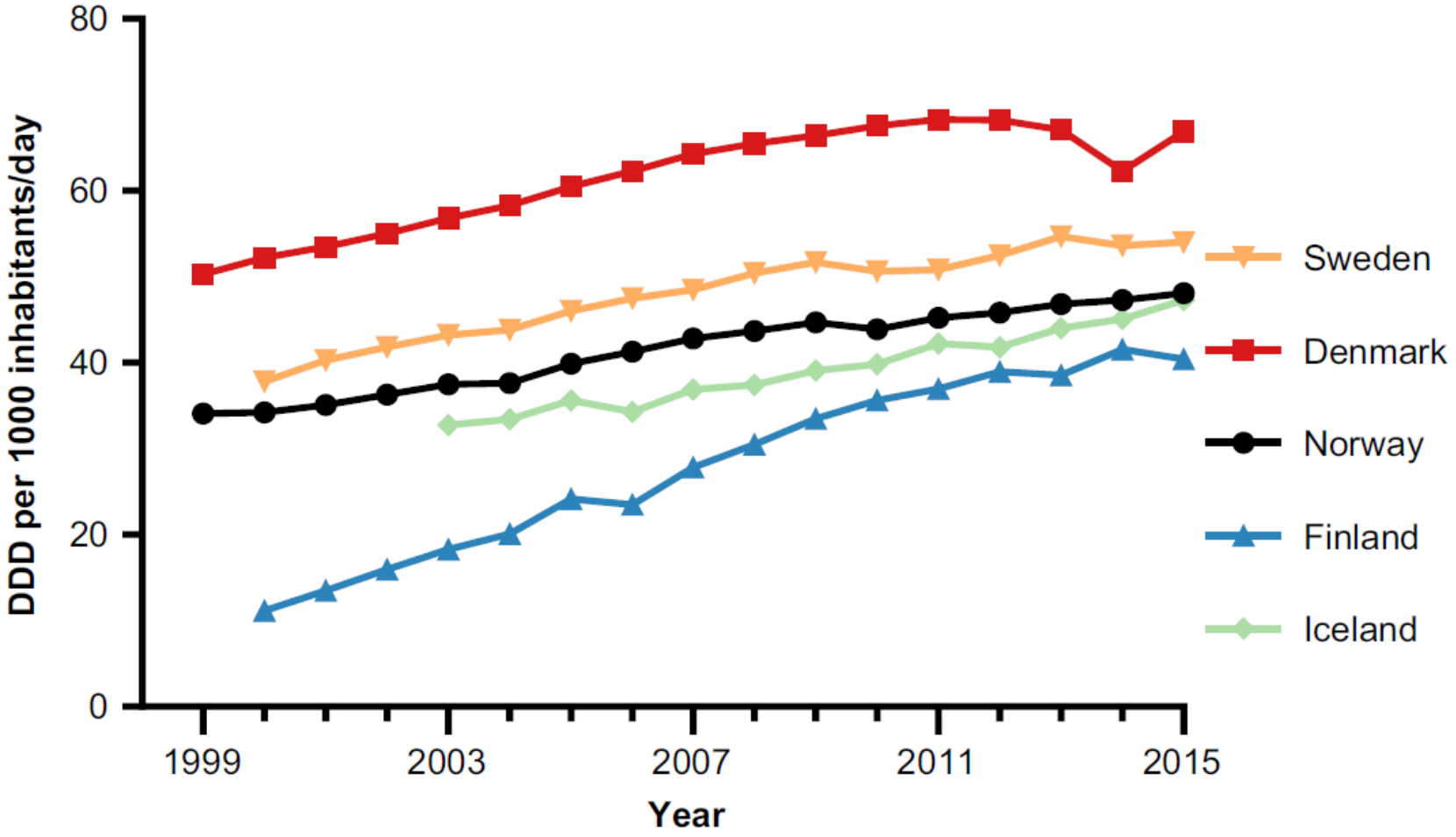
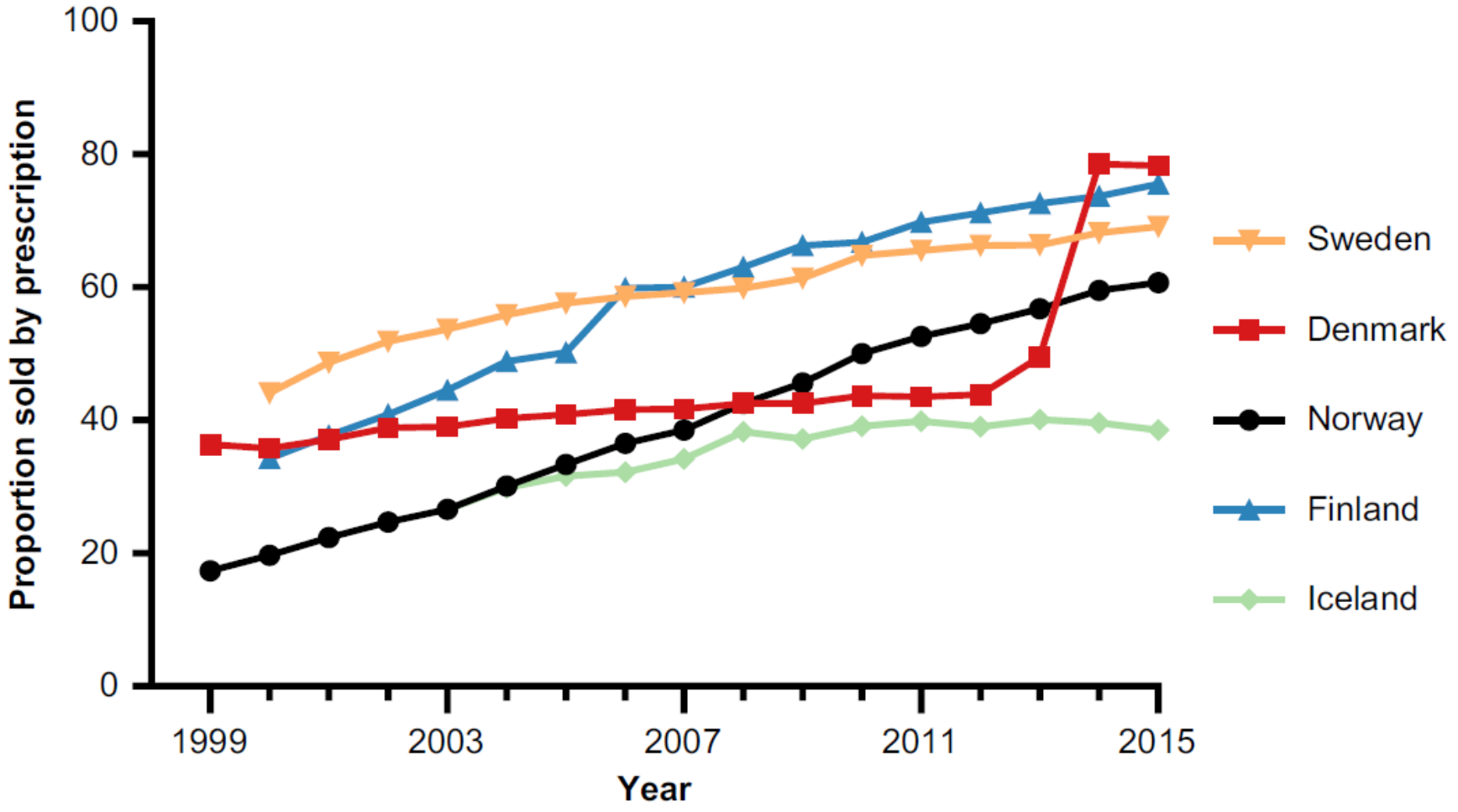
Abstract: Paracetamol (acetaminophen) is one of the most commonly used analgesics in Europe; however, both the safety and efficacy of paracetamol have recently been questioned. Little is known about cross-national differences in the sales of paracetamol. Using national wholesale statistics and nationwide prescription drug registers, we investigated trends in total and prescribed use of paracetamol in the Nordic countries. The total sales of paracetamol (Anatomical Therapeutic Chemical (ATC) classification system code: N02BE01) measured as defined daily doses (DDD) per 1000 inhabitants/day, and the sales by prescription (users per 1000 inhabitants/year), increased in the Nordic countries from 2000 to 2015. The total sales were highest in Denmark throughout the period, with 65 DDD per 1000 inhabitants/day and lowest in Iceland with 30 DDD per 1000 inhabitants/day in 2015. The cross-national difference in total sales of paracetamol was smaller in 2015 than in 2000. The proportion of paracetamol (DDD per 1000 inhabitants/day) sold by prescription was also highest in Denmark (78%), compared with 75% in Finland, 69% in Sweden, 61% in Norway and 38% in Iceland. Paracetamol by prescription was more common at older ages and among women. Total and prescribed sales of paracetamol have increased in all five Nordic countries over time. Cross-national differences exist, with highest sales per capita in Denmark throughout the period.

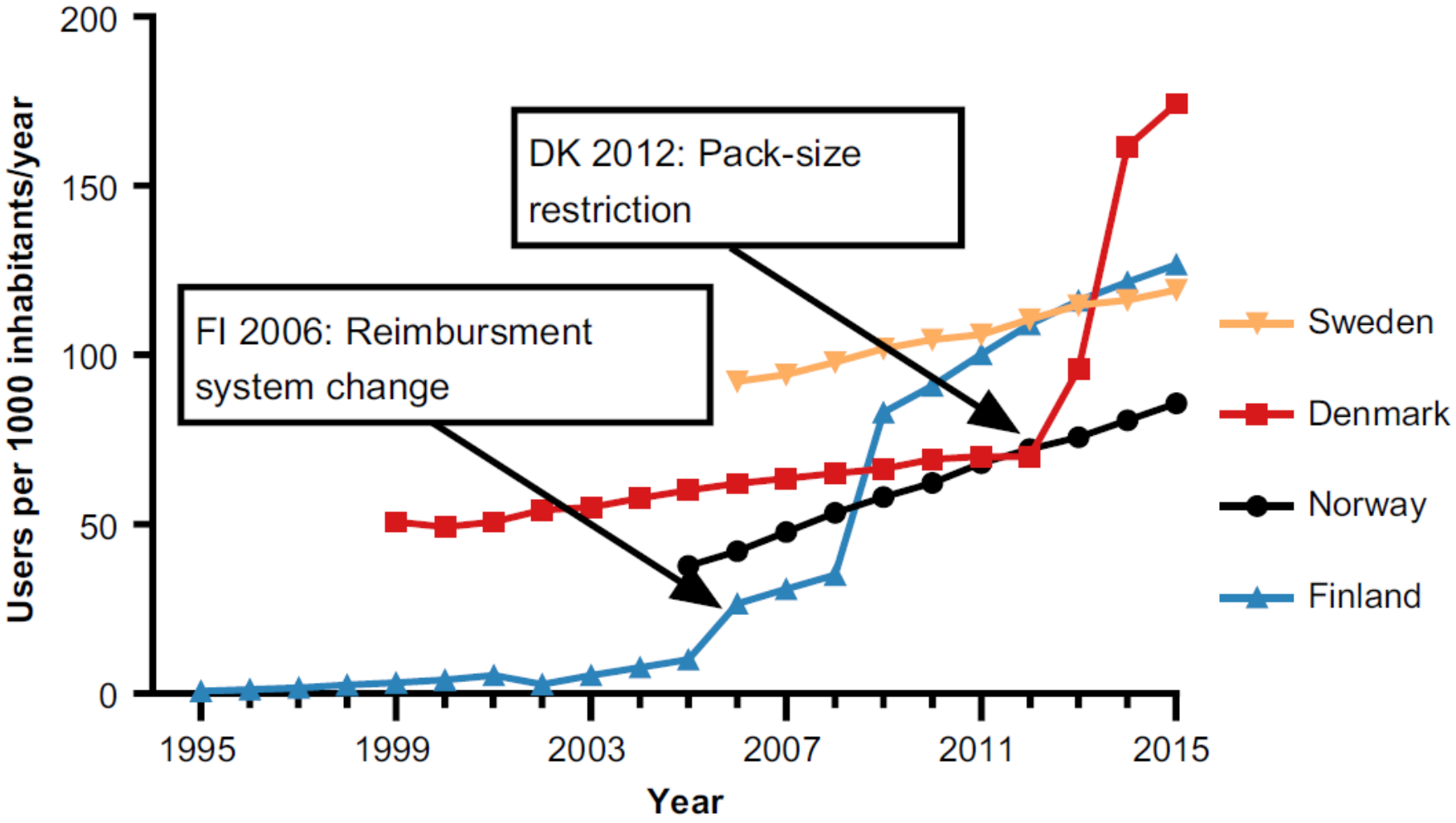
Paracetamol/acetaminophen is one of the most commonly used analgesic drugs in Europe [1], but relatively little is known about cross-national differences in paracetamol sales. Paracetamol has a favourable safety profile and is endorsed as first-line treatment for many pain conditions [2] and for both acute and persistent pain in geriatric patients [3].

However, the safety of paracetamol, especially for chronic use, has, recently been questioned. A randomized controlled trial found elevated aminotransferase activities after recurrent

Given that the efficacy of paracetamol has been questioned for some of its main indications [5,11] and the unclear safety profile of high-dosage paracetamol [4,5], it is important to understand how paracetamol is used at the national level. Cross-national comparison of drug use is necessary to distinguish between trends and changes influenced by nation-specific factors (e.g. guidelines and drug formulary), and can be used to generate hypothesis and inform health policy to facilitate the rational use of drugs. By combining wholesale statis-


80
60
40
20
0
DDD per 1000 inhabitants/day
1999
2003
2007
2011
2015
Year
Sweden
Denmark
Norway
Finland
Iceland


Proportion sold by prescription
100
80
60
40
20
0
1999
2003
2007
2011
2015
Year
Sweden
Denmark
Norway
Finland
Iceland


200
150
100
50
0
Users per 1000 inhabitants/year
1995
1999
2003
2007
2011
2015
Year
DK 2012: Pack-size restriction
FI 2006: Reimbursment system change
Sweden
Denmark
Norway
Finland

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Overview data availability and access for this study.

Figure S1. Total sales paracetamol + codeine combinations (N02AA59) in DDD per 1000 inhabitants/day, all Nordic countries 1999–2015.

Figure S2. Total sales paracetamol + caffeine combinations (N02BE51) in DDD per 1000 inhabitants/day, all Nordic countries 1999–2015.

Figure S3. Female/male ratio of the use of plain paracetamol (N02BE01) sold by prescription, users per 1000 inhabitants yearly, all Nordic countries except Iceland (no data available) 1995–2015.

Figure S4. Female/male ratio in 2015 subtracted with Female/male ratio in 2006 of the use of plain paracetamol (N02BE01) sold by prescription, users per 1000 inhabitants yearly, the Nordic countries except Iceland and Finland.

PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLE

Nonaspirin Nonsteroidal Antiinflammatory Drug Use in the Nordic Countries from a Cardiovascular Risk Perspective, 2000–2016: A Drug Utilization Study

Kasper Bruun Kristensen,[1,*] Øystein Karlstad,[2] Jaana E. Martikainen,[3] Anton Pottegård,[1] Jonas W. Wastesson,[4] Helga Zoega,[5,6] and Morten Schmidt[7,8]

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Study Objective Evidence on the cardiotoxicity of nonaspirin nonsteroidal antiinflammatory drugs (NSAIDs), particularly diclofenac and the newer selective cyclooxygenase (COX)-2 inhibitors, has accumulated over the last decade. Our objective was to examine whether the use of NSAIDs in the Nordic countries changed with the emerging evidence, regulatory statements, and clinical guidelines advocating caution for the use of specific NSAIDs.

Design Drug utilization study.

Data Sources Nationwide wholesale statistics and prescription registries in Denmark, Finland, Iceland, Norway, and Sweden (2000–2016).

Measurements and Main Results Our main outcome measures were yearly total sales, expressed as number of sold defined daily doses (DDDs)/1000 inhabitants/day, and yearly prevalence of prescription use, expressed as number of prescription users per 1000 inhabitants. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Total sales of

Eur J Clin Pharmacol
DOI 10.1007/s00228-016-2125-y

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

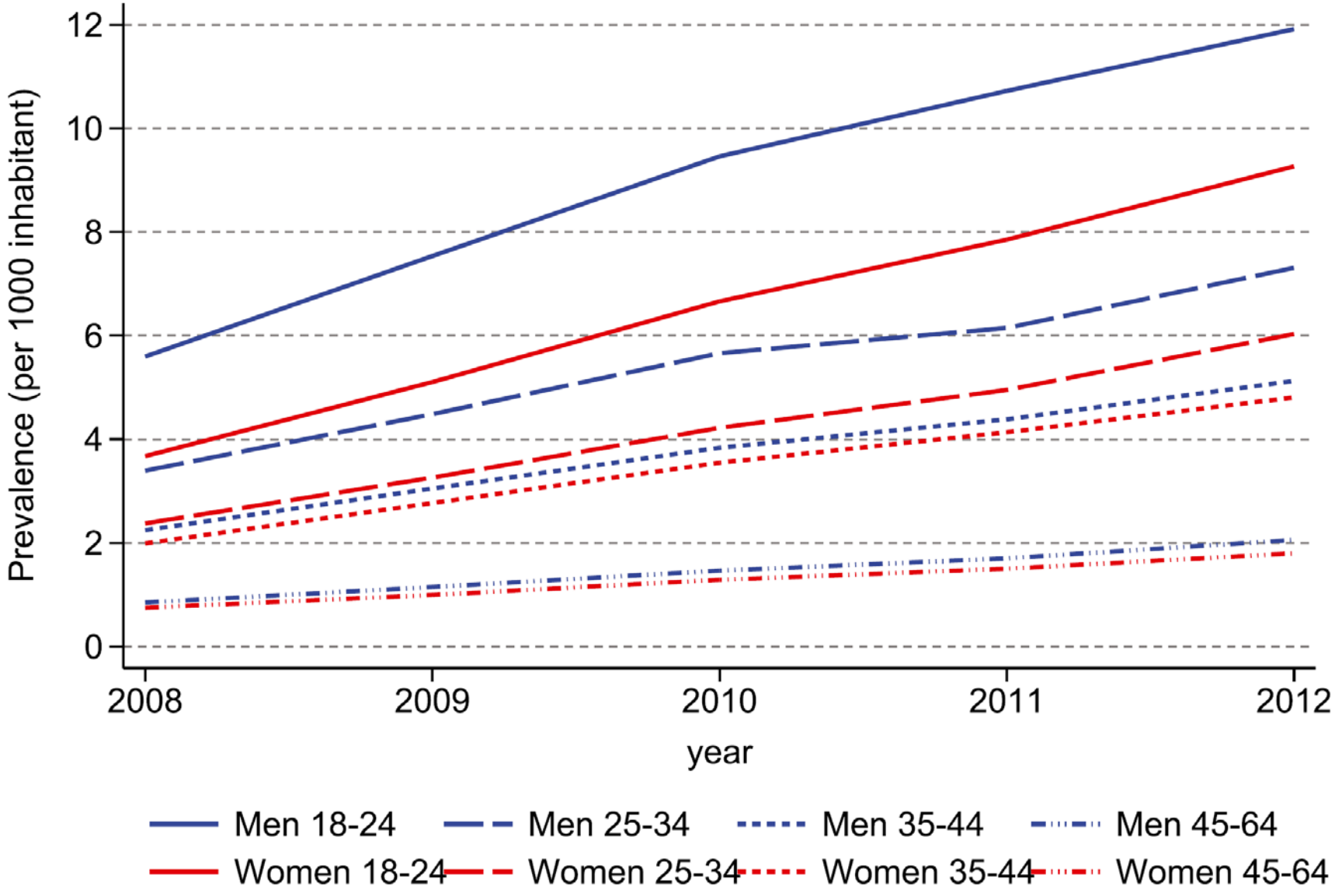
Use of drugs for ADHD among adults—a multinational study among 15.8 million adults in the Nordic countries

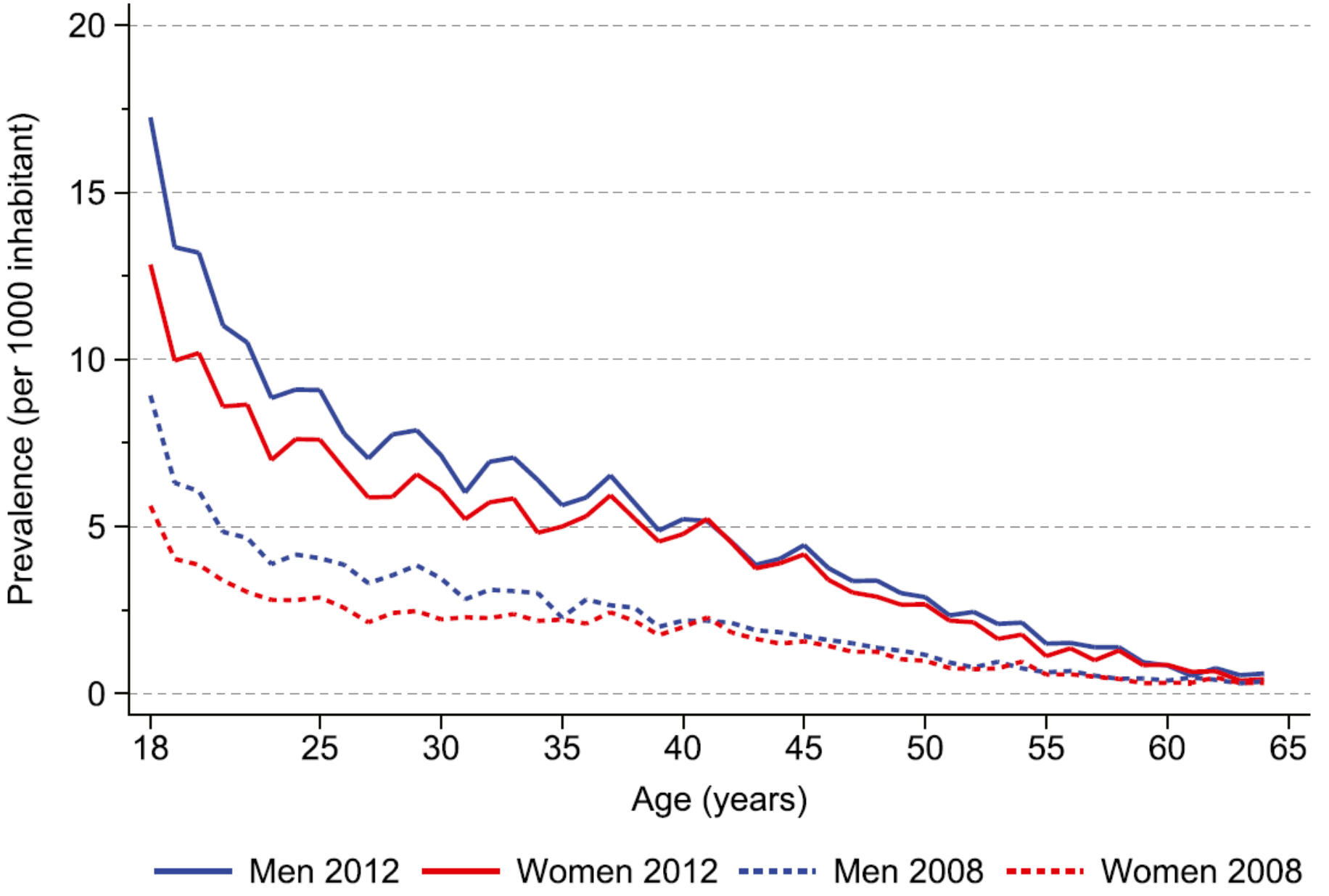
Øystein Karlstad[1] · Helga Zoëga[2] · Kari Furu[1] · Shahram Bahmanyar[3] · Jaana E Martikainen[4] · Helle Kieler[3] · Anton Pottegård[5]

Received: 25 April 2016 / Accepted: 25 August 2016

Abstract
Purpose The use of ADHD drugs among adults is controversial and has until recently not been approved for use in adults in most countries. The aim was to investigate use of ADHD drugs (stimulants and atomoxetine) among the entire adult population in the Nordic countries.
Methods We conducted a multinational population-based prescription register study based on the entire adult population in the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden). All users of ADHD drugs aged 18–64 years during 2008–2012 were included, which for 2012 comprised 76,896 drug users among 15.8 million adult inhabitants.
Results Annual prevalence of drug use increased during the study period for both genders and all age groups. The overall prevalence increased from 2.4 to 5.3 per 1000 men and 1.8 to 4.4 per 1000 women. Incidence also increased, but to a lesser extent in the last part of the study period. Methylphenidate was used by 88 % of drug users. Treatment was discontinued within the first year by 21 % of new drug users. Among all users of ADHD drugs, 53 % of men and 64 % of women concurrently used other psychotropic drugs, most frequently antidepressants and hypnotics. Psychotropic co-medication increased with age and was more pronounced among women than men.
Conclusions Use of ADHD drug among adults more than doubled over a 5-year period, and a majority were concurrently treated with other psychotropics. Adults constitute a substantial proportion of persons treated with ADHD drugs. Thus, evidence for long-term efficacy and safety in adults is urgently needed.

Keywords ADHD · Psychostimulants · Adults · Pharmacoepidemiology · Nordic countries


Prevalence (per 1000 inhabitant)
0
2
4
6
8
10
12
2008
2009
2010
2011
2012
year
Men 18-24
Men 25-34
Men 35-44
Men 45-64
Women 18-24
Women 25-34
Women 35-44
Women 45-64


Prevalence (per 1000 inhabitant)
20
15
10
5
0
18
25
30
35
40
45
50
55
60
65
Age (years)
Men 2012
Women 2012
Men 2008
Women 2008

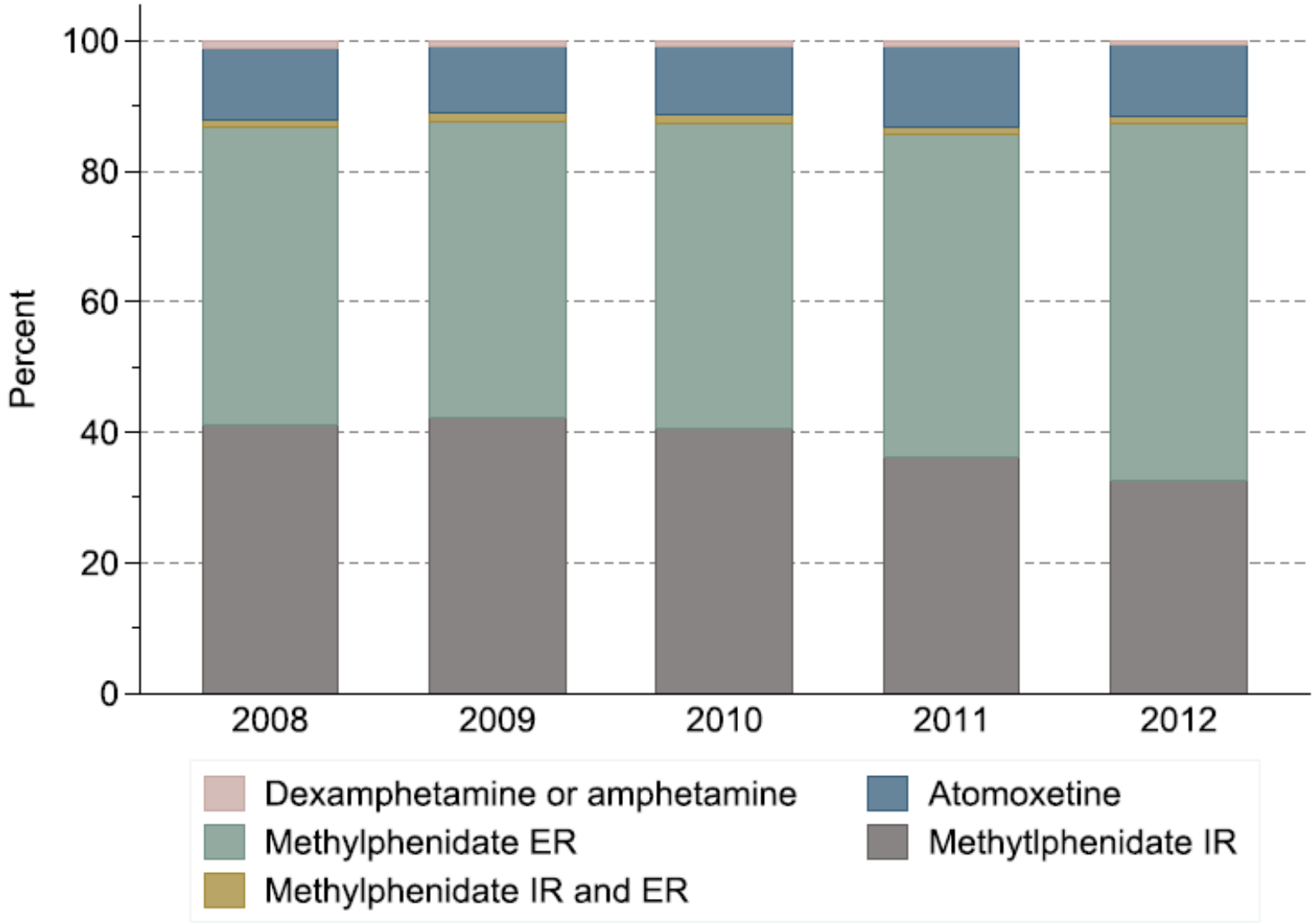


Fig. 4 Type of ADHD drug used at treatment initiation during 2008–2012 among persons aged 18–64 years in the Nordic countries, by year. *IR* immediate release formulation, *ER* extended release formulation

Gender	Men				
Age group	18–24	25–34	35–44	45–64	18–64
ADHD users (*n*)	14,396	11,972	9059	7023	42,450
Any psychotropic	38	56	62	67	53
Antidepressants	20	32	37	40	30
Antiepileptics	7	15	16	17	13
Antipsychotics	14	20	20	19	18
Anxiolytics	7	17	21	25	16
Hypnotics	15	23	27	31	23
Melatonin	7	6	5	5	6
Other hypnotics	10	20	24	29	19

Early discontinuation and switch in treatment

Among 62,144 new users of ADHD drugs during 2008–2011, 13 % filled only the initial prescription and 9 % filled only one more prescription, while 79 % filled 3 or more prescriptions of any ADHD drug during the first year of treatment. When restricting to users who initiated treatment on methylphenidate, 21 % filled only one or two prescriptions of any ADHD drug during the first year (discontinuation), while 8 % received atomoxetine within the first year (switching). Among users who initiated treatment on atomoxetine, 25 % filled only one or two prescriptions while 32 % received methylphenidate within the first year.

Eur Child Adolesc Psychiatry
DOI 10.1007/s00787-014-0523-1

ORIGINAL CONTRIBUTION

Use of SSRIs among Danish children: a nationwide study

Anton Pottegård · Helga Zoëga · Jesper Hallas · Per Damkier

Received: 15 August 2013 / Accepted: 20 January 2014

Abstract Our objective was to describe the use of selective serotonin reuptake inhibitors (SSRIs) in the entire Danish population of children and adolescents from 1995 to 2011. Data on filled SSRIs were obtained for all children in Denmark aged 5–17 during 1995–2011. The amount and type of SSRIs filled were calculated as well as incidence rates and prevalence proportions. Furthermore, we looked at concurrent use of other psychotropic drug treatment duration. A total of 23,547 children aged 5–17 used SSRIs during the study period, most commonly sertraline followed by citalopram. Overall, the incidence rate increased from 0.57 per 1,000 person years in 1997 to 3.30 in 2010 and fell to 2.55 in 2011, while the prevalence proportion rose from 0.1 per 1,000 children at the end of 1995 to 3.3 at the end of 2011. However, these findings were driven entirely by an concurrently, most notably antipsychotics (12–28 %) and psychostimulants (10–33 %). About 50 % of adolescents and 40 % of children discontinued treatment within 12 months of initiation. We found a marked increase in the use of SSRI drugs among adolescents in Denmark between 1995 and 2011. Whether this increase reflects a true increase in disorder occurrence, an increase in diagnostic intensity or more aggressive treatment remains uncertain.

Keywords SSRIs · Antidepressants · Drug utilization study · Children · Adolescents

Introduction

Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study

Anton Pottegård, Anne Broe, Jesper Hallas, Ove B. Schaffalitzky de Muckadell, Annmarie T. Lassen and Anders B. Lødrup

Ther Adv Gastroenterol
1–8
DOI: 10.1177/1756283X16650156

Abstract

Background: The use of proton-pump inhibitors (PPIs) has increased over the last decade. The objective of this study was to provide detailed utilization data on PPI use over time, with special emphasis on duration of PPI use and concomitant use of ulcerogenic drugs.

Methods: Using the nationwide Danish Prescription Registry, we identified all Danish adults filling a PPI between 2002 and 2014. Using descriptive statistics, we reported (i) the distribution of use between single PPI entities, (ii) the development in incidence and prevalence of use over time, (iii) measures of duration and intensity of treatment, and (iv) the prevalence of use of ulcerogenic drugs among users of PPIs.

Results: We identified 1,617,614 adults using PPIs during the study period. The prevalence of PPI use increased fourfold during the study period to 7.4% of all Danish adults in 2014. PPI use showed strong age dependency, reaching more than 20% among those aged at least 80 years. The proportion of users maintaining treatment over time increased with increasing age, with less than10% of those aged 18–39 years using PPIs 2 years after their first prescription, compared with about 40% among those aged at least 80 years. The overall use of ulcerogenic drugs among PPI users increased moderately, from 35% of users of PPI in 2002 to 45% in 2014.

Conclusions: The use of PPIs is extensive and increasing rapidly, especially among the elderly.

Keywords: proton-pump inhibitor, prescription registry, general population, prevalence, incidence, ulcerogenic drugs

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Anton Pottegård, MScPharm, PhD
Anne Broe, MD

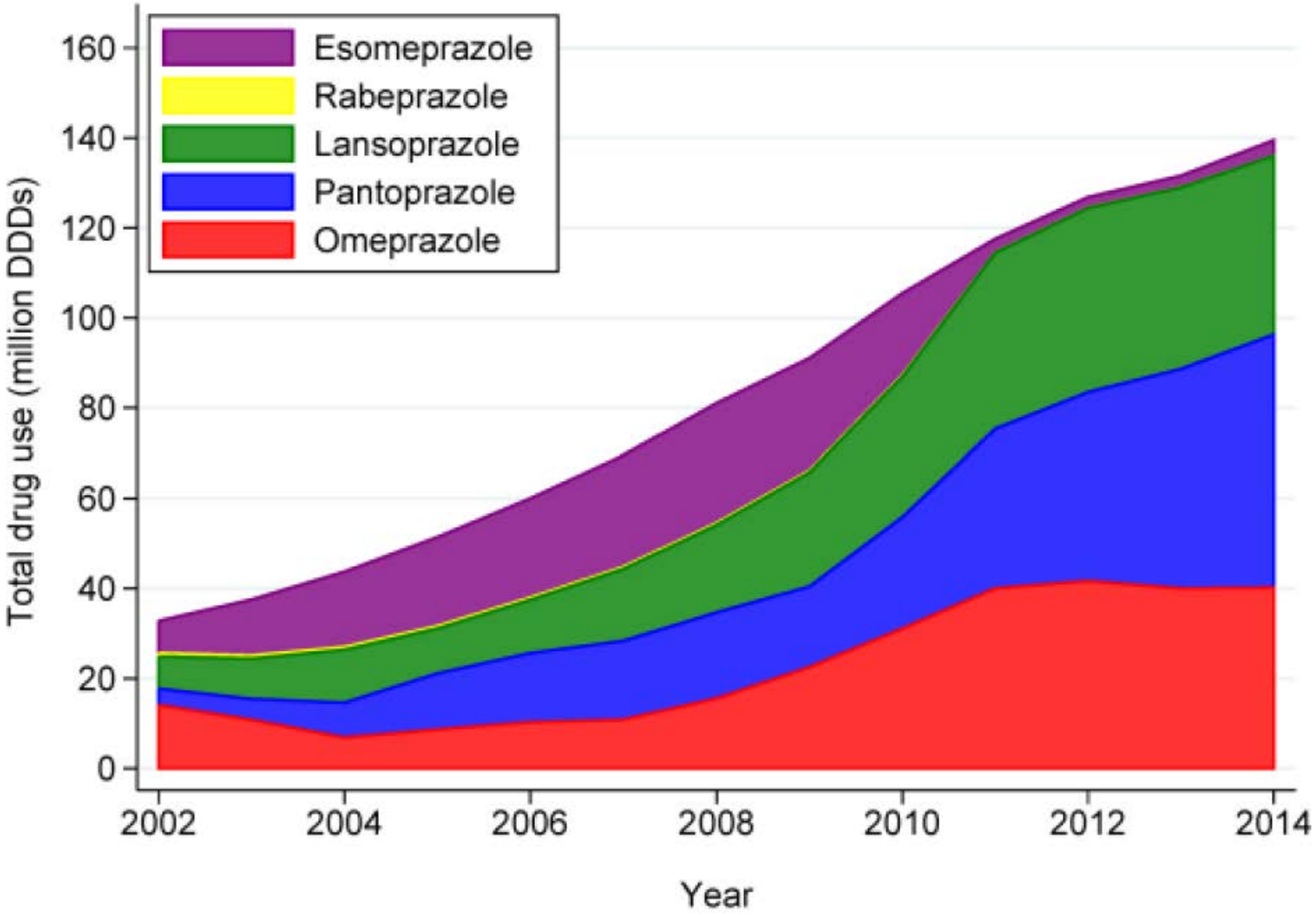
Introduction

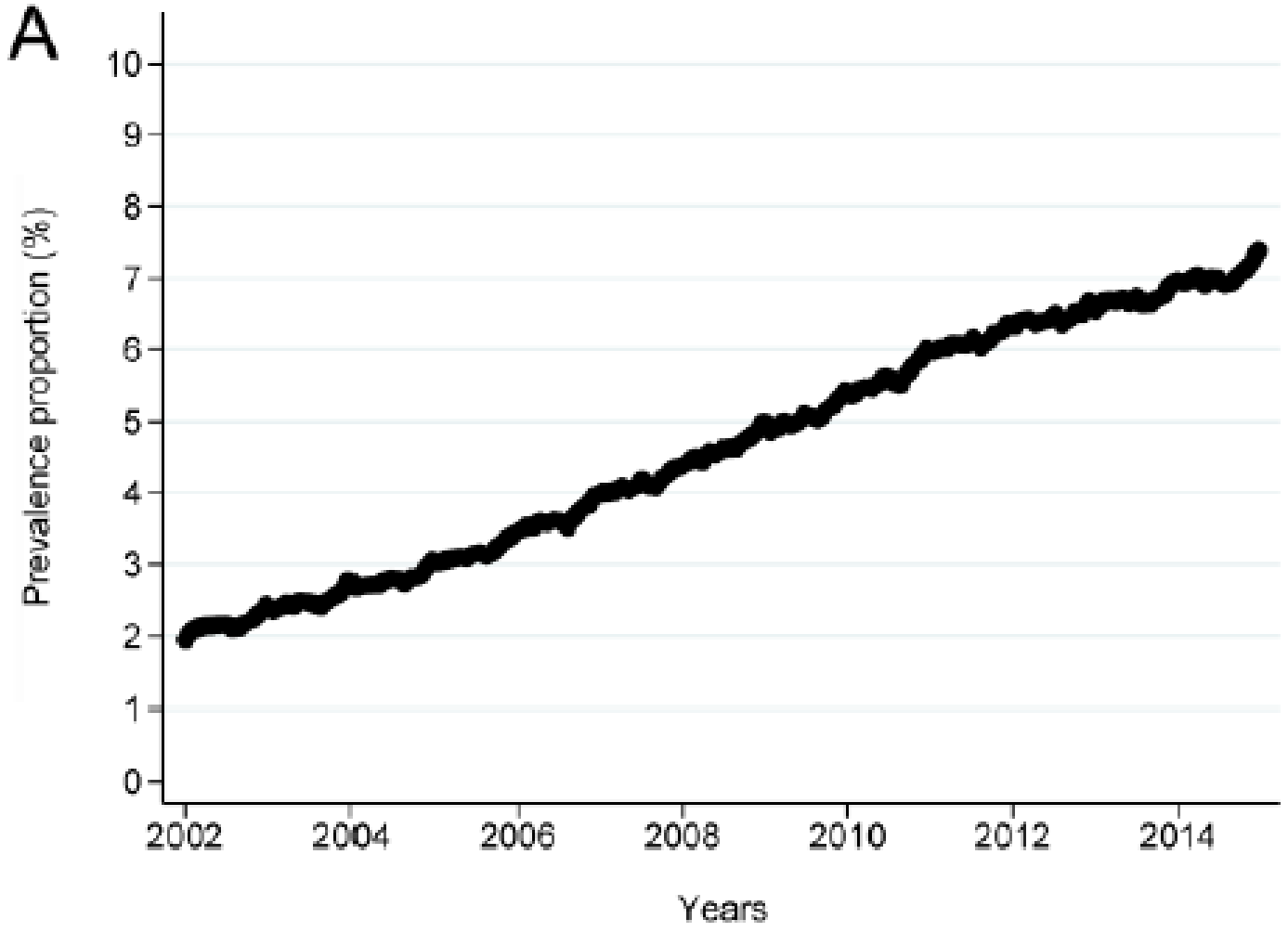
Proton-pump inhibitors (PPIs) have for many years been the cornerstone of treatment of gas-

Further, concerns have been raised regarding possible associations between long-term PPI use and increased risk of neuroendocrine gastrointestinal

Results

We identified 1,617,614 adults filling 18,963,535 prescriptions for PPIs throughout the study period. 517,000 (32%) filled only one prescription, whereas 449,272 (28%) and 739,339 (46%) filled two to four, and five-plus prescriptions, respectively. The median number of DDDs filled per prescription was 56 (interquartile range 28–98).


Esomeprazole
Rabeprazole
Lansoprazole
Pantoprazole
Omeprazole
Total drug use (million DDDs)
0
20
40
60
80
100
120
140
160
2002
2004
2006
2008
2010
2012
2014
Year


A
Prevalence proportion (%)
0
1
2
3
4
5
6
7
8
9
10
2002
2004
2006
2008
2010
2012
2014
Years

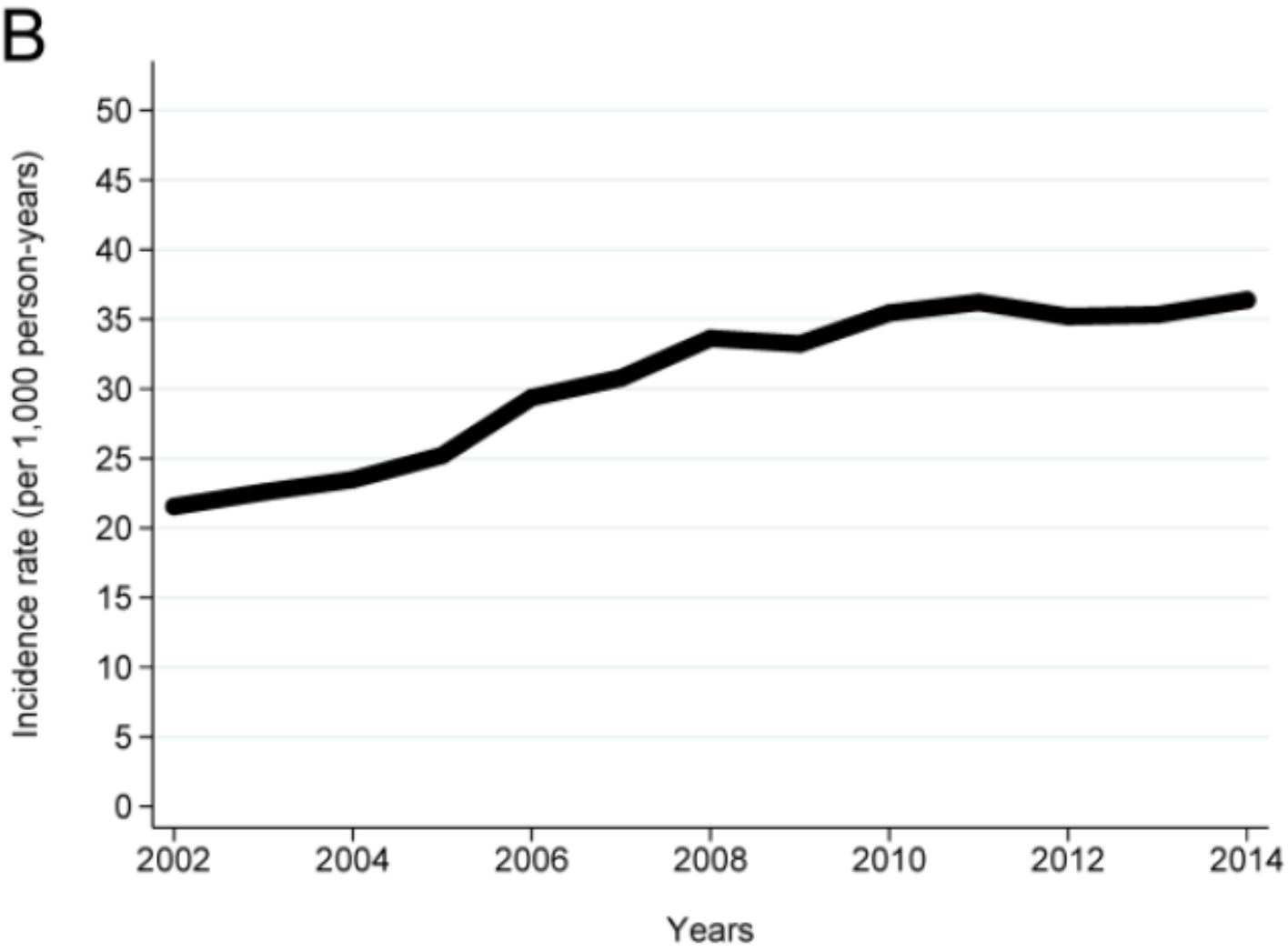
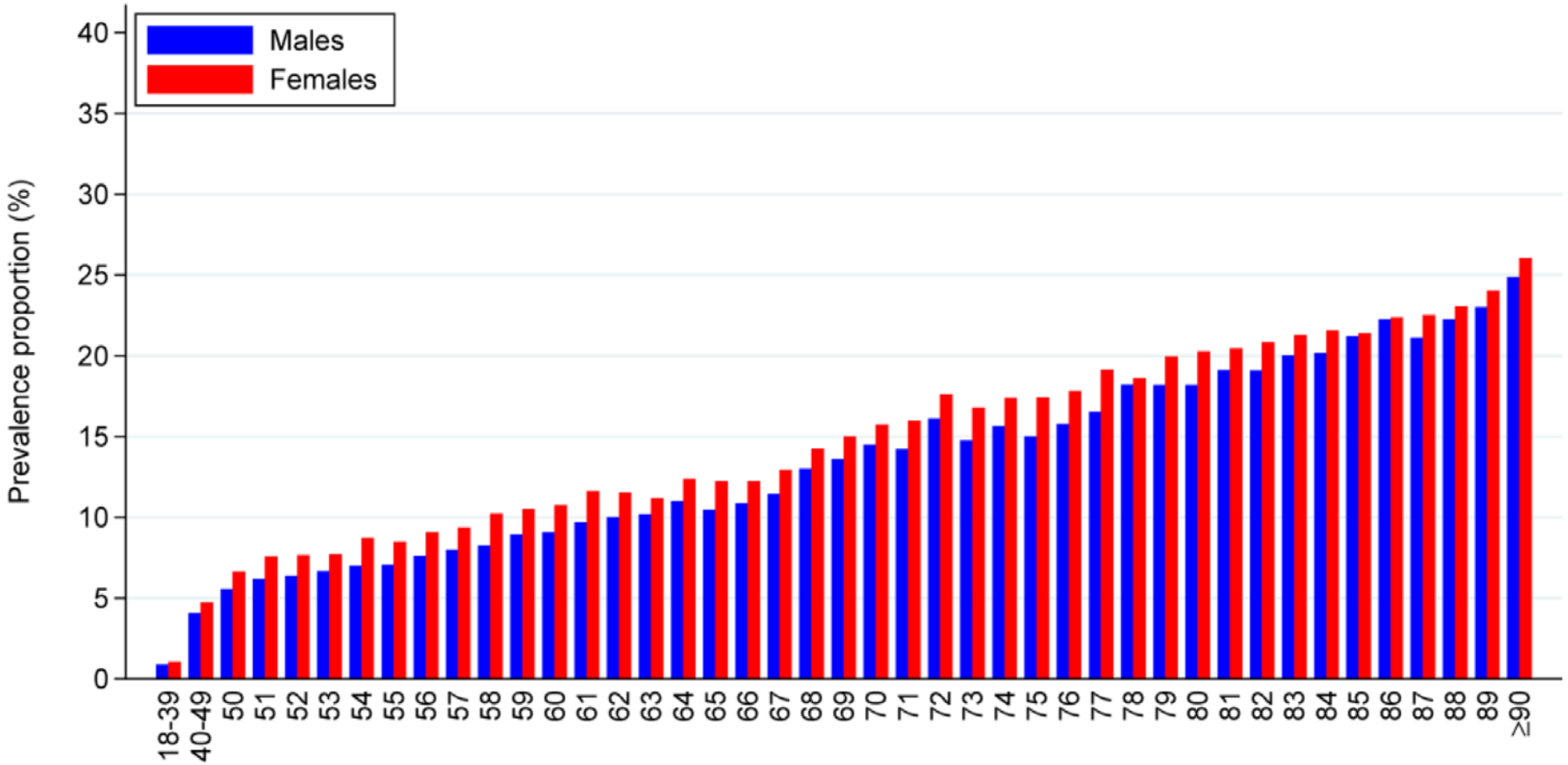
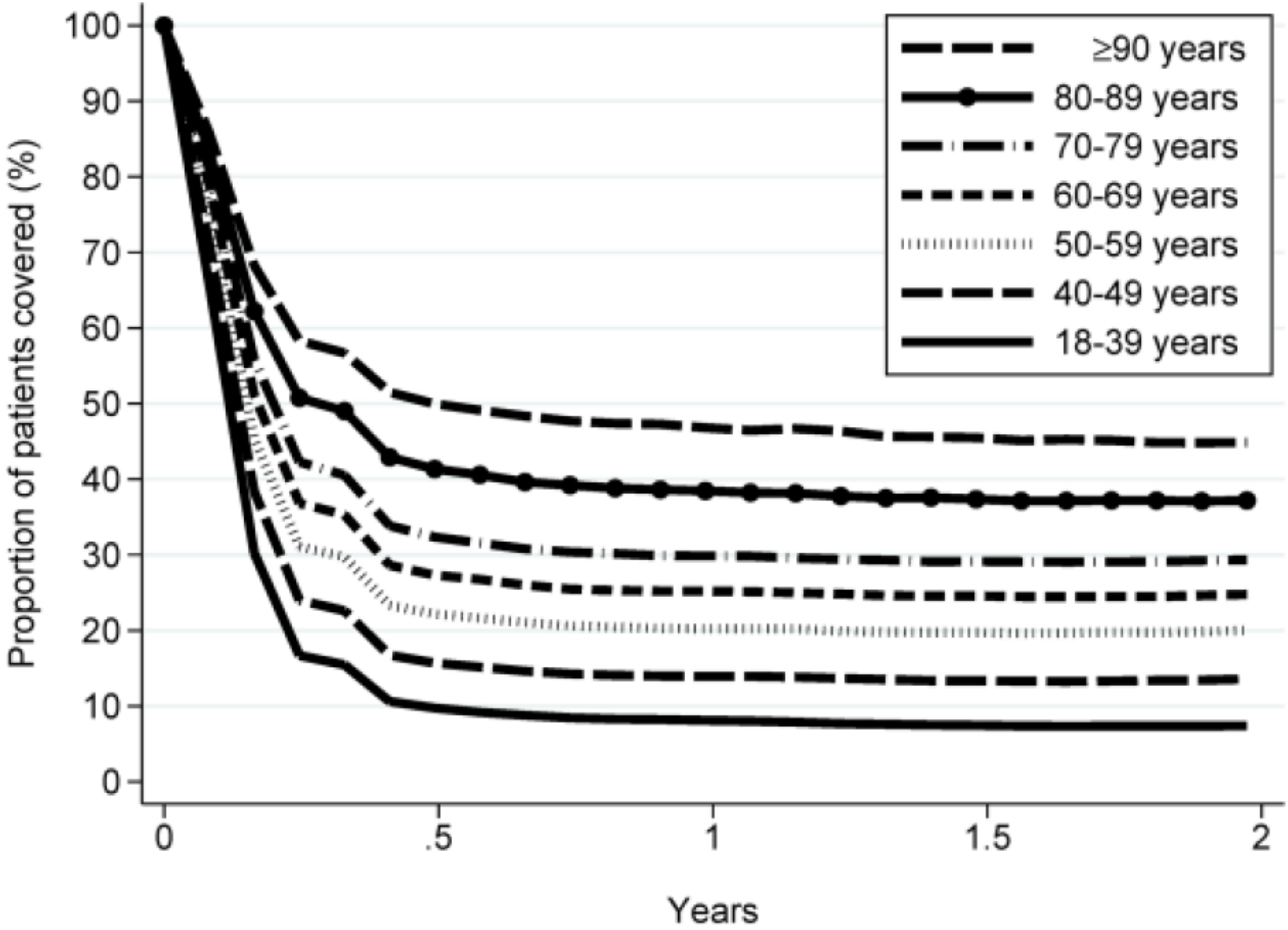
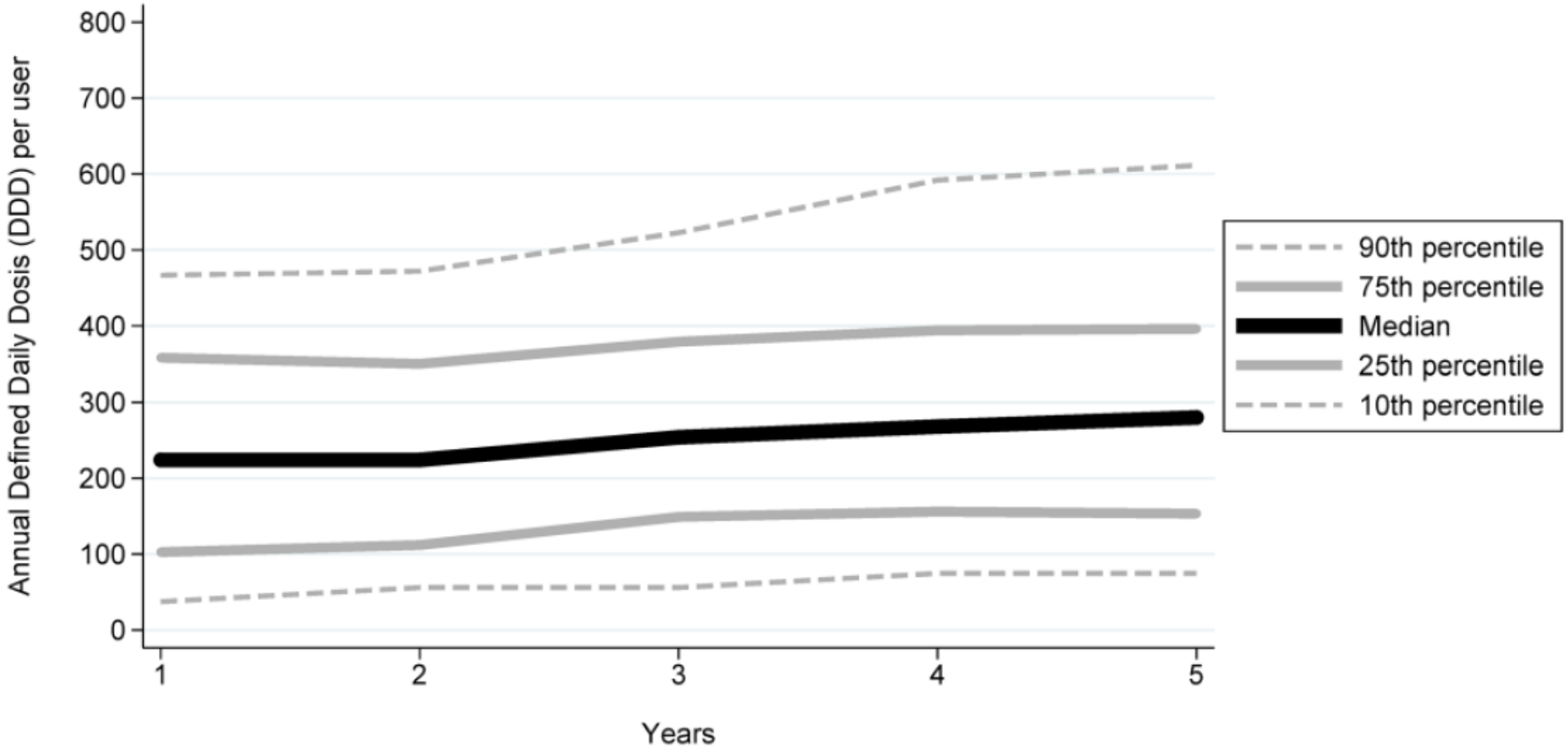
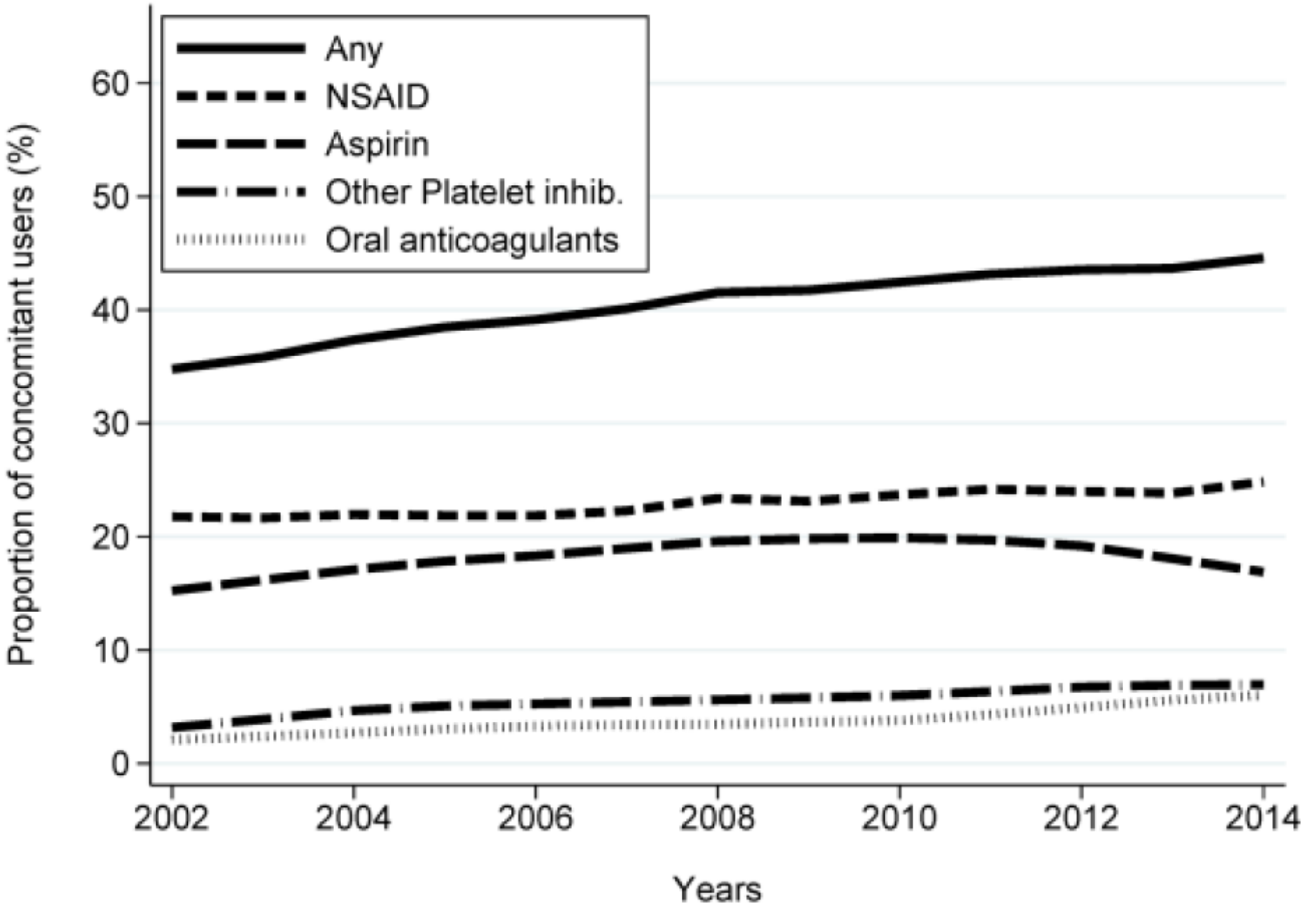

B
Incidence rate (per 1,000 person-years)
0
5
10
15
20
25
30
35
40
45
50
2002
2004
2006
2008
2010
2012
2014
Years

Figure 2. (A) Number of users (point-prevalence proportion), and (B) number of new users (incidence rate) of proton-pump inhibitor use among adults (⩾18 years) in Denmark from 2002 to 2014.


Males
Females
Prevalence proportion (%)
0
5
10
15
20
25
30
35
40
18-39
40-49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
≥90


Proportion of patients covered (%)
100
90
80
70
60
50
40
30
20
10
0
0
.5
1
1.5
2
Years
≥90 years
80-89 years
70-79 years
60-69 years
50-59 years
40-49 years
18-39 years


Annual Defined Daily Dosis (DDD) per user
800
700
600
500
400
300
200
100
0
1
2
3
4
5
Years
90th percentile
75th percentile
Median
25th percentile
10th percentile


Any
NSAID
Aspirin
Other Platelet inhib.
Oral anticoagulants
Proportion of concomitant users (%)
0
10
20
30
40
50
60
2002
2004
2006
2008
2010
2012
2014
Years

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Use of topical ocular antibiotics in young children: a Scandinavian drug utilization study

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ABSTRACT.

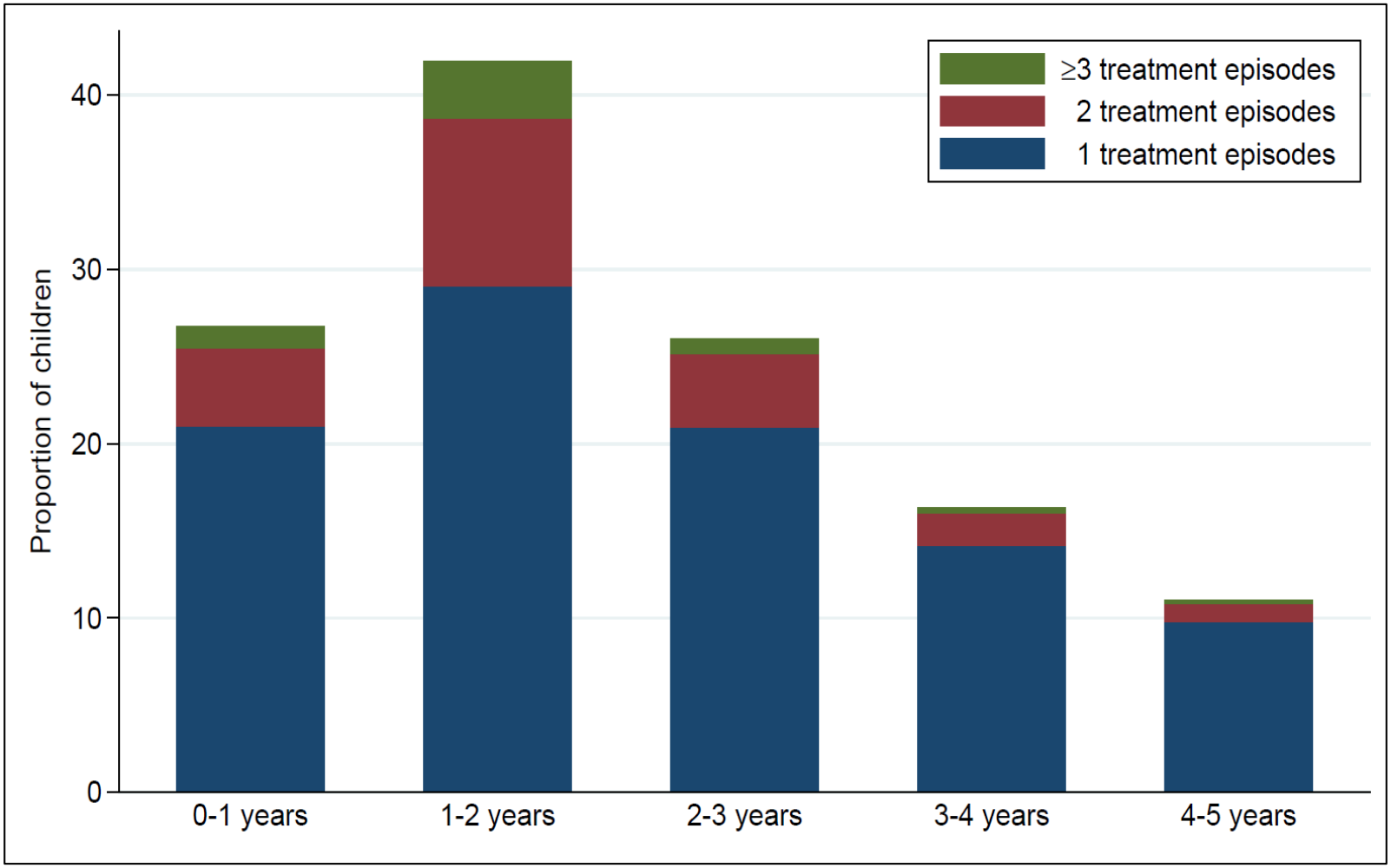
Purpose: **Acute infectious conjunctivitis is a common disease. While usually self-limiting, children often receive treatment to be accepted back into nursery, day care or school. We aimed to describe trends in the utilization of topical ocular antibiotics in young children aged 0–4 years in Denmark, Norway and Sweden.**

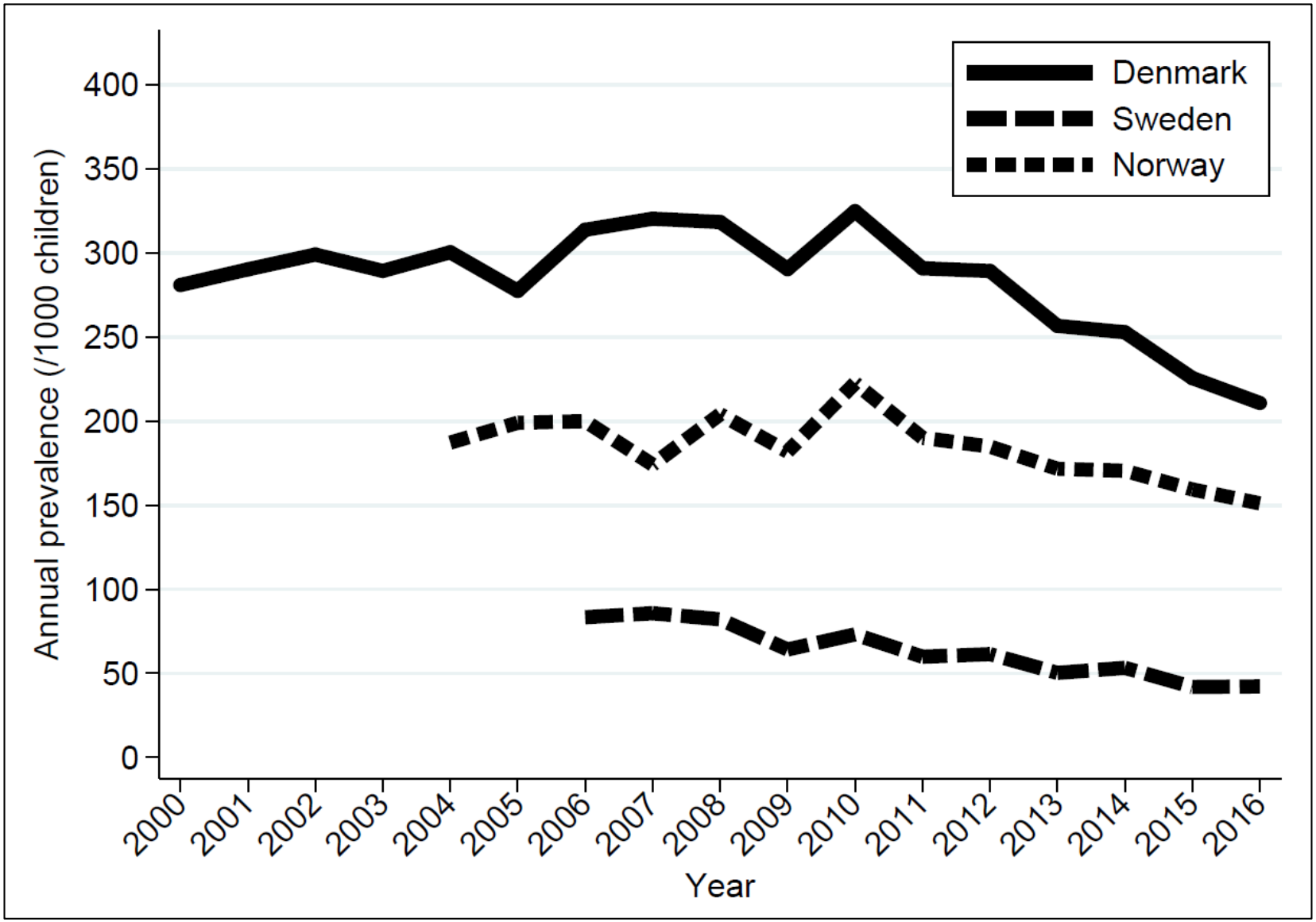
Methods: **Using individual-level data from the Danish National Prescription Registry (2000–2015), we provided detailed descriptions of treatment patterns at the individual level, stratified by age (0–1 years, 2–4 years) and antibiotic substance. Aggregate-level data for Danish, Norwegian and Swedish children (0–4 years) were obtained from publicly available data sources (2000–2016).**

Results: **We identified 107 581 Danish children aged 0–4 years receiving 271 980 treatment episodes. The incidence rate was relatively stable between 2000 and 2010 (on average, 637 and 283/1000 person-years for 0- to 1- and 2- to**

in eight children has symptoms of acute conjunctivitis and the percentage is even higher among younger children (Høvding 2008). The majority of patients with acute conjunctivitis are treated by general practitioners rather than ophthalmologists (Azari & Barney 2013).

The difficulty in distinguishing between viral and bacterial conjunctivitis is a common problem (Høvding 2008; Sheikh et al. 2012; Azari & Barney 2013). In young children, 50–


≥3 treatment episodes
2 treatment episodes
1 treatment episodes
Proportion of children
0
10
20
30
40
0-1 years
1-2 years
2-3 years
3-4 years
4-5 years


Denmark
Sweden
Norway
Annual prevalence (/1000 children)
400
350
300
250
200
150
100
50
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year

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