Use of NSAIDs in the Nordic countries

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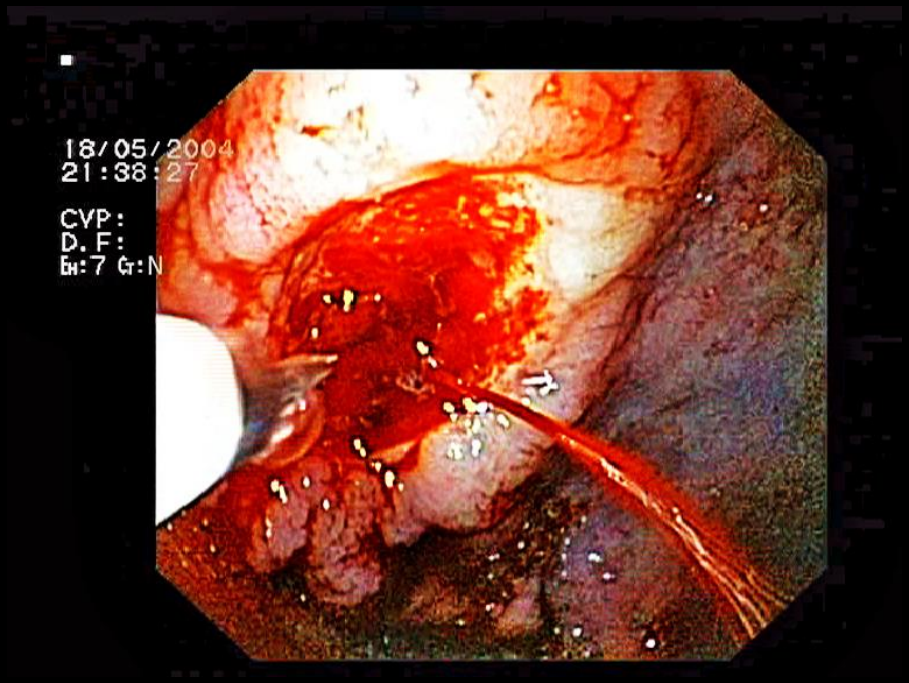
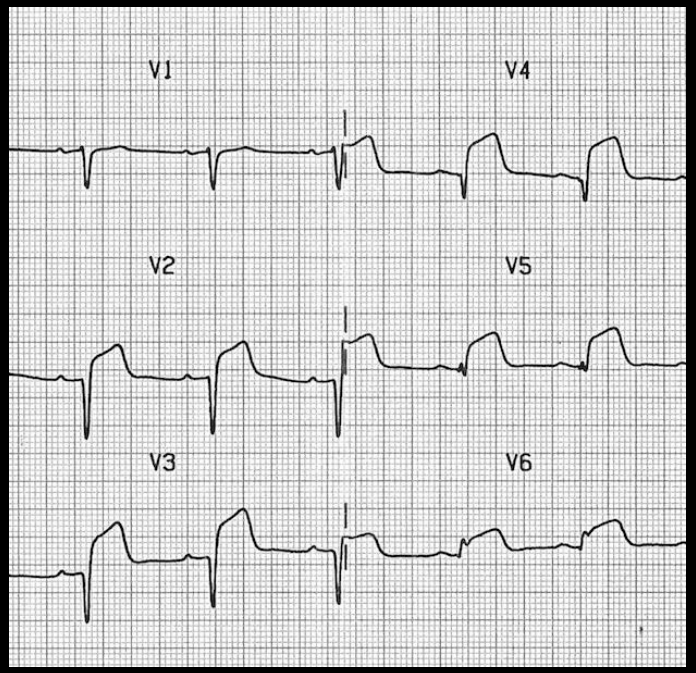
n=26.800.000

NSAIDs are commonly used worldwide but increase the risk of upper GI bleed and cardiovascular events





NSAIDs differ with regards to cardiovascular risk

Highest cardiovascular risk:
COX-2 selective inhibitors (coxibs)
Diclofenac

Lowest cardiovascular risk:
Ibuprofen < 1.200 mg
Naproxen < 500 mg

European Heart Journal (2016) **37**, 1015–1023
doi:10.1093/eurheartj/ehv505

CURRENT OPINION

Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology

Morten Schmidt[1*], Morten Lamberts[2], Anne-Marie Schjerning Olsen[2], Emil Fosbøll[3], Alexander Niessner[4], Juan Tamargo[5], Giuseppe Rosano[6,7], Stefan Agewall[8,9], Juan Carlos Kaski[10], Keld Kjeldsen[11,12], Basil S. Lewis[13], and Christian Torp-Pedersen[14]

The cardiotoxic potential of NSAIDs – particularly diclofenac and the newer selective COX–2 inhibitors – has been increasingly recognized during the last ~15 years

We aimed to examine whether use of NSAIDs in the Nordic countries 2000-2016 changed accordingly

WHO Collaborating Centre for
Drug Statistics Methodology

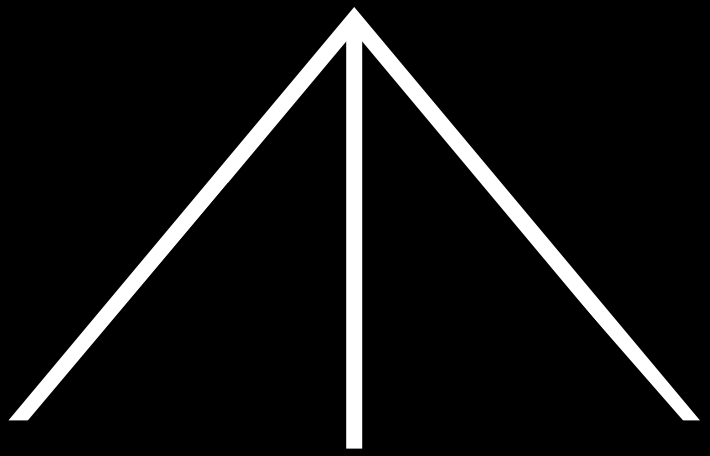
- News
- ATC/DDD Index
  - Updates included in the ATC/DDD Index
- ATC/DDD methodolog
- ATC
- DDD
- ATC/DDD alterations, cumulative lists
- ATC/DDD Index and Guidelines

M MUSCULO-SKELETAL SYSTEM
M01 ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS
M01A ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
M01AA Butylpyrazolidines
M01AB Acetic acid derivatives and related substances
M01AC Oxicams
M01AE Propionic acid derivatives
M01AG Fenamates
M01AH Coxibs
M01AX Other antiinflammatory and antirheumatic agents, non-steroids

~~M01AX05 glucosamine~~
~~M01AX25 chondroitin sulfate~~

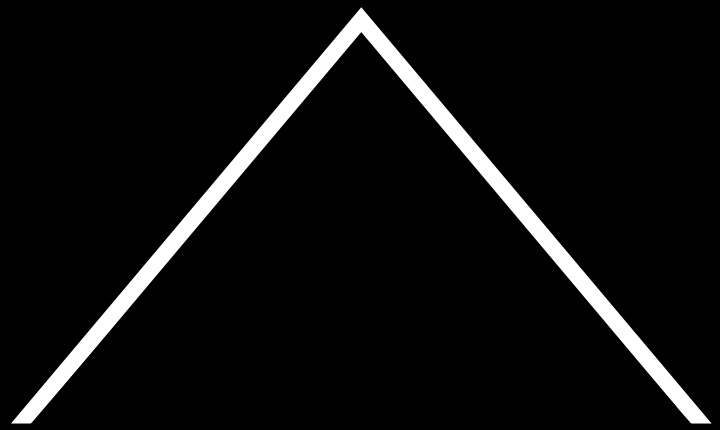
NSAIDs of special interest based on their cardiovascular risk profile:

Sales:
DDDs/1.000 inh./day



Total Prescription OTC

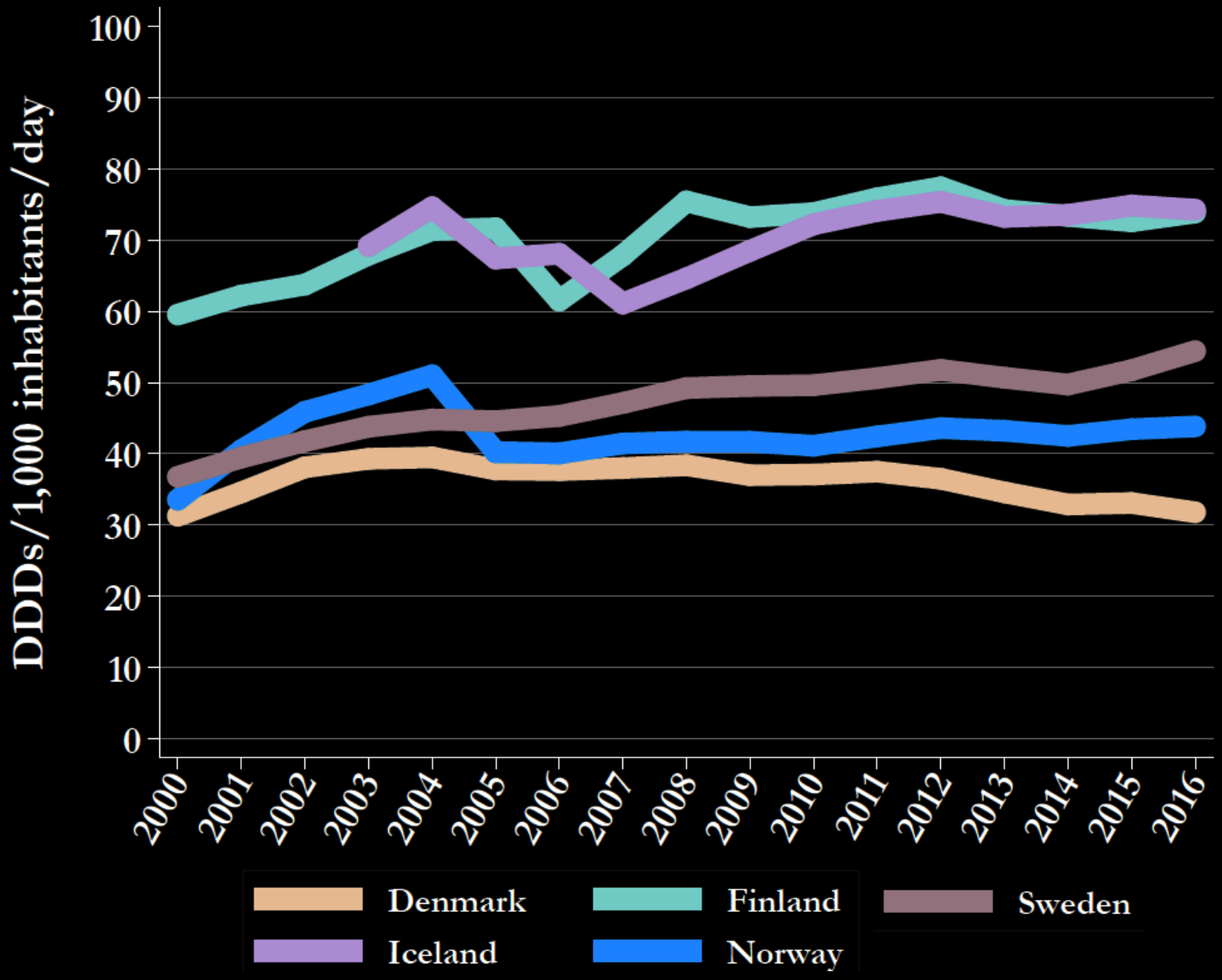
Prescription use:
Prescription users/1.000 inh



Age Sex

Total sales

(DDD/1.000 inh/day)


DDDs/1,000 inhabitants/day
100
90
80
70
60
50
40
30
20
10
0
2000
2001
2002
2003
2004
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2006
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2008
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2011
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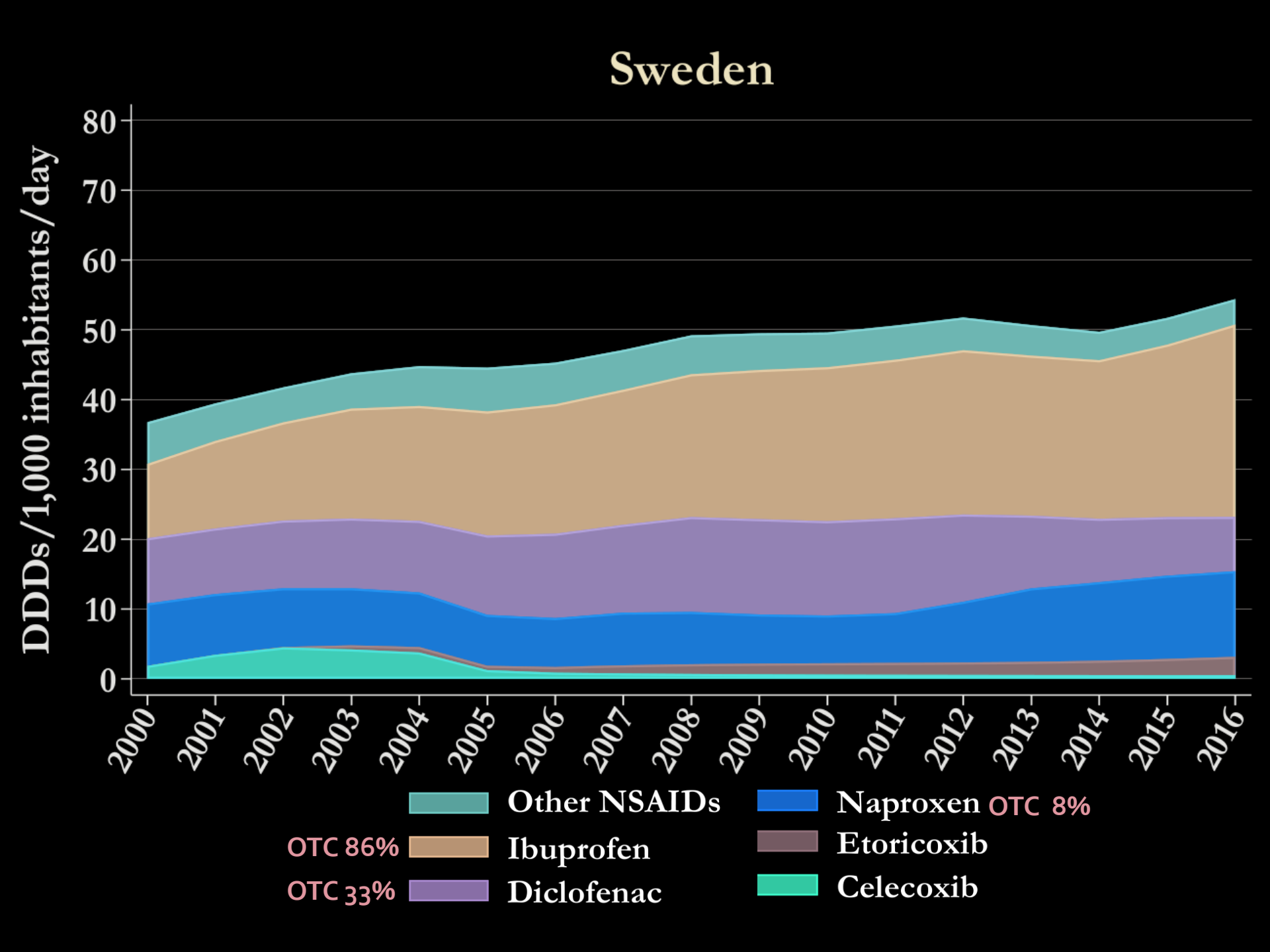
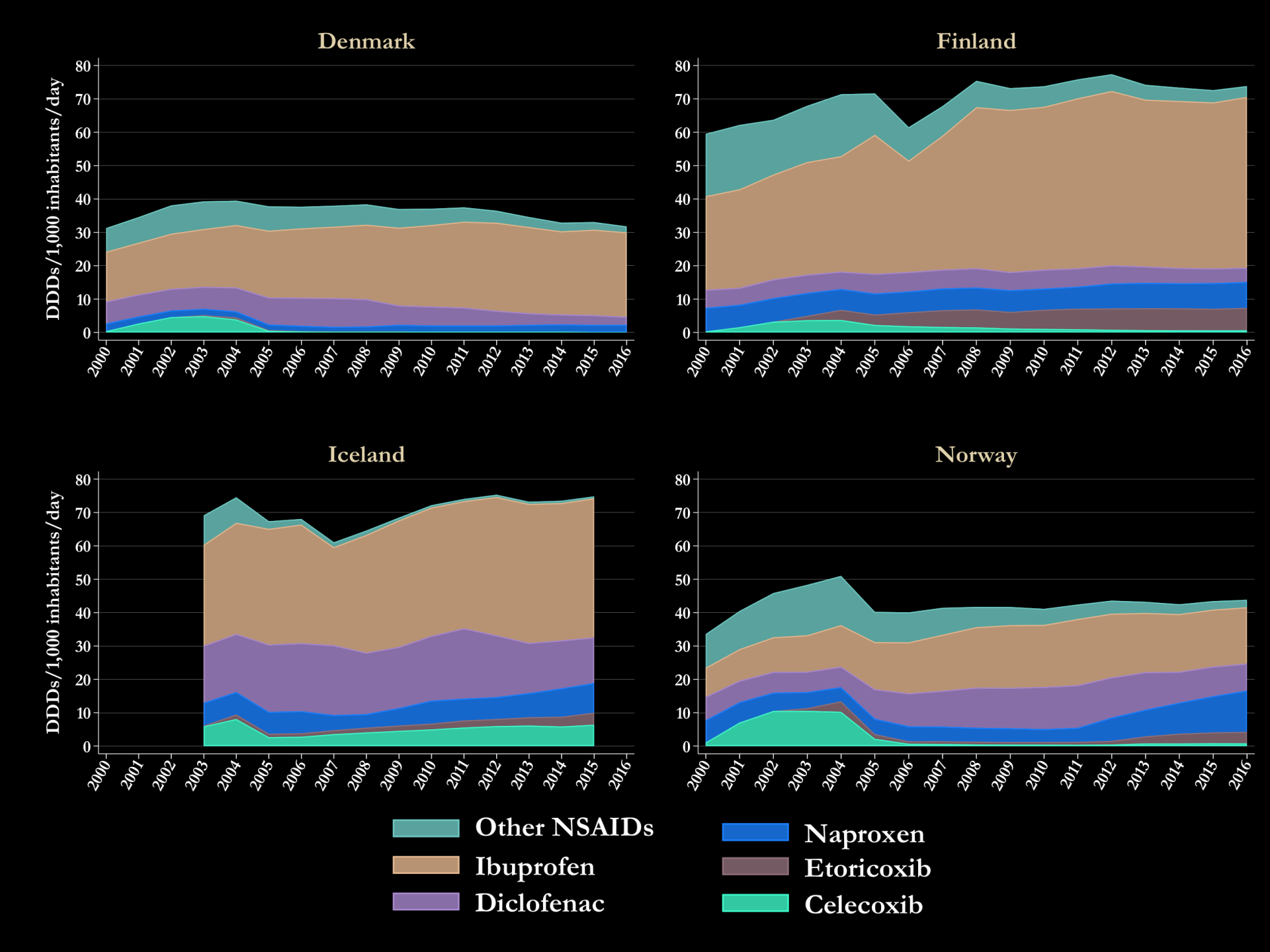
2013
2014
2015
2016
Denmark
Finland
Sweden
Iceland
Norway


Sweden
DDDs/1,000 inhabitants/day
80
70
60
50
40
30
20
10
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Other NSAIDs
OTC 86%
Ibuprofen
OTC 33%
Diclofenac
Naproxen
OTC 8%
Etoricoxib
Celecoxib


Denmark
Finland
Iceland
Norway
DDDs/1,000 inhabitants/day
0
10
20
30
40
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60
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2000
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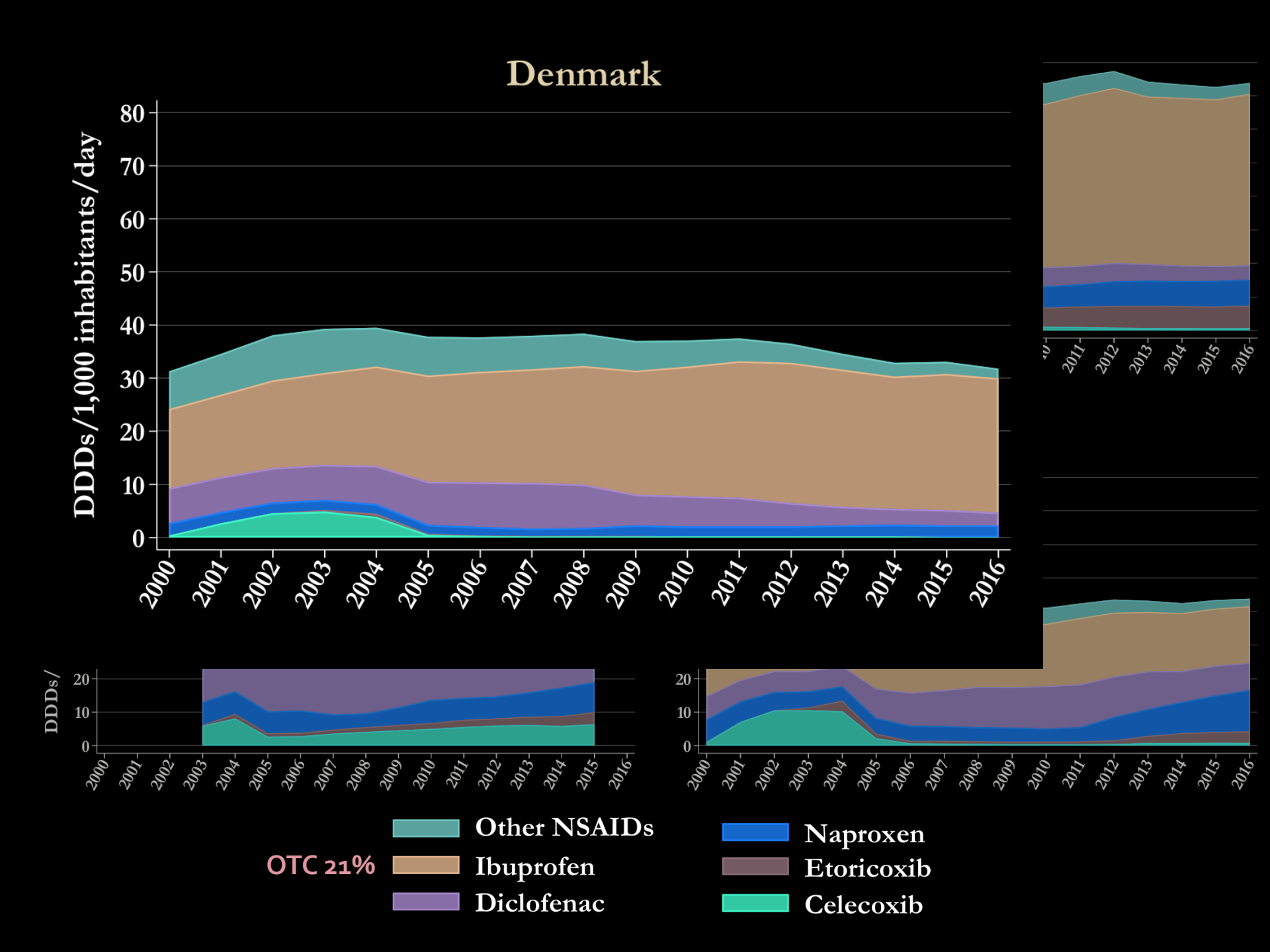
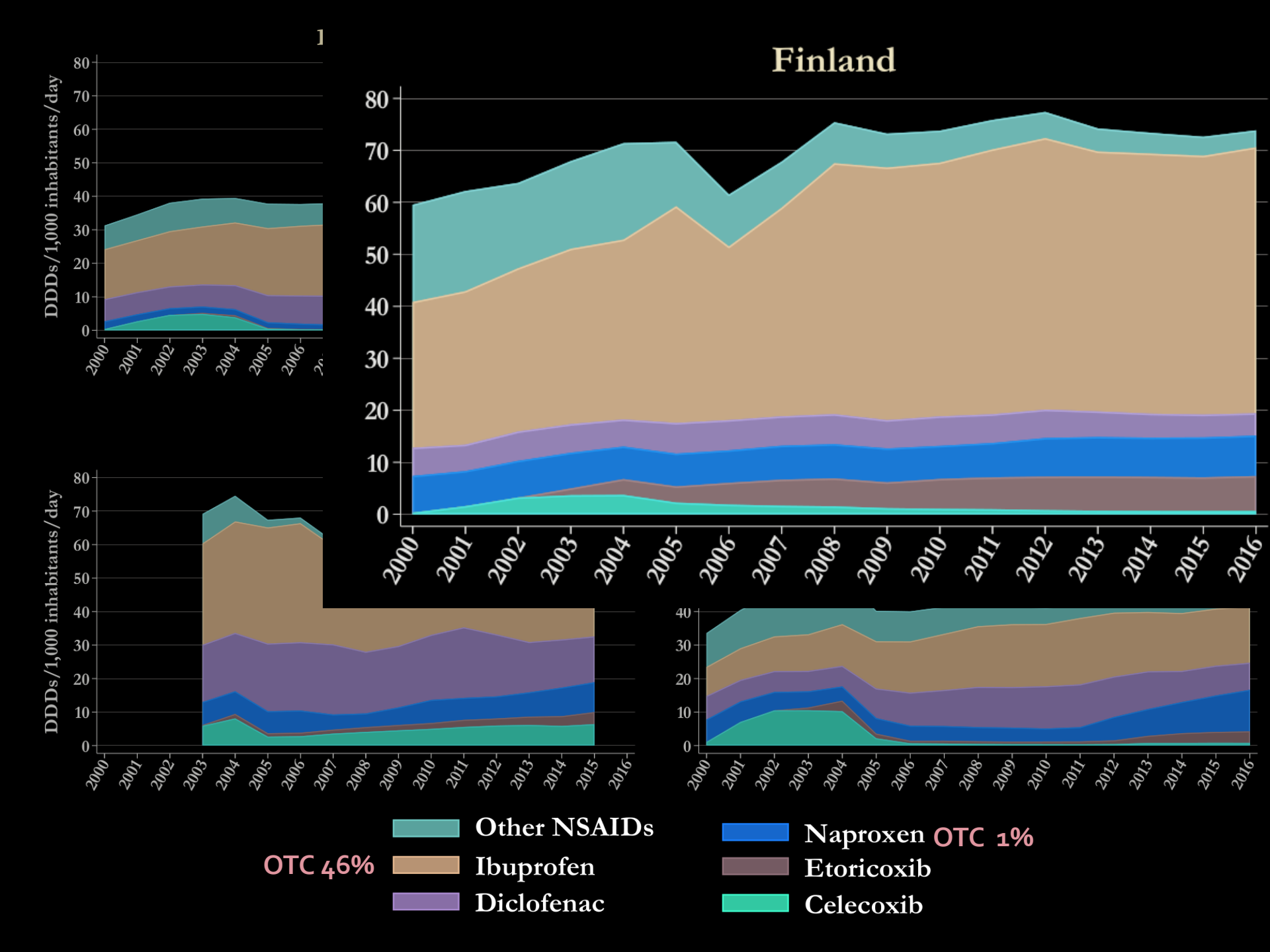
2016
Other NSAIDs
Ibuprofen
Diclofenac
Naproxen
Etoricoxib
Celecoxib


Denmark
DDDs/1,000 inhabitants/day
80
70
60
50
40
30
20
10
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
DDDs/
20
10
0
OTC 21%
Other NSAIDs
Ibuprofen
Diclofenac
Naproxen
Etoricoxib
Celecoxib


Finland
DDDs/1,000 inhabitants/day
0
10
20
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40
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60
70
80
2000
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2006
2007
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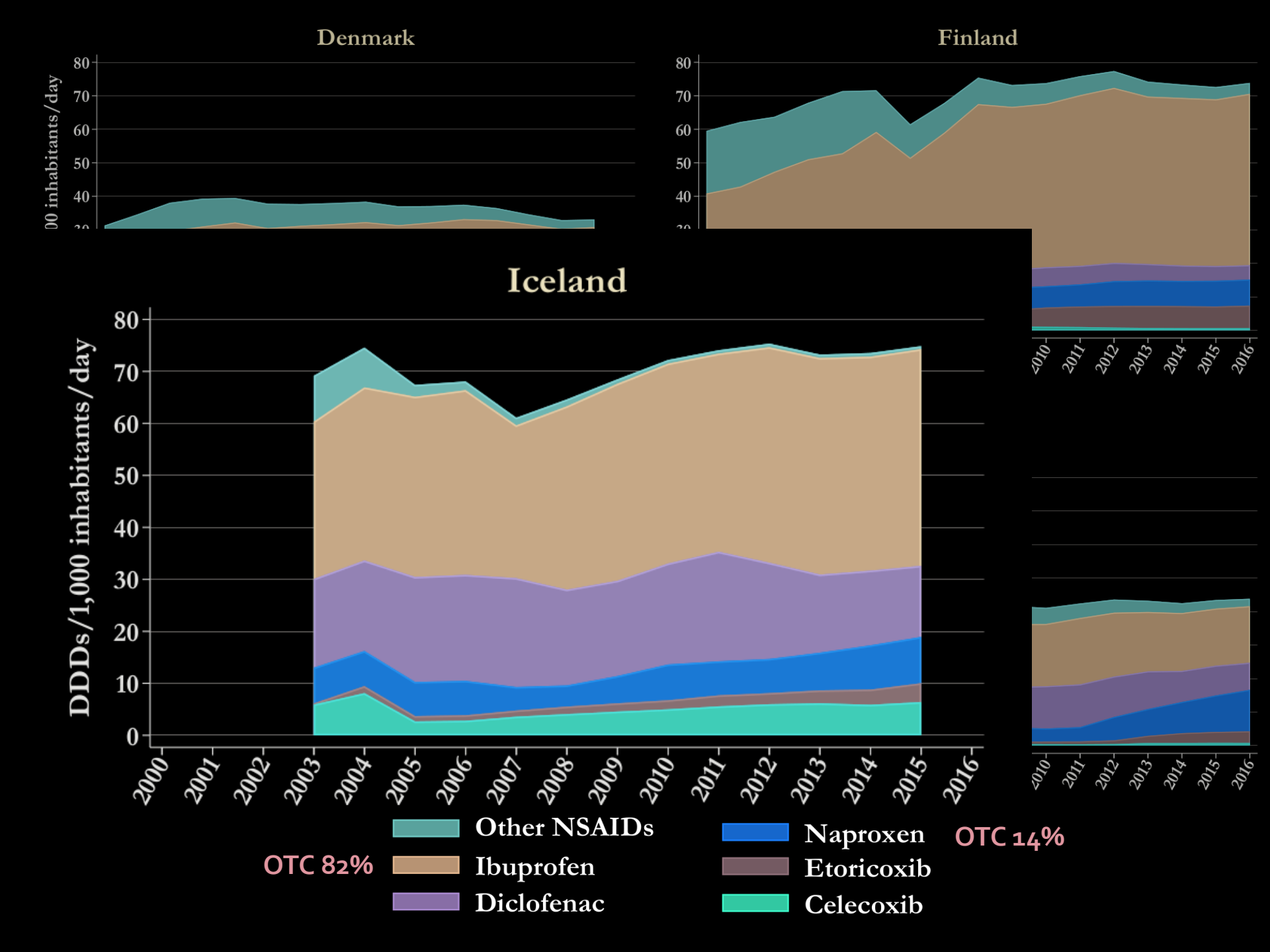
2016
OTC 46%
Other NSAIDs
Ibuprofen
Diclofenac
Naproxen
Etoricoxib
Celecoxib
OTC 1%


Denmark
Finland
Iceland
DDDs/1,000 inhabitants/day
00 inhabitants/day
80
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2006
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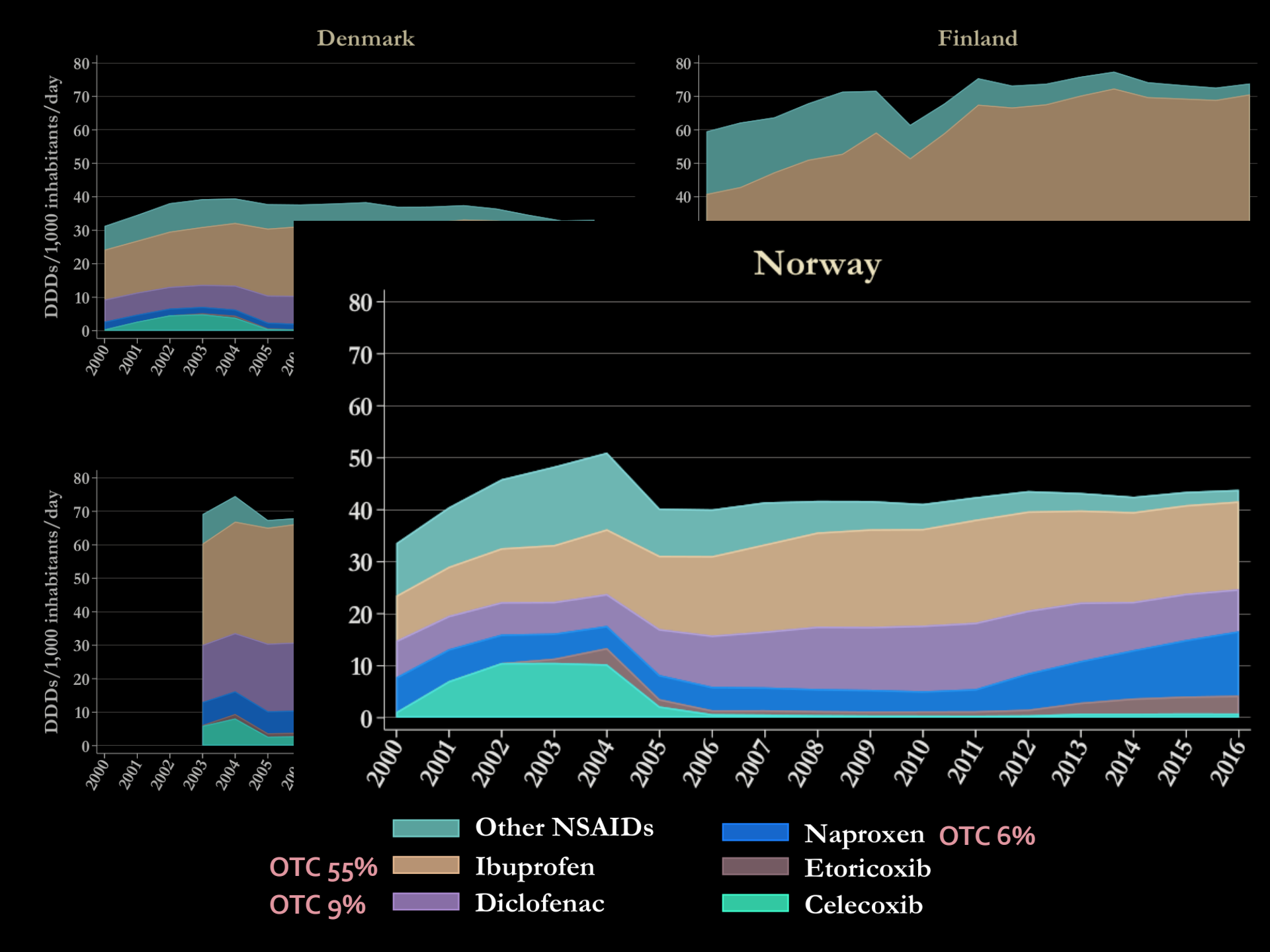
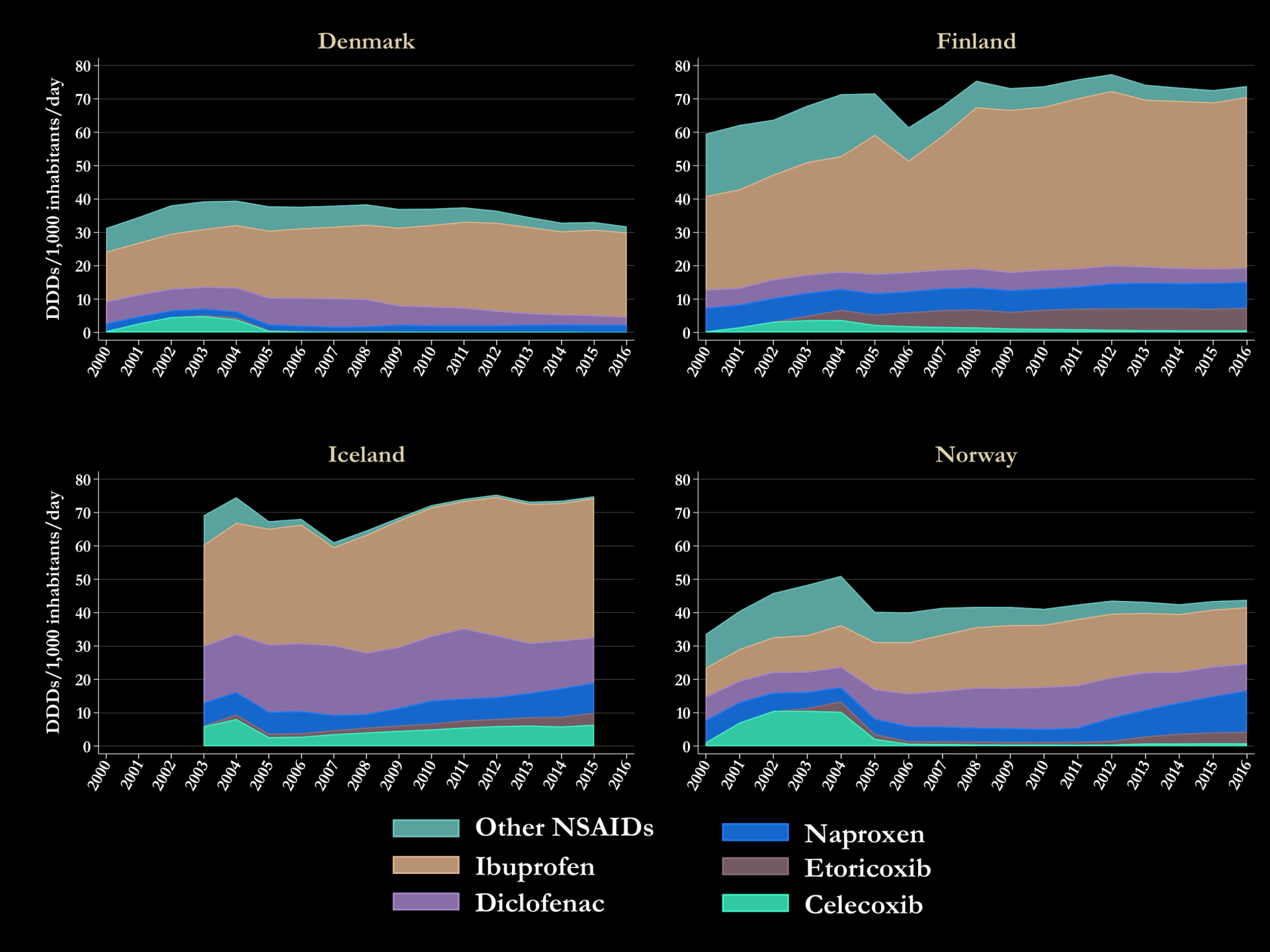
2016
Other NSAIDs
Ibuprofen
Diclofenac
Naproxen
Etoricoxib
Celecoxib
OTC 82%
OTC 14%


Denmark
Finland
Norway
DDDs/1,000 inhabitants/day
DDDs/1,000 inhabitants/day
Other NSAIDs
Ibuprofen
Diclofenac
Naproxen
Etoricoxib
Celecoxib
OTC 55%
OTC 9%
OTC 6%


Denmark
Finland
Iceland
Norway
DDDs/1,000 inhabitants/day
0
10
20
30
40
50
60
70
80
2000
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2002
2003
2004
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2006
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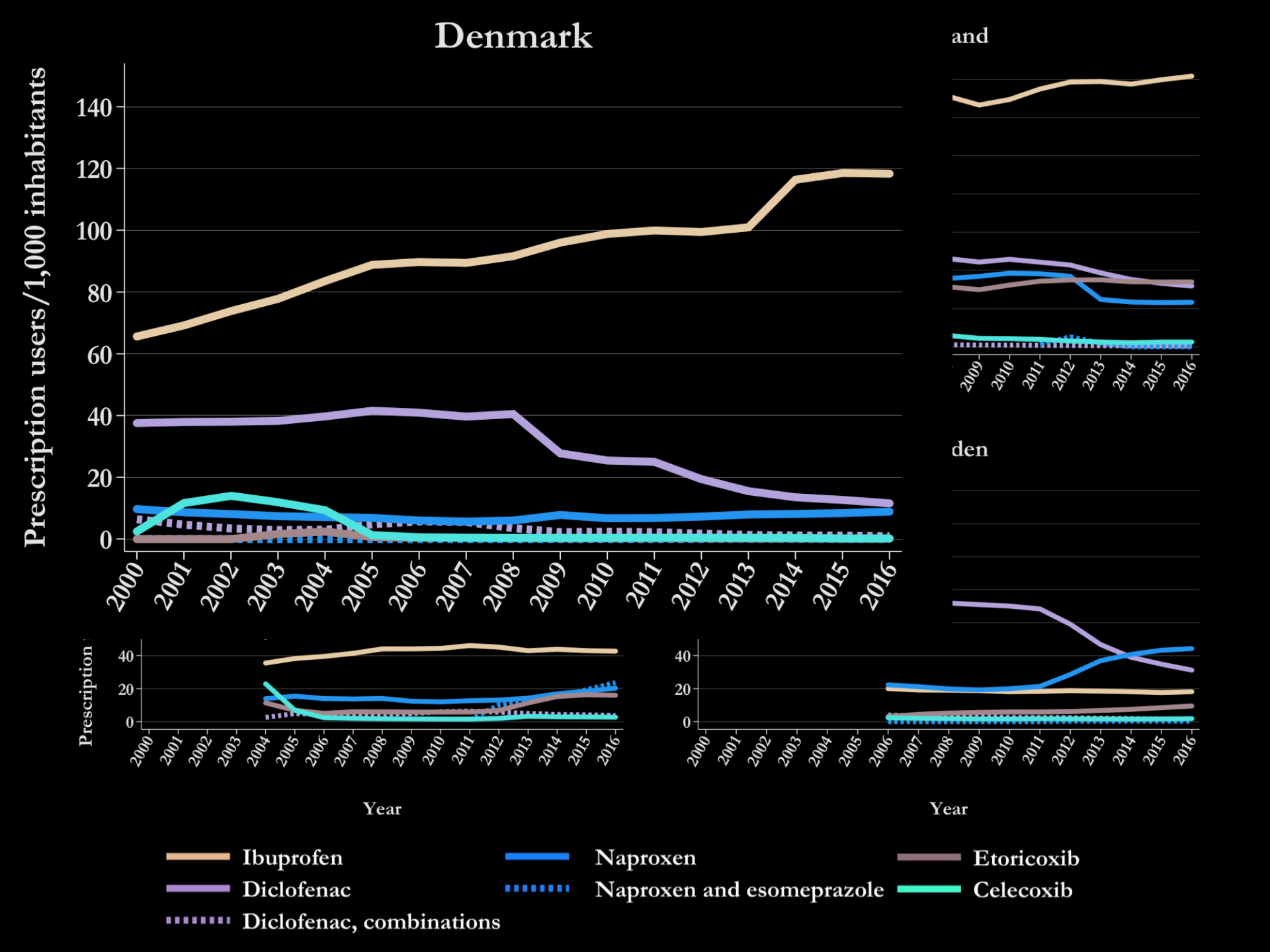
2010
2011
2012
2013
2014
2015
2016
Other NSAIDs
Ibuprofen
Diclofenac
Naproxen
Etoricoxib
Celecoxib

Prescription use

(users / 1.000 inh)


Denmark
Prescription users/1,000 inhabitants
0
20
40
60
80
100
120
140
2000
2001
2002
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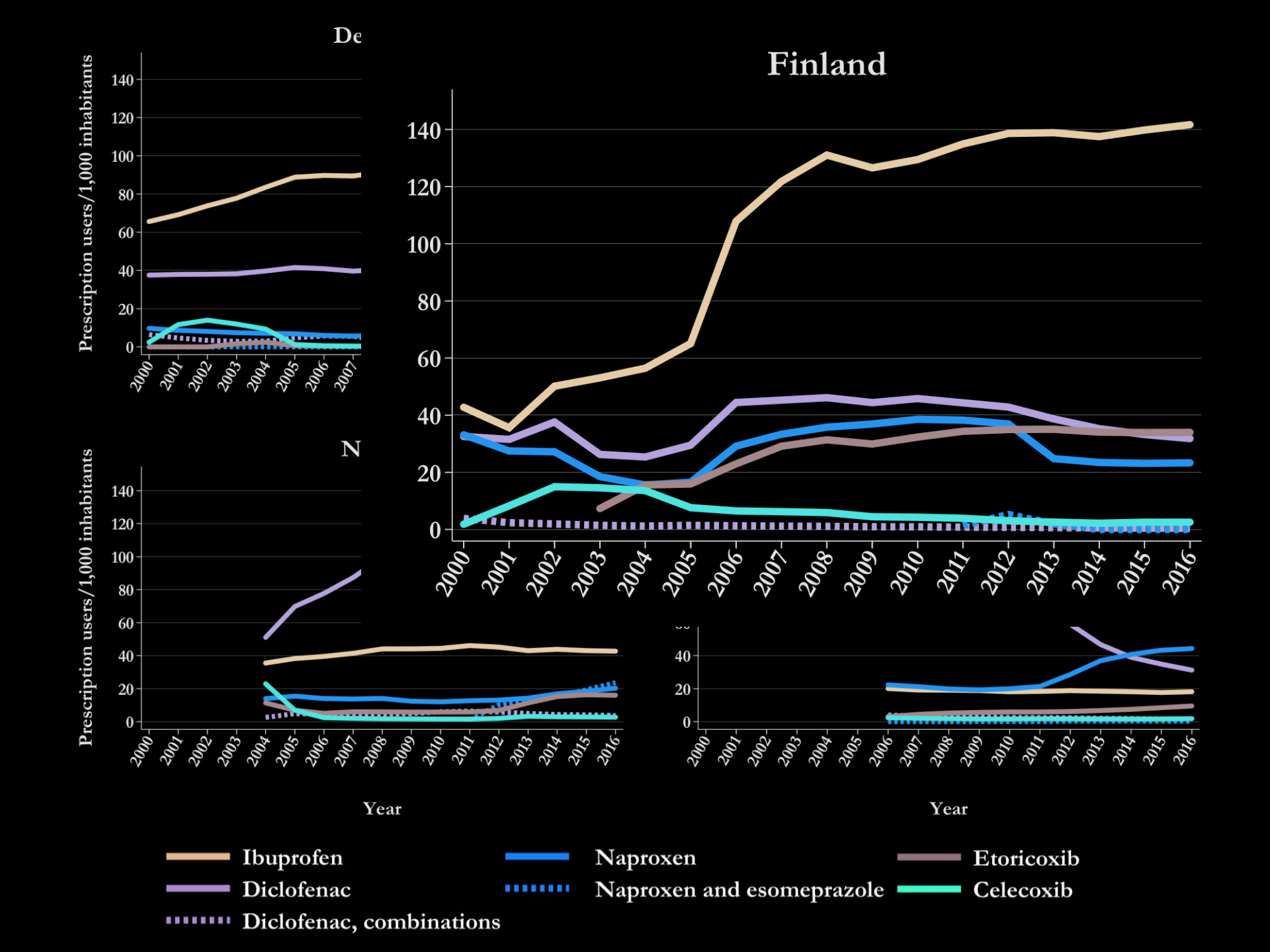
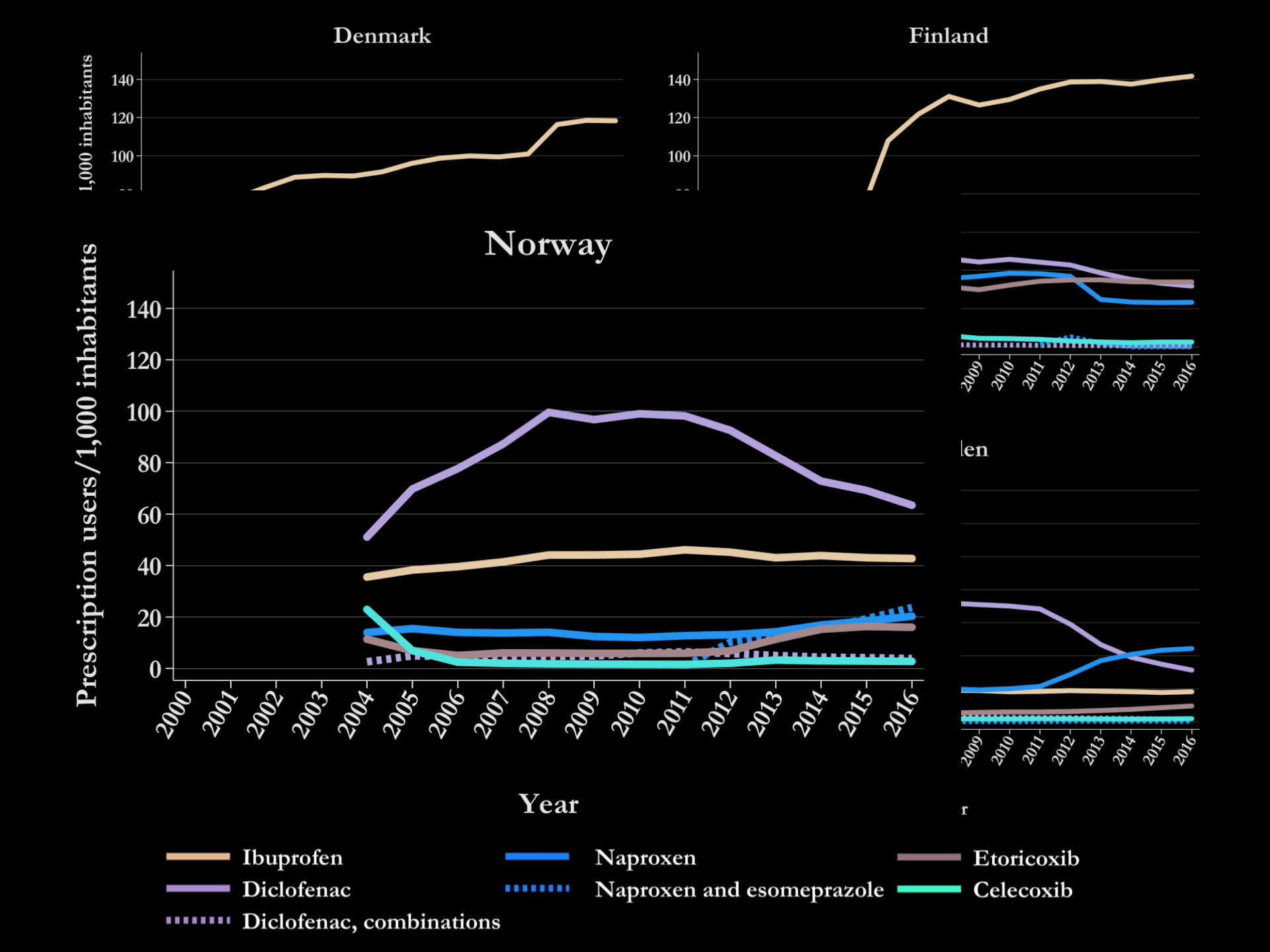
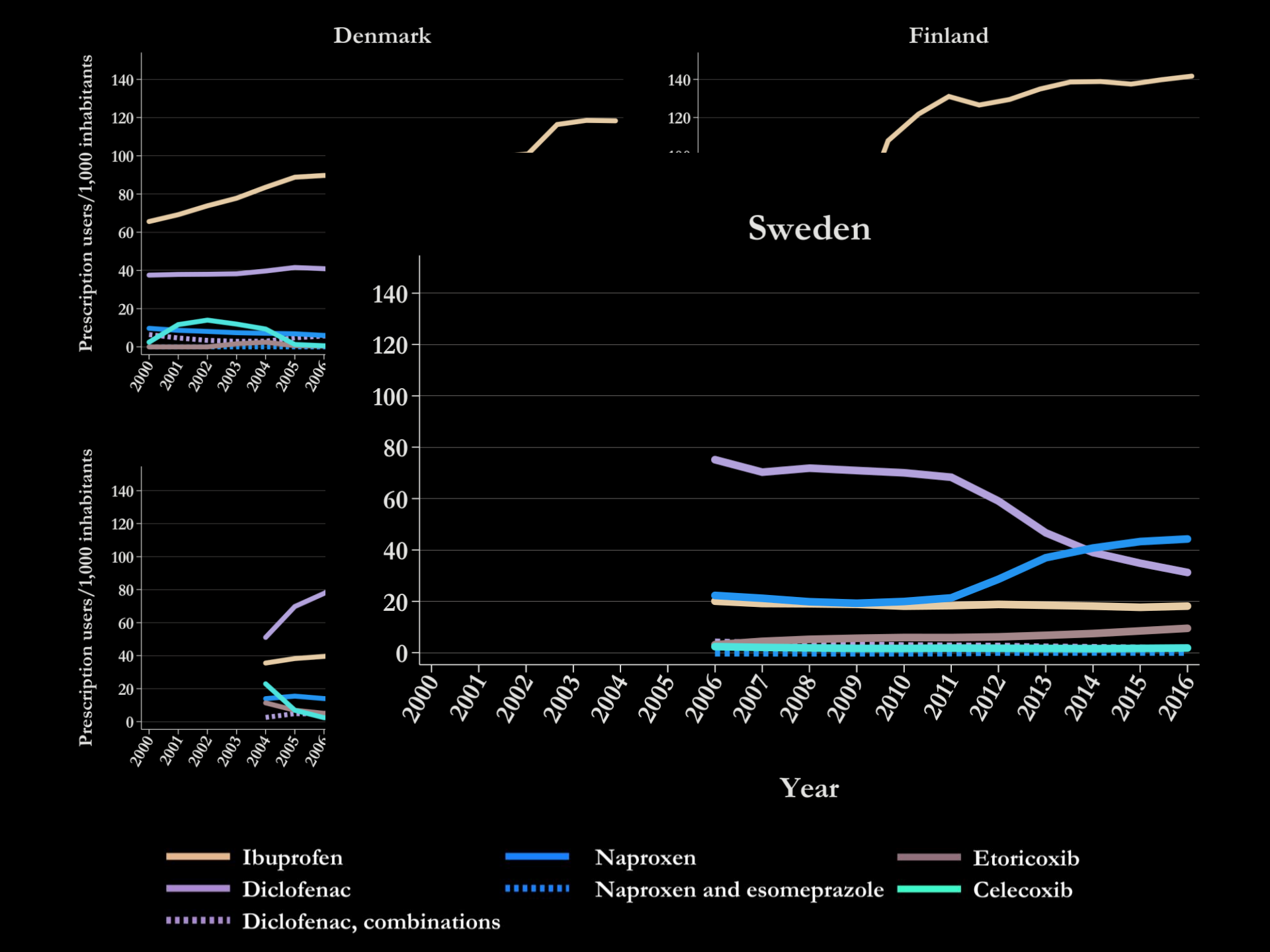
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
and
den
Prescription
Year
Year
Ibuprofen
Diclofenac
Diclofenac, combinations
Naproxen
Naproxen and esomeprazole
Etoricoxib
Celecoxib


De
Finland
N
Prescription users/1,000 inhabitants
Year
Ibuprofen
Diclofenac
Diclofenac, combinations
Naproxen
Naproxen and esomeprazole
Etoricoxib
Celecoxib


Denmark
Finland
Norway
1,000 inhabitants
Prescription users/1,000 inhabitants
Year
Ibuprofen
Diclofenac
Diclofenac, combinations
Naproxen
Naproxen and esomeprazole
Etoricoxib
Celecoxib


Denmark
Finland
Sweden
Prescription users/1,000 inhabitants
Prescription users/1,000 inhabitants
0
20
40
60
80
100
120
140
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
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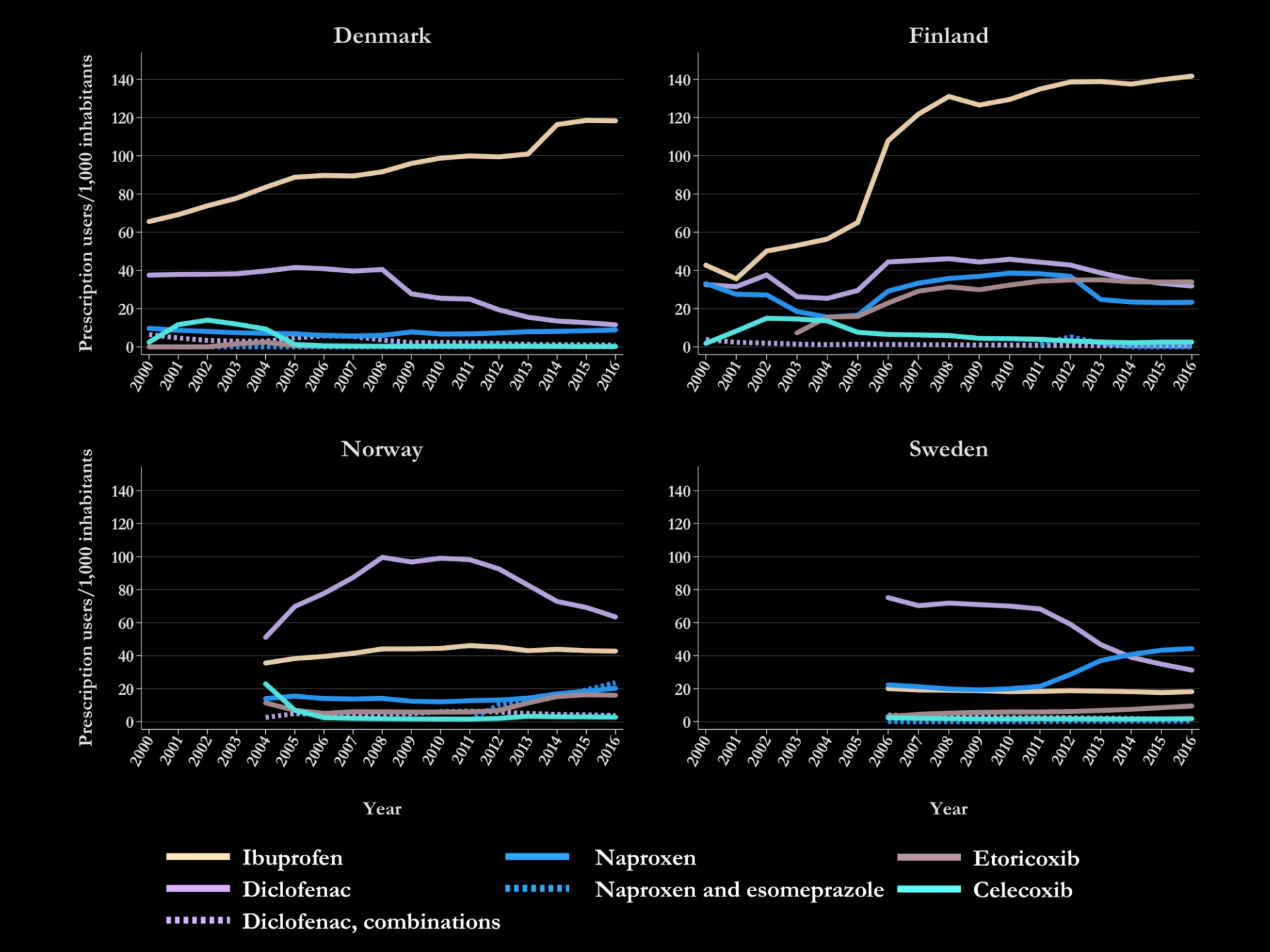
2012
2013
2014
2015
2016
Year
Ibuprofen
Diclofenac
Diclofenac, combinations
Naproxen
Naproxen and esomeprazole
Etoricoxib
Celecoxib


Denmark
Finland
Norway
Sweden
Prescription users/1,000 inhabitants
Year
Ibuprofen
Diclofenac
Diclofenac, combinations
Naproxen
Naproxen and esomeprazole
Etoricoxib
Celecoxib

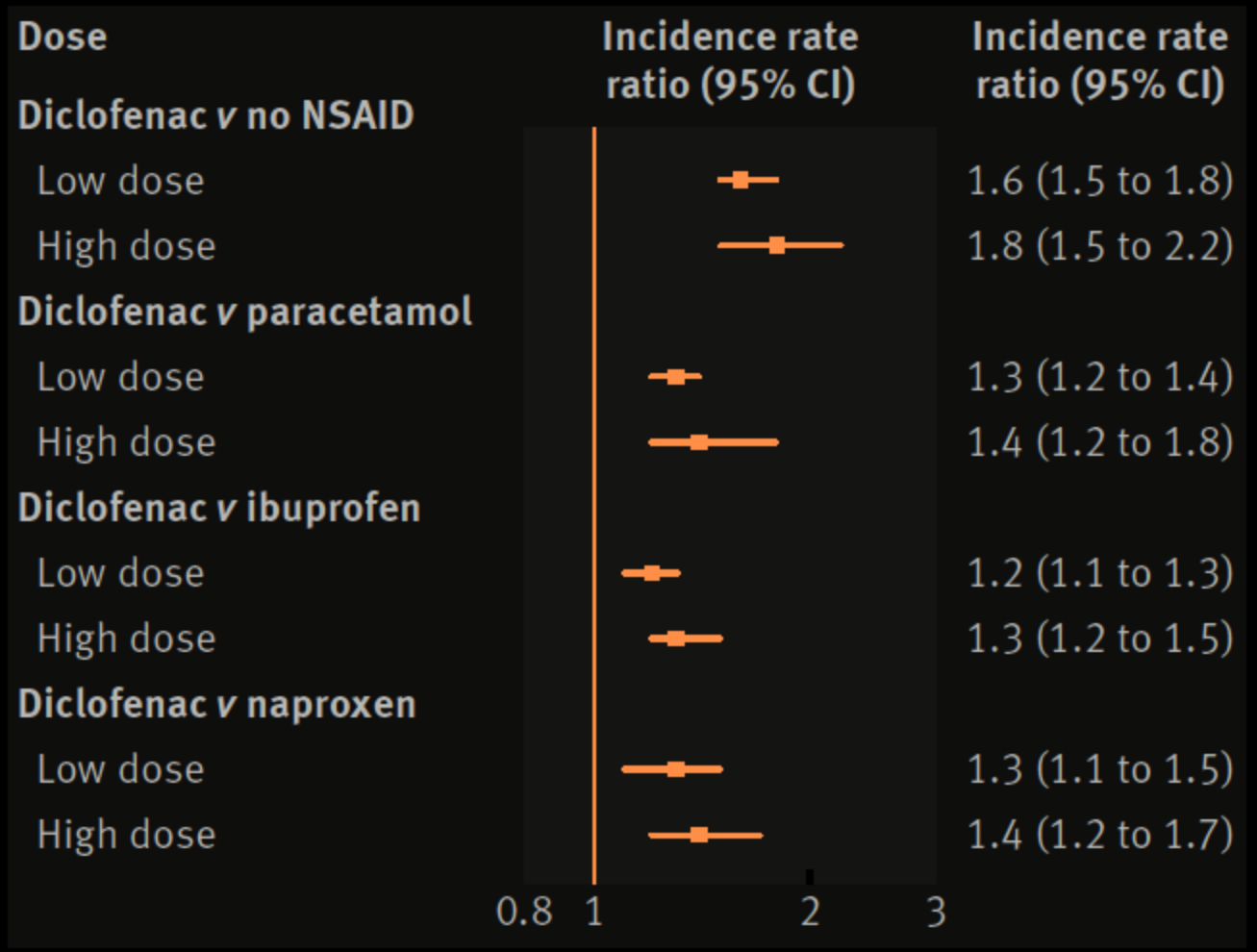
Conclusions

Sales of ibuprofen and naproxen increased while sales of diclofenac decreased.

However…

Diclofenac remains commonly used in Iceland, Norway, and Sweden and is available OTC in the latter two countries.

OTC sales of diclofenac constituted 33% of total diclofenac sales in 2016 in Sweden and 9% in Norway.



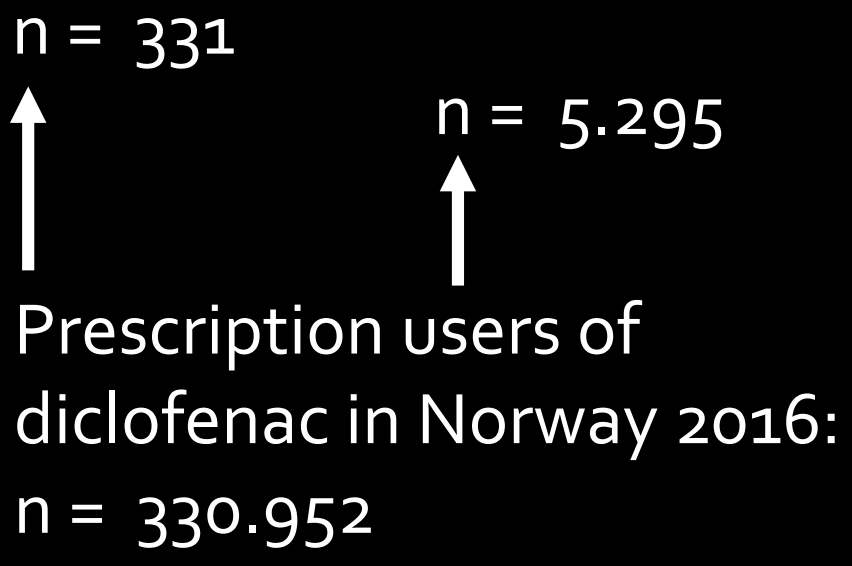
Schmidt et al:
BMJ 2018;362:k3426

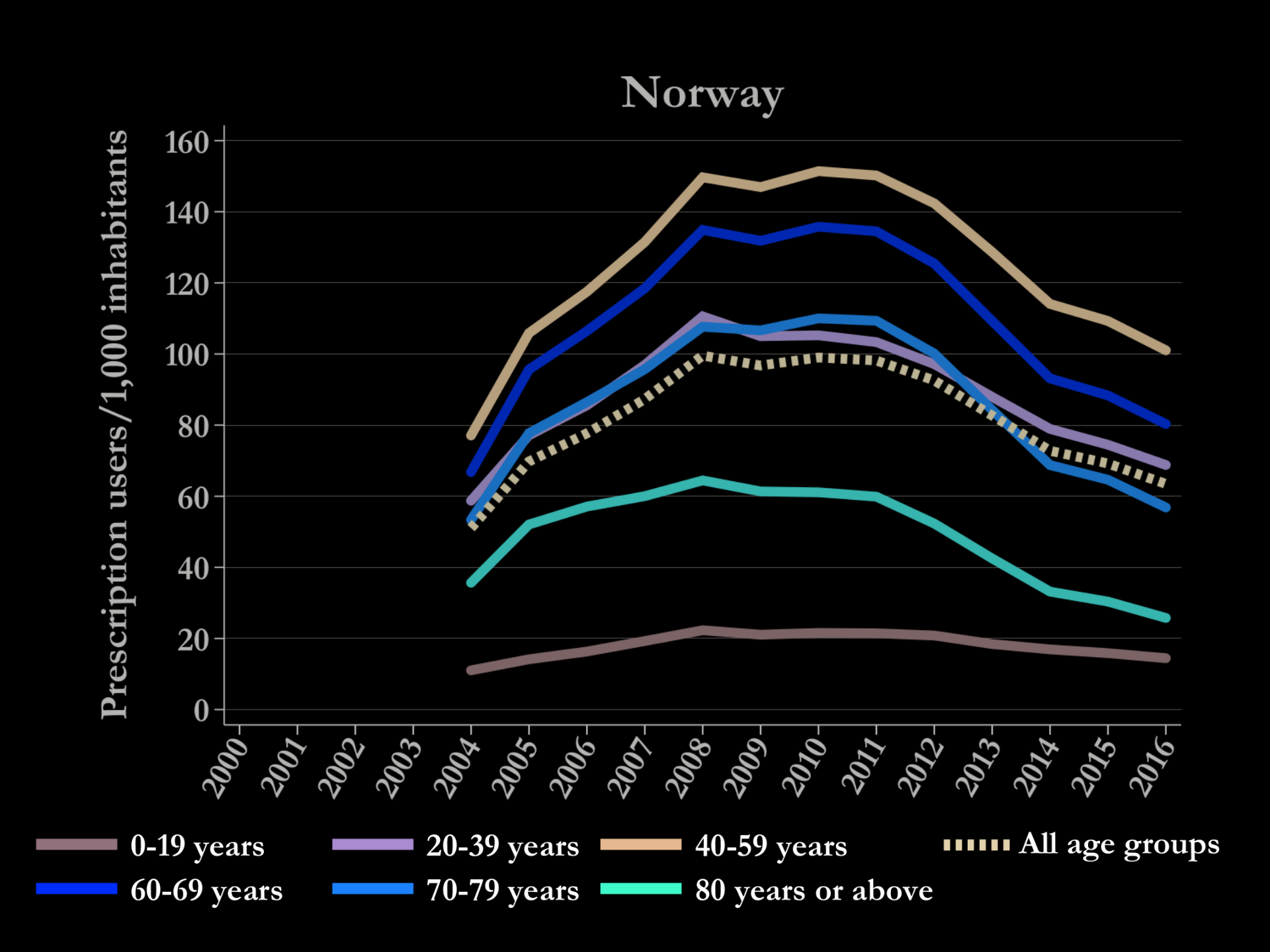
Fig 5 | Risk of major adverse cardiovascular events comparing initiation of low and high dose diclofenac with no NSAID initiation or initiation of paracetamol, ibuprofen, or naproxen. NSAID=non-steroidal anti-inflammatory drug

Absolute risk increase of cardiovascular event 30 days after initiation of diclofenac vs. ibuprofen

Low risk: 1/1.000
High risk: 16/1.000

Schmidt et al:
BMJ 2018;362:k3426




Norway
Prescription users/1,000 inhabitants
160
140
120
100
80
60
40
20
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
0-19 years
20-39 years
40-59 years
All age groups
60-69 years
70-79 years
80 years or above

Use of etoricoxib has increased in all Nordic countries except Denmark.

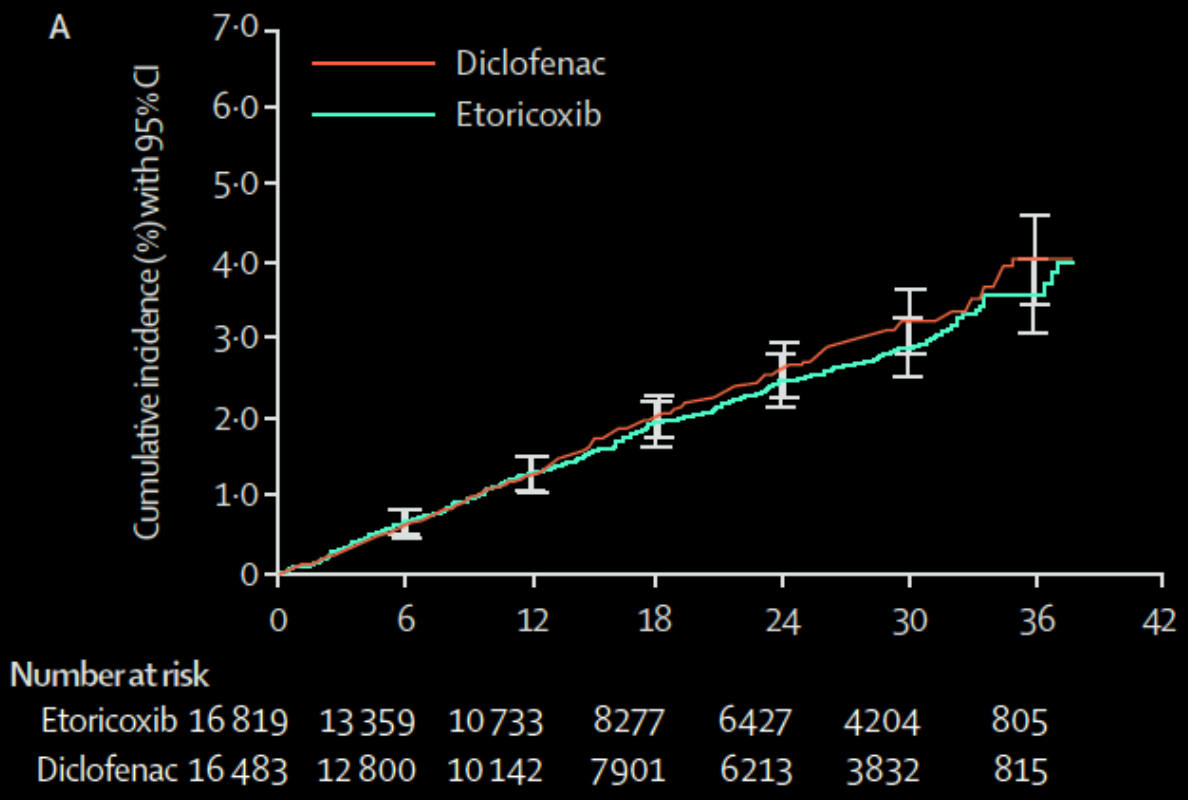
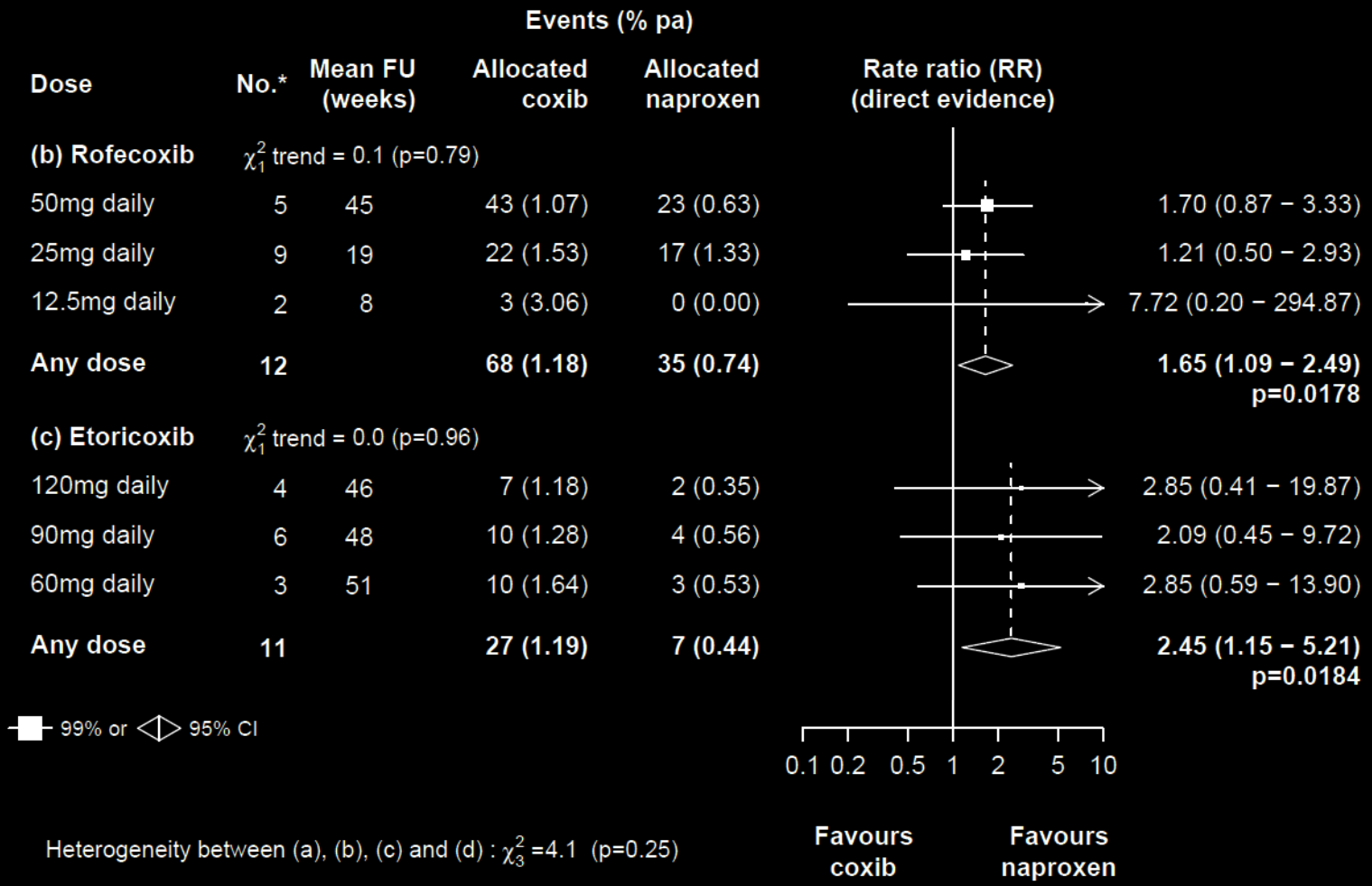


Figure 2: **Time-to-event per-protocol analysis**
(A) Cumulative incidence of thrombotic cardiovascular events. (B) Cumulative incidence of arterial thrombotic events. (C) Cumulative incidence of APTC[23] events (myocardial infarction, stroke, or vascular death).

Lancet 2006; 368: 1771–81

Webfigure 18: Effect of different coxib regimens on major vascular events, by dose: trials of a coxib vs naproxen



Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =4.1 (p=0.25)

* Number of comparisons with at least one event

Lancet 2013; 382: 769–79

?

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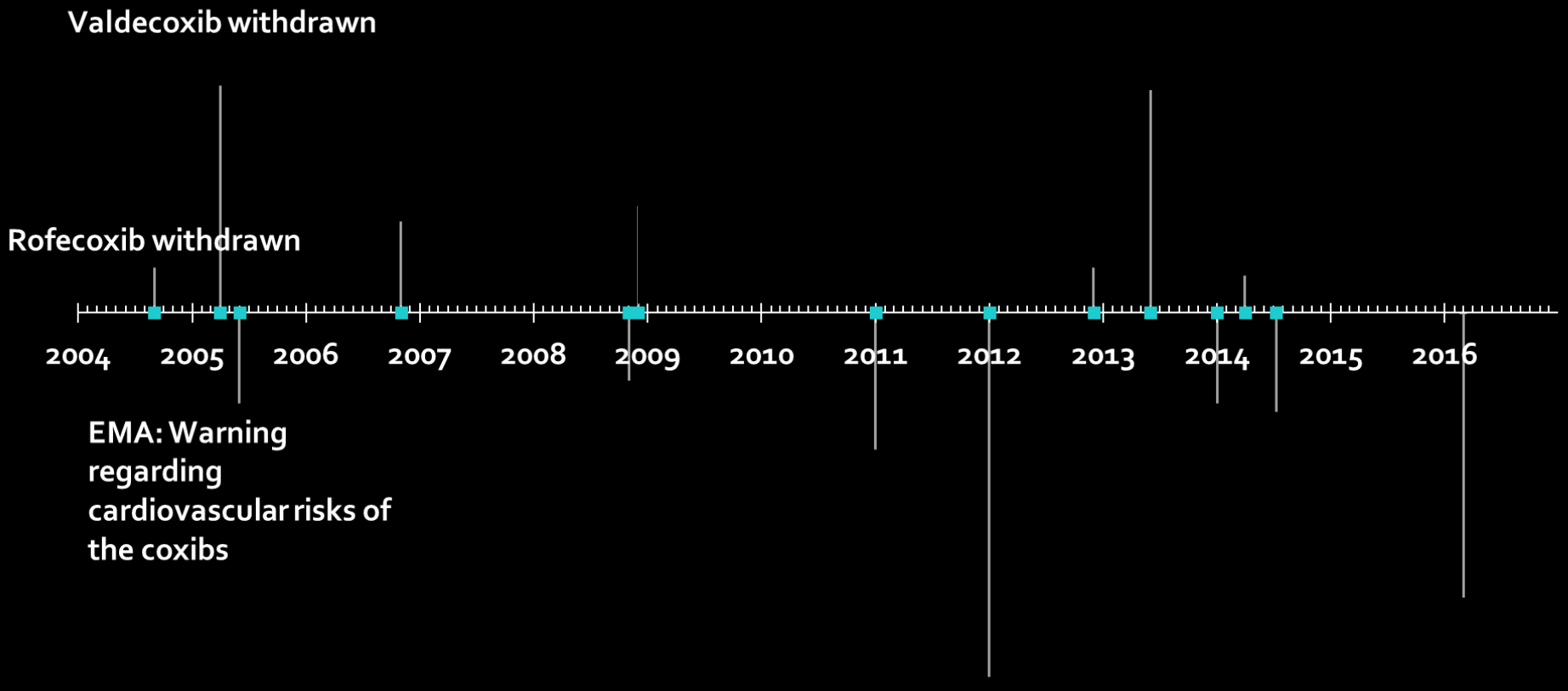
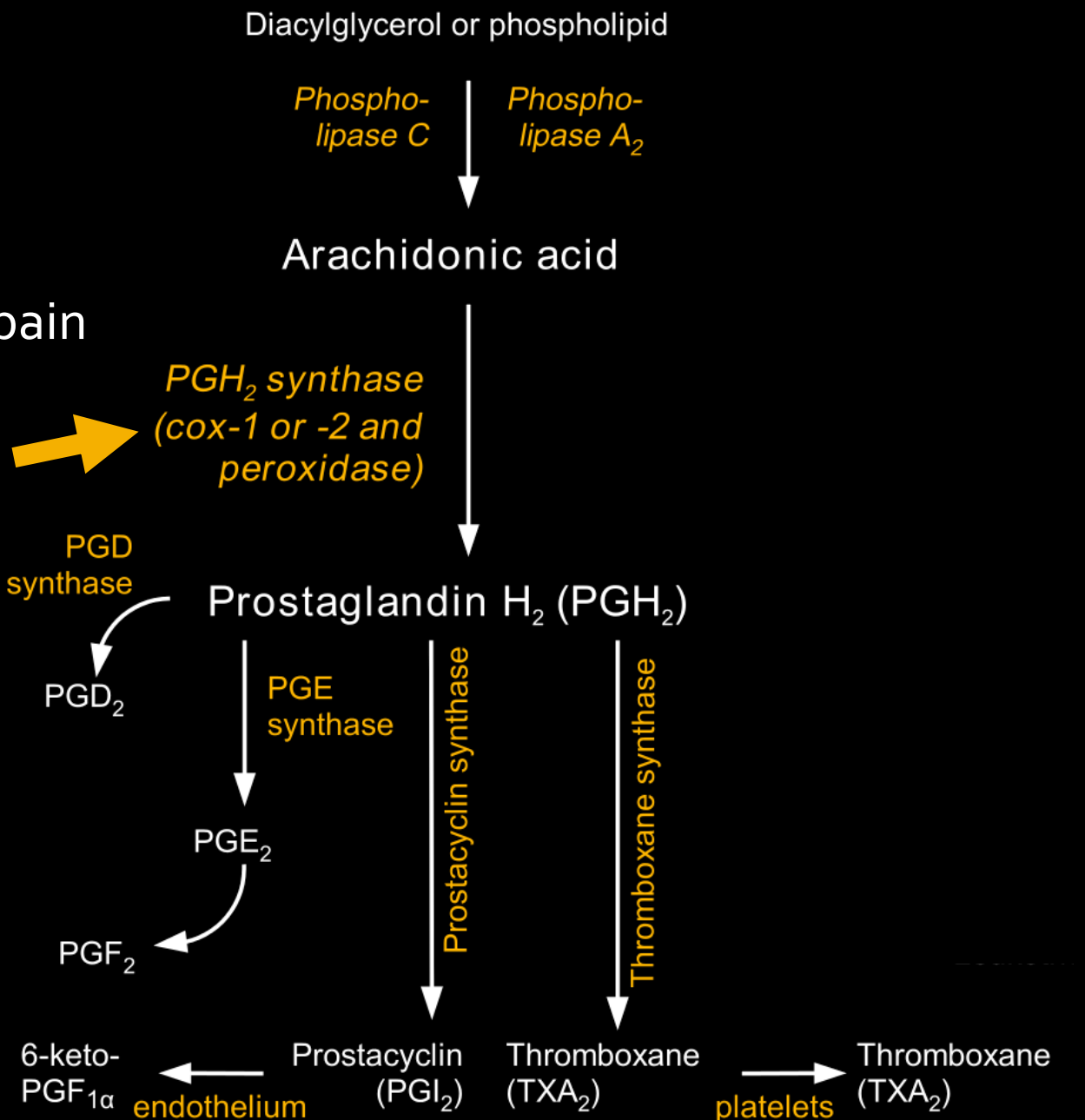

Valdecoxib withdrawn
Rofecoxib withdrawn
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
EMA: Warning regarding cardiovascular risks of the coxibs

NSAIDs

Used to treat inflammation, fever, pain

Mechanism of action: COX inhibition



NSAIDs differ with regards to cardiovascular risk

EDITORIALS

Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med 2000;343:1520-8.

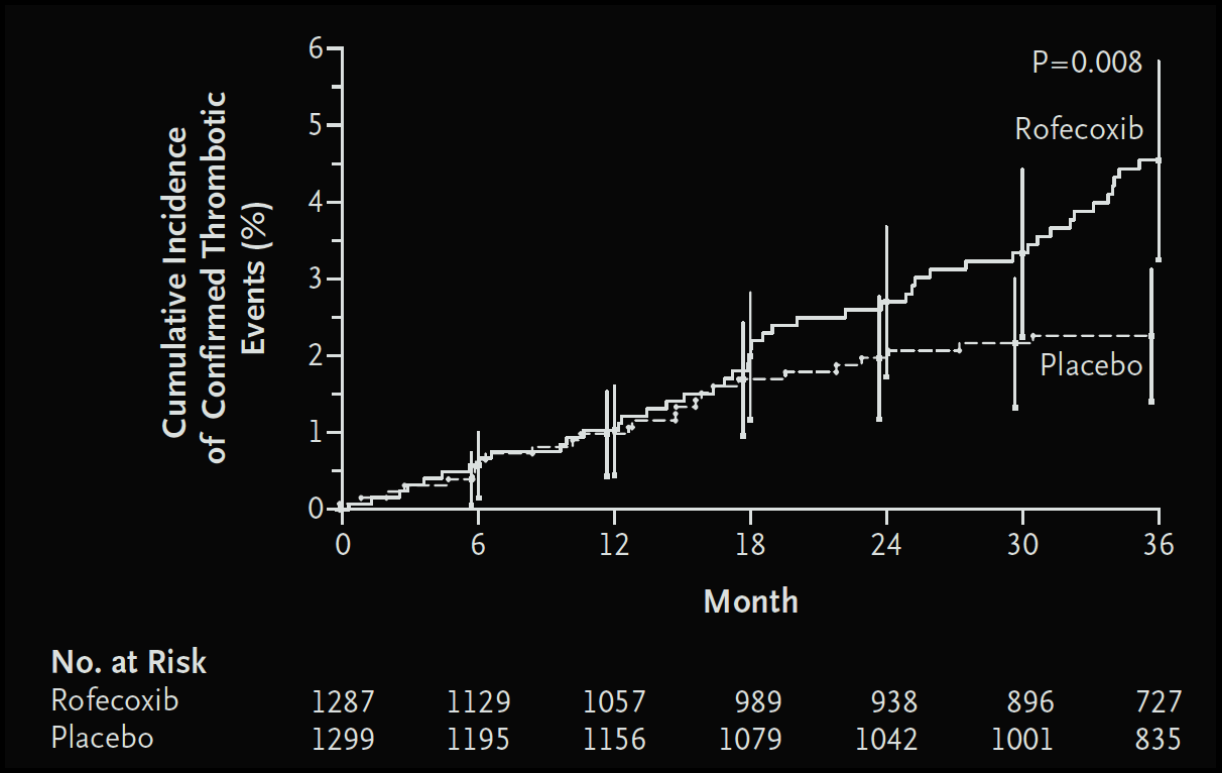
Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffrey M. Drazen, M.D.

Table 2. Data on Myocardial Infarctions Including the Three Events.*

Study Group	Person-Years of Exposure	No. of Myocardial Infarctions	Relative Risk	95% CI
Total				
Rofecoxib	2698	20	5.00	1.68 to 20.13
Naproxen	2699	4		

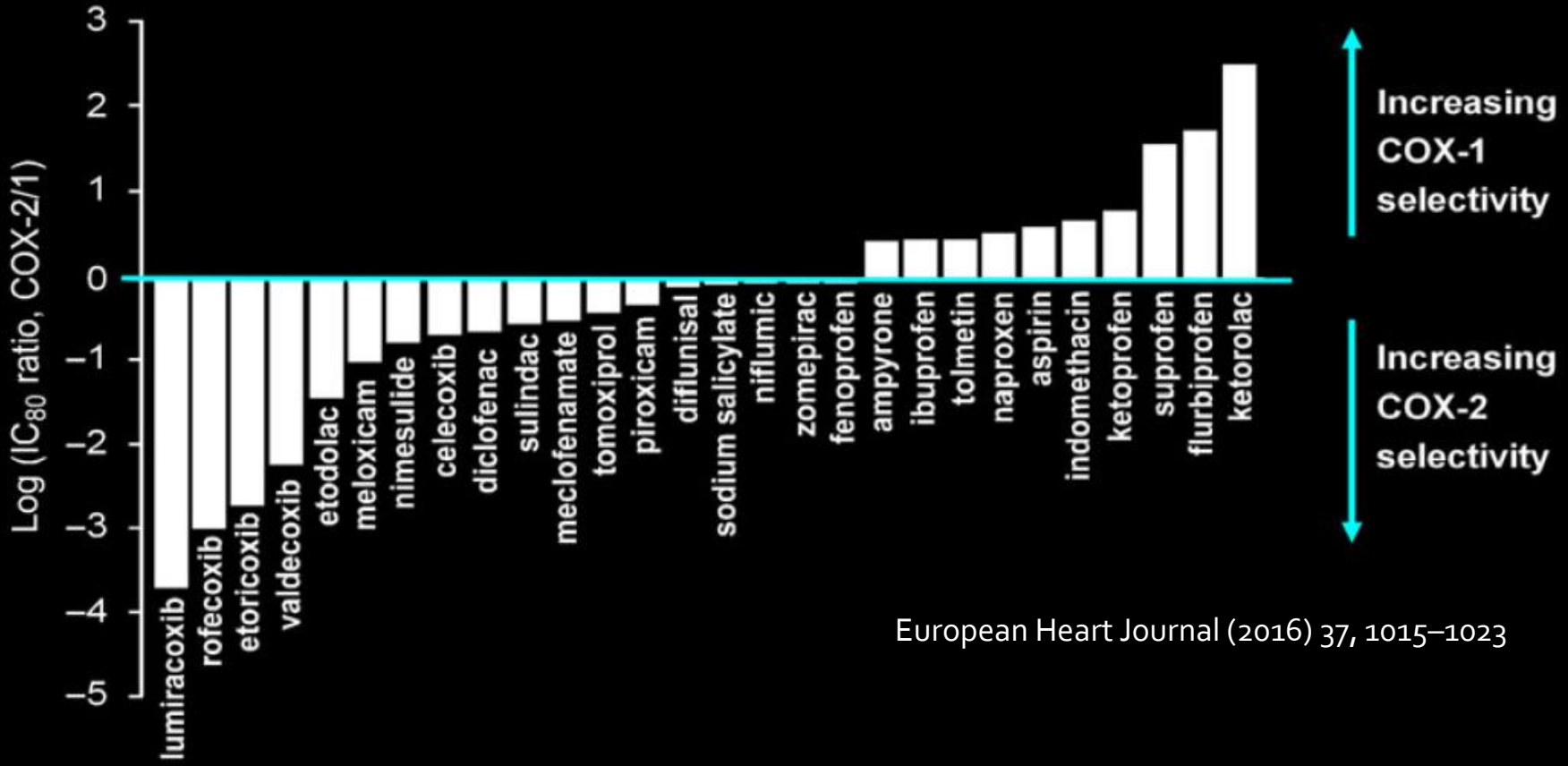
NSAIDs differ with regards to cardiovascular risk

2004: Rofecoxib APPROVe Trial

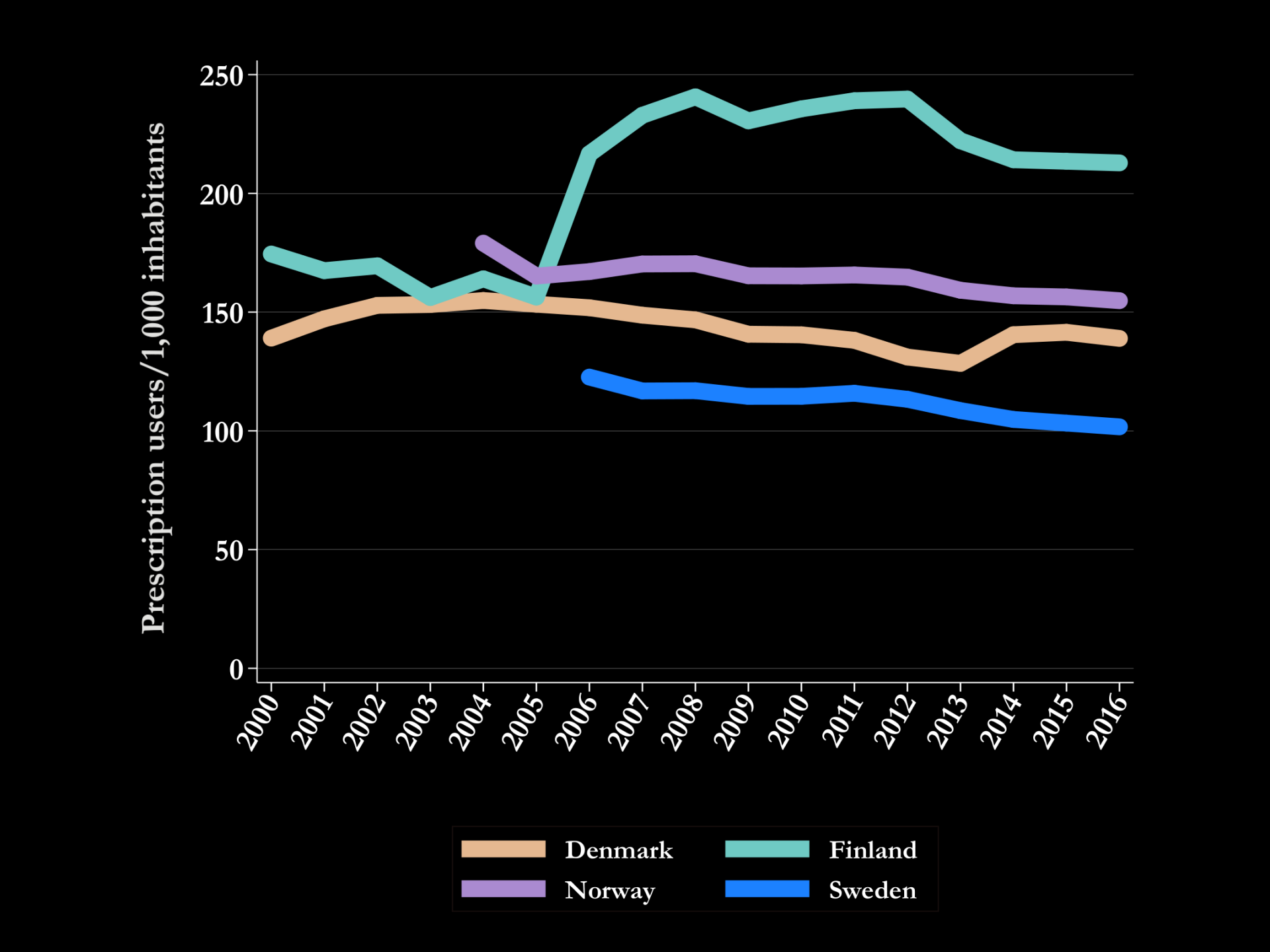


N Engl J Med 2005;352:1092-102.

NSAIDs differ with regards to cardiovascular risk



European Heart Journal (2016) 37, 1015–1023


Prescription users/1,000 inhabitants
250
200
150
100
50
0
2000
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2002
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2011
2012
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2016
Denmark
Finland
Norway
Sweden