

# 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 daily intake of 4 g of paracetamol for 14 days in healthy adults [4]. Furthermore, a systematic review from 2015 on the safety of paracetamol for back pain and osteoarthritis found four times increased risk of abnormal liver function tests in the paracetamol-treated groups compared with the placebo groups [5]. Paracetamol is considered the leading cause of liver failure in most high-income countries [6,7]. Reports of an increasing number of paracetamol poisonings, especially among adolescents, have led to legislative restrictions in the sales of paracetamol in many countries, such as pack size restrictions and age limits [8–10]. The efficacy of paracetamol to treat chronic pain has also been put to question. Systematic reviews suggest no or limited effects on chronic pain among patients with osteoarthritis [5,11,12] and no effect on lower back pain [5]. Paracetamol is, however, beneficial in acute or temporary pain, such as migraine [13], post-operative pain [14] and post-partum pain [15].

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 statistics and the high-quality prescription drug registers, we aimed to investigate trends in total and prescribed use of paracetamol in the Nordic countries.

## Materials and Methods

We investigated trends in the sales of paracetamol in the five Nordic countries – Sweden, Denmark, Norway, Finland and Iceland. Both aggregate-level wholesale data and nationwide prescription drug data on paracetamol sales were retrieved. In 2015, these data sources covered a total population of 26.8 million people; Sweden: 10.0 million; Denmark: 5.7 million; Norway: 5.2 million; Finland: 5.5 million; and Iceland: 0.3 million inhabitants [16].

**Data sources: wholesale statistics.** Wholesale statistics of paracetamol were available from public authorities in each country. The wholesale statistics were available for different periods in each country, ranging from 1999 to 2015 (2005–2015 in Sweden, 1999–2015 in Denmark, 1999–2015 in Norway, 2000–2015 in Finland and 2003–2015 in Iceland). For all countries, it was possible to break down the wholesale statistics by the prescription status of the products/packages: available as prescription only, available over-the-counter (OTC) and

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requisitions (drugs administered in institutions, for example hospitals, nursing homes or other institutions).

*Data sources: prescription register data.* The Nordic prescription registers are nationwide registers covering all drugs dispensed by prescription at community pharmacies, except for Finland where only prescriptions reimbursed by the national health insurance are covered. For a description of all the Nordic registers, see Furu *et al.* [17] or the country-specific descriptions [18–22]. The data in the registers have been collected on the individual level. However, in this study, we rely on aggregated data on paracetamol use by prescription presented by age and sex. For this study, the prescription drug data were available for the years 2006–2015 in Sweden, 1999–2015 in Denmark, 2004–2015 in Norway and 1995–2015 in Finland. We did not have access to prescription data for Iceland. An overview of data sources and data availability is summarized in Table S1.

*Paracetamol products.* Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system [23] in all Nordic countries (version 2016). We were primarily interested in sales and use of plain paracetamol (single substance, ATC code N02BE01). Some paracetamol combinations [paracetamol + codeine combinations (N02AA59, only on prescription) and paracetamol + other active ingredients excluding combinations with psycholeptics (e.g. caffeine) (N02BE51)] are presented as Supplementary material. Paracetamol combinations only available for specific time periods in the various countries were not included as the

sales of these combinations were generally low (<5% of the total DDDs of paracetamol sales in a given year) (e.g. N02AX52, N02AC54, M03BA52).

A short overview of the legislative changes in paracetamol sales in the Nordic countries is provided in table 1. Plain paracetamol was sold over-the-counter during the whole study period in all Nordic countries. Plain paracetamol has been sold in other outlets than pharmacies (e.g. grocery stores and gas stations) in Denmark (from 2002 and onwards), Sweden (2009–2015) and Norway (from 2003 and onwards). Pack size restrictions for OTC sales of paracetamol were issued in all countries at different time-points during the study period. Age restrictions on OTC sales exist in some of the countries (restricted to persons aged  $\geq 18$  years).

*Data analysis.* Wholesale statistics are presented as defined daily doses (DDD) per 1000 inhabitants per day (DDD/1000/day) for the sales of paracetamol (N02BE01), paracetamol + caffeine combinations (N02BE51) and paracetamol + codeine combinations (N02AA59). The DDD for plain paracetamol (N02BE01) is 3 g. The DDD for paracetamol combinations differs between products. Hence, we did not find it meaningful to present the results for plain paracetamol and paracetamol combinations combined. The proportion of plain paracetamol sold by prescription was calculated by dividing the sales by prescription by the total sales of plain paracetamol. The prescription register data were aggregated from individual-level data and presented as users (having filled a prescription for paracetamol) per 1000 inhabitants per year (users/1000 inhabitants/year).

Table 1.

Overview of legislation and restrictions regarding OTC paracetamol sales in the different countries during the study period.

	Available OTC	Available outside of pharmacy	Pack size restrictions	Age restrictions
Denmark	Yes	Yes (from 2002 – onward)	Packages of paracetamol containing $\geq 30$ tablets were labelled with red box warnings alerting users to read the warnings in the package leaflet and to store the medicine in a safe place (from 2004 – onward). Each dispensing of OTC paracetamol was restricted to pack sizes containing a maximum of 10 g (i.e. 20 tablets $\times$ 500 mg) (from 2013 – onward)	OTC sales of paracetamol were restricted to persons aged $\geq 18$ years and at maximum one package per person per day (from 2011 – onward)
Finland	Yes	No	Each dispensing of OTC paracetamol was restricted to pack sizes containing 6 g (12 tablets $\times$ 500 mg) (until 2009). Each dispensing of OTC paracetamol was restricted to pack sizes containing 15 g (i.e. 30 $\times$ 500 mg, 15 $\times$ 1 g) (from 2009 – onward)	
Iceland	Yes	No	Each dispensing of OTC paracetamol restricted to a maximum of 30 tablets (i.e. 30 tablets $\times$ 500 mg or 30 tablets $\times$ 60 mg) or 60 ml of 24 mg/ml per person (current regulations)	
Norway	Yes	Yes (from 2003 – onward)	Each dispensing of OTC paracetamol was restricted to at maximum one package per person per day. Pack sizes containing a maximum of 10 g (i.e. 20 tablets $\times$ 500 mg) (from 1982 – onward).	OTC sales of paracetamol from other outlets than pharmacies were restricted to persons aged $\geq 18$ years (2003 – onward)
Sweden	Yes	No (was available from 2009 to 2015).	Each dispensing of OTC paracetamol was restricted to pack sizes containing 10 g (20 tablets $\times$ 500 mg). (from 2009 – onward)	Some pharmacy retailers have internal guidelines to restrict OTC sales of paracetamol to a maximum one package per person per day for persons aged <18 years.

OTC, Over-the-counter; DDD, defined daily doses.

*Ethical approval.* No ethical approval was needed for this study as the results were based on aggregate-level data only.

## Results

### *Wholesale statistics.*

Total sales of plain paracetamol products (ATC code: N02BE01) increased in all five Nordic countries during 1999–2015 (fig. 1). The sales were highest in Denmark throughout the period, with 50.0 DDD/1000/day in 2000 and 65.1 DDD/1000/day in 2015. The sales were lowest in Finland with 5.7 DDD/1000/day in 2000 and in Iceland in 2015 (30.3 DDD/1000/day). The total sales of paracetamol + codeine combinations (N02AA59) remained stable or decreased during the period (Figure S1). The sales of paracetamol + caffeine (N02BE51) were more frequent in Iceland than in the other Nordic countries (Figure S2).

The amount and proportion of plain paracetamol (N02BE01) sold by prescription increased over time in all Nordic countries. The proportion of paracetamol sold by prescription was highest in Denmark, Finland and Sweden in 2015 (78.3%, 75.5% and 69.1%, respectively; fig. 2). In Norway and Iceland, the proportion of sales by prescription was lower over the entire period (60.7% and 38.5%, respectively, in 2015). In Denmark, there was a large increase in the proportion of paracetamol sold by prescription from 2013 (49.5%) to 2014 (78.5%).

### *Prescription register statistics.*

The number of plain paracetamol users per 1000 inhabitants per year increased in all Nordic countries (fig. 3; data for Iceland not available). In Denmark, there was a limited increase in the percentage of the population using plain paracetamol

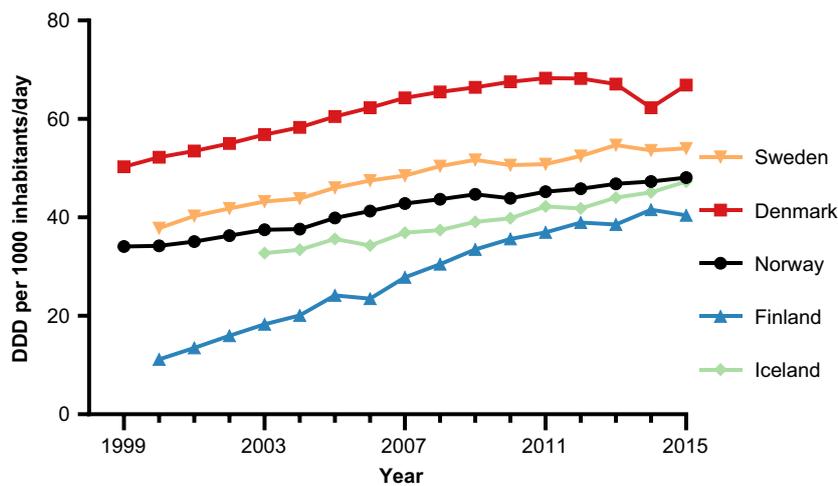


Fig. 1. Total sales of plain paracetamol products (N02BE01) in DDD per 1000 inhabitants/day, all Nordic countries 1999–2015. DDD, defined daily doses.

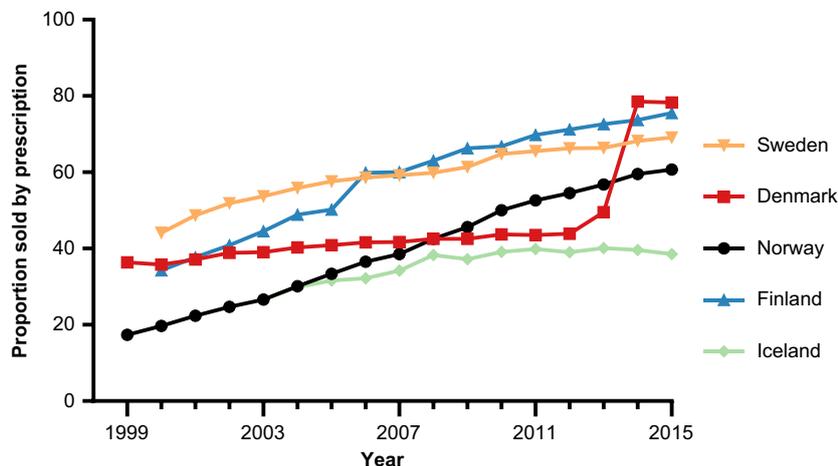


Fig. 2. The proportion of DDD per 1000/day of plain paracetamol products (N02BE01) sold by prescription, all Nordic countries 1999–2015. DDD, defined daily doses.

sold by prescription from 1999 (5.1%) to 2013 (9.6%), followed by a sharp increase to 16.2% in 2014. There was a modest increase from 3.8% (2005) to 8.6% (2015) in Norway and 9.2% (2006) to 11.9% (2015) in Sweden. In Finland, <1% used (reimbursed) paracetamol in 1995, increasing to 12.7% in 2015, with the largest increase between 2005 and 2009.

Prevalence of use of plain paracetamol (N02BE01) by prescription was highest at older ages (table 2). In 2015, the use was highest among those aged 80–84 years in Sweden (40.3%), aged 85+ years in Norway (31.2%) and in Finland (51.0%), and those 80+ years in Denmark (62.4%). The use increased in all age groups between 2006 and 2015, except for those aged 0–9 years in Sweden and 0–4 years in Finland and Denmark. In Sweden, the relative increase was 14–55% across age groups. In Norway, the relative increase was higher and most pronounced in people aged 15–69 years (90–131% increase). In Finland and Denmark, the relative increase was higher, with four times increase in persons aged 15–64 years in Finland and aged 10–39 years in Denmark.

Paracetamol (N02BE01) sales by prescription were more frequent among women than men in all countries and all years (Figure S3). The sex difference diminished over time in all countries, from a female/male ratio of 2.4 in Finland 1995 to between 1.6 and 1.8 in all countries in 2015. The diminishing sex difference in the populations was driven by a more similar paracetamol use pattern by older women and men. In the younger part of the populations (age 10–40 years), the sex differences were increasing as women were increasing their use at a faster rate than men.

## Discussion

The total sales of paracetamol and the proportion of sales by prescription increased in the Nordic countries from 2000 to 2015. Denmark had the highest total sales of plain paracetamol across the entire study period. Women had a higher use

of paracetamol on prescription than men, and the use of paracetamol increased with age in all countries.

Paracetamol is one of the most frequently used analgesics in Europe [1], and we showed that the sales of paracetamol have increased in all Nordic countries. The sales of paracetamol have previously been reported to increase from 2003 to 2009 in Denmark, Norway and Finland [24]. We showed that this trend continued through 2015. In addition, we showed that also Sweden and Iceland shared this upward trend. Similar to previous work, we found that Denmark had the highest use of paracetamol in the Nordic countries [24]. The increase in paracetamol use has been almost parallel in the Nordic countries, with a slight convergence in the latter period, the other Nordic countries are approaching the level of Denmark.

The use of paracetamol is relatively high in the Nordic countries compared to other European countries [1,24], but also France and United Kingdom display high levels of paracetamol use [1,25,26]. All Nordic countries have implemented pack size restrictions of paracetamol, which is in line with policy implementation in most other European countries [27]. Cross-national comparison studies are needed to disentangle if trends in paracetamol use can be explained by the overall levels of analgesic use in the country, or by a preference towards paracetamol compared to other analgesics.

Sales restrictions (age restrictions, pack size restrictions and rules for OTC sales) of paracetamol were enforced in the countries at different time-points, often after reports of paracetamol poisoning becoming more frequent [9,10]. The country variations in sales restrictions were not obviously linked to the level of paracetamol use in the various countries in this study. Sweden, Denmark and Norway have allowed OTC sales of paracetamol outside pharmacies, and these countries also had the highest sales of paracetamol. This could suggest that less restrictive regulations are linked to a higher use; however, the use of paracetamol was higher in these countries also before the OTC sales were implemented. Furthermore, the data presented here do not support any major time-

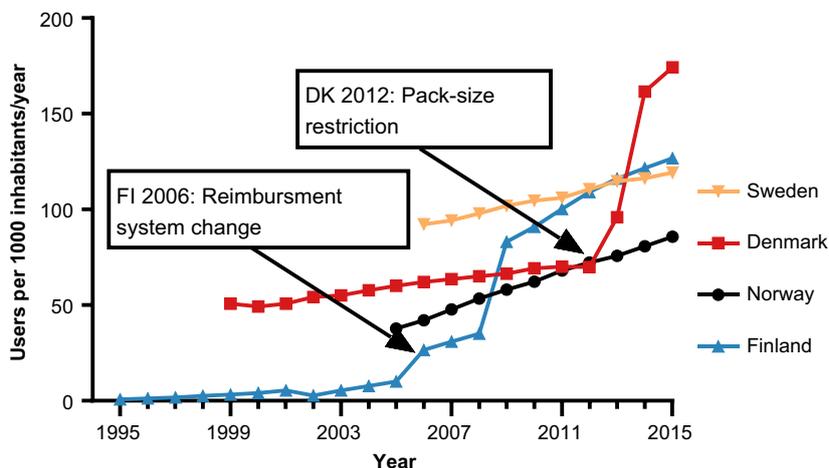


Fig. 3. Users of plain paracetamol products (N02BE01) by prescription per 1000 inhabitants per year, all Nordic countries except Iceland (data not available) 1995–2015.

Table 2. Time trend in users of paracetamol by prescription per 1000 inhabitants per year (N02BE01) by age group, 2006–2015, Sweden, Norway, Finland and Denmark.

	Sweden				Norway				Finland				Denmark <sup>1</sup>			
	2006	2015	Difference <sup>2</sup>	Ratio <sup>3</sup>	2006	2015	Difference <sup>2</sup>	Ratio <sup>3</sup>	2006	2015	Difference <sup>2</sup>	Ratio <sup>3</sup>	2006	2015	Difference <sup>2</sup>	Ratio <sup>3</sup>
	0-4	13.2	5.9	-7.2	0.45	2.6	4.1	1.5	1.60	0.2	0.1	-0.1	0.50	11.0	10.4	-0.6
5-9	11.1	6.2	-5.0	0.55	1.8	3.3	1.5	1.81	2.7	2.9	0.2	1.07	2.3	5.3	3.0	2.26
10-14	7.4	8.4	1.1	1.14	2.8	5.1	2.2	1.79	5.7	18.2	12.5	3.19	1.9	13.9	12.0	7.40
15-19	16.7	25.4	8.7	1.52	8.8	19.5	10.6	2.20	6.8	47.6	40.8	7.00	4.1	39.0	34.9	9.61
20-24	25.1	36.6	11.5	1.46	14.0	32.4	18.3	2.31	8.2	66.2	58.0	8.07	6.5	63.4	56.9	9.72
25-29	31.9	49.5	17.6	1.55	19.1	40.0	20.9	2.10	11.0	81.1	70.1	7.37	9.5	88.6	79.1	9.30
30-34	42.1	62.6	20.5	1.49	25.4	50.8	25.4	2.00	13.6	91.9	78.3	6.76	14.6	112.6	98.1	7.74
35-39	55.1	74.9	19.8	1.36	34.1	64.9	30.8	1.90	14.2	97.1	82.9	6.84	21.7	137.6	115.9	6.34
40-44	71.4	89.0	17.6	1.25	40.4	83.1	42.7	2.06	15.1	104.3	89.2	6.91	32.7	166.3	133.6	5.08
45-49	82.6	109.1	26.5	1.32	45.3	101.6	56.3	2.24	17.5	116.6	99.1	6.66	44.5	192.6	148.1	4.33
50-54	96.7	139.1	42.4	1.44	52.0	115.7	63.8	2.23	21.7	131.6	109.9	6.06	60.8	225.3	164.5	3.71
55-59	109.1	157.4	48.3	1.44	59.2	128.1	68.9	2.16	26.9	150.7	123.8	5.60	75.1	247.5	172.4	3.29
60-64	135.9	176.9	41.1	1.30	64.6	141.5	76.9	2.19	32.4	165.0	132.6	5.09	95.9	263.5	167.6	2.75
65-69	159.8	190.4	30.6	1.19	75.2	151.9	76.7	2.02	46.6	182.5	135.9	3.92	136.1	293.9	157.8	2.16
70-74	197.4	250.1	52.7	1.27	93.1	170.9	77.8	1.84	68.3	228.1	159.8	3.34	187.6	354.9	167.3	1.89
75-79	256.7	323.5	66.9	1.26	118.8	216.3	97.5	1.82	96.1	309.6	213.5	3.22	250.1	431.4	181.3	1.72
80-84	332.9	402.6	69.7	1.21	152.0	267.5	115.5	1.76	132.9	394.2	261.3	2.97	340.8	505.0	164.3	1.48
85+	81.2	106.8	25.6	1.32	183.6	312.2	128.6	1.70	180.5	510.3	329.8	2.83	503.1	624.4	121.3	1.24

<sup>1</sup>Derived from 1-year age groups (divided by the number of age categories).

<sup>2</sup>Calculated by subtracting the value of 2015 from the value of 2006.

<sup>3</sup>Calculated by dividing the value of 2015 by the value of 2006.

specific influence of the restrictions on the sales of paracetamol. The one exception was the large increase in the proportion of paracetamol sales by prescription from 2013 to 2014 in Denmark. This was most likely due to a legislative change, where larger pack sizes of paracetamol were restricted to prescription only in Denmark in September 2013. Another notable change in the trend in paracetamol use was the rapid increase in number of users of paracetamol by prescription in Finland between 2005 and 2009. The increase began in 2005 and is partly linked to a change in the Finnish reimbursement system for drugs. Before 2006, Finnish patients had to pay a fixed non-reimbursable sum (10 Euro in 2005) per purchase. This meant that products cheaper than the fixed deductible were not reimbursed and recorded in the Finnish register. In 2006, the deductible was abolished and the coverage of the Finnish prescription register improved. Partly the increase might also be due to changes in reimbursement status of paracetamol products in the Finnish drug reimbursement system.

In the Nordic countries, prescription paracetamol was most commonly used by people aged 80 years and older. The high use of prescription paracetamol among older adults is likely explained by high levels of chronic pain at these ages, combined with high rates of comorbidities. In the Nordic model for reimbursement of medications, the high use of drugs in old age will channel older adults towards the use of prescription paracetamol rather than OTC paracetamol, to reduce out-of-pocket expenses. In addition, the frequent administration of drugs via multi-dose dispensing (portion-packed plastic pouches) in older adults in the Nordic countries has been linked to a lack of re-evaluation (and discontinuation) of drug treatments [28] and could also add to the high levels of prescription paracetamol use in older adults. If paracetamol for chronic use indeed has a negative effect on liver function as has been suggested [4,5], caution is needed when prescribing paracetamol to older adults for whom physiological changes in the ageing body make them more sensitive to the toxic effects of drugs [29]. We also found a higher use of paracetamol in women than in men, although this sex difference was decreasing over time. This is in line with earlier research showing more frequent reporting of pain in women [30] and a higher use of analgesics [31]. Interestingly, the reduced sex difference was only apparent in the older population, whereas the sex difference actually increased in people aged 10–40 years. This is in line with previous reports of an increasing use of paracetamol among younger women [9].

Paracetamol is the first-line treatment for many pain conditions [2], thereby contributing to the high levels of paracetamol use. Recent studies have questioned the efficacy of paracetamol for some of its main indications and the safety of high-dosage paracetamol [4,5]. However, lowering the use of paracetamol is difficult as safe pharmaceutical alternatives are lacking, especially in the elderly population and those with cardiac comorbidity, for which non-steroidal anti-inflammatory drug and opioids are advised against [32,33]. The continuously increasing sales of paracetamol in the Nordic countries should be closely monitored in the future.

### *Strengths and limitations.*

The main strength of this study was the use of nationwide data, including both the high-quality drug registers (used as aggregated data) and wholesale data [17–20,34]. The wholesale data were available from all Nordic countries, and aggregate-level data from prescription registers were available from all Nordic countries except Iceland. However, there are some noteworthy limitations. The national drug formularies were different in the countries. In this study, we focused on plain paracetamol, and to a lesser extent paracetamol combinations with either caffeine or codeine as these were the most frequently sold paracetamol combinations. Some paracetamol combinations, which were only available in a specific country or during a limited time period, are not included in the study. Hence, the total sales of paracetamol in the Nordic countries during 1999–2015 were underestimated in our data. Different measurement units were used when presenting results from wholesale data and national prescription registers, which limits the possibility of making comparisons between the two data sources. However, we believe that combining the two units provides an added value. The total sales unit ‘DDD per 1000 inhabitants/day’ can change because either an increasing proportion of the population is prescribed paracetamol and/or because of an increase in the amount of paracetamol prescribed to the pre-existing paracetamol users. While for the individual-based unit ‘users per 1000 inhabitants per year’, we know that the measurement unit is strictly related to changes in the proportion of users in the population.

### **Conclusion**

The sales of plain paracetamol increased in all Nordic countries over the last decades. Cross-national differences existed, with highest sales per capita in Denmark throughout the period. The share of paracetamol by prescription also rose in all countries during the study period. Older people were the main users of paracetamol by prescription, and women used more paracetamol than men.

### **Conflict of Interest**

The authors have no conflict of interest to declare.

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### 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.