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REVIEW

Psychotropic drug use among children and adolescents in the Nordic countries: a systematic review

D. R. Ollerup[1] · L. Rasmussen[1] · S. L. Elkrog[1] · M. H. Stoltz-Andersen[1] · H. Stubmark[1] · R. Wesselhoeft[1,2]

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Abstract

The Nordic countries have rather homogenous populations and similar health care systems, and one could therefore expect comparable levels of psychopathology and psychotropic drug use. However, recent studies show pronounced variations in psychotropic drug use among children and adolescents from different Nordic countries. Therefore, we aimed to conduct a systematic review of the literature examining the use of psychotropic drugs among children and adolescents in the Nordic countries. This review followed PRISMA guidelines. We searched PsycINFO, EMBASE and MEDLINE for population-based studies published 2010 or later that investigated prevalent or incident use of antidepressants, psychostimulants, antipsychotics, hypnotics, anxiolytics, and mood stabilizers among 0–19-year-olds in the Nordic countries. Two reviewers assessed all studies. Twenty-two out of 2142 eligible studies were included in the final review covering data collected from 1995 to 2018. The use of psychotropic drugs, except for anxiolytics, increased in most of the Nordic countries, but at different rates. Prevalent use of antidepressants was two to four times higher among Swedish children and adolescents compared to Danish and Norwegian peers. Prevalent use of psychostimulants, on the other hand, was two to sixfold higher in Iceland compared to the other Nordic countries. Finally, the prevalence of antipsychotic use was threefold higher in Finland compared to Sweden, Denmark, and Norway. This systematic review provides a thorough overview of psychotropic treatment of youths in the Nordic countries. We demonstrate a pronounced national variation in use of psychotropics that should be addressed further to facilitate rational pharmacotherapy in youths with psychiatric disorders.

Keywords Psychotropic drugs · Children and adolescents · Drug utilization · Nordic countries

Introduction

Mental disorders have been ranked as the main contributors to disease burden among children in the Nordic countries from 1990 to 2019 [1]. In 2019, approximately one out of ten youths worldwide were estimated to have a mental disorder, and this ranged from 12 to 14% in the Nordic countries [2]. First-line treatment for childhood mental disorders are non-pharmacological interventions, but when these are considered insufficient, psychotropic drugs are used in addition [3–6]. There has been an increase in psychotropic drug use among children and adolescents throughout the last decades [7–9] but the extent of use varies markedly across pediatric populations [7–11]. A study comparing prevalent use of antipsychotics between 16 countries in 2013 found as much as a 62-fold difference between youths from Lithuania and Taiwan who had the lowest and highest use, respectively [7]. Recent Nordic comparison studies also show a pronounced national variation in psychotropic drug use and trends over time [7, 8, 12–14], regardless of quite homogeneous populations, cultures, and free access to tax-financed health care services [15, 16]. The variation in psychopharmacological treatment in populations otherwise considered comparable, is not directly understood. It could rely on national variation in prevalence proportions of mental disorders, clinical decision making, or access to mental health care specialists. A systematic review of the literature will provide detailed information on the extent of variation in psychotropic drug use between the Nordic countries and broaden our understanding of these differences.

✉ R. Wesselhoeft
rwesselhoeft@health.sdu.dk

[1] Clinical Pharmacology, Pharmacy and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark

[2] Child and Adolescent Psychiatry, Mental Health Services in the Region of Southern Denmark, Odense, Denmark

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Therefore, we aimed to conduct a systematic review of the literature outlining descriptive measures (prevalence, incidence, and time trends) of psychotropic drug utilization among children and adolescents aged 0–19 years in the five Nordic countries; Sweden, Denmark, Norway, Finland, and Iceland, including the three autonomous islands (Greenland, the Faroe Islands, and the Åland Islands).

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines [17]. The protocol (identification number: CRD42022309202) was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/PROSPERO/).

Search strategy

We systematically searched three scientific databases: MEDLINE (Ovid), PsycINFO (Ovid), and EMBASE (Ovid). The search strings (Online Resource 1) were composed in collaboration with a librarian from University of Southern Denmark and followed the Population, Comparison, Outcome – model (PCO-model) [18]. Two filters, English language and publication date between January 1st, 2010, and November 5th, 2021, were added before references were imported to Covidence (https://www.covidence.org/).

The studies were eligible for inclusion if all six inclusion criteria (IC) were fulfilled (Table 1).

The review process and data extraction

The review process consisted of three phases: (1) Screening of titles and abstracts, (2) Full-text screening, and (3) Data extraction, including quality assessment. The three phases were performed independently by the authors DRO, SLE, MHS-A and HS in pairs following Preferred Reporting Items for Reviews and Meta-Analyses (PRISMA) guidelines to enhance objectivity and avoid exclusion of relevant studies [17]. DRO and RW made the final decisions if disagreement occurred between reviewers regarding study inclusion. The authors were contacted if additional information was needed to decide whether inclusion criteria were fulfilled. If no response was received after three e-mail contacts, the study was excluded.

Data was extracted using Covidence and later transferred to Microsoft® Excel®. We extracted the following data: General information (authors, publication title, year of publication, aim), study characteristics (country, design, study period, sample size, sample age range, male/female ratio, nationwide sample (yes/no), data source, drug classes studied), study outcomes of drug utilization (measures of prevalence or incidence, time trends, male/female ratio), potential conflicts of interest and study conclusions.

Quality assessment was performed independently by DRO, SLE, MHS-A and HS in pairs according to "Quality Assessment for Observational Cohort and Cross-Sectional Studies" developed by National Heart, Lung, and Blood Institute [19]. Due to the focus on descriptive drug utilization measures, we excluded quality assessment sections related to intervention studies (exposures and outcomes), leaving us with six sections (Table 3). If disagreement occurred regarding the collected data, a consensus decision was made between DRO and RW.

Pilot test

Two inter-rater reliability tests were performed by the reviewers (DRO, SLE, MHS-A, HS and RW) prior to initiation of the review to ensure satisfactory agreement on study inclusion. The interrater reliability tests were performed on titles and abstracts from 20 randomly selected references.

Table 1 Inclusion criteria

Inclusion criteria	
IC1	Children and adolescents ≤ 19 years old[1]
IC2	Nordic country (Denmark, Sweden, Norway, Finland, Iceland, Greenland, the Faroe Islands and/or the Åland Islands)
IC3	Psychotropic drugs (antidepressants, psychostimulants, antipsychotics, hypnotics, anxiolytics and/or mood stabilizers)[2]
IC4	Population-based study
IC5	Drug utilization study, cross-sectional study, longitudinal study, or cohort study[3]
IC6	Original data

Online Resource 2 provides a detailed list of inclusion and exclusion criteria

[1]The study was excluded if any in the study population were aged above 19 years

[2]The study was excluded if psychotropic drugs were not classified as any of these drug classes, for instance if anti-epileptics and antihistamines were not classified as mood stabilizers or hypnotics

[3]In the full-text screening, we excluded studies that described use of psychotropic drugs in selected cohorts in an undefined study period

The required agreement between all reviewers was set to Cohen's $\kappa > 0.6$, which corresponded to "substantial" [20, 21] prior to screening initiation. Minor specifications were made to the inclusion criteria between the two inter-rater reliability tests.

Results

The first inter-rater reliability test provided Cohen's κ-values between 0.32 and 1.00. The second inter-rater reliability test provided Cohen's κ-values between 0.83 and 1.00, indicating an "almost perfect to perfect" agreement [20].

The literature search generated 2,142 eligible studies, of which 301 were duplicates. A total of 1,636 studies were excluded in the first screening phase and 183 studies were excluded in the second, leaving 22 studies for final inclusion (Fig. 1).

Study characteristics

The 22 included studies covered data collected within the time period from 1995 to 2018. Three studies examined psychotropic drug use in more than one Nordic country. Norway was the most frequently represented country with ten studies, followed by Denmark (n = 8), Finland (n = 6), Sweden (n = 5), and Iceland (n = 1). No studies covered data from the three autonomous islands (Greenland, the Faroe Islands, and the Åland Islands).

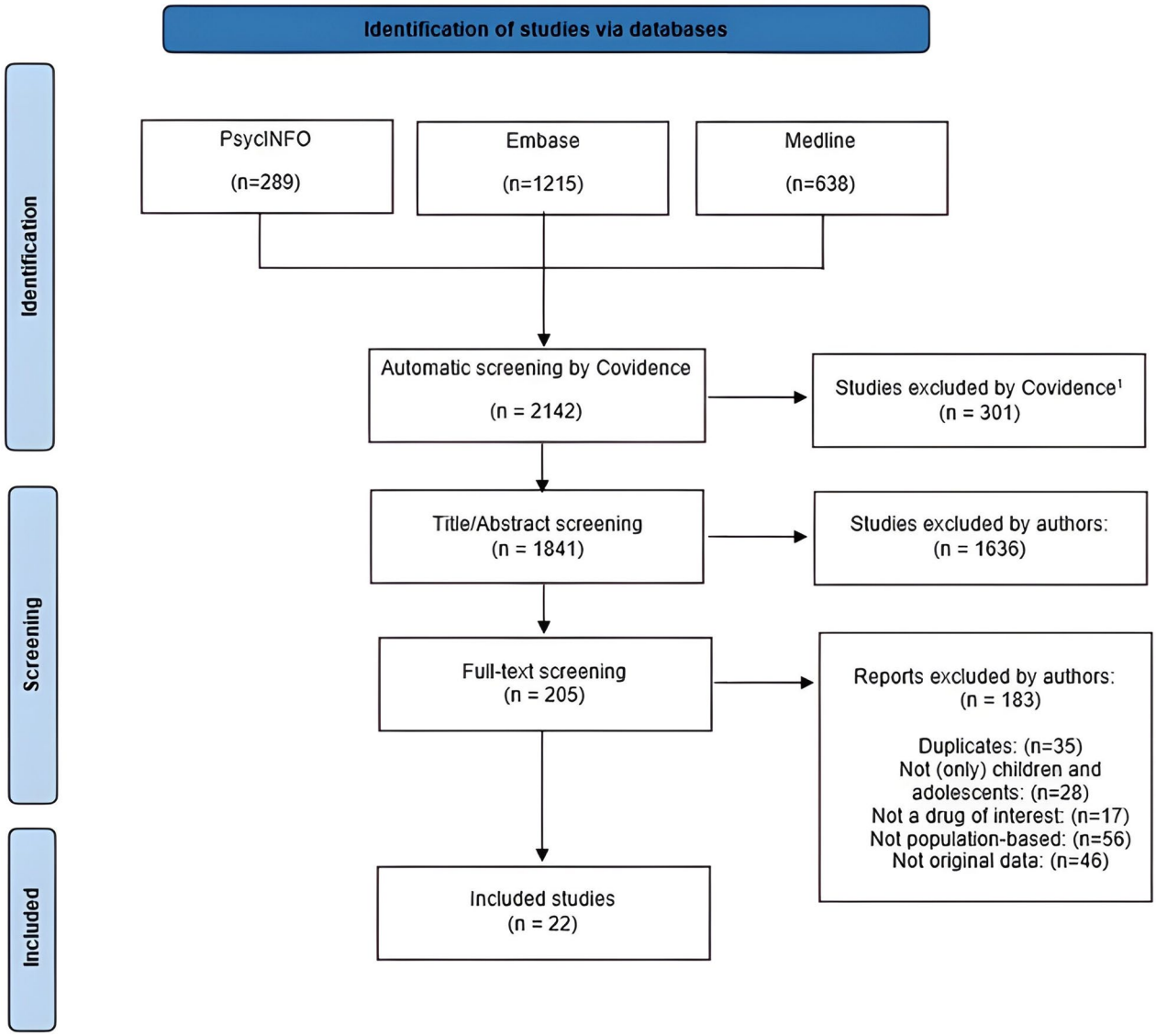

Fig. 1 Flow chart. [1]Duplicates identified by Covidence and double-checked by the first author (DRO). Flow chart created in Microsoft Office

Most studies (n = 18) reported the use of a single psychotropic drug class, while four studies reported the use of several psychotropic drug classes. Antidepressants was the most examined drug class (n = 10), followed by hypnotics (n = 9), antipsychotics (n = 6), psychostimulants (n = 5) and anxiolytics (n = 3). No studies examined the use of mood-stabilizers. All studies, except one, examined trends in drug use over time, and all were based on nationwide health care registers covering an entire population (i.e., nationwide sample). Drug use was mostly reported as prevalence proportions (n = 17), followed by incidence rates (n = 8), and the numeric numbers of new users (n = 1) (Table 2).

All included studies were considered of high quality (Table 3) with the most frequent quality limitation being missing information about population size. However, since all included studies were based on the entire population size justification or power calculations were irrelevant.

Combined psychotropic drug classes

Prevalence

One study examined prevalent use of a any psychotropic drug defined as use of antidepressants, psychostimulants, antipsychotics, anxiolytics, sedatives, or hypnotics among three Nordic countries from 2008 to 2017 [13]. It showed an increase in use of psychotropic drugs among Swedish 0–19-year-olds (153%), Danish 0–17-year-olds (58%) and Norwegian 0–19-year-olds (44%) [13]. Similarly, two Norwegian studies found a general increase in psychotropic drug use [22, 23]. One examined the prevalence of any psychotropic drug defined as use of alimemazine, hypnotics, sedatives, psychostimulants, antidepressants, antipsychotics, or anxiolytics and found an increase among Norwegian boys (31 to 35/1000) and girls (19 to 25/1000) under 18 years from 2004 to 2014 [22]. The other looked specifically at 15–16-year-olds and showed an increase in prevalent use of hypnotics, antidepressants and anxiolytics combined from 2006 to 2010 among boys (14 to 22/1000) and girls (20 to 25/1000) [23] (Fig. 2).

Antidepressants

Prevalence

Eight studies examined the prevalent use of antidepressants in Sweden, Denmark, Norway, and Finland, either separately or comparing across countries. Overall, the studies found that prevalent use of antidepressants increased markedly in Sweden and Finland, and to a smaller extent in Norway, whereas it decreased in Denmark after 2010 [11, 13, 14, 22–25].

Two studies compared antidepressant use across countries among 0–17- or -19-year-olds [13] and 5–19-year-olds [14] and found that the prevalence was at least twofold higher among Swedish youths (14/1000 and 18/1000) compared to Norwegian (6/1000 and 8/1000) and Danish (4/1000 and 8/1000) youths in 2017 [13, 14]. Furthermore, there was a steeper increase in antidepressant use in Sweden (91%) than in Norway (43%) from 2008 to 2017 [13].

In Norway, the prevalence of antidepressant use increased from 6.4/1000 in 2004 to 9.1/1000 in 2013 among 13–17-year-olds [24], while it increased from 6.0/1000 in 2006 to 7.0/1000 in 2010 among 15–16-year-olds [23]. A third Norwegian study examined the prevalence among youths under 18 years from 2004 to 2014 and found a threefold increase among girls (3.1 to 10.0/1000) while use was rather stable among boys (2.1 to 2.0/1000) [22]. In Finland, prevalent use of antidepressants increased from 2.2/1000 in 1998 to 5.9/1000 in 2005 among 0–19-year-olds [25]. In Denmark, on the other hand, there was a 60% increase in antidepressant use among 0–19-year-olds from 2005 to 2012 [11] and an approximate 33% increase in use of selective serotonin reuptake inhibitors (SSRIs) among 5–17-year-olds from 1995 to 2011 [26], followed by a decrease after 2010 [11, 13, 14]. This decrease led to an overall decrease by 31% among Danish 0–17-year-olds [13].

The prevalence of antidepressant use was approximately twice as high among girls compared to boys [11, 13, 14, 22–24, 26] and it increased with age [11, 13, 14, 22, 24, 26] (Fig. 3).

Incidence

Four studies examined incident use of antidepressants over time in Denmark, Norway, or Finland [24–27]. In Norway, the rates of new users increased slightly among boys from 2007 to 2013, whereas it increased among girls from 2009 [24]. A Finnish study found an increase in incident antidepressant use from 1999 to 2005 among 0–19-year-olds rising from 2.0 to 3.1/1000 person years [25]. The use of SSRIs increased from 1.0/1000 person years in 1999 to 1.6/1000 person years in 2004 among Finnish 0–17-year-olds and peaked in 2003 with 1.8/1000 person years [27]. In Denmark, incident SSRI use increased markedly among 5–17-year-olds from 1997 to 2010 (0.6 to 3.3/1000 person years) followed by a decrease to 2.6/1000 person years in 2011, where the study period ended [26].

Sex differences reflected those observed for prevalent use with approximately twice as many girls initiating antidepressant use compared to boys, and with a rising incidence with increasing age among both sexes [24, 26, 27]. A Danish study examined median age at first prescription of antidepressants and found that it was slightly lower for boys (15 years) than girls (16 years) [28].

Table 2 Characteristics of included studies

#	1st author, year of publication	Age range	Country (population size)	Study period	Psychotropic drug classes	Prevalence[1, 3]	Incidence[2,3]	Time trend
Combined psychotropic drugs								
1	Gomez-Lumbreras A, 2021 [13]	0–19 years	Sweden (-)	2008–2017	Antipsychotics, antidepressants, psychostimulants, anxiolytics, hypnotics, sedatives	♂♀: 26.1;66.1*	–	♂♀: + 152.8%
		0–17 years	Denmark (-)	2008–2017	Antipsychotics, antidepressants, psychostimulants, anxiolytics, hypnotics, sedatives	♂♀: 19.8;31.3*	–	♂♀: + 58.2%
		0–19 years	Norway (-)	2008–2017	Antipsychotics, antidepressants, psychostimulants, anxiolytics, hypnotics, sedatives	♂♀: 30.1;43.3*	–	♂♀: + 43.9%
2	Hartz I, 2016 [22]	0–17 years	Norway (1.1 million)	2004–2014	Alimemazine, hypnotics, sedatives, stimulants, antidepressant, antipsychotics, anxiolytics	♂: 30.6;35.3 ♀: 19.2;25.0	–	–
3	Steffenak A.K.M, 2012 [23]	15–16 years	Norway (128.012)	2006, 2008, 2010	Hypnotics, antidepressant, anxiolytics	♂: 13.9;21.5 ♀: 19.7;24;7	–	–
Antidepressants								
1	Bachmann C.J, 2016 [11]	0–19 years	Denmark (1.203.817)	2005–2012	Antidepressants	♂♀: 6.1;9.8 ♂: 4.0;6.2 ♀: 8.3:13.5	–	♂♀: + 60.5%
2	Foulon V, 2010 [25]	0–19 years	Finland (27.676)	1998, 2002, 2005	Antidepressants	♂♀: 2.23;5.93	♂♀: 2.01;3.12	–
3	Gomez-Lumbreras A, 2021 [13]	0–19 years	Sweden (-)	2008–2017	Antidepressants	♂♀: 7.18;13.68 ♂: 5.06;9.33 ♀: 9.43;18.33	–	♂♀: + 90.5%*
		0–17 years	Denmark (-)	2008–2017	Antidepressants	♂♀: 4.49;3.1 ♂: 3.08;2.3 ♀: 5.98;4.11	–	♂♀: -30.9%
		0–19 years	Norway (-)	2008–2017	Antidepressants	♂♀: 4.17;5.95 ♂: 2.95;3.58 ♀: 5.46;8.45	–	♂♀: + 42.7%*
4	Hartz I, 2016 [24]	13–17 years	Norway (-)	2004–2013	Antidepressants	♂♀: 6.4;9.1	*♂: 2.5;3.25* *♀: 5.2;7.7*	–
5	Hartz I, 2016 [22]	0–17 years	Norway (1.1 million)	2004–2014	Antidepressants	♂: 2.1;2.0 ♀: 3.1;10.0	–	–
6	Pottegård A, 2014 [26]	5–17 years	Denmark (838.000[4])	1995–2011	Antidepressants (SSRI)	Point prevalence: ♂♀: 0.1;3.3	Incidence-rate ♂♀: 0.57;2.55	–

Table 2 (continued)

#	1st author, year of publication	Age range	Country (population size)	Study period	Psychotropic drug classes	Prevalence[1, 3]	Incidence[2,3]	Time trend
7	Steffenak A.K.M, 2012 [23]	15–16 years	Norway (128.012)	2006, 2008, 2010	Antidepressants	♂: *6.0;7.1* ♀: 7.8;9.0		–
8	Saastamoinen L.K, 2012 [27]	0–17 years	Finland (10.376)	1999–2004	Antidepressants (SSRI)	-	♂♀: 0.10%-0.16%*	–
9	Wesselhoeft R, 2020 [14]	5–19 years	Sweden (1.693.565)	2007–2017	Antidepressant	♂♀: 8.98;18.03	–	–
			Denmark (1.012.855)	2007–2017	Antidepressant	♂♀: 9.27;7.52	–	–
			Norway (959.237)	2007–2017	Antidepressant	♂♀: 5.08;7.6	–	–
10	Nielsen E.S, 2017 [28]	0–17 years	Denmark (29,851)	2006–2012	Antidepressants	–	–	–
Psychostimulants								
1	Bachmann C.J, 2017 [30]	0–19 years	Denmark (1.203.817)	2005–2012	Psychostimulants	♂♀: 3.8;15.4* ♂: 6.2;22.2 ♀: 1.3;8.3	–	♂♀: + 302.7%
2	Furu K, 2017 [29]	0–17 years	Sweden (1.92 million)	2008–2012	Psychostimulants	♂♀: 8.18;16.62* ♂: 12.26;23.41* ♀: 3.88;9.44*	♂: 5.56;5.94*[5] ♀: 2.30;4.82*[5]	–
			Denmark (1.2 million)	2008–2012	Psychostimulants	♂♀: 8.21;13.54* ♂: 12.79;19.93* ♀: 3.39;6.82*	♂: 6.00;4.75*[5] ♀: 1.90;2.48*[5]	–
			Norway (1.12 million)	2008–2012	Psychostimulants	♂♀: 13.69;15.03* ♂: 17.79;21.23* ♀: 7.28;8.51*	♂: 6.14;5.94*[5] ♀: 3.27;3.13*[5]	–
			Finland (1.08 million)	2008–2012	Psychostimulants	♂♀: 4.57;8.80* ♂: 7.74;14.53* ♀: 1.27;2.81*	♂: 3.47;6.14*[5] ♀: 0.68;1.58*[5]	–
			Iceland (0.08 million)	2008–2012	Psychostimulants	♂♀: 30.70;38.94* ♂: 45.82;55.11* ♀: 14.95;22.00*	♂: 13.99;16.99*[5] ♀: 5.03;8.49 *[5]	–
3	Gomez-Lumbreras A, 2021 [13]	0–19 years	Sweden (-)	2008–2017	Psychostimulants	♂♀: 7.66;22.17 ♂: 11.36;29.3 ♀: 3.762;14.556	–	♂♀: + 189.4%
		0–17 years	Denmark (-)	2008–2017	Psychostimulants	♂♀: 8.09;13.54 ♂: 12.63;19.10 ♀: 3.312;7.697	–	♂♀: + 67.4%*
		0–19 years	Norway (-)	2008–2017	Psychostimulants	♂♀: 13.25;15.72 ♂: 18.97;21.59 ♀: 7.236;9.513	–	♂♀: + 18.6%*
4	Hartz I, 2016 [22]	0–17 years	Norway (1.1 million)	2004–2014	Psychostimulants	♂: 15.0;20.8 ♀: 3.8;8.5	–	♂: + 40% ♀: + 120%

Table 2 (continued)

#	1st author, year of publication	Age range	Country (population size)	Study period	Psychotropic drug classes	Prevalence[1, 3]	Incidence[2,3]	Time trend
5	Vuori M, 2020 [31]	6–17 years	Finland (-)	2008–2018	Psychostimulants	♂ Age 6–12: 1.26%;4.42% ♂ Age 13–17:0.93%; 4.21% ♀ Age 6–12: 0.21%: 0.99% ♀ Age 13–17:0.14%: 1.28%	–	–
Antipsychotics								
1	Gomez-Lumbreras A, 2021 [13]	0–19 years	Sweden (-)	2008–2017	Antipsychotics	♂♀: 1.77;2.79 ♂: 1.99;3.01 ♀: 1.54;2.55	–	♂♀: + 57.6%
		0–17 years	Denmark (-)	2008–2017	Antipsychotics	♂♀: 2.47;2.40 ♂: 2.98;2.53 ♀: 1.94;2.27	–	♂♀: -2.8%
		0–19 years	Norway (-)	2008–2017	Antipsychotics	♂♀: 2.24;3.25 ♂: 2.61;3.22 ♀: 1.84;3.29	–	♂♀: + 45.1%
2	Hartz I, 2016 [22]	0–17 years	Norway (1.1 million)	2004–2014	Antipsychotics	♂: 1.6;2.2 ♀: 1.1;1.6	–	–
3	Kalverdijk L.J, 2017 [33]	0–19 years	Denmark (-)	2005–2012	Antipsychotics	♂♀: 2.6;4.8 ♂: 3.1;5.6 ♀: 2.2;4.0	–	♂♀: + 83.9%
4	Nesvåg R, 2016 [34]	0–18 years	Norway (1.174.347)	2010	Antipsychotics	♂♀: 1.8 ♂: 2.3 ♀: 1.3	–	–
5	Varimo E, 2021 [35]	1–17 years	Finland (70.012)	2008–2017	Antipsychotics (SGA)	–	–	–
6	Varimo E, 2020 [32]	1–17 years	Finland (26.353)	2008–2017	Antipsychotics	*♂♀: 4.7;9.2* *♂: 5.3;9.3* *♀: 3.7;9.2*	♂♀: 2.1;3.8 *♂: 2.2;3.1* *♀: 1.9;4.5*	–
Anxiolytics/Hypnotics								
1	Furster C, 2015 [39]	0–19 years	Sweden (-)	2006–2013	Hypnotics (Melatonin)	–	Number of new users *♂ Age 0–4: 100* [3] *♂ Age 5–9: 850* [3] *♂ Age 10–14: 1600* [3] *♂ Age 15–19: 1700* [3] *♀ Age 0–4: 50* [3] *♀ Age 5–9: 275* [3] *♀ Age 10–14: 750* [3] *♀ Age 15–19: 2000* [3]	–

Table 2 (continued)

#	1st author, year of publication	Age range	Country (population size)	Study period	Psychotropic drug classes	Prevalence[1, 3]	Incidence[2,3]	Time trend
2	Gomez-Lumbreras A, 2021 [13]	0–19 years	Sweden (-)	2008–2017	Anxiolytics/ Hypnotics	♂♀: 11.47;33.36 ♂: 10.16;31.88 ♀: 12.86;34.93	–	♂♀: + 190.8%
		0–17 years	Denmark (-)	2008–2017	Anxiolytics/ Hypnotics	♂♀: 4.72;12.15 ♂: 4.73;10.69 ♀: 4.73; 13.53	–	♂♀: + 157.4%*
		0–19 years	Norway (-)	2008–2017	Anxiolytics/ Hypnotics	♂♀: 12.03;20.75 ♂: 12.56;20.72 ♀: 11.46;20.79	–	♂♀: + 72.5%*
3	Hartz I, 2012 [36]	0–17 years	Norway (1.089.158)	2004–2011	Hypnotics	♂♀: 8.94;12.32	–	♂♀: + 30 + %
4	Hartz I, 2015 [37]	4–17 years	Norway (869.989)	2004–2012	Hypnotics (Melatonin)	♂: 3.4;11.0 ♀: 1.5;7.7	–	–
5	Hartz I, 2016 [22]	0–17 years	Norway (1.1 million)	2004–2014	Anxiolytics	♂: 4.7;3.9 ♀: 4.5;3.9	–	–
					Hypnotics	♂: 4.2;10.8 ♀: 2.6;8.8	–	–
6	Holdø I, 2013 [40]	0–35 months	Norway (59.325)	2008–2010	Hypnotics (Alimemazine)	–	3-year incidence: ♂♀: 30 ♂: 34 ♀: 26	–
7	Kimland E.E, 2020 [38]	0–17 years	Sweden (2.099.005)	2006–2017	Hypnotics (Melatonin)	♂: 1.3;19.2 ♀: 0.7;15.2	♂: 1.3;8.2 ♀: 0.7;7.9	–
8	Steffenak A.K.M, 2012 [23]	15–16 years	Norway (128.012)	2006, 2008, 2010	Anxiolytics	♂: 2.3;2.3 ♀: 3.7;3.4	–	–
					Hypnotics	♂: 9.3:17.3 ♀: 11.7;17.4	–	–
9	Nielsen E.S, 2017 [28]	0–17 years	Denmark (29,851)	2006–2012	Hypnotics	–	–	–

[1]One-year prevalence in per 1000, unless otherwise is stated

[2]One-year incidence in per 1000, unless otherwise is stated

[3]First year; last year

[4]On average through the study years

[5]Among 6–17 year-olds

♂ = data for boys

♀ = data for girls

♂♀ = data for both genders

– = not reported

Italic: extracted from figures

* = values provided by author

Psychostimulants

Prevalence

Five studies examined prevalent use of psychostimulants in a least one Nordic country, and all showed an increase over time [13, 22, 29–31]. A study comparing the five Nordic countries, showed that Iceland had the highest prevalent use among 0–17-year-olds (39/1000 in 2012, numbers provided by authors), which was minimum twofold higher than the proportions reported in other countries [29]. The lowest prevalent use of psychostimulants was found among Finnish youths (2012: 8.8/1000) [29]. Another comparison study found a higher use of psychostimulants in Sweden (0–19 years: 22/1000) in 2017, than in Norway (0–19 years: 16/1000) and Denmark (0–17 years: 14/1000), and the

Table 3 Quality assessment of included studies using "Quality Assessment for Observational Cohort and Cross-Sectional Studies" developed by National Heart, Lung, and Blood Institute

1st author, year of publication	Q^1	Q^2	Q^3	Q^{4a}	Q^{4b}	Q^5
Bachmann C.J, 2017 [30]	✓	✗	✓	✓	✓	–
Bachmann C.J, 2016 [11]	✓	✗	✓	✓	✓	–
Foulon V, 2010 [25]	✓	✓	✓	✓	✓	–
Furster C, 2015 [39]	✓	✗	✓	✓	✓	–
Furu K, 2017 [29]	✓	✓	✓	✓	✓	–
Gomez-Lumbreras A, 2021 [13]	✓	✓	✓	✓	✓	–
Hartz I, 2012 [36]	✓	✓	✓	✓	✓	–
Hartz I, 2015 [37]	✓	✓	✓	✓	✓	–
Hartz I, 2016 [24]	✓	✗	✓	✓	✓	–
Hartz I, 2016 [22]	✓	✓	✓	✓	✓	–
Holdø I, 2013 [40]	✓	✓	✓	✓	✓	–
Kalverdijk LJ, 2017 [33]	✓	✗	✓	✓	✓	–
Kimland EE, 2021 [38]	✓	✓	✓	✓	✓	–
Nesvåg R, 2016 [34]	✓	✓	✓	✓	✓	–
Nielsen ES, 2017 [28]	✓	✓	✓	✓	✓	–
Pottegård A, 2014 [26]	✓	✓	✓	✓	✓	–
Steffenak AKM, 2012 [23]	✓	✓	✓	✓	✓	–
Saastamoinen LK, 2012 [27]	✓	✓	✓	✓	✓	–
Varimo, 2021 [35]	✓	✓	✓	✓	✓	–
Varimo, 2020 [32]	✓	✓	✓	✓	✓	–
Vuori M, 2020 [31]	✓	✗	✓	✓	✓	–
Wesselhoeft, 2020 [14]	✓	✓	✓	✓	✓	–

Q^1 Was the research question or objective in the paper clearly stated?

Q^2 Was the study population clearly specified and defined?

Q^3 Was the participation rate of eligible persons at least 50%?

Q^{4a} Were all the subjects selected or recruited from the same or similar populations (including the same time period)?

Q^{4b} Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?

Q^5 Was a sample size justification, power description, or variance and effect estimated provided?

✓ = criterion fulfilled, ✗ = criterion not fulfilled, *NR* not reported, – = not relevant

prevalence proportions increased by 189%, 19% and 67%, respectively, from 2008 to 2017 [13]. A Danish study performed earlier (2005 to 2012) found that prevalent use increased markedly (303%) among 0–19-year-olds, but that the rise levelled off after 2010 [30]. A Norwegian study covering data from 2004 to 2014 among 0–17-year-olds showed an increase by 120% among girls and 40% among boys, also with a decreasing slope after 2010 [22]. In Finland, prevalent use of psychostimulants increased three to fivefold among children (6–12 years), fourfold among adolescent boys (13–17 years), and ninefold among adolescent girls from 2008 to 2018 [31].

The prevalence proportions of psychostimulant use were at least twofold higher among boys compared to girls [13, 22, 29–31]. The sex difference decreased over time in Denmark [30] and Finland [31] due to a steeper increase in use among girls.

Prevalent psychostimulant use peaked in late childhood among boys and in adolescence among girls in Sweden, Denmark, Norway, and Iceland [13, 22, 29]. In Finland, however, prevalent use peaked earlier among girls (8 years) than boys (10 years) [29]. A cross-country comparison study that included Denmark as the only Nordic country, found that psychostimulant use peaked at age group 10–14-years among Danish children and adolescents (both sexes combined) [30] (Fig. 4).

Incidence

A single study examined incident use of psychostimulants and found an increase among Swedish and Finnish youths (6–17 years) from 2008 to 2012 [29]. In Denmark and Norway, incidence rates decreased after 2010, while there was only a brief drop in Iceland around 2010 to 2011 [29].

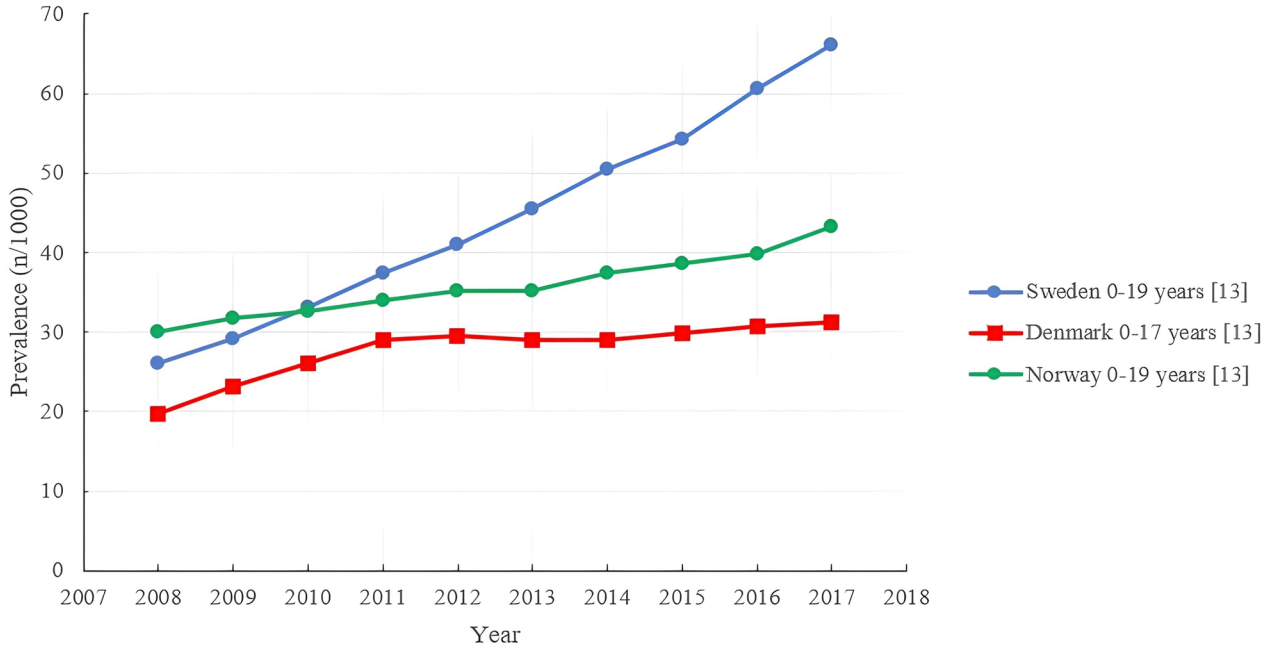

Fig. 2 Prevalence[1] of combined psychotropic drug use over time for Sweden, Denmark, and Norway. [1]Prevalence results are only presented for studies including broad age groups and both sexes. This leaves out studies on selected age groups [23] and girls or boys separately [22, 23]. Figure created in Microsoft Office

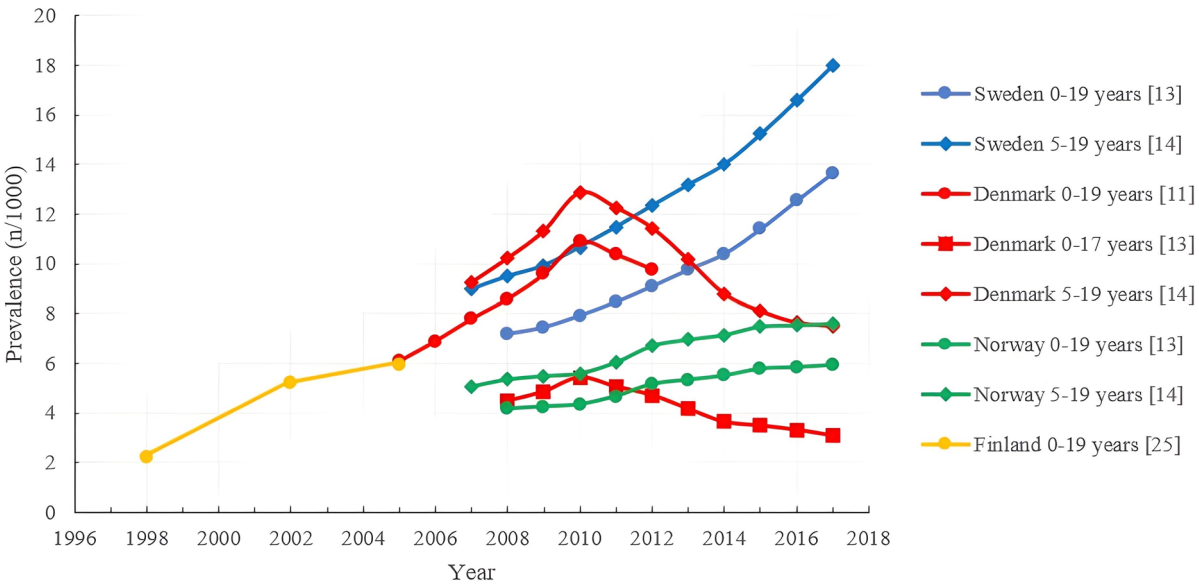

Fig. 3 Prevalence[1] of antidepressant use over time for Sweden, Denmark, Norway, and Finland. [1]Prevalence results are only presented for studies including broad age groups and both sexes. This leaves out studies on selected age groups [23, 24], girls or boys separately [22, 23] and SSRIs only [26, 27]. Figure created in Microsoft Office

When comparing all five countries in 2012, Danish boys (4.8/1000 person years) and Finnish girls (1.6/1000 person years) were least likely to initiate psychostimulant use, whereas Icelandic boys (17.0/1000 person years) and girls (8.5/1000 person years) had the highest incidence rates [29].

Antipsychotics

Prevalence

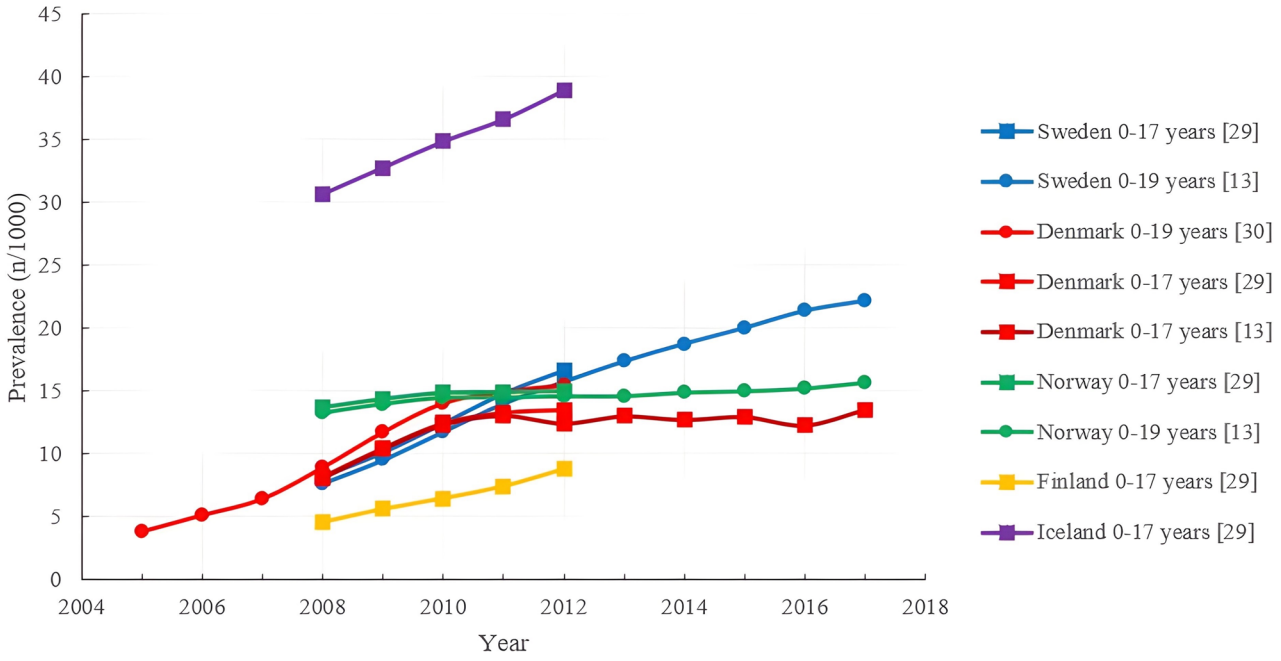

Fig. 4 Prevalence[1] of psychostimulant use over time for Sweden, Denmark, Norway, Finland, and Iceland. [1]Prevalence results are only presented for studies including broad age groups and both sexes. This leaves out studies on girls or boys separately [22, 31]. Figure created in Microsoft Office

Five studies examined prevalent use of antipsychotics in Sweden, Denmark, Norway, or Finland, either separately or as cross-country comparisons. Overall, they found that prevalent use of antipsychotics increased in Sweden, Norway, and Finland, while it peaked in Denmark in 2012 and then declined [13, 22, 32, 33]. One of these studies examined use from 2008 to 2017 and found that the prevalence increased by 58% in Sweden and 45% in Norway among 0–19-year-olds, while it decreased by 2.8% among Danish 0–17-year-olds [13]. In 2017, Norwegian 0–19-year-olds had the highest prevalence (3.3/1000) followed by Swedish 0–19-year-olds (2.8/1000) and Danish 0–17-year-olds (2.4/1000) [13]. A Danish study with an earlier study period (2005–2012) showed that the use of antipsychotics increased from 2.6/1000 to 4.8/1000 among 0–19-year-olds, corresponding to an 84% increase [33]. A Norwegian study covering data from 2004 to 2014 found that the prevalence increased by approximately 40%, leading to prevalence proportions of 2.2/1000 among boys and 1.7/1000 among girls [22]. In Finland, the prevalent use of antipsychotics increased almost twofold between 2008 and 2017 among children and adolescents (1–17 years), reaching approximately 9/1000 in 2017 [32].

Generally, the prevalence of antipsychotic use was slightly higher among boys compared to girls in Sweden, Denmark, Norway, and Finland [13, 22, 32–34]. In 2015 to 2017, however, the prevalence was higher among Norwegian girls [13] and a Finnish study found that the sex difference diminished from 2008 onwards and was eliminated in 2017 [32].

Use of antipsychotics increased with age in Sweden, Denmark, and Norway [13, 22, 33, 34] (Fig. 5).

Incidence

A Finnish study examined the incident use of antipsychotics and found an increase from 2.1/1000 person years in 2008 to 3.8/1000 person years in 2017 among 1–17-year-olds [32].

Incident antipsychotic use was slightly higher among Finnish boys from 2008 to 2010, whereas it was somewhat higher among girls from 2011 to 2017 [32]. However, another Finnish study found no sex difference in the incidence of second generation antipsychotics among youths (1–17 years) who initiated and discontinued treatment between 2008 and 2017 [35].

The incident use of antipsychotics increased with age among Finnish children and adolescents [32].

Hypnotics/anxiolytics

Prevalence

Six studies examined prevalent use of hypnotics, anxiolytics, and/or sedatives in Sweden, Denmark, or Norway. One study

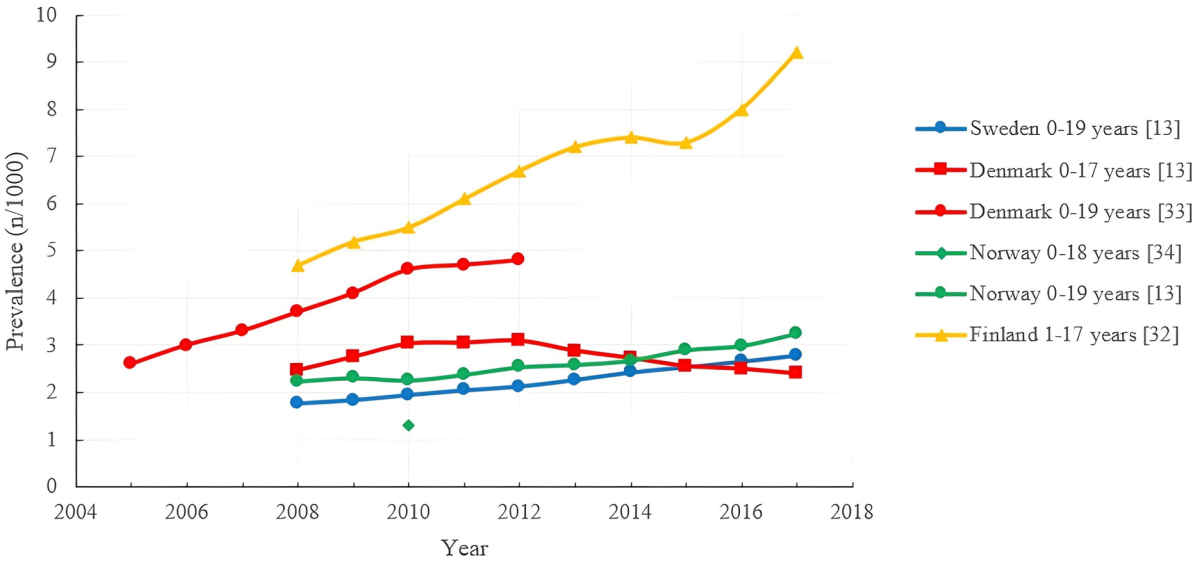

Fig. 5 Prevalence[1] of antipsychotic use over time for Sweden, Denmark, Norway, and Finland. [1]Prevalence results are only presented for studies including broad age groups and both sexes. This leaves out studies on girls or boys separately [22] and SGA only [35]. Figure created in Microsoft Office

examined these drugs combined and showed that Swedish youths had the highest prevalent use in 2017 (33/1000), followed by Norwegian (21/1000) and Danish (12/1000) youths [13]. Furthermore, there was an increase in use from 2008 to 2017, which was higher among Swedish 0–19-year-olds (191%), compared to Danish 0–17-year-olds (157%), and Norwegian 0–19-year-olds (73%) [13]. A Norwegian study found that the use of melatonin specifically increased from 2.1 in 2004 to 6.8/1000 in 2011 among 0–17-year-olds [36].

Three Norwegian studies of different age groups found that prevalent use of hypnotics and melatonin increased, while the use of anxiolytics was stable or slightly decreasing [22, 23, 37]. All studies looked at the sexes separately and one showed that use of hypnotics and sedatives (including melatonin) increased two- and threefold from 2004 to 2014 among boys and girls (0–17 years), respectively, and use of anxiolytics decreased from 4.7/1000 among boys and 4.5/1000 among girls to 3.9/1000 among both sexes [22]. This was also observed among 15–16-year-old Norwegians from 2006 to 2010, where hypnotic use increased among boys (9.3 to 17.3/1000) and girls (11.7 to 17.4/1000), but anxiolytic use was stable at 2.3/1000 among boys and decreased from 3.7/1000 to 3.4/1000 among girls [23]. The last Norwegian study found that 4–17-year-old boys had an increasing use of melatonin (3.4 to 11.0/1000), but the prevalence increased more among girls (1.5 to 7.7/1000) from 2004 to 2012 [37]. In Sweden, they observed a dramatic increase in prevalent use of melatonin from 2006 to 2017 by 20-fold (0.7 to 15.2/1000) among girls and 15-fold (1.3 to 19.2/1000) among boys aged 0–17 years [38].

The prevalent use of hypnotics, sedatives and anxiolytics was generally higher among boys compared to girls [13, 22, 37, 39]. One study examined the prevalent use of hypnotics, sedatives, and anxiolytics in Sweden, Denmark, and Norway from 2008 to 2017, and found that boys had a higher use in childhood, while girls had a higher use in adolescence [13]. One study found that Norwegian boys consumed approximately 60% more hypnotics/sedatives (including melatonin) compared to girls in 2004, but the sex difference was reduced to approximately 20% in 2014 [22]. Similarly, a study of Norwegian 15–16-year-olds showed that girls used more hypnotics in 2006 and 2008, but that this sex difference was almost eliminated in 2010 [23].

Generally, the use of anxiolytics, hypnotics, and sedatives increased with age among both sexes in Sweden, Denmark, and Norway [13]. Prevalent melatonin use peaked at the age of ten years among Norwegian boys, whereas use increased continuously with age among girls [37] (Fig. 6).

Incidence

There was a marked increase in new melatonin users in Sweden [38, 39], and a rise in incidence rates was observed from 2008 to 2017, in specific from 1.3 to 8.2/1000 person years among boys and from 0.7 to 7.9/1000 person years among girls [38]. A Norwegian study followed newborns in 2008 and until 35 months of age and found that the 3-year incident use of alimemazine was 30/1000 person years [40].

Incident use of melatonin was generally higher among Swedish boys than girls from 2008 to 2011 [38]. After 2012, initiation of melatonin treatment was more common

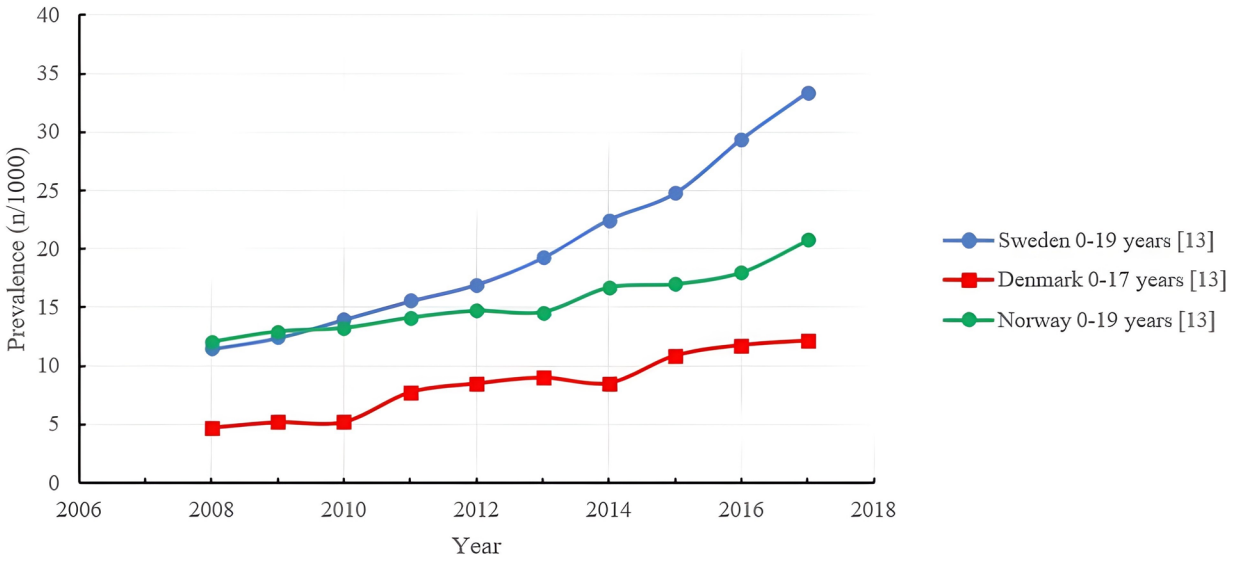

Fig. 6 Prevalence[1] of anxiolytic, hypnotic, and sedative use combined over time for Sweden, Denmark, and Norway. [1]Prevalence results are only presented for studies including broad age groups and both sexes. This leaves out studies on selected age groups [23, 40], girls or boys separately [22, 23, 37–39], melatonin [37–39] or alimemazine [40] only, and hypnotics separately [36]. Figure created in Microsoft Office

among boys in childhood, whereas it was more common among girls in adolescence [38, 39]. The 3-year incidence of alimemazine use among Norwegian infants was also higher among boys (3.4%) compared to girls (2.6%) [40].

Incidence of melatonin use increased with age in Sweden [38, 39] and the rates of alimemazine use peaked between age 12 and 23 months among Norwegian infants [40]. In Denmark, the median age at first prescription of sedatives and hypnotics was 12 years among boys and 15 years among girls [28].

Discussion

This systematic literature review included 22 studies covering data collected from 1995 to 2018. The review showed a marked variation between the Nordic countries in psychotropic drug use among children and adolescents despite comparable heath care and welfare systems [15, 16]. With a few exceptions, the use of psychotropic drugs increased in the Nordic countries, but at a very different pace. The included studies were all based on national register data involving nationwide samples and characterized by low risk of bias [16]. No included studies examined the use of psychotropic drugs in Greenland, the Faroe Islands or the Åland Islands, and no studies examined the use of mood stabilizers.

The review showed an overall increase in psychotropic drug use among children and adolescents in most Nordic countries. This is in line with a systematic review that documented a rise in mental health problems among youths in Sweden, Denmark, Norway and Finland from 1996 to 2013 [41]. In addition, depressive and anxiety symptoms increased in Icelandic youths from 2006 to 2016 [42]. Furthermore, reduced stigma over time may have encouraged youths to seek mental health care [43], which may have led to more youths being diagnosed with mental disorders and subsequently receiving psychotropic treatment. There were, however, exceptions to the general increase in psychotropic drug use. In Denmark, prevalent use of antidepressants and antipsychotics decreased around 2010–2012 [11, 13, 14]. In Norway, there was an isolated decrease in utilization of anxiolytics after 2007 [22], which has also been observed in United Kingdom [44] and Germany [45]).

The drop in use of antidepressants and antipsychotics observed in Denmark could be related to the national media criticizing the efficacy and safety of these drugs in youths at the same time [46]. A subsequent revision of Danish prescription legislations restricting initiation and maintenance of medical treatment for children and adolescents with mental disorders to child and adolescent psychiatrists only [47, 48], could also have contributed. Finally, the announced plan for publication of a Danish clinical guideline for treatment of childhood psychosis in 2013 [49] could have caused reluctancy to prescribe antipsychotics to youths before then.

In general, our review demonstrated a pronounced variation across countries in the extent of psychotropic drug use. Sweden had the highest use of antidepressants and hypnotics/anxiolytics [13, 14], Finland had the highest use of antipsychotics [32], while Iceland had the highest use of psychostimulants [50]. All Nordic countries rely on

tax-based welfare [15] mainly free of charge [16], but the observed variations could rely on differences in access to mental health care. Sweden and Iceland provide the opportunity to self-refer to child and adolescent psychiatric specialists (Iceland until 2017) [16]. This is likely to lower the help seeking threshold and hence increase the possibility of pharmacological treatment. Also, Sweden has twice as many child and adolescent psychiatrists per youth compared to Denmark and Norway [51], which could have contributed to the high Swedish use of psychotropics. The use of psychostimulants was markedly higher in Iceland than in any other Nordic country. This could be influenced by the fact that many Icelandic child and adolescent psychiatrists are clinically trained in the United States of America [52], where psychotropic utilization rates are among the highest worldwide [9, 10]. Finland had the highest rates of antipsychotic use. A lack of a clear prioritization of medication choices in the Finnish clinical treatment guideline for childhood psychosis, as opposed to Swedish and Danish guidelines, could lead to a nonrestrictive prescription practice [53].

There was a clear distinction in utilization of psychotropic drugs between the sexes, except for antipsychotics. Antidepressants were more commonly used among girls, and psychostimulants were more commonly used among boys, which correlates well with the sex-specific prevalence rates of depression and Attention-Deficit Hyperactivity Disorder (ADHD) worldwide [54, 55]. Our review showed, however, that the sex difference in use of psychostimulants decreased over time in Denmark [30] and Finland [31]. This could be due to increased awareness, diagnosis, and treatment of girls with ADHD [56, 57]. Hypnotic use was more common among boys in childhood and among girls in adolescence, which is in line with sex-specific rates of age-related sleep problems [58–60]. Antipsychotic use was quite similar between boys and girls reflecting the rates of schizophrenia, and schizophrenia spectrum disorders [61–63].

Finally, the use of antidepressants, antipsychotics and hypnotics/anxiolytics increased with age in the Nordic countries, which reflects the patterns of the respective disorder rates [55, 58, 61, 64]. In all Nordic countries, except Finland, the utilization of psychostimulants peaked in childhood among boys and in adolescents among girls. This is in accordance with the sex-specific incidence rates of ADHD diagnoses found in Denmark [64].

Methodological strengths and limitations

This systematic review was conducted according to PRISMA statement guidelines [17] and based on searches in three databases. An inter-rater reliability test was performed to ensure satisfactory reviewer agreement. All studies were assessed by two reviewers, which minimized the risk of bias in study selection and quality assessment. All included studies were considered of high quality and were based on nationwide prescription databases that have high validity and completeness [16] and no selection- or recall bias.

There are, however, also some limitations. Even though we conducted a broad search string in collaboration with a librarian, it is possible that we have missed relevant studies. The first screening phase was based on abstracts, and studies that did not reported sufficient details in the abstract could have been missed. This review focuses on individuals aged 0–19 years, and studies including adults were excluded even though they could contain data on children and adolescents separately.

Conclusion

This review demonstrates a remarkable variation in pharmacological treatment of childhood mental disorders between the Nordic countries. Generally, the prevalence and incidence of psychotropic drug use increased among Nordic children and adolescents from 1995 to 2018. However, youths in Sweden, Iceland and Finland were more likely to receive treatment with psychotropic medications than youths in Denmark and Norway. These findings could rely on national differences in the rates of childhood mental disorders. However, national variation in clinical practice and access to mental health care may be more plausible explanations. Furthermore, the huge discrepancies in the psychotropic drug utilization rates between countries raise concern about the reliability and validity of the diagnostic evaluation performed across the Nordic mental health care units. A concern that is intensified by a lack of national treatment guidelines in some Nordic countries.

We therefore suggest future studies to compare the rates of clinical psychiatric disorders as well as self-reported mental health problems between Nordic youth populations. We also recommend a joint effort within the Nordic countries to establish updated clinical treatment guidelines facilitating rational pharmacotherapy across countries.

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Author contributions Conceptualization: Rikke Wesselhoeft (RW), Debbie Rosenlyst Ollerup (DRO) and Lotte Rasmussen (LR). Literature search: DRO under supervision of RW. Screening, data extraction and quality assessment of studies: DRO, Sophie Lund Elkrog (SLE), Maria Højgaard Stoltz-Andersen (MHS-A) and Heidi Stubmark (HS) under supervision of RW. DRO wrote the main manuscript text and created figures and tables, supervised by RW and LR. Writing: DRO, RW, and LR. All authors reviewed and contributed to the final manuscript.

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Code availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Not applicable.

Informed consent Not applicable.

Consent for publication All authors have consented to the content of this publication.

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