

Utilization of Stimulants and Atomoxetine for Attention-Deficit/Hyperactivity Disorder among 5.4 Million Children Using Population-Based Longitudinal Data

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Abstract: Use of stimulants to treat attention-deficit/hyperactivity disorder (ADHD) has increased over the past two decades and varies substantially between countries. The objective of this multinational population-based study was to examine utilization of ADHD drugs (stimulants and atomoxetine) including comedication with other psychotropic drugs in the entire child population in the five Nordic countries. We included longitudinal data on dispensed ADHD drugs from five Nordic prescription registers during 2008–2012, which in 2012 comprised 48,296 individuals among 5.42 million inhabitants aged 0–17 years. Prevalence of filling ≥ 1 prescriptions of ADHD drugs among children aged 6–17 years increased during 2008–2012 from 5.9 to 11.2 and 19.4 to 31.0 per 1000 girls and boys, respectively. Prevalence by country showed that Iceland, Finland and Sweden had a steady increase during the study period, while in Norway the prevalence was quite stable and in Denmark it levelled off from 2010. Use in preschoolers (aged 0–5 years) was rare. Iceland had much higher prevalence and incidence than the other Nordic countries. The incidence of ADHD drug use increased during the study period, from 4.0 to 4.9 and from 1.5 to 2.3 per 1000 boys and girls, respectively. The increasing number of new users levelled off somewhat after 2010. Comedication with other psychotropic drugs was more common among girls (33.9%) than boys (27.0%) and was mainly melatonin, followed by antidepressants and antipsychotics. Overall prevalence of ADHD drug use increased among Nordic girls and boys aged 6–17 years, whereas the incidence increased slightly during 2008–2010 but levelled off through 2012. The substantial differences in ADHD drug use across the Nordic countries and high degree of comedication with other psychotropic drugs underscore the importance of close monitoring of treatment for ADHD among children.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurobehavioural disorders in childhood [1,2] and is estimated to affect 3–6% of children worldwide [3]. The disorder is managed by behavioural therapy and pharmacological treatment, mainly with stimulants and atomoxetine. The efficacy of these drugs to relieve the core symptoms of ADHD has been established [4–6].

The use of stimulants to treat ADHD has increased markedly over the past two decades throughout the entire Western world [7–12]. Nevertheless, stimulant use varies markedly between countries and regions of the world, with some countries such as France and Italy reporting as little as 0.2% and 0.02% of their paediatric population receiving pharmacological treatment [13,14]. Some of the differences may be due to limited access to ADHD drugs or differences in preferring behavioural therapy with and without concomitant pharmacological treatment in some countries. ADHD is diagnosed and treated more often in boys than in girls, and studies suggest that girls may be consistently underdiagnosed [15,16]. Concomitant psychotropic drug use in children treated with ADHD drugs has been shown to be common [17]. Detailed knowledge of treatment patterns,

including comedication with other drugs, is crucial to ensure the rational use of pharmacological treatment of ADHD. The use of stimulants in children remains controversial, and there has been a broad public concern also in the Nordic countries regarding the increasing use of psychostimulants for ADHD in children. A Nordic cross-sectional study with data from 2007 on use of stimulants in children showed considerable variation between the Nordic countries [18]. There is a need to do a follow-up study to explore in more detail the use of stimulants and changes over time in the Nordic countries. Leveraging data from the five nationwide prescription registers in the Nordic countries, we sought to examine the utilization of stimulants and atomoxetine, including comedication with other psychotropic drugs, over the five-year period of 2008–2012 in the entire Nordic paediatric population aged 0–17 years.

Materials and Methods

Study setting, population and data sources. In this population-based study, data on dispensed drugs from 2006 to 2012 were extracted from the nationwide prescription databases in the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden). Individual data were pooled into a common Nordic dataset on a server at Statistics Denmark. Information on filled prescriptions is sent electronically from all pharmacies to the national register holders, allowing individual drug use to be tracked over time in the databases

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by using the unique, personal identity number assigned to each resident at birth or immigration [19].

Age- and sex-specific population statistics, used as denominator in prevalence and incidence measures, were retrieved from national population registers (Social Insurance Institution (Kela) in Finland and the bureau of statistics in the other countries). The number of inhabitants aged 0–17 years in 2012 was 1.20 million in Denmark, 1.08 in Finland, 0.08 in Iceland, 1.12 in Norway, and 1.92 in Sweden, amounting to 5.40 million children in total.

Study drugs. Medical products in the Nordic countries are coded according to the Anatomical Therapeutic Chemical (ATC) classification system [20]. In this study, ADHD drugs were defined as amphetamine (ATC code N06BA01), dexamphetamine (N06BA02), methylphenidate (N06BA04) and atomoxetine (N06BA09). These were the only drugs with an approved indication for ADHD in the Nordic countries during the study period. Methylphenidate was further classified in extended release and immediate release formulations. Danish data did not include amphetamine, which is not marketed and thus rarely used in Denmark.

For individuals who received any ADHD drug, data on filled prescriptions for other psychotropic drugs during study period were retrieved. Other psychotropic drugs were classified into antipsychotics (ATC code N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A) and anti-epileptics (N03A).

Data analysis. Individual-based analyses of a pooled data set from the Nordic prescription registers, based on filled prescriptions during 2006–2012, were performed. The study period was 2008–2012 and data from 2006–2007 were used to ensure a 24-month drug-free period for all incident users.

ADHD drug utilization was examined using the following definitions:

Prevalence: Annual prevalence of ADHD drug use was defined as the number of children per calendar year who filled at least one prescription for an ADHD drug per 1000 in the population that same year. The denominator for prevalence was composed by the number of children in each country at the beginning of each relevant year according to population statistics, stratified by sex and age.

Incidence (new users): Annual incidence of ADHD drug use was defined as the number of children per calendar year who filled their first prescription for an ADHD drug, that is after a period of at least 24 months with no filled ADHD drug prescriptions, per 1000 in the population the same year. The denominator was composed by the number of children in each country at the beginning of each relevant year, stratified by sex and age. Incidence was calculated for prescription fills occurring from 2008 and onwards and was calculated for use of any ADHD drug and by each specific ADHD drug.

Type of ADHD drug at treatment initiation: Type of ADHD drug on the first prescription fill was assessed among new users (defined as above) in 2008–2012.

Early discontinuation of drug treatment: Among new users during 2008–2011 (defined as above), early discontinuation of treatment was defined as filling no more than two prescriptions of ADHD drugs (regardless of type of ADHD drug) during the 365 days after start of treatment (including the index prescription). Prescriptions for chronic

diseases are normally filled for maximum of three months' treatment. Prescriptions filled on the same date were counted as one prescription.

Comedication with other psychotropic drugs: For all individuals who filled a prescription for an ADHD drug in one calendar year, the proportion (%) who also filled at least one prescription for another psychotropic drug (defined as above) concomitantly with an ADHD drug (within 3 months before or after) was calculated.

We performed analyses stratified by sex and three age groups (0–5, 6–12 and 13–17 years) with the primary focus on children aged 6–17 years, that is the ages for which ADHD drugs are mainly licensed [21]. Prevalence and incidence of ADHD drug use are presented combined for the Nordic countries as well as by country. We set up a negative binomial regression model to evaluate the simultaneous effect of countries, age, year and sex.

Ethics. Personal identity numbers were encrypted before researchers received the data files. No ethical approval was needed for use of the Danish, Finnish and Norwegian data [22]. The study was approved by the Icelandic Bioethics Committee (VSNb2013010018/03.07) and the Icelandic Data Protection Authority (2013010062TS/–), and in Sweden by the regional ethics committee at Karolinska Institutet.

Results

Prevalence.

In 2008, the prevalence of ADHD drug use was 8.9 per 1000 Nordic children aged 0–17 years (48,296 children of 5.42 million) increasing to 14.4 per 1000 in 2012 (77,604 children of 5.40 million). Restricting to children aged 6–17, the corresponding values were 12.8 per 1000 children (47,226 children of 3.68 million) and 21.4 per 1000 children (76,362 children of 3.57 million). The annual prevalence increased among both six- to 12-year-olds and 13- to 17-year-olds for both sexes and was stable in the youngest age group (fig. 1, table 1). The prevalence was 70% higher in 2012 than in 2008 (table 2). Iceland, Finland, and Sweden had a steady increase during the study period, while in Norway the prevalence was quite stable

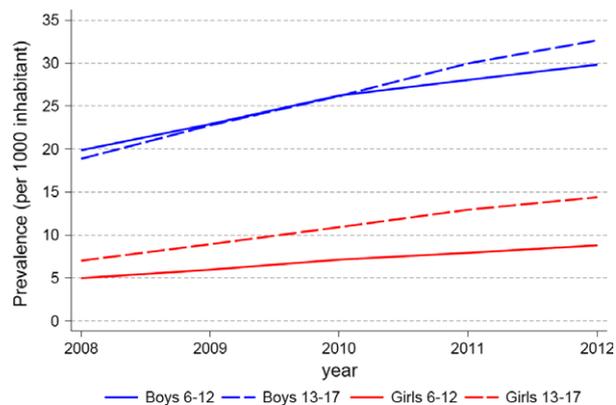


Fig. 1. Annual prevalence (per 1000 children) of ADHD drug use among girls and boys (6–12 years and 13–17 years old) in the Nordic countries in 2008–2012.

Table 1.

Annual prevalence (per 1000 children) of ADHD drug use by age group among girls and boys in the Nordic countries in 2008 and 2012.

Age group	Girls		Boys	
	2008 Per 1000	2012 Per 1000	2008 Per 1000	2012 Per 1000
0–5	0.3	0.3	0.9	1.0
6–12	5.0	8.8	19.9	29.8
13–17	7.0	14.4	18.9	32.7
0–17	4.1	7.5	13.5	20.9
6–17	5.9	11.2	19.4	31.0

Table 2.

Prevalence ratios of ADHD drug use by country, calendar year, sex and age group¹.

Covariate	Prevalence ratio	95% confidence interval	
Country			
Denmark	1.0	Ref	
Finland	0.5	0.41	0.57
Iceland	3.3	2.77	3.83
Norway	1.4	1.20	1.66
Sweden	1.2	0.98	1.35
Year			
2008	1.0	Ref	
2009	1.2	1.02	1.40
2010	1.4	1.18	1.62
2011	1.5	1.31	1.81
2012	1.7	1.44	2.00
Sex			
Boys	1.0	Ref	
Girls	0.3	0.28	0.35
Age (years)			
6–12	1.0	Ref	
13–17	1.1	0.98	1.21

¹The simultaneous effect of countries, age, year and sex estimated by a negative binomial regression model.

and in Denmark it levelled off from 2010 (fig. 2). The prevalence was highest in Iceland and lowest in Finland throughout the period (fig. 2, table 2). The prevalence among girls was 69% lower than among boys (table 2).

The age-specific prevalence reached its maximum at age 12 among boys (26.0 per 1000 in 2008, 42.8 per 1000 in 2012) (fig. 3). Among girls, the prevalence rose with each age year and peaked at age 16 (8.05 per 1000 in 2008, 16.7 per 1000 in 2012) (fig. 3). The sex ratio (boys *versus* girls) of prevalence decreased slightly during the study period, from 3.3 in 2008 to 2.8 in 2012. Iceland had the highest prevalence for all ages, while there were small differences between the other four countries among children up to 11 years (fig. 4).

Incidence.

The incidence of ADHD drug use among Nordic children increased during the study period, from 4.0 to 4.9 per 1000

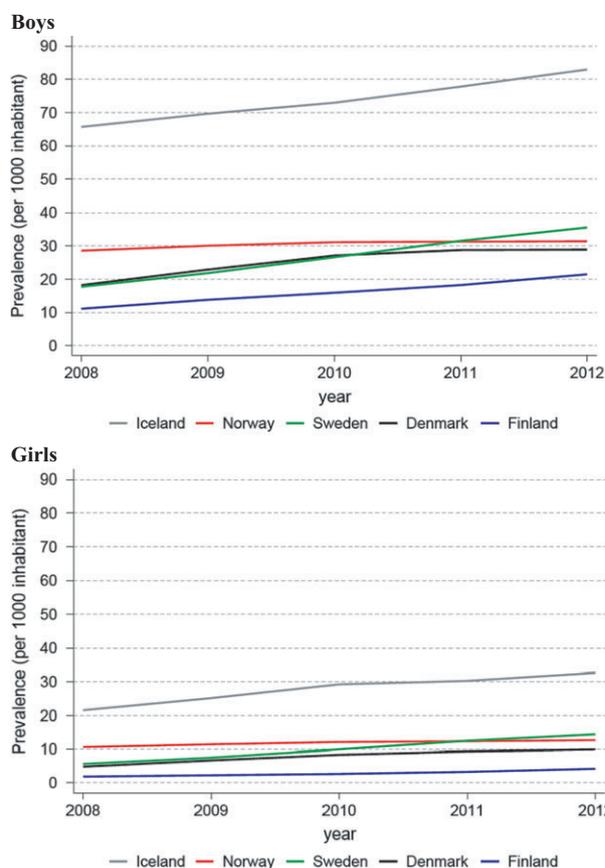


Fig. 2. Annual prevalence (per 1000 boys/girls) of ADHD drug use among boys, and among girls aged 6–17 years by country, 2008–2012.

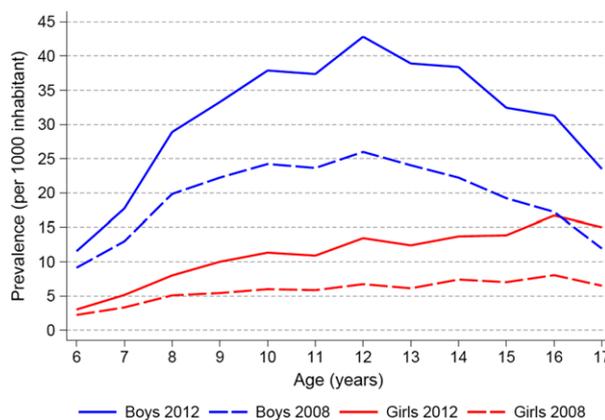


Fig. 3. Annual prevalence (per 1000 children) of use of ADHD drugs by age among girls and boys in the Nordic countries, 2008 and 2012.

boys and from 1.5 to 2.3 per 1000 girls. The increasing number of new users levelled off somewhat after 2010 in all age groups and both sexes (fig. 5). Among Nordic boys, the incidence was highest in the age group 6–12 years (8.3 per 1000 in 2012), while among girls it was highest in the age group 13–17 years (4.1 per 1000 in 2012) (fig. 5). The incidence of ADHD drug use remained stable throughout the study period

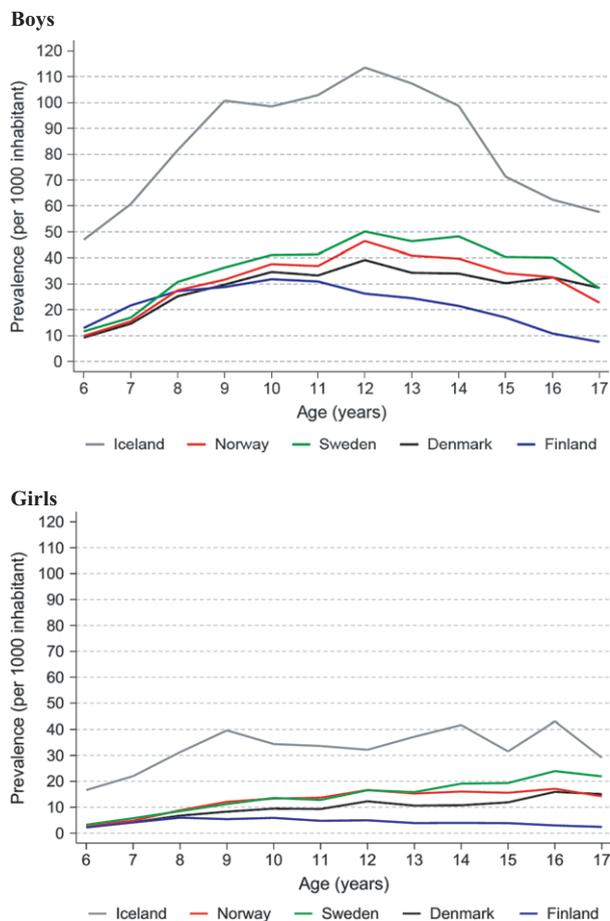


Fig. 4. Annual prevalence (per 1000 boys/girls) of ADHD drug use in 2012 among boys and girls aged 6–17 years by country.

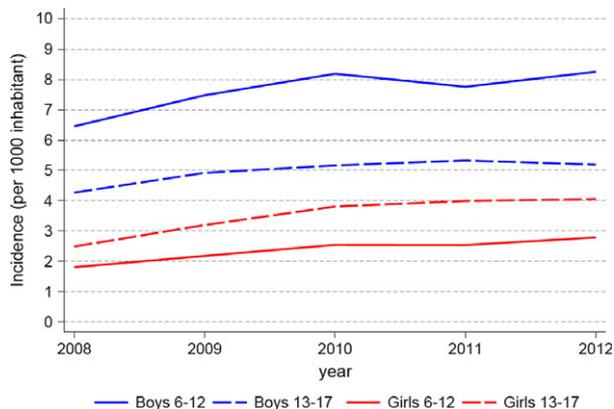


Fig. 5. Annual incidence (new users per 1000 children) of ADHD drug use among boys and girls aged 6–17 years in the Nordic countries, 2008–2012. New users defined as not filling a prescription for ADHD drugs during the previous 24 months.

among the youngest children (0–5 years) at 0.8 per 1000 boys and 0.2 per 1000 girls.

Annual incidence by country showed that Iceland had much higher incidence than the other Nordic countries. In 2012, incidence of ADHD drug use among ages 6–17 years

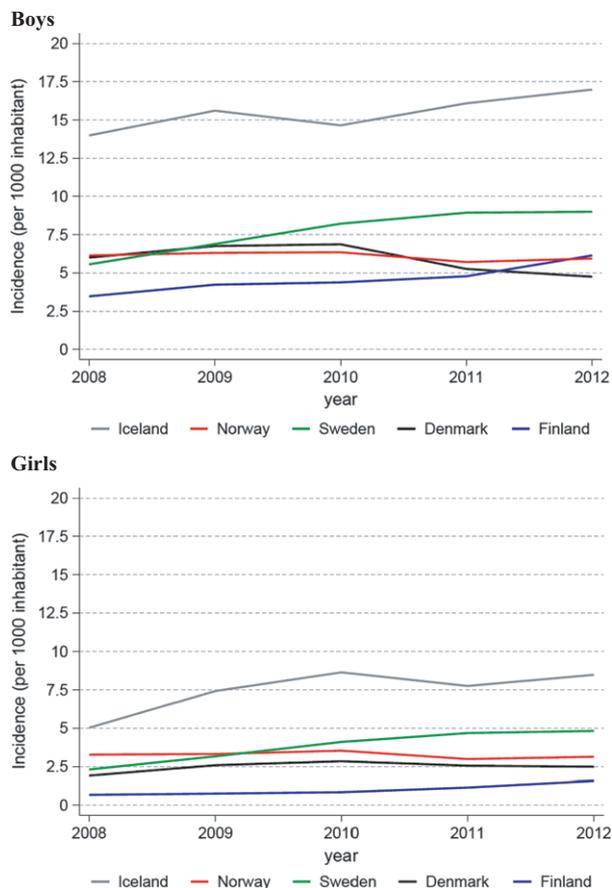


Fig. 6. Annual incidence (new users per 1000 boys/girls) of ADHD drug use among boys and girls aged 6–17 years by country, year 2008–2012. New users defined as not filling a prescription for ADHD drugs during the previous 24 months.

was highest in Iceland (17.0 per 1000 boys, 8.5 per 1000 girls) and lowest in Denmark for boys (4.8 per 1000 boys) and in Finland for girls (1.6 per 1000 girls) (fig. 6).

The median age at initiation of ADHD drug treatment among Nordic children was 11 years throughout the study period, varying slightly between countries, from 9 years in Finland to 12 years in Sweden.

Type of ADHD drug at treatment initiation.

Methylphenidate was the predominant ADHD drug used at treatment initiation throughout the study period, and 94% of new users in 2012 received methylphenidate on the first prescription fill. In 2008, 66% of new methylphenidate users received extended release formulations of methylphenidate, increasing to 83% of new users in 2012.

Early discontinuation of drug treatment.

Among 64 469 new users (aged 6–17 years) of any ADHD drugs, 6.5% filled only the initial prescription and 5.9% filled only one more prescription during the 365 days after start of treatment; that is, 87.6% filled three or more prescriptions during the first year of treatment.

Table 3.

Proportion (%) of Nordic children aged 6–17 years with concomitant prescription fills for any ADHD drug and other psychotropic drugs¹.

Sex	Girls (%)		Boys (%)	
	6–12 years	13–17 years	6–12 years	13–17 years
ADHD users in 2012 (n)	8753	10,765	31,088	25,756
Any psychotropic	29.5	37.6	27.6	26.3
<i>Any psychotropic excl. melatonin</i>	<i>12.2</i>	<i>26.7</i>	<i>11.9</i>	<i>16.0</i>
Antidepressants	4.0	17.4	3.0	7.3
Anti-epileptics	3.3	4.2	2.2	2.1
Antipsychotics	4.6	6.5	6.8	7.3
Anxiolytics	2.7	5.3	1.9	2.2
Hypnotics	21.5	20.2	19.3	15.0
<i>Melatonin</i>	<i>21.2</i>	<i>18.0</i>	<i>19.1</i>	<i>14.1</i>
<i>Hypnotics excl. melatonin</i>	<i>0.6</i>	<i>3.7</i>	<i>0.3</i>	<i>1.4</i>

¹Text in *italic* is subgroups of the drug group in the line above.

Comedication with other psychotropic drugs.

Among children using ADHD drugs in 2012, comedication with other psychotropic drugs – including and excluding melatonin – was more common among girls aged 6–17 years (33.9% incl. melatonin and 20.2% excl. melatonin) than among boys (27.0% and 13.8%). Melatonin was the psychotropic drug most frequently used with ADHD drugs in both sexes and age groups, followed by antidepressants and antipsychotics (table 3). Other hypnotics than melatonin were very rarely used among children aged 6–12 years. When excluding melatonin, 12% of the children aged 6–12 years used other psychotropic drugs with no differences between the sexes. Among adolescents (13–17 years), girls were more commonly comedicated than boys (27% versus 16%), mainly due to the higher use of antidepressants (table 3).

Discussion

This study provides population-based longitudinal data of ADHD drug utilization from 2008 through 2012 among 5.4 million children aged 0–17 years in the five Nordic countries. Iceland had much higher prevalence and incidence of ADHD drug use than the other Nordic countries in all ages and throughout the study period. The prevalence in Norway was quite stable across time, while all the other countries increased, also Iceland. Among Nordic boys, the incidence was highest in the age group 6–12 years (8.3 per 1000 in 2012), while among the girls it was highest in the age group 13–17 years (4.1 per 1000 in 2012). Methylphenidate was the drug of choice, and four of five new users of methylphenidate used the extended release formulation. Approximately one-third of children aged 6–17 years on ADHD drugs were comedicated with other psychotropic drugs, mainly melatonin followed by antidepressants and antipsychotics.

The primary strength of the study is the multi-country setting, including high-quality nationwide prescription registers with population-based longitudinal data and mandatory

reporting providing age- and sex-specific information on all drugs prescribed by all physicians regardless of workplace and medical specialization and dispensed to all children in ambulatory care [19]. This approach eliminates the possibility of selection and recall bias, which may be the case for utilization estimates based on prescribing in general practice or surveys with self- or parent-reported drug use [12,23]. Further, data on dispensed drugs decrease the likelihood of misclassification of drug exposure, which may arise with prescribed data on drugs due to primary non-adherence [24]. The study also has limitations. Firstly, as in other register-based studies on dispensed drugs, we do not know whether the dispensed drug is actually consumed by the children. However, the majority of the children had repeated prescription fills which should indicate consumption of the previously dispensed drugs. Secondly, we have no information about drugs administered to hospitalized children. However, very few children in the Nordic countries are in institutions for longer periods and we do not expect that this lack of information will influence the estimates for prevalence and incidence. The hospital dispensing of ADHD drugs are likely to be a very small proportion of the overall dispensing of ADHD drugs. For example in Norway and Denmark, it is <1% of total amount dispensed (in Defined daily doses). Lastly, we lack information on the underlying ADHD diagnosis in this study, which precludes solid conclusions on appropriateness of the treatment.

During the five-year study period, there was an increase in prevalence of use of ADHD drugs among children in the Nordic countries except Norway which had a quite stable prevalence across time. However, the overall 2.1% prevalence of ADHD drug use among six- to 17-year-old Nordic children in 2012 was substantially lower than 6.1% prevalence reported for four- to 17-year-old children in the United States in 2011 [12]. The overall Nordic prevalence was comparable to that of the Netherlands, about 2% for 0- to 19-year-olds in 2006 [25], but much higher than in UK and Australia, where the reported prevalence of pharmacologically treated children with ADHD was 0.74% in 2008 and 1.24% in 2010, respectively [26,27]. A recent meta-analysis of 175 eligible studies reported a pooled prevalence estimate of 7.2% for the diagnosis of ADHD in children aged ≤18 years [28]. Our study showed that there are still substantial differences concerning use of ADHD drugs across the Nordic countries. Given that the social and health structures are comparable in these countries, it is quite surprising. Each Nordic country has developed its own guidelines for diagnosing and treating ADHD. A group of Nordic researchers in the field of ADHD have suggested the exploration of possibilities for joint Nordic guidelines to reduce variability in rates of treatment [29]. It is difficult to explain why the prevalence of ADHD drug use in Iceland, which is comparable to that in the United States, remains much higher than in the other Nordic countries. As there is no known biological cause of a geographical variation in ADHD, the observed variation in drug treatment between the Nordic countries is assumed to stem from professional and cultural differences in recognizing and treating ADHD [30]. These results underscore the importance of continued promotion of

rational use of stimulants and other psychotropics in treatment of children with ADHD.

As expected, Nordic boys were about three times more likely to receive ADHD drugs than Nordic girls. This may be due to girls tending to have an inattentive presentation of ADHD, thus being more difficult to recognize which may result in later diagnosis and treatment, or underdiagnosing and lack of treatment [15,31,32]. However, the boys/girls ratio decreased during the study period and suggests increased awareness of ADHD in girls in the Nordic countries.

Psychiatric comorbidities in individuals with ADHD are common [11,17]. Although we do not have access to underlying diagnoses or indication for drug use in our data, comedication with other psychotropic drugs may function as an indicator of psychiatric comorbidity [27]. Children treated with stimulants such as methylphenidate are at higher risk of sleep problems [33]. This may explain our finding that about 20% of Nordic children treated with ADHD drugs are comedicated with melatonin. However, the single melatonin formulation registered for human use in the Nordic countries, Circadin[®], is only approved for short-term treatment of primary insomnia in people aged 55 years and over [34,35]. Future studies should investigate the appropriateness of this treatment. Two other studies on use of antidepressants in the general adolescent population show that adolescent girls are more likely to receive antidepressants than adolescent boys [36,37]. Higher exposure to antidepressants in girls medicated with ADHD drugs may support earlier findings that girls tend to have a more inattentive type of ADHD [15,31,32].

In conclusion, we found that the overall prevalence of ADHD drug use in the Nordic countries increased among girls and boys aged 6–17 years, whereas the incidence increased slightly during 2008–2010 and then levelled off. There were substantial differences in both prevalence and incidence across the Nordic countries. Comedication with other psychotropic drugs was highly prevalent among children treated with ADHD drugs, reflecting a high degree of psychiatric comorbidity among these children.

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Author Contributions

Furu had the idea, conceptualized and designed the study and drafted the initial manuscript. Pottegård and Karlstad conceptualized and designed the study and carried out the analysis. Pottegård collected the Danish data and Karlstad collected the Norwegian data. Zoega collected the Icelandic data, Kieler and Bahmanyar collected Swedish data, and Martikainen collected Finnish data. All authors critically reviewed and revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Financial Disclosure

The authors have no financial relationships relevant to this article to disclose.

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