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ORIGINAL ARTICLE

The Effect of Different Algorithms on Prevalence of Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder in Secondary Healthcare Data in Five European Countries: A Contribution from the ConcePTION Project

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Abstract

To assess the effect on prevalence estimates of using different algorithms to identify children with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in healthcare data. Three algorithms were developed and run on administrative/research data in Finland, France (Haute Garonne), Italy (Emilia Romagna), Norway and Wales: (1)≥1 ADHD or ASD diagnoses recorded in specialist settings, (2)≥2 ADHD or ASD diagnoses recorded in primary care and (3)≥1 prescription for medication to manage ADHD. Prevalence rates per 1000 children for each algorithm were calculated. 3,130,162 children (born 1996–2020) with 29,291,204 years of follow-up were included. ADHD prevalence per 1000 children in specialist settings ranged from 3.9 (Emilia Romagna) to 24.1 (Finland); and was 7.0 in primary care (Finland). Based on prescriptions, ADHD prevalence ranged from 0.1 (Emilia Romagna) to 9.9 (Haute Garonne). ASD prevalence in specialist settings ranged from 5.6 (Wales) to 9.7 (Finland), and in primary care from 1.0 (Finland) to 2.0 (Wales). Prevalence of ADHD and ASD was greater among children with longer follow-up. In Finland and Wales, 1.7% and 19.4% of children were diagnosed with ASD in primary care only respectively. The male:female ratio was 3–4:1. Whilst there was considerable geographical variation in the length of follow-up available, and prevalence of ADHD and ASD, specialist diagnoses recorded in healthcare data were key to identifying children with these disorders. These data sources can be complemented by using primary care diagnoses and prescription data to identify affected children more comprehensively.

Keywords Autism spectrum disorder · Attention deficit disorder with hyperactivity · Routinely collected health data · Data linkage

Introduction

Access to routinely collected administrative data for research has increased, due in part to its population-based coverage, timely information, increased efficiency, minimal attrition, and reduced costs. The ability to accurately identify children with neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in secondary data sources is important for several reasons including surveillance of these conditions,

The subheadings Statistics and Ethical Approval should use Section 2 font

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healthcare resource planning, healthcare delivery, educational support, the provision of special educational needs, and pharmacoepidemiological research assessing the effects of exposure to medication in pregnancy and breastfeeding on the child.

Most evidence relating to the impact of medication exposure on neurodevelopment is derived from observational studies, as enrolling pregnant individuals into interventional trials poses both practical and ethical challenges. While studies based on primary data collection typically perform direct assessment of the child resulting in more reliable data across a range of outcomes, they are typically limited by volunteer bias, sample size, follow-up duration, and high costs (Jordan et al., 2013; Wang et al., 2019). Population-based cohorts created using secondary data can explore a broader range of maternal medication exposures and facilitate longer follow-up periods. However, these cohorts typically rely on the presence or absence of diagnostic codes, which can lead to discrepancies in findings due to misclassification, under-recording, changes in disease coding over time (Wang et al., 2019) and underdiagnosis (O'Nions et al., 2023).

Search criteria to identify individuals with ADHD and ASD in secondary data sources are based on defined lists of codes or algorithms (Morkem et al., 2020), but there is little information on the composition of the optimal algorithm to correctly identify children with these conditions. The aim of this study is to estimate the prevalence of ADHD and ASD by birth cohort, age and sex, based on algorithms developed to identify children with these outcomes in administrative data sources across five European countries.

Methods

The Innovative Medicines Initiative ConcePTION Project is a large consortium of academic, regulatory and industry partners ('ConcePTION', 2019), with the primary aim of establishing a trusted ecosystem that can generate and disseminate reliable, evidence-based information for individuals planning pregnancy and their healthcare providers regarding the effects of medications used during pregnancy and breastfeeding. Five partners in ConcePTION Work Package 1 with access to data relating to ASD or ADHD participated in the study (Finland, France (Haute Garonne), Italy (Emilia Romagna), Norway and Wales), (Table 1). They extracted, transformed and loaded (ETL) some or all

Table 1 Country, geographic coverage, data sources, birth years, total sample of children, years of follow-up and the maximum age at the end of follow-up for each country/region

Country/region	Geographic coverage	Source of births	Birth years included	Total sample of children	Total years of follow-up	Mean years of follow-up	End of follow-up
Finland	National	Medical Birth Register (MBR)	1996–2018	1,317,890	15,621,755	11.9	17 years[a]
France: EFEMERIS	80% of the population of the Haute-Garonne region	EFEMERIS	01/07/2005–31/12/2013	75,485		8	8 years[b]
France: POMME 2010	Subsample of EFEMERIS		01/07/2010–30/06/2011	8363	76,969	9.2	10½ years
France: POMME 2015	Subsample of EFEMERIS		01/07/2015-30/06/2016	10,476	50,539	4.8	5½years
Italy: Emilia Romagna	Emilia Romagna region	Certificato di assistenza al parto (CedAP—births)	2010–2020	413,867	2,442,668	5.9	10 years
Norway	National	Medical Birth Registry (MBRN)	2008–2019	678,772	4,348,321	6.4	11 years
Wales	National[c]	Office for National Statistics (ONS)	2000–2020	644,148	6,750,952	10.5	17 years[a]
Total[d]			1996–2020	3,130,162	29,291,204	9.4	

EFEMERIS Evaluation chez la Femme Enceinte des MEdicaments et de leurs RISques; *POMME* PrescriptiOn Médicaments Mères Enfants; *RHE31* Registre des handicaps de l'enfant

[a]Longer follow-up is possible, but the study was restricted to children < 18 years of age

[b]Children are not followed up in EFEMERIS or in the RHE31 disability register; instead, assessments of ASD are recorded at 5 and 8 years of age

[c]Wales holds national data, with 100% coverage, for all datasets except primary care records of prescribing and diagnoses. About 85% of primary care practices contribute data, voluntarily

[d]The children in EFEMERIS are included in the total but not those in POMME 2010 and 2015 as these are subsamples of EFEMERIS and including them in the total would be double counting

their administrative healthcare data into the ConcePTION common data model (CDM) (Thurin et al., 2022).

The start year of the birth cohorts in each country or region was determined by the year when administrative data on maternal medication exposure during pregnancy and administrative data on neurodevelopmental outcomes in children became available, which ranged from 1996 in Finland to 2010 in Emilia Romagna. In each country/region, all children (< 18 years) born during the study period who were present in the dataset for at least 28 days (8 days for Haute Garonne), and who were 6 months of age or older at the end of follow-up were included. In Wales, 1.6% of children had gaps in follow-up, with the median gap 465 days. Observation periods following these gaps were not included in this study.

Emilia Romagna, Finland and Norway included all births in their region or country during the study period. Wales included all births to women resident in Wales whether they occurred in Wales or England. The EFEMERIS healthcare database includes pregnant women living in the Haute-Garonne region registered under the general state health insurance system (which covers around 80% of the population) and their children. Children with a confirmed diagnosis of ASD at the age 5 or 8 years registered in the RHE31 disability registry are identifiable in EFEMERIS. POMME is a subsample of the EFEMERIS database enriched with medication and healthcare data on the infant/child.

In all five countries/regions, a diagnosis of ADHD or ASD can only be made by a specialist such as a child psychologist, psychiatrist, paediatrician or neurologist with expertise in child development. Specialist diagnoses recorded in administrative healthcare data sources such as hospital inpatient or outpatient records, mental health services or disability registries were available in all five countries (Table 2). Non-specialists, such as primary care physicians or general practitioners (GP), refer children to specialists for assessment and may record diagnoses confirmed by a public or private sector specialist. Primary care diagnoses were only available in Finland and Wales for this study. ADHD may also be identified through specific prescriptions for medications to manage ADHD. In all countries/regions, ADHD prescriptions must be initiated by a specialist, though in some cases, a non-specialist (e.g. the GP) may adjust the dose upon a specialist's request. Finland did not have prescription records (dispensation or reimbursement) for children in this study and only those children in the POMME subsamples of EFEMERIS had prescription data available. Three algorithms were created to identify ADHD and ASD using the available data:

- Algorithm 1 required at least one diagnosis code recorded in a specialist setting
- Algorithm 2 required at least two diagnoses to be recorded, at least 28 days apart, in primary care (adapted from (Lindemann et al., 2017)).
- Algorithm 3 required at least one prescription or dispensation record for a medication used to treat ADHD.

Based on an agreed statistical analysis plan, a central analysis script was developed using the ConcePTION CDM to create the relevant tables. A list of diagnostic codes used to identify ADHD and ASD and medications used to manage ADHD was developed based on previous literature and input from data experts and clinicians in each country/region. This list was then reviewed by an expert on neurodevelopment (ND) (Supplementary Table 1—Supplementary Table 3). The central script was made available to the data access providers (DAPs) in each country/region using GitHub. After running the script locally, each DAP reviewed the results before uploading them to the myDRE secure research platform for collation. Due to data protection rules, Finland and Wales had restrictions preventing the release of counts < 5. On reviewing the preliminary results, individual years were collapsed to three eight-year birth cohorts (1996–2003, 2004–2011, and 2012–2019/2020) and children's ages were collapsed to 0–4, 5–6, 7–12, and 13–17-years age groups to allow the maximum granularity while meeting small number restrictions.

Statistics

The period prevalence of ADHD and ASD per 1000 children for the whole sample and by birth cohort was calculated for each algorithm in each country/region. Prevalence per 1000 child years was calculated by age group. The numerator was the number of child-years following diagnosis of ASD or ADHD in the age group concerned, and the denominator was the number of child-years in the age group. Once a child met the requirements of an algorithm identifying ADHD or ASD, they were considered to have ADHD or ASD in all subsequent years of follow-up. For algorithm 1 or 3, this was the date of the first diagnosis or prescription, while for algorithm 2, it was the date of the second diagnosis.

An example for ADHD in the 5–6 year age group is shown below.

$$\frac{\begin{array}{c}\text{Sum of the number of years that children aged } 5-6 \text{ years had} \\ \text{following ADHD diagnosis (in child} - \text{years)}\end{array}}{\begin{array}{c}\text{Total number of years children were} \\ \text{aged } 5-6 \text{ years (in child} - \text{years)}\end{array}} \times 1000$$

For countries/regions with data allowing them to test more than one algorithm for ADHD or ASD, we calculated the number of children identified by each algorithm and the number determined by more than one algorithm to assess

Table 2 Country, ND outcomes, data sources and available years used for ADHD and ASD algorithms

Country/region	ND outcomes	ADHD and ASD		ADHD specific
		Algorithm 1: At least one diagnosis recorded in a specialist setting Data sources (Coding classification system)	Algorithm 2: At least two diagnoses recorded in primary care Data sources (Coding classification system)	Algorithm 3: At least one prescription/ dispensation Data sources (Coding classification system)
Finland	ASD and ADHD	Care Register for Health Care (hospital inpatient 1996–2019 and outpatient records 1998–2019) (ICD-10)	Register of Primary Health Care visits 2013–2019 (ICD-10/ICPC2)	–
France: EFEMERIS	ASD	RHE31 disability registry 01/07/2005–31/12/2021[a] (ICD-10)	–	–
France: POMME 2010[b]	ADHD	–	–	Prescribing records 2010–2020 (ATC)
France: POMME 2015[b]	ADHD	–	–	Prescribing records 2015 to 2020 (ATC)
Italy: Emilia Romagna	ASD and ADHD	Sistema informativo regionale Neuropsichiatria infantile e dell'adolescenza (SinpiaER -Neuropsychiatry service for childhood and young people) and Sistema informativo salute mentale (SISM—regional mental health service) 2010–2020 (ICD-10)	–	Assistenza Farmaceutica Territoriale /Farmaci ad erogazione diretta(medications dispensed in public and private community pharmacies/ medications dispensed from hospital outpatient pharmacies) 2010–2020 (ATC)
Norway	ASD and ADHD	Norwegian Patient Registry (NPR) (hospital and outpatient specialist records) 2008–2019 (ICD-10)	–	Norwegian Prescription Database (NorPD) 2008–2019 (ATC)
Wales	ASD and ADHD	Patient Episode Database for Wales (hospital in-patient records) and Outpatient Dataset for Wales (hospital out-patient records) 2000–2020 for ASD only (ICD-10)	Primary Care GP dataset 2000–2020 for ASD only (Read v2)	Primary Care GP dataset (Prescribing records) 2000–2020 (ATC / Read v2)

[a]Assessments of ASD are recorded in the RHE31 disability register at 5 and 8 years of age

[b]Children in POMME were not linked to RHE31 as they were already to RHE31 as a subsample of EFEMERIS

ATC = Anatomical Therapeutic Chemical Classification; EFEMERIS = Evaluation chez la Femme Enceinte des MEdicaments et de leurs RISques, ICD-10 = International Classification of Diseases, 10th revision; ICPC2 = International Classification of Primary Care, 2nd edition; POMME = PrescriptiOn Médicaments Mères Enfants; RHE31 = Registre des handicaps de l'enfant

how different data sources allow the identification of additional cases.

We also explored how diagnostic and treatment practices varied across countries/regions in all children with a diagnosis of ADHD or ASD recorded in primary care, i.e. not just those with two or more diagnoses. In each country, we calculated the total number of children with a recorded diagnosis, the median (interquartile range, IQR), and mean (standard deviation, SD) age at first diagnosis for all children, by sex and diagnostic setting (specialist/primary care). We also calculated the ratio of males to females for ADHD and ASD, and for children with multiple diagnoses, the time in months between the first and second diagnosis. The number of children with a prescription for an ADHD medication and the age at first prescription was examined for males, females and the total population. For countries with both diagnostic and prescription data, the time interval between the first ADHD diagnosis and the first ADHD prescription/ dispensation was calculated.

A two-sample t-test was used to compare the mean age at first diagnosis of ADHD or ASD and age at first prescription for males and females in each country. A Bonferroni correction was performed for multiple comparisons and set the 95% significance level at $p < 0.004$.

Ethical Approval

An umbrella protocol was developed for partners to obtain local ethical and governance approval; see Statements and Declarations for additional information. The Ulster University Institute of Nursing and Health Research Ethics Filter Committee (FCNUR) gave ethical approval for this study,

approval number FCNUR-21-110; see the Ethics statement for the approvals for each data source.

Results

A total of 3,130,162 children were included and followed up for 29,291,204 child-years.

ADHD Prevalence

For algorithm 1 (diagnoses recorded in specialist setting), the overall prevalence of ADHD was 17.5 per 1000 children ranging from 3.9 in Emilia Romagna to 24.1 per 1000 children in Finland. For algorithm 2 (two or more diagnoses recorded in primary care), ADHD prevalence was 7.0 per 1000 children in Finland, which was the only country that had primary care ADHD diagnoses analysed in this study. For algorithm 3 (prescribed/dispensed ADHD medication), prevalence was 7.2 per 1000 children ranging from 0.1 per 1000 children in Emilia Romagna to 9.9 per 1000 children in the 2010 POMME cohort, Table 3

The prevalence of ADHD was generally greater among children in the earlier birth cohorts, Table 3. The prevalence of ADHD based on diagnoses recorded in specialist settings (algorithm 1) was similar in Finland and Norway (33.5 and 31.2 per 1000 children born 2004–2011 and 2008–2011 respectively), while it was lower in Emilia Romagna (9.0 per 1000 children born 2010–2011). In Finland, in primary care (algorithm 2) the prevalence was just over a third of that seen in specialist settings at 11.8 per 1000 children. The prevalence of ADHD based on prescribed medication (algorithm 3) ranged from 0.4 per 1000 children born 2010–2011 in Emilia Romagna to 24.0 per 1000 children born 2008–2011 in Norway. In Finland, the prevalence of ADHD was higher among children born between 2004–2011 than in children born between 1996–2003 for both algorithm 1 and 2.

All countries had some children with ADHD in the 0–4 age group (Fig. 1) and all except POMME 2015 had children with ADHD in the 5–6 year age group. The prevalence

Table 3 Number of children in each birth cohort and number of affected children and prevalence of ADHD per 1000 children based on algorithms 1–3 in each country/region

Country/region	Birth cohort	Total children in cohort	Algorithm 1: At least one diagnosis recorded in a specialist setting		Algorithm 2: At least two diagnoses recorded in primary care		Algorithm 3: At least one prescription/dispensation	
			Children identified (n)	Prevalence per 1000 children (95% CI)	Children identified (n)	Prevalence per 1000 children (95% CI)	Children identified (n)	Prevalence per 1000 children (95% CI)
Finland	1996–2003	459,319	14,617	31.8 (31.3–32.3)	3,506	7.6 (7.4–7.9)	–	–
	2004–2011	475,452	15,913	33.5 (33.0–34.0)	5,605	11.8 (11.5–12.1)	–	–
	2012–2018	383,119	1293	3.4 (3.2–3.6)	109	0.3 (0.2–0.3)	–	–
	All years	1,317,890	31,823	24.1 (23.9–24.4)	9220	7.0 (6.9–7.1)	–	–
France: POMME 2010	2010–2011	8363	–	–	–	–	83	9.9 (7.9–12.3)
France: POMME 2015	2015–2016	10,476	–	–	–	–	5	0.5 (0.2–1.1)
Italy: Emilia Romagna	2010–2011	93,822	842	9.0 (8.4–9.6)	–	–	40	0.4 (0.3–0.6)
	2012–2020	320,045	790	2.5 (2.3–2.6)	–	–	12	0.0 (0.0–0.1)
	All years	413,867	1632	3.9 (3.8–4.1)	–	–	52	0.1 (0.1–0.2)
Norway	2008–2011	245,824	7660	31.2 (30.5–31.9)	–	–	5904	24.0 (23.4–24.6)
	2012–2019	432,948	1098	2.5 (2.4–2.7)	–	–	545	1.3 (1.2–1.4)
	All years	678,772	8758	12.9 (12.6–13.2)	–	–	6449	9.5 (9.3–9.7)
Wales	2000–2003	162,008	–	–	–	–	2638	16.3 (15.7–16.9)
	2004–2011	243,566	–	–	–	–	3257	13.4 (12.9–13.8)
	2012–2020	238,574	–	–	–	–	196	0.8 (0.7–0.9)
	All years	644,148	–	–	–	–	6091	9.5 (9.2–9.7)
Total: All countries/regions combined[a]	1996–2003	621,327	14,617	31.8 (31.3–32.3)	3506	7.6 (7.4–7.9)	2638	16.3 (15.7–16.9)
	2004–2011	1,067,027	24,415	30.0 (29.6–30.3)	5605	11.8 (11.5–12.1)	9284	15.7 (15.4–16.0)
	2012–2020	1,385,162	3181	2.8 (2.7–2.9)	109	0.3 (0.2–0.3)	758	0.8 (0.7–0.8)
	All years	3,073,516	42,213	17.5 (17.3–17.7)	9220	7.0 (6.9–7.1)	12,680	7.2 (7.1–7.3)

[a] For each birth cohort in the Total rows the prevalence is based on only those countries/regions who ran the algorithm

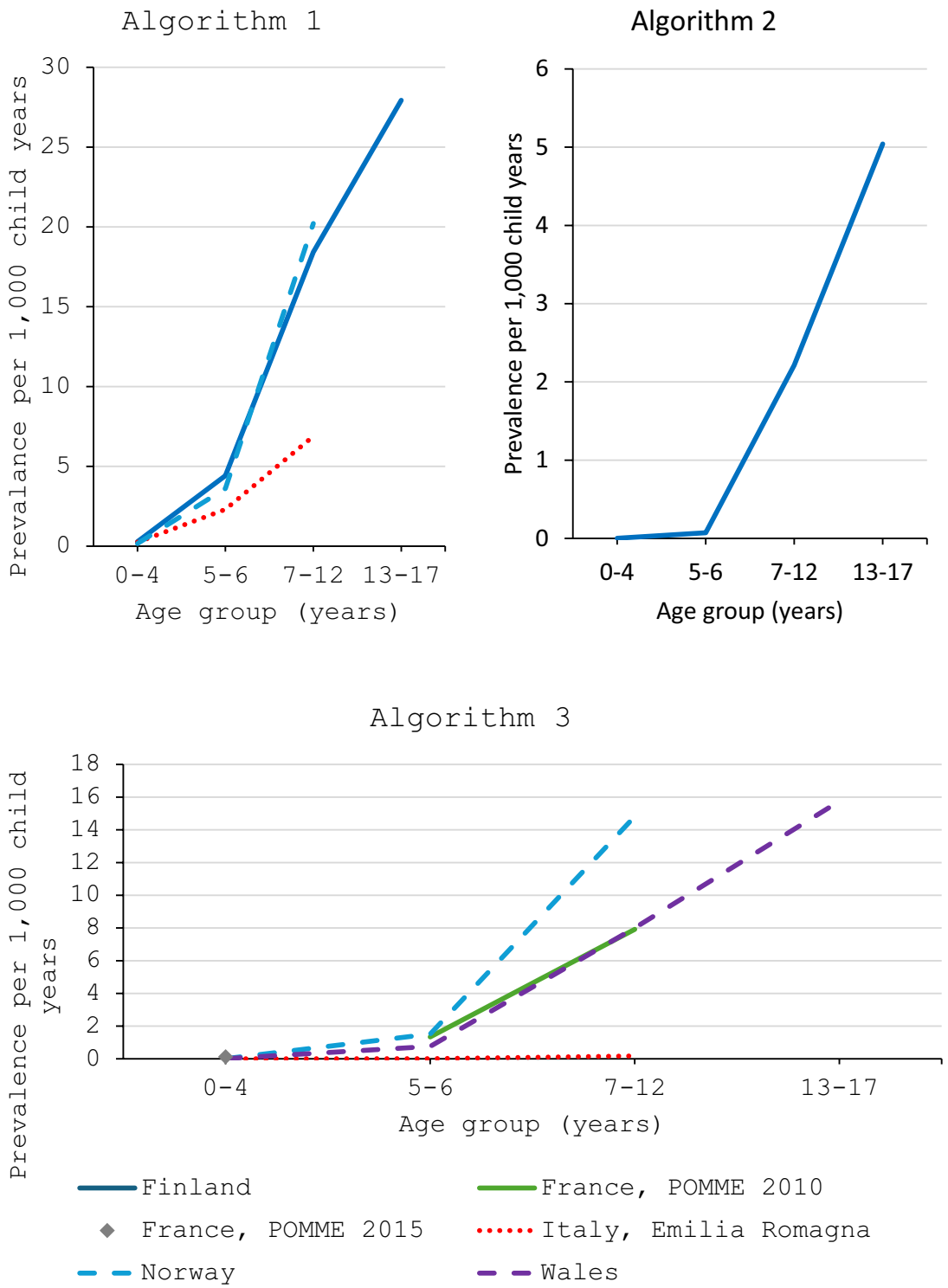

Fig. 1 Prevalence of ADHD per 1000 child years by age based on algorithm 1 (diagnoses in a specialist setting), algorithm 2 (diagnoses in primary care) and algorithm 3 (prescribed/dispensed ADHD medications)

of ADHD in children aged 5–6 years ranged from 2.3 per 1000 child years in Emilia Romagna to 4.4 per 1000 child years in Finland with algorithm 1, Fig. 1. The prevalence of ADHD based on algorithm 2 was much lower at 0.1 per 1000 child years in Finland. Very few children aged 5–6 years were treated with medication for ADHD in Emilia Romagna (0.01 per 1000 child years), with POMME 2010 and Norway having a similar prevalence of medication use

at 1.3–1.5 per 1000 child years and Wales having approximately half their prevalence (0.8 per 1000 child years).

ASD Prevalence

The overall prevalence of ASD was 8.0 per 1000 children for algorithm 1, ranging from 5.6 per 1000 children in Wales to 9.7 per 1000 children in Finland, (Table 4). Prevalence was similar in France and Norway at 6.6 and 6.9 per 1000 children, respectively, and slightly higher in Emilia Romagna at 8.4 per 1000 children. Based on diagnoses recorded in primary care (algorithm 2), the overall prevalence was 1.3 per 1000 children based on Finland (1.0 per 1000 children) and Wales (2.0 per 1000 children).

The prevalence of ASD was also greater in earlier birth cohorts. In a specialist setting (algorithm 1), the prevalence was similar in Emilia Romagna (7.2 per 1000 children born 2010–2011) and Wales (7.5 per 1000 children born 2004–2011). Finland had the highest prevalence at 11.1 per 1000 children born 2004–2011, followed by Norway at 9.9 per 1000 children born 2008–2011. France had the lowest prevalence at 6.2 per 1000 children born 2005–2011. Based on diagnoses recorded in primary care, Wales had a higher prevalence of ASD (2.3 per 1000 children born 2004–2011) than Finland (1.2 per 1000 children born 2004–2011).

The prevalence of ASD was typically higher than that of ADHD in children aged 0–4 years, with ADHD more prevalent as children get older. For ASD, Wales had the lowest prevalence in children aged 5–6 years (2.1 per 1000 child years) using algorithm 1, while Emilia Romagna had the highest prevalence (8.5 per 1000 child years) (Fig. 2). In EFEMERIS-RHE31, children are assessed at 5 and 8 years old rather than being followed up. The prevalence of ASD was 6.1 per 1000 children at 5 years of age in EFEMERIS-RHE31, and 6.6 per 1000 children at 8 years, which is in keeping with that seen for other countries. Emilia Romagna was an exception to the general increasing ASD prevalence with increasing age; based on algorithm 1 the prevalence of ASD was lower in the 7–12 age group (7.7 per 1000 child years) compared to the 5–6 age group (8.5 per 1000 child years) but the CIs overlapped.

Additional Children Identified by Algorithms

When available, primary care data identified children with ADHD or ASD that were not identified in specialist care records. 11.4% of children with ADHD and 1.7% of children with ASD in Finland had diagnoses recorded in primary care but not in specialist setting. Primary care was much more important in identifying ASD in Wales, where

Table 4 Number of children in each birth cohort and prevalence of ASD per 1000 children based on algorithms 1–2 in each country/region

Country/ region	Birth cohort	Total children in the cohort	Algorithm 1: At least one diagnosis recorded in specialist care		Algorithm 2: At least two diagnoses recorded in primary care	
			Children identified (n)	Prevalence per 1000 children (95% CI)	Children identified (n)	Prevalence per 1000 children (95% CI)
Finland	1996–2003	459,319	6332	13.8 (13.5–14.1)	670	1.5 (1.4–1.6)
	2004–2011	475,452	5299	11.1 (10.8–11.4)	573	1.2 (1.1–1.3)
	2012–2018	383,119	1143	3.0 (2.8–3.2)	34	0.1 (0.1–0.1)
	All years	1,317,890	12,774	9.7 (9.5–9.9)	1277	1.0 (0.9–1.0)
France, EFEMERIS-RHE31	2005–2011	54,705	340	6.2 (5.6–6.9)	–	–
	2012–2013	20,780	157	7.6 (6.4–8.8)	–	–
	All years	75,485	497	6.6 (6.0–7.2)	–	–
Italy, Emilia Romagna	2010–2011	93,822	676	7.2 (6.7–7.8)	–	–
	2012–2020	320,045	2796	8.7 (8.4–9.1)	–	–
	All years	413,867	3472	8.4 (8.1–8.7)	–	–
Norway	2008–2011	245,824	2423	9.9 (9.5–10.3)	–	–
	2012–2019	432,948	2236	5.2 (5.0–5.4)	–	–
	All years	678,772	4659	6.9 (6.7–7.1)	–	–
Wales	2000–2003	162,008	1106	6.8 (6.4–7.2)	572	3.5 (3.2–3.8)
	2004–2011	243,566	1833	7.5 (7.2–7.9)	572	2.3 (2.2–2.5)
	2012–2020	238,574	684	2.9 (2.7–3.1)	174	0.7 (0.6–0.8)
	All years	644,148	3623	5.6 (5.4–5.8)	1318	2.0 (1.9–2.2)
Total: All countries/ regions combined [a]	1996–2003	621,327	7,438	12.0 (11.7–12.2)	1242	2.0 (1.9–2.1)
	2004–2011	1,113,369	10,571	9.5 (9.3–6.7)	1145	1.6 (1.5–1.7)
	2012–2020	1,395,466	7,016	5.0 (4.9–5.1)	208	0.3 (0.3–0.4)
	All years	3,130,162	25,025	8.0 (7.9–8.1)	2595	1.3 (1.3–1.4)

[a] For each birth cohort in the Total rows, the prevalence is based on only those countries with data available

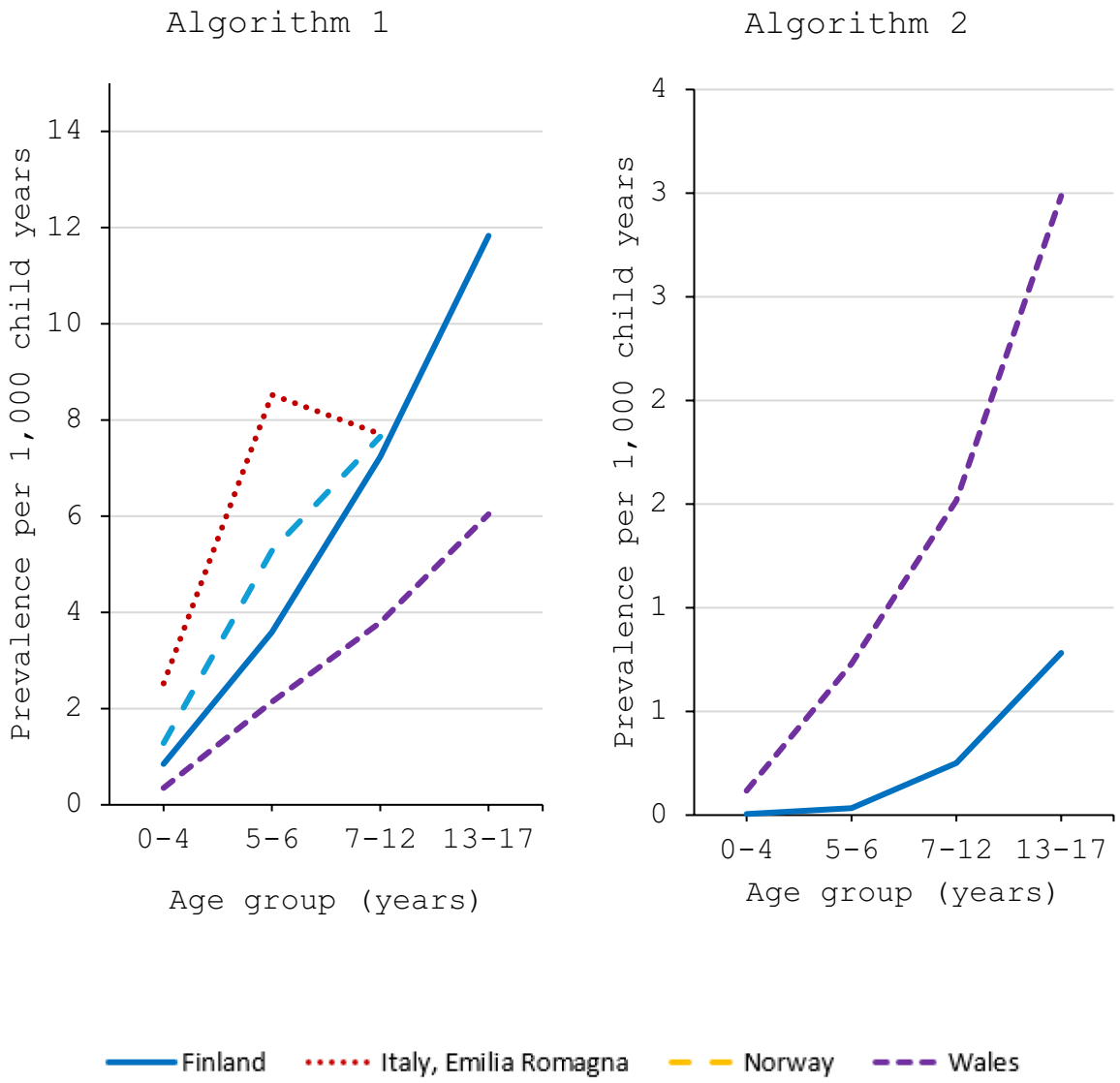

Fig. 2 Prevalence of ASD per 1000 child years by age based on algorithm 1 (diagnoses in a specialist setting) and 2 (diagnoses in primary care)

almost a fifth of all cases were identified in primary care but not specialist settings.

Using prescribing data identified an additional 0.6% of children with ADHD in Emilia Romagna and 2.8% of children with ADHD in Norway who did not have a diagnosis recorded in a specialist setting. However, most children with ADHD medication prescribed/dispensed had a diagnosis recorded in the specialist setting (80.1% in Emilia Romagna and 96.1% in Norway). The proportion of those with an ADHD diagnosis taking a medication increased with the increasing number of diagnoses recorded in both countries. Despite this, just 3.2% of those with an ADHD diagnosis were taking medication in Emilia Romagna compared with 73.6% in Norway.

Age at First Diagnosis of ADHD and ASD and Prescription for ADHD

The median age of first diagnosis for ADHD in specialist setting was similar in Emilia Romagna, Norway and Finland at 6 (IQR 5–7), 7 (IQR 6–8) and 8 (IQR 6–11) years respectively (Table 5). In primary care, the median age at first diagnosis in Finland was older at 10 (IQR 8–13) years of age. For ASD, the median age of first diagnosis in specialist setting was lowest in Emilia and Romagna and Norway at 3 (IQR 2–4) and 4 (IQR 3–6) years, respectively, with the median age in both Finland and Wales being 8 years, (Table 6). In primary care, the median age for recording a diagnosis in Wales was similar to that in specialist setting,

Table 5 Number of males and females with an ADHD diagnosis, Ratio of males to females, Median (Interquartile range) and Mean (standard deviation) age of first diagnosis for males, females and all children with ADHD and results of two-sample t-test for comparison of mean age at diagnosis for males and females in each country and setting

Country and setting	Total number of children with a diagnosis		Ratio (Male: Female)	Age at first diagnosis						
	Male (n)	Female (n)		Male		Female		*p-value*	Total	
				Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)		Median (IQR)	Mean (SD)
Finland: Specialist care	25,182	6641	3.8:1	8 (6–10)	8.5 (3.1)	9 (7–13)	9.7 (3.9)	<0.001	8 (6–11)	8.7 (3.3)
Finland: Primary care	15,974	3986	4:1	10 (8–13)	10.6 (3.2)	11 (8–14)	11.3 (3.5)	<0.001	10 (8–13)	10.8 (3.3)
Italy, Emilia Romagna	1329	303	4.4:1	6 (5–7)	5.9 (1.9)	6 (5–7)	5.9 (1.9)	1.0	6 (5–7)	5.9 (1.9)
Norway	6436	2322	2.8:1	7 (6–8)	7.2 (1.7)	7 (6–9)	7.3 (1.9)	0.02	7 (6–8)	7.2 (1.8)

The number of children with a diagnosis in primary care does not equal the number identified by algorithm 2 as the requirement for≥two primary care diagnoses was not used when exploring diagnostic variation across countries

Table 6 Number of males and females with an ASD diagnosis, Ratio of males to females, Median (Interquartile range) and Mean (standard deviation) age of first diagnosis for males, females and all children with ASD and results of two-sample t-test for comparison of mean age at diagnosis for males and females in each country and setting

Country and setting	Total number of children with a diagnosis		Ratio (Male: Female)	Age at first diagnosis						
	Male (n)	Female (n)		Male		Female		p-value	Total	
				Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)		Median (IQR)	Mean (SD)
Finland: Specialist setting	9754	3020	3.2:1	7 (4–11)	7.7 (4)	9 (4–13)	8.7 (4.7)	<0.001	8 (4–11)	8 (4.2)
Finland: Primary care	2904	757	3.8:1	12 (8–14)	11.3 (3.9)	13 (9–15)	11.7 (4)	0.01	12 (8–14)	11.4 (3.9)
Italy, Emilia Romagna	2748	724	3.8:1	3 (2–4)	3.4 (1.7)	3 (2–4)	3.2 (1.6)	0.0044	3 (2–4)	3.3 (1.7)
Norway	3713	946	3.9:1	4 (3–6)	4.5 (2.4)	4 (3–6)	4.5 (2.6)	1	4 (3–6)	4.5 (2.4)
Wales: Specialist setting	2866	757	3.8:1	7 (5–11)	8.1 (4.1)	9 (5–14)	9.2 (4.7)	<0.001	8 (5–12)	8.3 (4.3)
Wales: Primary care	7173	2008	3.6:1	7 (4–10)	7.5 (4)	9 (4–13)	8.7 (4.5)	<0.001	7 (4–11)	7.7 (4.1)

The number of children with a diagnosis in primary care does not equal the number identified by algorithm 2 as the requirement for≥two primary care diagnoses was not used when exploring diagnostic variation across countries

while for Finland, it was again much older than that in specialist setting at 12 (IQR 8–14) years of age.

The proportion of males with an ADHD or ASD diagnosis recorded was higher than the proportion of females. Among children with an ADHD diagnosis recorded in specialist setting, the ratio of males to females ranged from 2.8:1 in Norway to 4.4:1 in Emilia Romagna with the ratio similar in specialist and primary care in Finland (3.8:1 and 4:1 respectively) (Table 5). For those with ASD, the ratio in specialist settings was relatively consistent ranging from 3.2:1 in Finland to 3.9:1 in Norway. In primary care the ratio of males to females was similar to that seen in the specialist setting for both Finland and Wales.

The mean age of diagnosis for females with ADHD in Finland was older than that of males in both specialist (1.2 years older) and primary care settings (0.7 years older) ($p<0.05$), with no difference between males and females in other countries ($p>0.05$). Females with ASD were also diagnosed later than males in specialist settings in Finland (1 year older) and both specialist and primary care settings in Wales (1.1 and 1.2 years older, respectively).

For both ADHD and ASD, the time between the first and second diagnosis of ADHD or ASD within each setting was typically a few months except for primary care in Finland and both specialist and primary care in Wales, where it was a year or more (Supplementary Table 4).

The age at first prescription of ADHD medication was generally consistent across countries at 7 or 8 years of age, with just Wales starting medication slightly older at 9–10 years of age (Table 7). Despite there being no difference between males and females in terms of age at diagnosis in Norway and Wales, males were started on medication earlier than females in both countries. The number of children taking medication was small in Emilia Romagna and POMME (2010 and 2015) so there was low power to detect differences, but females in Emilia Romagna were started on medication a year younger than males. Only males were taking medication for ADHD in the POMME 2015 cohort and had their first prescription at a much younger age than the other countries. This is an artifact of the limited follow-up for these children (5½ years).

Emilia Romagna and Norway were the only countries to have both prescription and diagnoses available. The median

Table 7 Number of children in each country with prescribing data who have prescriptions for an ADHD medication, median and mean age at first prescription for males, females and all children and p-value for difference in mean age of first prescription between males and females

Country	Children with ≥ 1 ADHD medication			Age at first prescription						
				Males		Females		p-value	Total	
	Males	Females	Total	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)		Median (IQR)	Mean (SD)
France: POMME 2010	66	17	83	7 (6–8)	7.2 (1.4)	7 (7–9)	7.4 (1.6)	0.61	7 (6–8)	7.3 (1.4)
France: POMME 2015	5	0	5	4 (2–5)	3.4 (1.8)	-	0 (0)	-	4 (2–5)	3.4 (1.8)
Italy, Emilia Romagna	45	7	52	8 (7–9)	7.9 (1.2)	7 (7–9)	6.9 (3.2)	0.13	8 (7–9)	7.8 (1.6)
Norway	4750	1699	6449	8 (7–9)	7.6 (1.5)	8 (7–9)	7.8 (1.5)	< 0.001	8 (7–9)	7.7 (1.5)
Wales	5261	1162	6423	9 (7–11)	9.5 (3.1)	10 (8–13)	10.4 (3.5)	< 0.001	9 (7–12)	9.6 (3.2)

time between the first diagnosis and prescription of medication was 3 months (IQR 1–6)) in Norway but almost a year in Emilia Romagna (10 months, IQR 1.3–15.5). The corresponding mean times were 5.2 months (SD 7.6) in Norway and 13.9 months (SD 18) in Emilia Romagna.

In Finland, 61% of children had their first ADHD diagnosis recorded in a specialist setting, while for ASD, this was 77%. In contrast, in this study, just 28.3% of children in Wales had their first ASD diagnosis recorded in a hospital, with the majority having their first diagnosis recorded by their GP.

Discussion

This is the first study to investigate how prevalence of ADHD and ASD varies within and across countries/regions depending on the type of secondary data used (specialist v primary care) and the length of follow-up available. This information is important for accurate monitoring of these conditions and ensuring these children have timely access to specialist care. As children grow older, the prevalence of both ADHD and ASD increased across all algorithms (Salari et al., 2022, 2023; Sayal et al., 2018; Talantseva et al., 2023; Zeidan et al., 2022). While children in the earlier birth cohorts will have longer follow-up and therefore more opportunity to be diagnosed there was also evidence in Finland of increasing prevalence over time with those born in 2004–2011 having a higher prevalence of ADHD in both specialist and primary care settings than those born in 1995–2003. This finding is explained by the fact that children below school age (< 7 years) in Finland have annual health check-ups in primary care, but the primary care data was only available from 2013, hence primary care diagnoses were not captured for children born in the earlier birth cohort. The prevalence of both ASD (Salari et al., 2022; Talantseva et al., 2023; Zeidan et al., 2022) and ADHD [based on diagnoses (Salari et al., 2023) and medication use (Bachmann et al., 2017)] have increased over time. The rise in ADHD and ASD diagnoses may be attributed to changes in diagnostic criteria over time (Merten et al., 2017), actual increases in the conditions, as well as improvements in diagnostic methods, research quality, access to services, and awareness and acceptance within professional and non-professional communities (Talantseva et al., 2023). It has also been suggested that some of the increase may be due to overdiagnosis (Fombonne, 2023; Kazda et al., 2021; Merten et al., 2017).

It is difficult to compare our results with the literature due to different study designs and methodologies e.g. the data are heterogeneous in terms of the age of assessment, source of diagnosis (administrative healthcare records, parent or teacher ratings or reports, clinical evaluations and screening studies), and the time period included. In our study, the prevalence of ADHD based on diagnoses in Italy (Reale & Bonati, 2018), Finland (Malm et al., 2016), Norway (Hjorth et al., 2021; Wichstrøm et al., 2012) and medication use in Wales (Jick et al., 2004; McCarthy et al., 2012), Norway (Norum et al., 2014) and France (Ponnou & Thomé, 2022) were generally consistent with the literature. However, the prevalence of ADHD medication use in Emilia Romagna in our study was lower than that seen in 0–17 years olds in seven regions of Italy including Emilia Romagna between 2006 and 2011 (0.19 per 1000, 95% CI 0.18–0.21) (Piovani et al., 2016). In our study the maximum age at end of follow-up was 10 years in Emilia Romagna while in the Piovani study it was < 18 years which may explain variations in prevalence estimates. Variation in prevalence based on medication use seen in algorithm 3 reflects the recognised geographical variation in ADHD medication use by country and even regions within countries (Raman et al., 2018).

The prevalence of ASD based on algorithm 1 was also consistent with the literature for Finland (Delobel-Ayoub et al., 2020; Mattila et al., 2011), France (Delobel-Ayoub et al., 2020), Norway (Isaksen et al., 2012) and Italy/ (Narzisi et al., 2020; Valenti et al., 2019). In Wales, when combining both specialist and primary care diagnoses the prevalence was slightly lower than the 9.0 per 1000 children at 18 years of age among those born 1991–2000 (Langley et al., 2023). This can be explained by Langley et al.'s longer follow-up time and additional use of emergency department diagnoses.

Diagnoses recorded in specialist settings/disability registers were the most common source of information and identified the most children with ADHD and ASD. Only Finland accessed diagnostic data recorded in specialist and primary care to identify children with ADHD and ASD. Wales accessed both specialist and primary care data for ASD but relied solely on prescriptions for ADHD. Primary care and prescribing data identified additional affected children and may be the only data sources available in some settings. However, the time, effort and costs of linking to another data source should be balanced against the ability to identify more affected children. For example, linking to prescription data in Emilia Romagna only identified an additional 0.6% of children with ADHD.

The reliance on medication data alone to identify ADHD in France (POMME 2010 and 2015) and Wales will likely underestimate ADHD prevalence. ADHD management guidelines vary by country, with some countries preferring to use non-pharmacological interventions as first-line treatment choices and only use medication as a last resort to manage ADHD. This will affect medication use, which is highlighted by the contrast between Emilia Romagna (3.2% of children diagnosed on medication) and Norway (73.6% of children diagnosed on medication). Indeed, there are marked geographical disparities in ADHD medication use by country and region globally, as well as striking differences between northern and western Europe, with much more medication use in northern Europe (Raman et al., 2018). In the UK in 2016, it was estimated that 41.2% of children with ADHD were receiving stimulant medications (Hoang et al., 2019) which would suggest that the actual prevalence of ADHD in Wales in our study should be at least double that estimated based on prescribing data alone. However, in Wales, many children are diagnosed in non-medical or private services who then inform the GP of the diagnosis. Education, health visiting, and social services' data therefore hold the most complete records for developmental and neurological diversity in Wales, rather than hospital or GP records.

There was also heterogeneity between countries and healthcare settings within countries in terms of the mean/median age of the first recorded diagnosis. In Emilia Romagna, half of the children received a diagnosis of ASD before their 4th birthday, while in Finland, half of the children were aged 9 years before they received a diagnosis in specialist settings and aged 14 years before having a diagnosis captured/recorded in primary care. The median/mean age at first diagnosis for ADHD was higher than that for ASD. This is not surprising given that in Europe, the average age of first concern a child may have autism is 25.3 months (Manuel Posada de la Paz, 2018), while for ADHD, it is commonly concerns raised by teachers which lead to referral (Hodgkins et al., 2013). Globally, the peak age of recognition of ASD is 5.5 years (median age at onset 9 years, IQR 5–14) compared to 9.5 years (median age at onset 12 years, IQR 8–18) for ADHD (Solmi et al., 2022). The relatively low median/mean age of first diagnosis of ASD in Emilia Romagna is in keeping with that previously reported (median 4 years, IQR 3–8) among children aged 0–17 in Catania in Southern Italy (2004–2014) (Ferrante et al., 2015). In contrast, a systematic review of the age of onset and age of diagnosis for ADHD in Europe found the highest age of onset in Finland at 7.5 years, with the mean age at diagnosis in Finland ranging from 7.3 to 9.3 years (Rocco et al., 2021). The much higher age at first diagnosis in primary care in Finland in our study likely reflects the fact that electronic primary care data was only available in Finland from 2013, so initial diagnoses recorded in primary care may have been missed for the older birth cohorts. Also, this combined with our requirement for two diagnoses in primary care before a child is considered to have ADHD or ASD, may have also led to an increased age at first diagnosis.

The later age of diagnosis of both ADHD and ASD in females in Finland compared with males in both primary care and specialist settings was not seen in a previous study of ADHD in Finland, which used the Hospital Discharge Register and included children born 1991–2005 with follow-up to 2011 (mean age of diagnosis males 7.6, SD 2.9 and females 7.6, SD 3.2) (Joelsson et al., 2016). Preliminary results from a study using both diagnoses and prescriptions for those born 1994–2003 in Finland suggest that males are more often diagnosed in childhood (4–12 years) and females in adolescence (13–17 years) (Volotinen et al., 2023). This may indicate that a sex difference in age of diagnosis is present in the more recent birth years included in this study. Females have also been found to be older at the age of first diagnosis of ADHD than males in Sweden (2015) (Klefsjö et al., 2021) and for ADHD and ASD in Denmark (1995–2016) (Dalsgaard et al., 2020). Both ADHD and ASD are reported to present differently in females compared with males. For example, females with ADHD are less hyperactive than males and have fewer difficulties in terms of motor response inhibition and cognitive flexibility (Loyer Carbonneau et al., 2021). Females with ASD have better non-verbal communication (Rynkiewicz et al., 2016), fewer parental reports of repetitive, stereotyped behaviour and teacher-reported externalising and social problems (Mandy et al., 2012) which may mask other diagnostic features and put females at risk of under-diagnosis (Rynkiewicz et al., 2016). It has also been shown that diagnostic instruments are not as sensitive to the female ASD phenotype, creating considerably poorer diagnostic precision in females (Beggiato et al., 2017). There also appears to be a diagnostic sex

bias, meaning that females who meet the criteria for ASD are at disproportionate risk of not receiving a clinical diagnosis (Loomes et al., 2017). Indeed, the true male-to-female ratio may be lower than reported here given that the ratio is higher in studies with higher ascertainment bias and lower in studies with lower ascertainment bias. Similarly, studies which screened whole populations rather than just ascertaining pre-existing diagnoses found a lower male-to-female ratio (Loomes et al., 2017). Given that the secondary data sources used here contain pre-existing diagnoses, the true prevalence of ADHD and ASD among females may have been underestimated to some extent, with just those females who are most severely affected identified. This would be supported by the preponderance of males among those with ADHD and ASD diagnoses and ADHD medication.

All countries had some children diagnosed with ADHD or ASD or prescribed medication for ADHD in the 0–4 year age group, and these children will be the most severely affected. ADHD medications are not licenced for use in this age group (Mylan, 2022), and this is reflected in the relatively consistent age of first prescription across countries of 7–8 years of age. When exploring the risk of adverse outcomes following maternal medication exposure, including individuals diagnosed at 0–4 years may introduce a bias towards those with the most significant and early emerging difficulties which may be attributable to other factors such as monogenic or childhood metabolic conditions. These diagnoses and prescriptions may also represent data errors or may be records of suspected diagnoses. We know of one study which only included children diagnosed with ADHD and ASD from age 4 years (Posserud et al. 2021). However, excluding children < 5 years diagnosed with ADHD or ASD in Emilia Romagna would have excluded 11.5% of child years with ADHD diagnoses, 7.2% of child years with ADHD prescriptions and 41.5% of child years with ASD diagnoses. Early diagnosis of ASD in Italy has been reported previously in L'Aquila, with the prevalence of ASD 3–5 years of age increasing between 2004–2012 (Valenti et al., 2019). It is essential to recognise the variation in diagnostic practice across the regions and countries included in studies, as excluding affected children in this way would mask the adverse effects of medications and lead to biased results.

Lessons Learnt

When conducting research to identify children with ADHD and ASD, no single algorithm was optimal or identified all possible children with these outcomes. We recommend including all sources of diagnoses and ADHD prescribing data, where possible, to ensure that all true positives are identified. Diagnoses recorded in primary care may be dependent on visits to the GP for a different reason, or dependent on specialists in private, community or secondary care clinics informing the GP of the diagnosis. Using primary care data alone would not be recommended, as a considerable proportion of those with symptoms of the conditions under investigation would be overlooked, decreasing the power to detect an effect of medication in a drug safety study. A publication in the UK assessing the sensitivity of primary care data to identify the neurodevelopmental impact of antenatal valproate exposure reported similar findings (Charlton et al., 2017).

The length of follow-up is an important consideration for identifying children with ADHD and ASD using secondary data sources. The minimum follow-up period should be longer than the upper quartile of the median age of diagnosis or treatment in the country/setting, or ideally up to 18 years of age. ADHD is typically diagnosed at an older age than ASD, and females with ADHD or ASD are diagnosed later than males. Children born in the 2012–2018 birth cohort had less opportunity to be diagnosed, particularly if they were born in the latter half of this birth cohort. Those who are more severely affected will also be diagnosed earlier than those with milder symptoms, who may not be diagnosed in administrative datasets relying on passive case ascertainment. If a neurodevelopmental toxin leads to atypical symptoms, affected children may not be recorded with a diagnosis in administrative data, leading to underreporting. Therefore, pharmacovigilance studies using electronic healthcare data should be one of a complementary set of investigations used for pregnancy and breastfeeding pharmacovigilance studies where neurodevelopmental outcomes are under investigation (Bromley et al. 2023; Hjorth et al., 2019; Jordan et al. 2022).

Strengths and Weaknesses

The main strength of this study is the large representative sample across five European countries with longer follow-up than would be feasible in prospective cohorts based on primary data collection, due to prohibitive costs and length of follow-up needed. The comprehensive list of diagnoses and medication codes was based on previous literature and were reviewed by an expert clinician.

Using secondary healthcare data has limitations in that those identified as having ADHD/ASD are those with access to services and who have been diagnosed. As a result, studies using insurance claims data and administrative data have the lowest prevalence of ASD (Talantseva et al., 2023). Observational research based on active case-finding approaches, where the whole population is screened irrespective of symptoms, may identify additional children with ND disorders who have been missed by services (Baird

et al., 2006; Loomes et al., 2017; Talantseva et al., 2023). For example, an Italian study found that systematic screening followed by a standardised diagnostic interview identified an additional 15% of children with ASD (Narzisi et al., 2020). However, such active screening approaches may be limited by population coverage, sample representativeness, and response rates from participants (Zeidan et al., 2022).

There also will be some degree of under-ascertainment of ADHD and ASD as children who receive a diagnosis in a private healthcare setting will not necessarily be identified in the administrative healthcare datasets. If private diagnoses are reported to primary care doctors, relying on two diagnoses in the primary care setting will have compounded this issue. Similarly, children whose ADHD or ASD was undiagnosed at the end of follow-up will not be identified, which is more likely to impact on children with more moderate phenotypes (Hjorth et al., 2019; O'Nions et al., 2023) or those in resource-poor regions with long waiting lists. Children with symptoms of these conditions but who do not quite meet the diagnostic criteria or do not have a certain level of severity to lead to specialist assessment would not be detected in this study. This issue may be less critical in countries with some level of free universal screening and health care.

Another key limitation is the lack of external validation of ADHD or ASD diagnoses in secondary data sources. The algorithms used here assumed that once a child met the criteria for ADHD or ASD they continued to have the condition for the rest of their follow-up. However, as a child develops their symptoms may change and they may no longer meet the diagnostic criteria for an earlier diagnosed neurodevelopmental condition. In addition, an error made at the time of first diagnosis may be corrected or, as the symptoms get more specific to the clinician, the initial diagnosis may be refuted and changed. As a result, we do not know what proportion of original diagnoses have been or would be confirmed if the child's clinical notes were reviewed in detail or if they were examined by a different child psychologist, psychiatrist or paediatrician. This may explain some of the use of medication for ADHD in the 0–4 age group and among children with no diagnosis recorded. In Norway, a medical note review of children born 1999–2009 confirmed ADHD diagnoses recorded in the Norwegian Patient Registry in 98% of children, with the remaining 2% of recorded diagnoses appearing to have been registered in error (Surén et al., 2018). A similar study in Finland found that 88% of children diagnosed in 2011 met the full diagnostic criteria of DSM-IV for ADHD, with 95% meeting the symptoms criteria of DSM-IV, 99% of teachers reported ADHD-related behaviour, and 95% of parents considered the symptoms to be impairing (Joelsson et al., 2016).

There may also be some overestimation of ADHD if some of those taking ADHD medications are taking these to control hyperactivity symptoms in patients with other disorders, such as ASD (Raman et al., 2018). In contrast, some medications, such as bupropion or modafinil, may be used off-label to treat ADHD, therefore these children may be misclassified as not having ADHD if there is no diagnosis information recorded or available. Such off-label use will be rare, though, and is preferable to classifying all children taking these medications as having ADHD.

Conclusion

The administrative and research data sources included in this study varied considerably in terms of type of data (specialist/primary care), the periods covered, follow-up available, and the prevalence of ADHD and ASD recorded. While diagnoses recorded in a specialist setting are a crucial source of information, combining them with those recorded in primary care or prescription data enables researchers to identify more potentially affected children. Using primary care data alone was not found to be reliable. The proportion of ADHD diagnoses that would be missed by using only prescription data varies considerably and depends on the prescribing practices within the country. Irrespective of the data source used, it is important to have sufficient length of follow-up available to identify children, particularly girls, who were diagnosed at older ages. In our study, the optimal algorithm for identifying children with ADHD and ASD in administrative datasets is to use a combination of all three algorithms i.e. specialist diagnosis, diagnosis recorded in primary care and medications for ADHD in the five countries/regions of Europe.

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Author Contributions The Principal Investigator was MLo, who conceptualised the study. MLo and JG developed the study protocol and the statistical analysis plan (SAP). All authors reviewed and commented on these documents. JG analysed the data from each country. OP wrote the syntax analysis scripts based on the SAP and liaised with the DAPs to run them. RB reviewed all the diagnostic ADHD and ASD codes in each country. The first draft of the manuscript was written by JG. All authors commented on all versions of the manuscript. All authors contributed to the interpretation, discussed the results and approved the submitted manuscript. *Finland* MLe applied for the study approval and obtained the Finnish data in this study. VM and MLe were responsible for the mapping of the Finnish data onto the ConcePTION CDM. VM was responsible for data curation, running scripts on the Finnish data and debugging. MLe contributed to data interpretation and benchmarking of the Finnish data in the study. MLe reviewed the aggregated Finnish results and approved their upload to the DRE (safe server at UMC). *France* CDM applied for the study approval and obtained the French data in this study. CDM and ABB were responsible for the mapping of the French data onto the ConcePTION CDM. AC was responsible for data curation, running scripts on the French data and debugging. CDM and ABB contributed to data interpretation and benchmarking of the French data in the study. ABB reviewed the aggregated French results and approved their upload to the DRE (safe server at UMC). *Italy* EB and AN applied for the study data and obtained all required approvals for the Italian data in this study. AP was responsible for the mapping of the Italian data onto the ConcePTION CDM. MM was responsible for data curation, running scripts on the Italian data and debugging. AP and MM contributed to data interpretation and benchmarking of the Italian data in the study. MM reviewed the aggregated Italian results and approved their upload to the DRE (safe server at UMC). *Norway* HN applied for the study data and obtained all required approvals for the Norwegian data in this study. HN contributed to data curation and was responsible for the mapping of the Norwegian data onto the ConcePTION CDM. HN contributed to data interpretation and benchmarking of the Norwegian data in the study and signed off on the aggregated Norwegian data that was uploaded to the DRE (safe server at UMC). *Wales* SJ applied for the study data and obtained all required approvals for the Wales data in this study. Daniel Thayer mapped the SAIL data onto the ConcePTION CDM. AC ran and cleaned the scripts, with help from HTE. SJ curated and interpreted the data, benchmarked to published data, and approved uploading of aggregated data.

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Data Availability All relevant data are within the paper and its Supporting Information files. Authors may not share the study data due to regulations which restrict access and distribution to those with ethical and legal permission to use the data. The study material is available to other researchers upon an application to relevant register holders. The datasets generated and analysed for Wales are not publicly available and can only be accessed within the SAIL Trusted Research Environment as part of an approved project. Project application enquiries to the SAIL Databank can be submitted at: https://saildatabank.com/. We confirm that data that are not publicly available are not part of the minimal data set. The study protocol was registered in the EUPAS Registry (EUPAS43385) and is also available in the zenodo repository. All code lists and scripts can be found at: https://github.com/IMI-ConcePTION/DP2_SSRI-SNRI/releases/tag/DP2_v4.0

Declarations

Conflict of interest None.

Ethical Approval Ethical approval for this study was given by the Ulster University Institute of Nursing and Health Research Ethics Filter Committee (FCNUR), approval number FCNUR-21-110. *Finland* Ethical approval is not required for register-based studies. Institutional Review Board at the Finnish Institute for Health and Welfare approved the study and waived the requirement for obtaining informed consent for the secondary use of health administrative data from study participants (THL/543/6.02.00/2021). Data were handled and stored in accordance with the General Data Protection Regulation. *France* The EFEMERIS cohort was approved by the French Data Protection Authority on 7 April 2005 (authorization number 05-1140). This study was performed on anonymized patient data. The women included in the EFEMERIS database were informed of their inclusion and of the potential use of their anonymized data for research purposes. They could oppose the use of their data at any time. The women included in the EFEMERIS database know that their collected and anonymized data can be used for medical research purposes and can thus be published. The study was approved by the EFEMERIS steering group. Data were handled and stored in accordance with the General Data Protection Regulation. *Italy* The study was approved by the local ethical committee (approval number 593/2023/Oss/UniFe). Data were handled and stored in accordance with the General Data Protection Regulation and in agreement with the Authority for Healthcare and Welfare, Emilia Romagna Regional Health Service, Bologna, Italy. We thank Elisa Ballardini and Aurora Puccini for their contributions to this work. *Norway* The study was approved by the Regional Committee for Research Ethics in South-East Norway (approval number 85224) and by the Data Protection Officer at the University of Oslo (approval number 519858). Data were handled and stored in accordance with the General Data Protection Regulation. *Wales* This study uses anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank.[1,2] The SAIL Databank independent Information Governance Review Panel (IGRP) approved the study as part of project 0823, on 16th October 2020.

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