

Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases



Sudha R Raman*, Kenneth K C Man*, Shahram Bahmanyar, Anick Berard, Scott Bilder, Takoua Boukhris, Greta Bushnell, Stephen Crystal, Kari Furu, Yea-Huei KaoYang, Øystein Karlstad, Helle Kieler, Kiyoshi Kubota, Edward Chia-Cheng Lai, Jaana E Martikainen, Géric Maura, Nicholas Moore, Dolores Montero, Hidefumi Nakamura, Anke Neumann, Virginia Pate, Anton Pottegård, Nicole L Pratt, Elizabeth E Roughead, Diego Macias Saint-Gerons, Til Stürmer, Chien-Chou Su, Helga Zoega, Miriam C J M Sturkenboom, Esther W Chan, David Coghill, Patrick Ip, Ian C K Wong

Summary

Background The use of medications to treat attention deficit hyperactivity disorder (ADHD) has increased, but the prevalence of ADHD medication use across different world regions is not known. Our objective was to determine regional and national prevalences of ADHD medication use in children and adults, with a specific focus on time trends in ADHD medication prevalence.

Methods We did a retrospective, observational study using population-based databases from 13 countries and one Special Administrative Region (SAR): four in Asia and Australia, two in North America, five in northern Europe, and three in western Europe. We used a common protocol approach to define study populations and parameters similarly across countries and the SAR. Study populations consisted of all individuals aged 3 years or older between Jan 1, 2001, and Dec 31, 2015 (dependent on data availability). We estimated annual prevalence of ADHD medication use with 95% CI during the study period, by country and region and stratified by age and sex. We reported annual absolute and relative percentage changes to describe time trends.

Findings 154·5 million individuals were included in the study. ADHD medication use prevalence in 2010 (in children aged 3–18 years) varied between 0·27% and 6·69% in the countries and SAR assessed (0·95% in Asia and Australia, 4·48% in North America, 1·95% in northern Europe, and 0·70% in western Europe). The prevalence of ADHD medication use among children increased over time in all countries and regions, and the absolute increase per year ranged from 0·02% to 0·26%. Among adults aged 19 years or older, the prevalence of any ADHD medication use in 2010 varied between 0·003% and 1·48% (0·05% in Asia and Australia, 1·42% in North America, 0·47% in northern Europe, and 0·03% in western Europe). The absolute increase in ADHD medication use prevalence per year ranged from 0·0006% to 0·12%. Methylphenidate was the most commonly used ADHD medication in most countries.

Interpretation Using a common protocol and data from 13 countries and one SAR, these results show increases over time but large variations in ADHD medication use in multiple regions. The recommendations of evidence-based guidelines need to be followed consistently in clinical practice. Further research is warranted to describe the safety and effectiveness of ADHD medication in the short and long term, and to inform evidence-based guidelines, particularly in adults.

Funding None

Copyright © 2018 Elsevier Ltd. All rights reserved.

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children, with estimated worldwide prevalences in school-aged children of 5–7%.^{1,2} Although ADHD is often perceived as a disorder of childhood and adolescence, there is increasing evidence that symptoms and impairments can persist into adulthood for up to 65% of children with ADHD, and that ADHD is present in approximately 2·5% of adults.^{3,4} ADHD is associated with a diverse range of adverse health, academic, and psychosocial outcomes⁵ and is associated with other

mental health disorders, such as depression, anxiety, and substance misuse.⁵ Although the epidemiological evidence suggests that the prevalence of ADHD is similar across the world, there is considerable variation in the rate of diagnosis between different countries.^{1,7}

Behavioural interventions and drug treatments are frequently used to manage ADHD symptoms and impairments. Guidelines for children from North America, the UK, and Europe recommend the use of stimulants, such as methylphenidate and amphetamines, and non-stimulants, such as atomoxetine, when pharmacological intervention is considered appropriate for the management

Lancet Psychiatry 2018

Published Online
September 13, 2018
[http://dx.doi.org/10.1016/S2215-0366\(18\)30293-1](http://dx.doi.org/10.1016/S2215-0366(18)30293-1)

See Online/Comment
[http://dx.doi.org/10.1016/S2215-0366\(18\)30317-1](http://dx.doi.org/10.1016/S2215-0366(18)30317-1)

*Contributed equally

Department of Population Health Sciences, Duke University School of Medicine, Durham, NC, USA (S R Raman PhD); Department of Paediatrics and Adolescent Medicine

(K K C Man MPH, P Ip MBBS, Prof I C K Wong PhD) and Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy (K K C Man, E W Chan PhD, Prof I C K Wong), Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; Research Department of Policy and Practice, University College London School of Pharmacy, London, UK (K K C Man, Prof I C K Wong); Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands (K K C Man,

Prof M C J M Sturkenboom PhD); Department of Social Work and Social Administration, Faculty of Social Science, The University of Hong Kong, Hong Kong, China (K K C Man); Centre for Pharmacoepidemiology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden (S Bahmanyar PhD, Prof H Kieler PhD); Centre for Psychiatry Research, Karolinska Institutet and Stockholm Health Care Services, Stockholm, Sweden (S Bahmanyar); Faculty of

Pharmacy, University of Montreal, and CHU Ste-Justine Research Center, Montreal, Quebec, Canada (Prof A Berard PhD, T Boukhris MSc); Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA (S Bilder PhD, Prof S Crystal PhD); Department of Epidemiology, University of North Carolina, Chapel Hill Gillings School of Global Public Health, Chapel Hill, NC, USA (G Bushnell PhD, V Pate MS, Prof T Stürmer MD); Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway (K Furu PhD, Ø Karlstad PhD); School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan (Prof Y-H KaoYang BS Pharm, E C-C Lai PhD, C-C Su MSc); Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan (E C-C Lai); Drug Safety Research Unit, Tokyo, Japan (Prof K Kubota PhD); Research Unit, Social Insurance Institution, Helsinki, Finland (J E Martikainen PhD); Department of Studies in Public Health, French National Health Insurance, Paris, France (G Maura PharmD, A Neumann PhD); Bordeaux PharmacEpi, INSERM CIC1401, Université de Bordeaux, Bordeaux, France (Prof N Moore PhD); Spanish Agency for Medicines and Medical Devices, Madrid, Spain (D Montero PhD, D Macias Saint-Gerons PhD); Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Valencia, Spain (D Macias Saint-Gerons); Clinical Research Center, National Center for Child Health and Development, Tokyo, Japan (H Nakamura PhD); Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense, Denmark (A Pottegård PhD); Quality Use of Medicines and Pharmacy Research Centre, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia (N L Pratt PhD, Prof E E Roughead PhD); Centre of Public Health Sciences,

Research in context

Evidence before this study

We searched PubMed for studies written in English published from Jan 1, 1966, to June 21, 2017, with the following terms: “treatment” OR “medication” AND “prevalence” OR “trend” OR “utilization” AND “attention deficit hyperactivity disorder or ADHD or hyperkinetic disorder”. The search yielded 3832 articles. We excluded articles that we deemed not to be relevant on the basis of their titles. We reviewed abstracts of the remaining articles to identify potentially relevant articles and scanned reference lists of relevant articles. The primary criterion was that the study reported attention deficit hyperactivity disorder (ADHD) medication use prevalence. Most previous studies were from Europe and North America, with a few studies from Asia and Australia. However, only studies from northern European countries, the USA, and the UK investigated the prevalence of ADHD medication use in adults. Two multinational studies were identified (in children): one included the five Nordic countries and the other one

included four western European countries and the USA. However, differences in study designs create difficulties in comparing the estimates directly.

Added value of this study

In this cross-national comparison of ADHD medication use, leveraging a common protocol and standard definitions and data from 14 sources relating to more than 150 million individuals, we showed marked differences between countries and multiple world regions, with large absolute and relative increases in the prevalence over time of ADHD medication use in both children and adults.

Implications of all the available evidence

Increasing ADHD medication use in both children and adults supports a need for monitoring medication safety and effectiveness in exposed populations, particularly in adults, because of the scarcity of knowledge about ADHD medication use in this age group.

of ADHD.^{8–12} Compared with children, there are fewer clinical treatment guidelines for adults with ADHD, and fewer medications specifically licensed for the treatment of this disorder in adults.^{10–12} Nevertheless, available guidelines recommend pharmacological treatment as the first-line therapy for ADHD in adults.^{10–12}

In the past few decades, an increased prevalence of ADHD and increased use of ADHD medications have been observed in several countries,^{13–15} raising concerns about possible overdiagnosis and inappropriate prescribing of ADHD medications. In this context, in July, 2013, the UK National Institute for Health and Care Excellence (NICE) issued a guidance to avoid the use of methylphenidate in children and young people with mild and moderate ADHD, amid concerns about stimulant safety and effectiveness.¹⁶

Estimates of the trends of ADHD medication use over time and across countries are needed to give insight about the population-level distribution of medication use. Additionally, because most previous studies have focused on children and adolescents, little is known about the use of ADHD medication in adults. Moreover, some studies have focused on medication use only among individuals diagnosed with ADHD,¹⁷ which might underestimate the exposure to ADHD medication, because it is not uncommon for ADHD medications to be prescribed to control hyperactivity symptoms in patients with other disorders, such as autism spectrum disorder. Therefore, we aimed to describe the prevalence and trends in prevalence over time of ADHD medication use in children, adolescents, and adults, focusing on different age groups, sex, and type of ADHD medications across countries in four regions: Asia and Australia, North America, northern Europe, and western Europe.

Methods

Study design

We used a common protocol to study the prevalence of ADHD medication use in 15 participating sites from 13 different countries and one Special Administrative Region (SAR) across four regions: Asia and Australia (Hong Kong, Japan, Taiwan, and Australia), North America (Canada and two sites in the USA), northern Europe (Denmark, Finland, Iceland, Norway, and Sweden), and western Europe (France, the UK, and Spain). The sites were chosen on the basis of availability of national administrative data. Where such data were not available (USA, Canada, and the UK), we prioritised data sources that had a defined population to serve as the denominator, with data in which we could measure the study parameters (medication prescription and dispensation). Because countries within the research networks of the Nordic Pharmacoepidemiological Network (NorPEN) have a common data and research structure, similar underlying health systems, and have jointly published in this area previously,¹⁸ we decided to maintain the NorPEN countries as one of two European regions. Each country contributed data from administrative databases for the study period, between Jan 1, 2001, and Dec 31, 2015.

All data sources were generated from the automated capture of patient-level electronic data from either administrative clinical records or administrative claims records in a defined population or portion thereof. Additional details about the databases, source populations, health-care systems, methods of medication information capture, coding systems used, and other aspects of data collection are shown in table 1 and the appendix (pp 3–4).

Data collection

In each site, the study population consisted of all individuals who were aged 3 years or older during the study period (subject to data availability in each site). Individuals were grouped by age: 3–5 years (kindergarten or preschool), 6–11 years (primary school), 12–16 years (secondary school), 17–18 years (older adolescent), and 19 years or older (adults). Because data from Canada included only children aged 11 years or younger, Canada was excluded from age-specific analyses for individuals aged 12 years or older.

Where possible, the total number of individuals at each site in each calendar year served as the denominator to calculate prevalence. Otherwise, for databases without universal coverage, census or population data were used

to determine denominator data, defined as the total number of the target age group population in the middle (July) or end (December) of each calendar year in the population database. The numerator (ADHD medication use) was ascertained by examining the medication records of all individuals with data available for each year (table 1; appendix pp 3–4).

Ethical review of or approval for the use of each data source was obtained by the contributing authors and ethics organisations in participating countries: the National Bioethics Committee and Data Protection Authority of Iceland, the French Data Protection Agency, the Health Improvement Network Scientific Review Committee (UK), the Institutional Review Board of the Hospital Authority HK West Cluster (Hong Kong), the

Faculty of Medicine, University of Iceland, Reykjavik, Iceland (Prof H Zoega PhD); Medicines Policy Research Unit, Centre for Big Data Research in Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia (Prof H Zoega); Julius Global Health, University Medical Center Utrecht, Utrecht, Netherlands (Prof M C J M Sturkenbroom); Departments of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC, Australia (Prof D Coghill MD);

	Region	Database	Study start year	Number of years under study	People included (% national population)	Denominator	Health system or data source	Child data (3–18 years)	Adult data (≥19 years)
Norway	Northern Europe	Norwegian Prescription Database	2004	10	5.3 million (100%)	Number of residents at start of year	Universal	Yes	Yes
Denmark	Northern Europe	Danish National Prescription Registry	2001	13	5.6 million (100%)	Number of residents at start of year	Universal	Yes	Yes
Sweden	Northern Europe	Swedish Prescribed Drug Register	2005*	8	9.8 million (100%)	Number of residents at end of year	Universal	Yes	Yes
Finland	Northern Europe	Finnish Prescription Register	2005	8	5.5 million (100%)	Number of residents at end of year	Universal	Yes	Yes
Iceland	Northern Europe	Icelandic Medicines Registry	2003	11	0.33 million (100%)	Number of residents at start of year	Universal	Yes	Yes
France	Western Europe	French National Health Insurance	2006	7	52 million (75%)	Number of insured persons at end of year	Universal	Yes	Yes
Spain	Western Europe	Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria	2001	14	4.8 million (9%)	Number of enrollees at midyear	Universal	Yes	Yes, 19–45 years
UK	Western Europe	The Health Improvement Network	2001	14	11.1 million (6%)	Number of residents at midyear	Universal	Yes	Yes
Hong Kong, China	Asia and Australia	Hong Kong Clinical Data Analysis and Reporting System	2001	15	7 million (100%)	Number of residents at midyear	Universal	Yes	Yes
Taiwan	Asia and Australia	Taiwan National Health Insurance Research Database	2002	9	1 million (5%)	Number of residents at midyear	Universal	Yes	Yes
Japan	Asia and Australia	Japan Medical Data Center Database	2010	6	4 million (3%)	Number of enrolled people at midyear	People enrolled in the insurance plans	Yes	Yes
Australia	Asia and Australia	Australian Pharmaceutical Benefits Scheme	2009	6	22 million (100%)	Number of residents at midyear	Universal	Yes	Yes
Canada	North America	Quebec Pregnancy Cohort†	2001	9	†	Number of insured persons at end of year	People insured by the Régie de l'Assurance Maladie du Québec prescription drug insurance plan	Yes, 3–11 years	No
USA—US MarketScan (private)	North America	Truven MarketScan	2001	14	40 million (about 13%)	Number of enrolled people at midyear	Commercially insured people	Yes	Yes, 19–64 years
USA—US Medicaid (public)	North America	Medicaid Analytic Extract	2001	10	29–38 million (about 20%)	Number of enrolled people at midyear	Publicly insured people (low-income and disabilities)	Yes	Yes

*The Swedish Prescribed Drug Register started recording individual data in July, 2005. †Canadian data are from the Quebec Pregnancy Cohort, a population-based cohort study of over 289 000 pregnancies in 186 000 women during 1998–2009; the data used in this study included 159 064 children.

Table 1: Data source characteristics, by country

and Murdoch Children's Research Institute, Melbourne, VIC, Australia (Prof D Coghill)

Correspondence to: Prof Ian CK Wong, Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China wongick@hku.hk

or Patrick Ip, Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China patricip@hku.hk

See Online for appendix

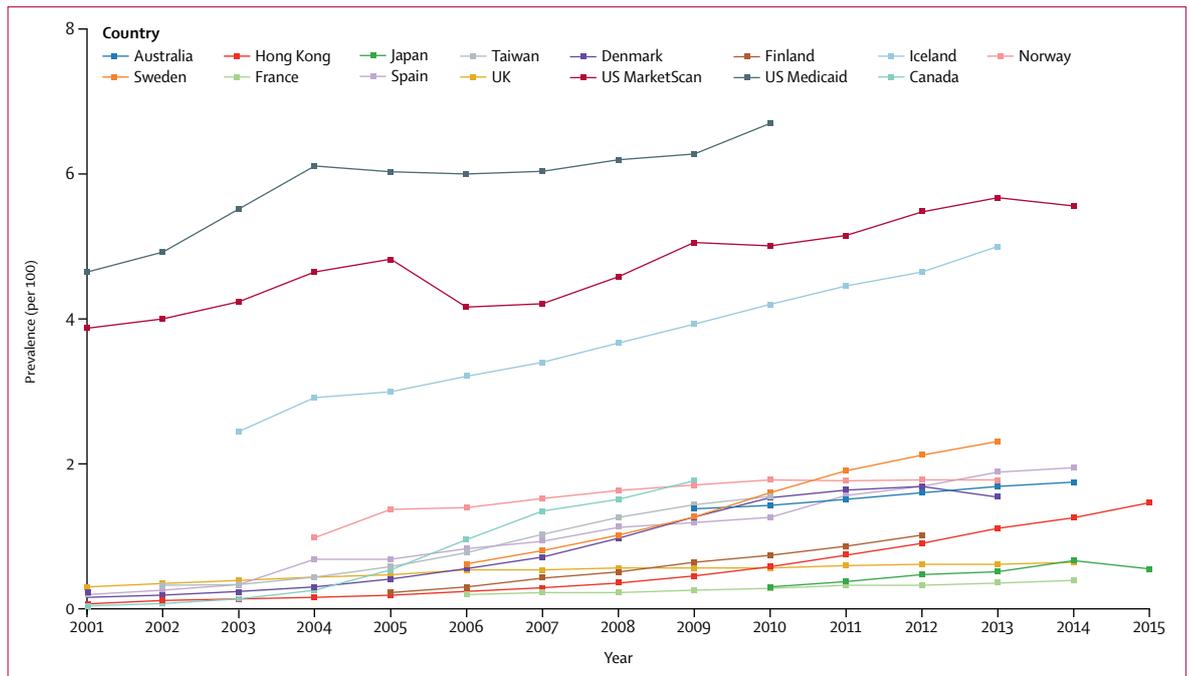


Figure 1: Overall annual prevalence of attention deficit hyperactivity disorder medication use in children aged 3–18 years

Taiwan National Cheng Kung University Hospital Institutional Review Board, the Ethics Review Board of the National Centre for Child Health and Development (Japan), the research ethics board of the Centre Hospitalier Universitaire Sainte-Justine Research Center (Canada), the University of North Carolina Institutional Review Board (USA), and the Rutgers Arts and Sciences Institutional Review Board (USA; appendix pp 5–6). Additional references for the data sources used in this study are listed in the appendix (p 7).

Medication definition

To identify ADHD medication, we examined WHO Anatomical Therapeutic Chemical (ATC) classification codes¹⁹ in the records for prescribed medication, dispensed medication, or insurance claims for dispensed medication. If medications were not coded using the ATC system in a particular database, drug ingredients were mapped to ATC terminology (appendix pp 3–4). Data about medications that were available and licensed for the treatment of ADHD in each country were compiled, with a focus on the most common medications used for ADHD (as listed in appendix pp 8–9). Exposure was defined as an ADHD medication record (either prescribed or dispensed) at least once in the relevant study year. We examined ADHD medication use regardless of a confirmed diagnosis of ADHD.

Data analysis

Only the country-level researchers or data custodians had access to individual-level data. In Australia, the analysis

of individual-level data was done by the staff within the Australian Government Department of Health and the deidentified, aggregate data was approved for release to the Australian researchers. All country-level researchers provided aggregate data to the primary authors (SRR and KKCM), who then assessed the patterns of medication use across the study period, comparing trends over time between the 14 countries and SAR. The annual prevalence of each medication was expressed as a percentage (per 100 individuals). Overall annual prevalence and prevalence by region and country were calculated with a 95% CI estimated by Poisson method.²⁰ Regional pooled prevalences with 95% CI were estimated using DerSimonian and Laird’s random-effects model²¹ to account for heterogeneity across different sites. A linear regression model, assuming a linear trend, was used to test for time trends in the annual prevalence and the absolute changes in prevalence for each year throughout the study period. We fitted one model per region, with year as the only predictor variable in the model. Relative changes in the prevalence per year were assessed as percentage change for each site by the following formula:

$$\frac{prevalence_{curr} - prevalence_{prev}}{prevalence_{prev}} \times 100$$

Age-specific and sex-specific analyses were done. Cross-sectional comparisons of prevalence, type of medications used, and sex ratio (annual ratio of male to female individuals of all ages) by country were made for the year 2010. The statistical significance level was set at $p < 0.05$. We

used Statistical Analysis System (SAS) v9.4 (SAS Institute, Cary, NC, USA), Review Manager 5.3 (Cochrane, London, UK), and Stata SE v11 (StataCorp, College Station, TX, USA) for data manipulation and analysis.

Results

Available data across all sites covered a total of 154.5 million individuals during the study period (table 1). The overall pooled prevalence of ADHD medication use in children and adolescents aged 3–18 years across all regions was 1.95% (95% CI 0.76–3.13; appendix pp 10–17, 29). For children aged 3–18 years, considerable national variation was evident in the prevalence of any ADHD medication use during the study period, ranging from 0.27% (France, 2010) to 6.69% (US Medicaid, 2010; figure 1). Regional prevalence was highest in North America, with a pooled prevalence of 4.48% (95% CI 2.86–6.10), followed by northern Europe (1.95%, 1.47–2.44); the lowest prevalences were observed in Asia and Australia (0.95%, 0.35–1.56) and western Europe (0.70%, 0.31–1.10).

The prevalence of ADHD medication use among children aged 3–18 years increased over time in all countries and regions; the absolute increase per year ranged from 0.02% to 0.26% (table 2). The magnitude of the annual relative increase also varied (appendix pp 10–17). The highest average relative percentage change per year was recorded in northern Europe (15.07% per year [95% CI 7.15–23.00], between 2001 and 2013), followed by Asia and Australia (11.35% per year [2.39–20.32], between 2001 and 2015), North America (10.34% per year [9.46–11.23], between 2001 and 2014), and western Europe (8.96% per year [4.96–12.95], between 2001 and 2014). The average relative percentage increase across all countries was 14.55% per year (95% CI 12.69–16.41), between 2001 and 2015. By country, Canada had the highest yearly increase, with average percentage increases of 45.11% (95% CI 43.50–46.71) per year (in 2001–09), followed by Hong Kong, Taiwan, Finland, Denmark, and Sweden, in order, with increases in prevalence ranging from 24.18% (23.94–24.42) in Hong Kong to 20.15% (19.91–20.39) in Sweden. The lowest average increase per year among all countries was observed in the USA; the two US data sources showed an average increase of 3.16% (95% CI 3.14–3.18, US Medicaid [2001–10]) and 2.83% (2.80–2.86, US MarketScan [2001–14]; appendix pp 10–17).

The age group with the highest annual prevalence of ADHD medication use was age 6–11 years in Asia-Pacific region, US Medicaid, and Finland, and 12–16 years in the remaining sites. The time trend in the age-group-specific prevalence of ADHD medication use was similar to the overall time trend in children (figure 2).

The overall pooled prevalence of ADHD medication use in adults was 0.39% (95% CI 0.31–0.47; appendix 18–25, 30). The national prevalence of any ADHD medication use for adults during the study period ranged from as low as 0.003% (2010) in Japan to as high as

	Children aged 3-18 years		Adults aged 19 years or older	
	Average absolute change per year (95% CI)	p value	Average absolute change per year (95% CI)	p value
Asia and Australia				
Australia	0.08% (0.06–0.09)	<0.0001	0.02% (0.01–0.02)	<0.0001
Hong Kong	0.10% (0.08–0.12)	<0.0001	0.0006% (0.0005–0.0008)	<0.0001
Japan	0.06% (0.02–0.10)	0.0161	0.01% (0.01–0.02)	0.0029
Taiwan	0.17% (0.15–0.20)	<0.0001	0.002% (0.002–0.003)	<0.0001
North America				
Canada	0.24% (0.19–0.29)	<0.0001	..	<0.0001
US MarketScan	0.13% (0.09–0.17)	<0.0001	0.12% (0.10–0.13)	<0.0001
US Medicaid	0.19% (0.11–0.26)	0.0004	0.09% (0.06–0.12)	<0.0001
Northern Europe				
Denmark	0.15% (0.12–0.17)	<0.0001	0.05% (0.04–0.06)	<0.0001
Finland	0.11% (0.11–0.12)	<0.0001	0.01% (0.00–0.02)	0.0055
Iceland	0.24% (0.22–0.26)	<0.0001	0.10% (0.08–0.11)	<0.0001
Norway	0.08% (0.05–0.11)	0.0005	0.04% (0.03–0.04)	<0.0001
Sweden	0.26% (0.24–0.27)	<0.0001	0.07% (0.07–0.08)	<0.0001
Western Europe				
France	0.02% (0.02–0.03)	<0.0001	0.002% (0.002–0.002)	<0.0001
Spain	0.14% (0.13–0.15)	<0.0001	0.007% (0.004–0.009)	<0.0001
UK	0.02% (0.02–0.03)	<0.0001	0.003% (0.003–0.004)	<0.0001

Linear regression models were used to test for time trends in the annual prevalence and the absolute changes in prevalence throughout the study period; separate linear regression models were fitted for each country.

Table 2: Absolute change in annual prevalence of attention deficit hyperactivity disorder medication use

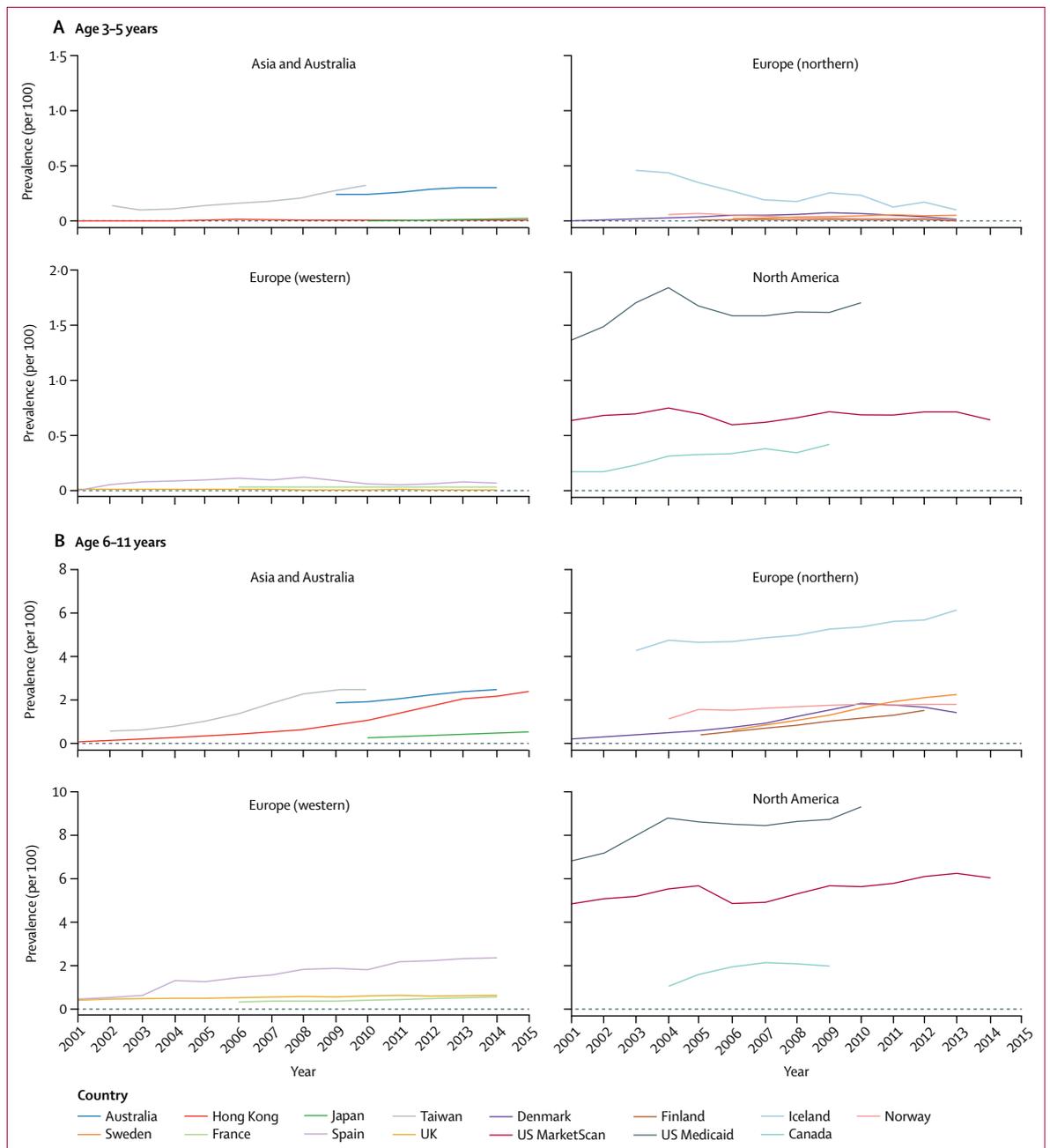
1.48% (2010) in US MarketScan (figure 3). Regional prevalence was highest in North America (1.42%, 95% CI 1.29–1.54), followed by northern Europe (0.47%, 0.31–0.62). The lowest prevalences were observed in Asia and Australia (0.05%, 0.004–0.10) and western Europe (0.03%, 0.01–0.04). The prevalence of ADHD medication use in adults increased in all countries over time; the absolute increase per year ranged from 0.0006% to 0.12% (0.0006–0.02% in Asia and Australia, 0.09–0.12% in North America, 0.01–0.10% in northern Europe, and 0.002–0.007% in western Europe; figure 4; appendix pp 18–25). The average yearly percentage increase across all countries was 18.87% (95% CI 16.25–21.49), with the highest increase in ADHD medication use being observed in the Asia and Australia region (25.06%, 17.65–32.46; 2001–15), followed by northern Europe (18.81%, 10.74–26.87; 2001–13) and western Europe (17.01%, 11.83–22.19; 2001–14). Both US data sources had a low average yearly increase, with a rate of 12.98% (95% CI 10.39–15.57) per year (US MarketScan 11.66%, 11.62–11.69 [2001–14] and US Medicaid 14.30%, 14.22–14.38 [2001–10]). By contrast with the low absolute prevalence of ADHD medication use in Japan, the annual rate of increase in adults was highest in this country, with an average increase of 75.88% per year (95% CI 70.55–81.21; 2010–15), followed by Denmark (28.84% per year, 28.61–29.06 [2001–13]) and Sweden (27.37% per year, 27.10–27.63 [2006–13]; appendix pp 18–25).

The overall male-to-female ratio among those with medication use was 2.0 to 1 across all countries. The lowest male-to-female ratios were found in US MarketScan (1.3 to 1) and Iceland (1.8 to 1). The male-to-female ratio was highest in Hong Kong (6.4 to 1), followed by Japan (4.6 to 1) and Finland (4.0 to 1).

The male-to-female ratio in medication use was greater in children (2.0–6.3 to 1) than in adults (0.9–2.7 to 1). The lowest male-to-female ratios in children were observed in Australia (2.0 to 1) and US MarketScan

(2.2 to 1), whereas the highest were observed in Finland (6.3 to 1), followed by Hong Kong (5.8 to 1) and the UK (5.4 to 1). In adults, the ratio was lowest in US MarketScan (0.9 to 1) and France (1.2 to 1), whereas the highest ratio was observed in Finland (2.7 to 1), the UK (2.3 to 1), and Hong Kong (2.0 to 1; appendix pp 31–32).

In 2010, methylphenidate was the most commonly used medication in all participating sites, except one (US MarketScan). Of individuals who used ADHD medication, more than 90% used methylphenidate in



(Figure 2 continues on next page)

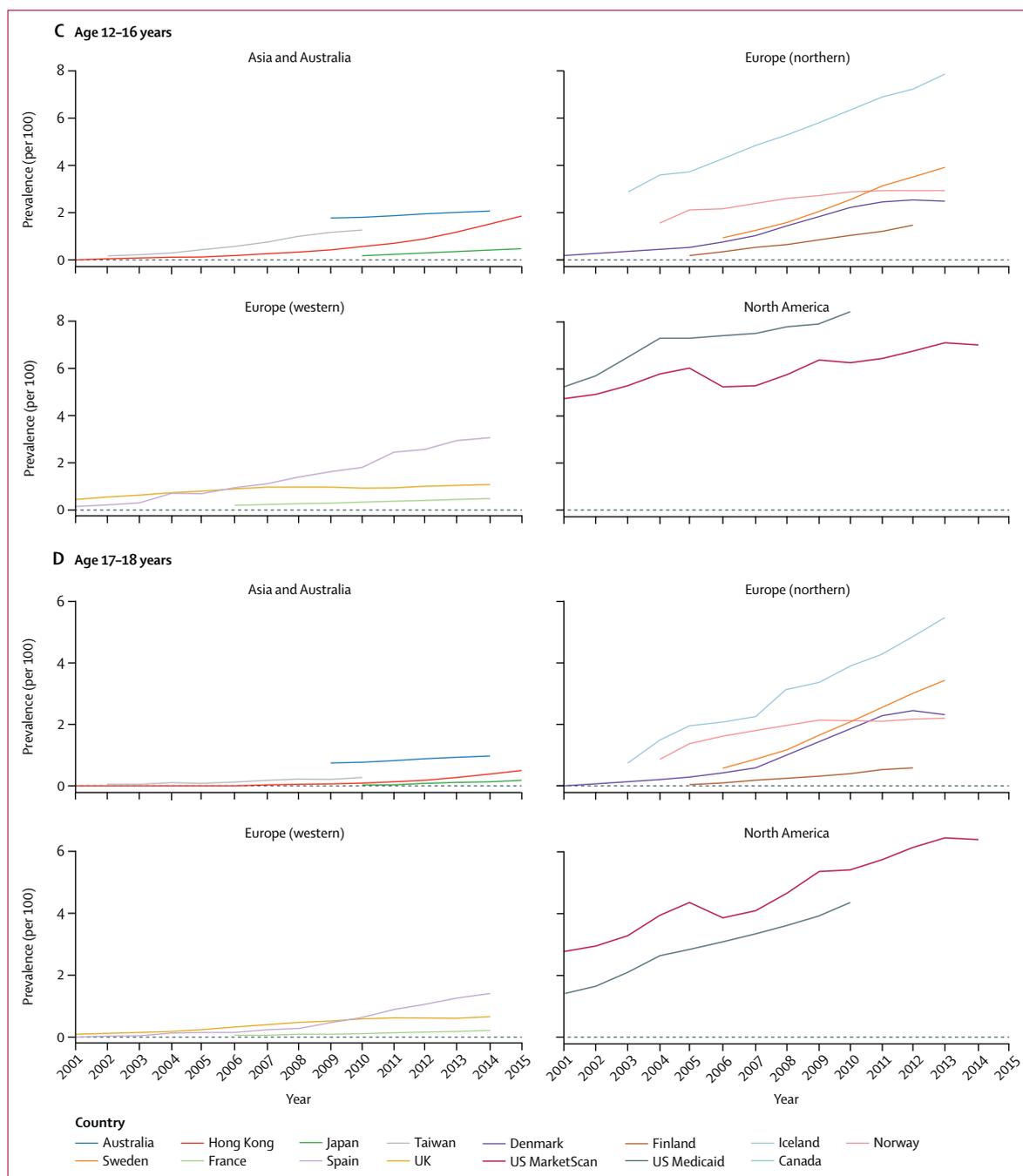


Figure 2: Annual prevalence of attention deficit hyperactivity disorder medication use in children, by region and age group

Hong Kong, Taiwan, Canada, Finland, and Spain (appendix p 26). In Japan, Denmark, Iceland, Norway, Sweden, and the UK, approximately 75% to 90% of patients received methylphenidate, whereas 59% of patients in Australia and 45% of patients in US Medicaid used this medication (appendix p 26). In US MarketScan, amphetamine was the most commonly used medication (41% of patients), followed by methylphenidate (34%) and

lisdexamfetamine (21%). Atomoxetine was the second most commonly used ADHD medication in ten countries or SAR (Hong Kong, Japan, Taiwan, Denmark, Finland, Iceland, Norway, Sweden, Spain, and the UK; appendix p 26). ADHD diagnosis prevalence estimates from studies included in the review by Thomas and colleagues² and the 2010 prevalence estimates for ADHD medication use in children aged 3–18 years from our

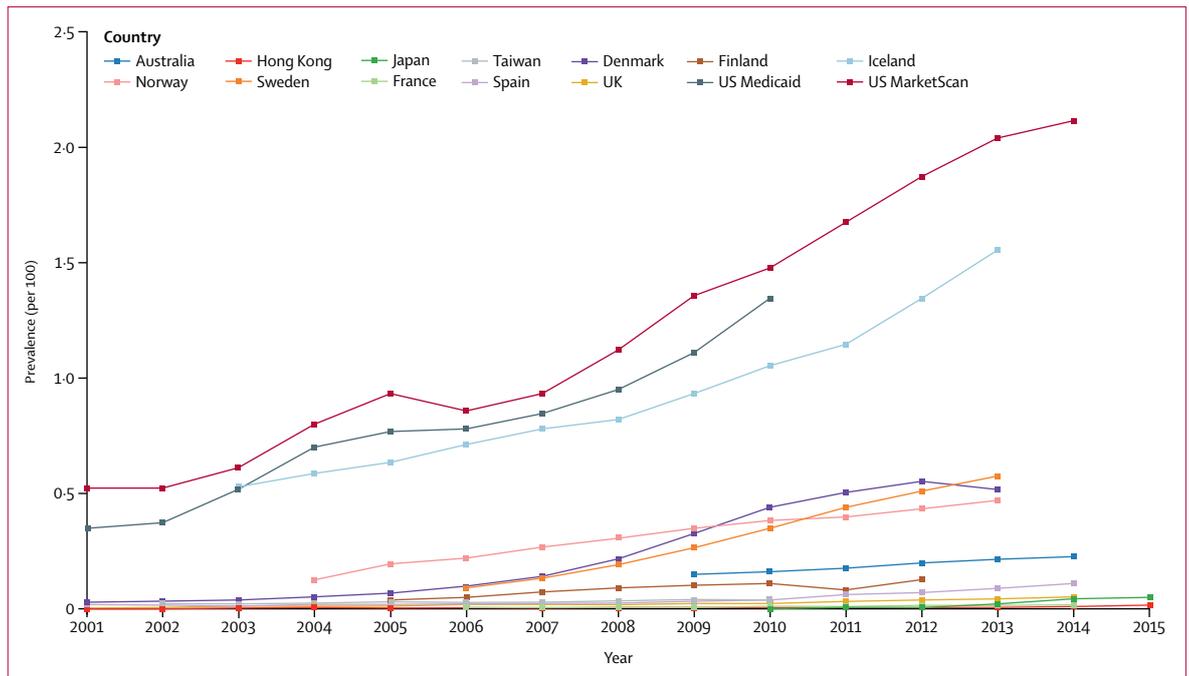


Figure 3: Overall annual prevalence of attention deficit hyperactivity disorder medication use in adults

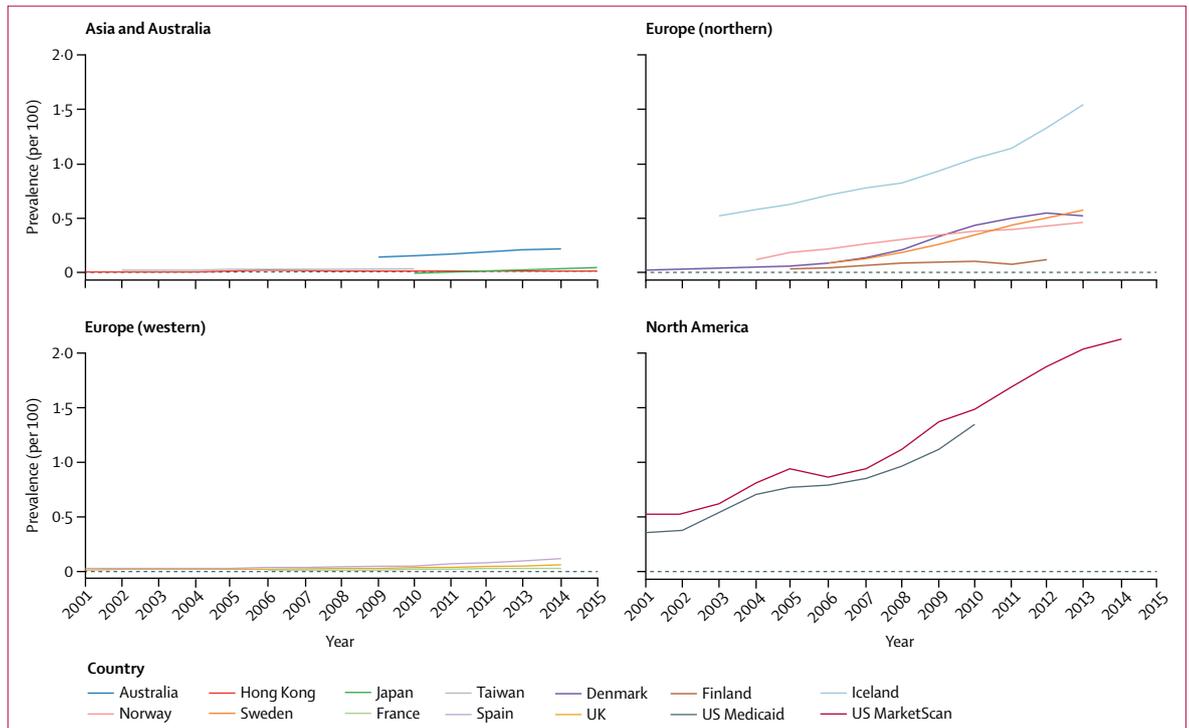


Figure 4: Annual prevalence of attention deficit hyperactivity disorder medication use in adults, by region

study can be found in the appendix (p 27). The variation in medication prevalence was much greater than that of the prevalence of ADHD diagnosis. All other additional results are included in the appendix (pp 28, 31–33).

Discussion

In this large, population-based study of 13 countries and one SAR, we noted sharp increases in ADHD medication prescription and marked geographical disparities in

medication use. We found wide variations by country and region in the prevalence of ADHD medication use, with the 2010 cross-sectional estimates in North America being markedly higher than those in other study regions. Across regions, the prevalence of ADHD medication use has increased strikingly since 2000. This consistent rise was notable in both children and adults in all four study regions. The high variation across regions, as well as within regions, suggests variation in clinical approach to the treatment of ADHD.

The prevalence of ADHD medication use and the increase over time varied widely across study regions. Within Europe, the contrast between patterns in northern Europe and western Europe was striking, as were the disparities between nations within a given region, with Iceland having the highest prevalence of all European countries. The average relative percentage increase per year was also higher among children and adults in the northern Europe region than in the western Europe region, leading to further increases in the regional disparity in medication use patterns over time.

The prevalence of ADHD observed in Asia and Australia in 2010 was similar or greater than the prevalence in western Europe. The average yearly percentage increase in the USA was the lowest of all countries and SAR, in both children and adults. However, because of the high absolute prevalence within the USA, this consistent increase is substantial.

Some of the disparities might reflect geographical differences in the epidemiological prevalence of ADHD. Although previous studies suggested that the epidemiological prevalence of an ADHD diagnosis might be higher in North America than in other regions^{1,2}—with reported estimates of about 8·8% in the USA,²² 3·5% to 5·6% in France,²³ and 3% to 5% in the UK²⁴—the analysis of Polanczyk and colleagues²⁵ suggests that these differences can be largely accounted for by methodological differences between studies. Notwithstanding the fact that ADHD could be overdiagnosed and overtreated in the USA, while underdiagnosed in some countries in Asia,²⁶ a consistent increase in the use of ADHD medication in all countries was observed in this study.

Given the evidence that the underlying epidemiological prevalence of ADHD is similar across the world when the diagnosis is made with consistent criteria and methods,¹ much of the absolute variation in ADHD medication use might be explained by differences in how diagnostic criteria are applied in practice by clinicians, the thresholds required by clinicians to initiate treatment for individuals with an ADHD diagnosis, and the persistence of ADHD medication treatment over time. The structure and funding of the health-care system, including factors such as direct access to specialists and other prescribers, availability and cost of medicines, and availability of non-pharmacological treatments for ADHD, might all influence the patterns of prescribing medication.²⁷ Additionally, some differences might be due to the

proportion of off-label use of ADHD medications.²⁸ Differences in regional clinical guidelines in ADHD treatment recommendations might also contribute to the difference in the prescribing prevalence across the world. Non-pharmacological treatment is recommended as first-line treatment for children and young people aged 6 years or older with ADHD in the NICE guidelines,¹² whereas medications are recommended as first-line treatment in the American Academy of Pediatrics⁸ and American Academy of Child and Adolescent Psychiatry guidelines.⁹ Cultural variations in the perception of ADHD and ADHD treatment, both within and between countries, might also contribute to variation in the use of ADHD medication;²⁹ for example, perceived stigma might influence the willingness of a parent or patient to use medication.²⁹ On the one hand, public attitudes towards psychotropic medication became more positive between 1998 and 2006 in the USA³⁰ and in a Swedish community between 1976 and 2003.³¹ On the other hand, in Hong Kong and Taiwan, where Chinese culture is dominant, conservative attitudes and resistance towards ADHD medications are common.¹⁵ Lastly, ADHD medication use might increase as clinicians and guidelines take into account emerging evidence about the effectiveness or safety of ADHD medications, such as the evidence that behavioural therapy in combination with medication is more effective than behavioural therapy alone.³²

The three previous multinational studies that compared prevalences of ADHD medication use did so across four European countries and the USA¹³ or across northern European countries.^{14,33} The estimates for two western European countries that could not be included in our study (Germany and the Netherlands) were higher than our western European estimates. Despite these differences, our findings support the between-country variation found in previous studies and add the comparison of two more world regions.

The two US data sources represent distinct populations, for the most part: those who were privately insured through employers (MarketScan) and those who were covered by Medicaid, a federal and state government social health-care programme for individuals with low incomes. The higher estimates in Medicaid for children and adults are likely to be due to a combination of factors, including the type of insurance, in terms of the cost and availability of medications and non-pharmacological treatments, and differences in the demographic characteristics of the populations. Factors affecting the Medicaid population, such as low financial resources, poor health of children and their parents, and insufficient resources of the public educational system, might affect the treatment decisions of providers and families.³⁴ For instance, families of higher socioeconomic status might have more resources for non-pharmacological treatment and therefore might be less likely to use ADHD medications. Although the two data sources represent only part of the US population, this evidence of

within-country variation is noteworthy and can be used to examine more closely the underlying determinants.

The results of this study have substantial implications for clinical practice, health systems, and policies. For individuals with ADHD, these results suggest that the type of pharmacological treatment prescribed might depend largely on where they live. Although there is no clear evidence as to the optimal rates of prescription, it seems likely that many patients might be undertreated (especially in low-use areas) and some might be overtreated with medication. For most countries, despite considerable increases in the prescribing of ADHD medications, these rates continue to be lower than the expected prevalence of ADHD (eg, in Japan)², and the increases observed in this study are likely to represent increased recognition of ADHD and the importance of effective treatment to avoid long-term problems. By contrast, in the USA, where rates of prescribing in many states are already higher than the generally accepted epidemiological prevalences,²² the continued increase in prescribing rate should be considered as a cautionary note for clinicians and regulators, who should ensure that they are not overdiagnosing and medicating children and young people. Given the adverse developmental and functional implications of undertreatment and the negative individual and societal effect of overtreatment (including diversion of stimulant drugs), it is important that clinical practices reflect the available evidence and are based on careful monitoring of children. To ensure that individuals with ADHD receive optimal treatment across nations, efforts are needed to assure that structured approaches are applied to the diagnosis and treatment of ADHD and to develop consensus on the best practices in light of available evidence. International organisations such as WHO might have a role to play in convening and supporting policy initiatives to improve the consistent identification and treatment of ADHD across the international community.

By contrast with the number of pharmacoepidemiological studies on the use of ADHD medications in children and adolescents, far fewer data are available for adults. We observed an increase in the prevalence of ADHD medication use among adults in all participating sites, with the USA having the highest prevalence in adults among all countries and SAR. Our results are similar to those reported in a previous meta-analysis.³ Although diagnosis and treatment guidelines for adult ADHD are emerging, research continues into the course of ADHD from childhood and presentation of ADHD in adulthood.³⁵ Overall, when considered in terms of epidemiological prevalence of ADHD in adults and the recommendations from guidelines that medication be a first-line treatment for adults with ADHD, the data suggest that ADHD medications are probably not being overprescribed in adults. The large differences observed between countries regarding the use of ADHD medications in adults raise questions about how well guidelines are being followed. To increase the confidence of clinicians treating adults, further

research is required to show the longer-term safety and effectiveness of ADHD medications in adult populations.

The results of this study must be taken in the context of the following limitations. Although the common protocol enabled us to standardise the measurement of populations and medications under study, there were some previously defined variables in each country's database. For example, medication data might reflect prescribed or dispensed medication and administrative or clinical records. Although most of the countries had data sources with almost complete population coverage, the denominator estimates might have differences in accuracy and generalisability because the data came from different sources (government census or administrative databases). The trends observed in the US private insurance data might have been influenced by shifts in the population who contributed to the data source. Several medications used for ADHD also have other indications or are used off-label or in the context of a differential diagnosis. Because we were not able to include the diagnoses and indications for the study groups, we could not investigate the clinical characteristics of patients who used ADHD medication. We examined the number of individuals exposed at least once to ADHD medication, but we did not measure exposure over time, which would reflect adherence to ADHD medication. Additionally, for each country or SAR, as discussed previously, the data might reflect differences in ADHD diagnosis and treatment practice. For example, most data sources only captured ambulatory or outpatient medication, but the extent of the capture (inclusion of specialist prescriptions or out-of-pocket medications) might have had an influence on the comparability of the estimates. These differences in the measurement of ADHD medication use might have influenced the absolute estimates of this study and might be a limitation for comparisons between countries or SAR. However, the trends in ADHD medication use over time are compelling and similar to previously published research.^{13,15} Linear regression models that assumed linear trends were used to estimate the overall trends in ADHD medication use. However, our assumptions were supported by post-hoc spline-based models that resulted in similar estimates. Additionally, we estimated the prescribing prevalences with the Poisson method, which might have resulted in conservative (wide) confidence intervals. However, the resulting confidence intervals were sufficiently narrow for the purposes of this study. Lastly, because of the nature of the data collected using the common protocol, we could not do several relevant analyses: medication use and trends among young adults (aged 18–25 years), estimates stratified by age and sex in three sites (Japan, Taiwan, and Canada), and age-specific estimates of medication use by medication type.

To our knowledge, this study presents the most comprehensive analysis to date of cross-sectional comparisons and longitudinal trends of ADHD medication use in children and adults, with representation from

several global regions. This study attempted to standardise the methodology that has been a source of much of the variation in previous estimates of ADHD medication prevalence, complementing the existing global ADHD diagnosis prevalence estimates³⁶ and ensuring an accurate representation of the dynamics of ADHD medication use in adults and children globally.

Further research is warranted to describe the safety and effectiveness of ADHD medication in the short and long term, and to inform evidence-based guidelines, particularly in adults. These results can also serve as a foundation for further insight into the potential effects of health-care access, the management of ADHD, and the use of ADHD medications.

Contributors

SRR, KKCM, PI, and ICKW had full access to the aggregate analysis data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ICKW, KKCM, and PI were responsible for the study concept, and ICKW, SRR, KKCM, and MCJMS were responsible for the study design. All authors were involved in the acquisition, statistical analysis, or interpretation of data. SRR, KKCM, and ICKW drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

Declaration of interests

SRR reports grants from GlaxoSmithKline, outside the submitted work. KKCM reports personal fees from IQVIA Holdings (previously known as QuintilesIMS Holdings), outside the submitted work. GB reports grants from the National Institute of Mental Health (F31MH107085), during the conduct of the study, and a graduate research assistantship with GlaxoSmithKline, outside the submitted work. SC and SBI report financial support from the Agency for Healthcare Research and Quality (U19SH021112, R18HS03258). EWC reports grants from Research Grant Council (Hong Kong, China), the Beat Drugs Fund of the Narcotics Division, Security Bureau (Hong Kong, China), the National Natural Science Fund of China, Bayer, Bristol-Myers Squibb, Janssen (a division of Johnson and Johnson), Pfizer, and Takeda, outside the submitted work. DC reports grants and personal fees from Shire, grants from Vifor, and personal fees from Eli Lilly, Novartis, and Oxford University Press, outside the submitted work. HK reports that the institution receives fees from Abbvie, Astellas, AstraZeneca, Bayer, Janssen Biotech, Novartis, Pfizer, and Reckitt Benckiser, outside the submitted work. HN reports grants from European Union FP7 programme, during the conduct of the study, and personal fees from Janssen Pharmaceutical KK, outside the submitted work. NLP and EER are members of the Australian Government Drug Utilisation Subcommittee of the Pharmaceutical Benefits Advisory Committee. TS reports other relationships as a member of the Center for Pharmacoepidemiology of the UNC Gillings School of Global Public Health with GlaxoSmithKline, Merck, UCB BioSciences, and Shire and grants from AstraZeneca and Novo Nordisk, outside the submitted work, and that he owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk, with none of these companies having any role in the research project. ICKW reports grants from Research Grant Council (Hong Kong, China), Innovative Medicines Initiative, Shire, Janssen-Cilag, Eli Lilly, Pfizer, and European Union FP7 programme, outside the submitted work; he was a member of the National Institute of Health and Care Excellence ADHD Guideline group and the British Association for Psychopharmacology ADHD guideline group, and he acted as an advisor to Shire. All other authors declare no competing interests.

References

- Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol* 2014; **43**: 434–42.
- Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* 2015; **135**: e994–1001.
- Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 2009; **194**: 204–11.
- Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 2006; **36**: 159–65.
- Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005; **366**: 237–48.
- Jensen CM, Steinhausen HC. Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *Atten Defic Hyperact Disord* 2015; **7**: 27–38.
- Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry* 2018; **5**: 175–86.
- Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2011; **128**: 1007–22.
- Pliszka S, Bernet W, Bukstein O, et al. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Psy* 2007; **46**: 894–921.
- Bolea-Alamanac B, Nutt DJ, Adamou M, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2014; **28**: 179–203.
- Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. *BMC Psychiatry* 2010; **10**: 67.
- National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: diagnosis and management. 2018. <https://www.nice.org.uk/guidance/ng87> (accessed June 13, 2018).
- Bachmann CJ, Wijaars LP, Kalverdijk LJ, et al. Trends in ADHD medication use in children and adolescents in five western countries, 2005–2012. *Eur Neuropsychopharmacol* 2017; **27**: 484–93.
- Karlstad O, Zoega H, Furu K, et al. Use of drugs for ADHD among adults—a multinational study among 15·8 million adults in the Nordic countries. *Eur J Clin Pharmacol* 2016; **72**: 1507–14.
- Man KKC, Ip P, Chan EW, et al. Attention-deficit/hyperactivity disorder (ADHD) drug prescribing trend is increasing among school-aged children and adolescents. *J Atten Disord* 2017; **37**: 711–21.
- National Institute for Health and Clinical Excellence. Avoid drug treatment for children and young people with moderate ADHD. 2013. <https://www.nice.org.uk/news/article/avoid-drug-treatment-for-children-and-young-people-with-moderate-adhd> (accessed Sept 7, 2018).
- McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong IC. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care. *BMC Pediatr* 2012; **12**: 78.
- Wettermark B, Zoega H, Furu K, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research—a literature review. *Pharmacoepidemiol Drug Saf* 2013; **22**: 691–99.
- WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2018. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2017.
- Rothman KJ, Greenland S. Modern epidemiology, 2nd edn. Philadelphia: Lippincott-Raven, 1998.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.
- Visser SN, Danielson ML, Bitsko RH, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003–2011. *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 34–46.
- Lecendreau M, Konofal E, Faraone SV. Prevalence of attention deficit hyperactivity disorder and associated features among children in France. *J Atten Disord* 2011; **15**: 516–24.
- Ford T, Goodman R, Meltzer H. The British Child and Adolescent Mental Health Survey 1999: the prevalence of DSM-IV disorders. *J Am Acad Child Adolesc Psychiatry* 2003; **42**: 1203–11.

- 25 Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007; **164**: 942–48.
- 26 Hamed AM, Kauer AJ, Stevens HE. Why the diagnosis of attention deficit hyperactivity disorder matters. *Front Psychiatry* 2015; **6**: 168.
- 27 Hodgkins P, Setyawan J, Mitra D, et al. Management of ADHD in children across Europe: patient demographics, physician characteristics and treatment patterns. *Eur J Pediatr* 2013; **172**: 895–906.
- 28 Sinita E, Coghill D. The use of stimulant medications for non-core aspects of ADHD and in other disorders. *Neuropharmacology* 2014; **87**: 161–72.
- 29 Hinshaw SP, Scheffler RM, Fulton BD, et al. International variation in treatment procedures for ADHD: social context and recent trends. *Psychiatr Serv* 2011; **62**: 459–64.
- 30 Mojtabai R. Americans' attitudes toward psychiatric medications: 1998–2006. *Psychiatr Serv* 2009; **60**: 1015–23.
- 31 Ineland L, Jacobsson L, Renberg ES, Sjolander P. Attitudes towards mental disorders and psychiatric treatment—changes over time in a Swedish population. *Nordic J Psychiatry* 2008; **62**: 192–97.
- 32 Catala-Lopez F, Hutton B, Nunez-Beltran A, et al. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: a systematic review with network meta-analyses of randomised trials. *PLoS One* 2017; **12**: e0180355.
- 33 Furu K, Karlstad Ø, Zoega H, et al. Utilization of stimulants and atomoxetine for attention-deficit/hyperactivity disorder among 5·4 million children using population-based longitudinal data. *Basic Clin Pharmacol Toxicol* 2017; **120**: 373–79.
- 34 Altman D, Frist WH. Medicare and Medicaid at 50 years: perspectives of beneficiaries, health care professionals and institutions, and policy makers. *JAMA* 2015; **314**: 384–95.
- 35 Sibley MH, Rohde LA, Swanson JM, et al. Late-onset ADHD reconsidered with comprehensive repeated assessments between ages 10 and 25. *Am J Psychiatry* 2018; **175**: 140–49.
- 36 Skounti M, Philalithis A, Galanakis E. Variations in prevalence of attention deficit hyperactivity disorder worldwide. *Eur J Pediatr* 2007; **166**: 117–23.