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


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 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 0·006% 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

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 3–7%.12 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.13 ADHD is associated with a diverse range of adverse health, academic, and psychosocial outcomes14 and is associated with other mental health disorders, such as depression, anxiety, and substance misuse.4 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.15 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
Education, University, New Brunswick, NJ, USA (S Crystal PhD); Department of Epidemiology, University of North Carolina, Chapel Hill (G Bushnell PhD, V Pats MSc, Prof T Stürmer MD); Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway (Prof K Kubota PhD); School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kong University, Tainan, Taiwan (Prof Y-H Kao/Yang BS Pharm, E C C Lai PhD, C C Su MSc); Department of Pharmacy, National Cheng Kong University Hospital, Tainan, Taiwan (E C C Lai); Drug Safety Research Unit, Tokyo, Japan (Prof K Kuwata 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 Maure Pharm); Neumann PhD); Bordeaux Pharmacopole, INSERM CIC 4601, Université de Bordeaux, Bordeaux, France (Prof N Moore PhD); Spanish Agency for Medicines and Medical Devices, Madrid, Spain (D Montero PhD, D Macias Saint-Genois PhD); Biomedical Research Networking Center for Mental Health Network (CIBERSAM), Valencia, Spain (D Macias Saint-Genois); Clinical Research Centre, National Center for Child Health and Development, Tokyo, Japan (H Nakamura PhD); Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense, Denmark (A Pottenborg PhD); Quality Use of Medicines and Pharmacy Research Centre, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia (NL Pratt PhD, Prof E C-C Lai). Center for Public Health Sciences, of ADHD.4–12 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.10–12 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.14

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, 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), northern Europe (Denmark, Finland, Iceland, Norway, and Sweden), and western Europe (France, the UK, and Spain). The sites were chosen on the basis of the 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,15 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 I 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); Medicine 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 Sturkenboom); Departments of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC, Australia (Prof D Coghill MD);

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

Table 1: Data source characteristics, by country

*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.
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:

\[
\frac{\text{prevalence}_{\text{curr}} - \text{prevalence}_{\text{prev}}}{\text{prevalence}_{\text{prev}}} \times 100
\]

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.
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 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%, 0·00–0·10) 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).

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Children aged 3-18 years</th>
<th>Adults aged 19 years or older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average absolute change</td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td>per year (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Asia and Australia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>0·08% (0·06–0·09)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>0·10% (0·08–0·12)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Japan</td>
<td>0·06% (0·02–0·10)</td>
<td>0·0161</td>
</tr>
<tr>
<td>Taiwan</td>
<td>0·17% (0·15–0·20)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Northern Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>0·24% (0·19–0·29)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>US MarketScan</td>
<td>0·23% (0·19–0·27)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>US Medicaid</td>
<td>0·19% (0·15–0·26)</td>
<td>0·0004</td>
</tr>
<tr>
<td>Western Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>0·25% (0·20–0·30)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Finland</td>
<td>0·22% (0·15–0·39)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Iceland</td>
<td>0·20% (0·14–0·26)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Norway</td>
<td>0·08% (0·05–0·11)</td>
<td>0·0055</td>
</tr>
<tr>
<td>Sweden</td>
<td>0·26% (0·24–0·28)</td>
<td>&lt;0·0001</td>
</tr>
</tbody>
</table>

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.
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 Asia and Australia Europe (northern)

Europe (western)

North America

Country
Australia Hong Kong Japan Taiwan Denmark Finland Iceland US MarketScan US Medicaid Canada

(Figure 2 continues on next page)
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 colleagues' and the 2010 prevalence estimates for ADHD medication use in children aged 3–18 years from our

Figure 2: Annual prevalence of attention deficit hyperactivity disorder medication use in children, by region and age group
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—with reported estimates of about 8·8% in the USA, 3·5% to 5·6% in France, and 3% to 5% in the UK—the analysis of Polanczyk and colleagues 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, 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, 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. Additionally, some differences might be due to the proportion of off-label use of ADHD medications. 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; whereas medications are recommended as first-line treatment in the American Academy of Pediatrics and American Academy of Child and Adolescent Psychiatry guidelines. 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; for example, perceived stigma might influence the willingness of a parent or patient to use medication. On the one hand, public attitudes towards psychotropic medication became more positive between 1998 and 2006 in the USA and in a Swedish community between 1976 and 2003. On the other hand, in Hong Kong and Taiwan, where Chinese culture is dominant, conservative attitudes and resistance towards ADHD medications are common. 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.

The three previous multinational studies that compared prevalences of ADHD medication use did so across four European countries and the USA or across northern European countries. 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. 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)\textsuperscript{3}, 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,\textsuperscript{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 under-treatment 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.\textsuperscript{1} 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.\textsuperscript{3} 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 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.\textsuperscript{1,15} 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 estimates 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.

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References
Why are stimulant medication prescriptions rising globally?

In The Lancet Psychiatry, Sudha Raman and colleagues\(^1\) provide a rich summary of cross-national longitudinal trends in the prescription of central nervous system stimulant and non-stimulant attention deficit hyperactivity disorder (ADHD) medications. They found the prevalence of ADHD medication in children aged 3–18 years in 2010 to be 0.95% in Asia and Australia, 4.48% in North America, 1.95% in northern Europe, and 0.7% in western and southern Europe. The prevalence of ADHD medication use among children increased over time in all countries and regions. Their study adds to a growing body of literature indicating rising rates of stimulant and non-stimulant attention deficit hyperactivity disorder (ADHD) medications. They found 55–66% of adults in the USA with a stimulant diagnosis were prescription do not have an ADHD diagnosis.\(^7\,8\) The prevalence of ADHD medication use also increased among adults aged 19 years or older in all the regions studied.\(^1\)

These data emerge amidst public concern that physicians overprescribe stimulant medications as a first resort for underperforming schoolchildren,\(^4\) to adolescents and young adults seeking cognitive enhancement,\(^5\) and to women interested in weight loss.\(^6\) Medical data support these claims, indicating that 55–66% of adults in the USA with a stimulant prescription do not have an ADHD diagnosis.\(^7\,8\) In children, this figure is 38%.\(^1\) In the study by Raman and colleagues, ADHD diagnoses were not recorded because of the known under-ascertainment of outpatient conditions in claims data.

No comprehensive worldwide data on the reasons why stimulants are prescribed have been published (discussed below). This information would help us understand if the same forces increasing US prescription rates operate cross-nationally. In the study by Raman and colleagues, it is unclear what proportion of the participants received stimulants for ADHD compared with commonly accepted non-ADHD indications (eg, hyperactivity associated with autism spectrum disorder or narcolepsy) and more controversial off-label uses. These proportions would be expected to vary by culture, age, sex, and geographic region.

Even patients with a documented ADHD diagnosis might be receiving stimulant medication for a reason other than ADHD. In one US study, up to 31% of college students self-referring for ADHD showed evidence of feigning cognitive deficits—this could reflect widespread deceiving by young adults who desire stimulant medication to boost academic productivity.\(^9\) The use of stimulant medication for cognitive enhancement among healthy individuals is controversial, with some medical professionals supporting this off-label use.\(^10\) It remains unclear whether using stimulants for cognitive enhancement is largely a cultural occurrence of north American young adulthood, is a cohort effect (ie, the so-called generation Adderall),\(^5\) or is occurring globally across the lifespan.

Additionally, diagnostic practices for ADHD vary widely.\(^11\) In fast-paced primary care settings, 5 minutes self-administered or parent-administered diagnostic checklists can be used, but research\(^12\) suggests that relying on these quick checklists can lead to high rates of false diagnoses. Unlike individuals feigning cognitive deficits, these false cases might have true cognitive symptoms, but from non-ADHD sources (ie, substance abuse, anxiety, depression, trauma, high demands, physical health problems, or sleep deprivation). A related concern is that stimulant medications are becoming default treatments for a broad range of cognitive-behavioural symptoms, which might prevent patients from receiving optimal treatment (eg, detoxification, behavioural sleep therapy, or antidepressant medications) on the basis of the cause of their difficulties.

The issues raised here are key to interpreting the findings of Raman and colleagues. The authors report cross-national prescription prevalences in children (ranging from 0.27% in France to 6.69% in the US Medicaid cohort) and adults (0.003% in Japan to 1.48% in US MarketScan), noting that they are substantially lower than global ADHD prevalence estimates (5–7% in children and 2.5% in adults).\(^1\) Raman and colleagues conclude that ADHD medications are probably not overprescribed among adults. However, the picture is far more complicated.

In sum, empirical data suggest that there probably is mixed prescription of stimulants to individuals who truly have ADHD, people who feign ADHD symptoms, misdiagnosed individuals, and those who openly receive medications for an off-label use endorsed by their prescriber. What offsets the ballooning use of stimulants...
by non-ADHD individuals is a markedly low use among many individuals with legitimate ADHD. Stigma, refusal to acknowledge deficits, poor access to behavioural health care, and problems with stimulant acceptability prevent many individuals who might benefit from ADHD medication from receiving treatment. Each cultural and geopolitical region presents its own set of factors that influence treatment referral and prescribing behaviours. It remains unclear whether conclusions drawn in North American contexts can be generalised worldwide. Furthermore, the evidence suggests that markedly different dynamics influence stimulant use, even within a broad developmental period (eg, young adulthood vs older adulthood or early childhood vs late childhood). These issues must be considered when interpreting global stimulant prevalences.

As noted by Raman and colleagues, there is an urgent need to refine evidence-based guidelines for stimulant medication. This mission extends beyond ADHD. Researchers should address pressing questions, including the following: which sources of cognitive dysfunction (eg, illness, sleep difficulties, stress, trauma, low intelligence quotient, high demands, or fatigue) are appropriate for stimulant prescription and under which circumstances is it appropriate to prescribe stimulants to cognitively healthy individuals (eg, weight loss or cognitive enhancement)? Resolving these issues represents an important step towards improving global stimulant medication practices. These parameters will require unique refinements for the age, sex, region, and cultural context of each patient.

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