# Evaluating ADHD medication trial representativeness: a Swedish population-based study comparing hypothetically trial-eligible and trial-ineligible individuals

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## Summary

**Background** Randomised controlled trials (RCTs) evaluating ADHD medications often use strict eligibility criteria, potentially limiting generalisability to patients in real-world clinical settings. We aimed to identify the proportion of individuals with ADHD who would be ineligible for medication RCTs and evaluate differences in treatment patterns and clinical and functional outcomes between RCT-eligible and RCT-ineligible individuals.

**Methods** We used multiple Swedish national registries to identify individuals with ADHD, aged at least 4 years at the age of diagnosis, initiating pharmacological treatment between Jan 1, 2007, and Dec 31, 2019, with follow-up up to Dec 31, 2020. Hypothetical RCT ineligibility was established using exclusion criteria from the international MED-ADHD dataset, including 164 RCTs of ADHD medications. Cox models evaluated differences in medication switching and discontinuation within 1 year between eligible and ineligible individuals. Quasi-Poisson models compared eligible and ineligible individuals on rates of psychiatric hospitalisations, injuries or accidents, and substance use disorder within 1 year of initiating ADHD medications. People with lived experience of ADHD were not involved in the research and writing process.

**Findings** Of 189 699 individuals included in the study cohort (112 153 men and boys [59%] and 77 546 women and girls [41%]; mean age 21·52 years [SD 12·83; range 4–68]) initiating ADHD medication, 53% (76 477 [74%] of 103 023 adults [aged >17 years], 12 658 [35%] of 35 681 adolescents [aged 13–17 years], and 10 643 [21%] of 50 995 children [aged <13 years]) would have been ineligible for RCT participation. Ethnicity data were not available. Ineligible individuals had a higher likelihood of treatment switching (hazard ratio 1·14, 95% CI 1·12–1·16) and a decreased likelihood of medication discontinuation (0·96, 0·94–0·98) compared with eligible individuals. Individuals ineligible for RCTs had significantly higher rates of psychiatric hospitalisations (ncidence rate ratio 9·68, 95% CI 9·57–9·78) and specialist care visits related to substance use disorder (14·78, 14·64–14·91), depression (6·00, 5·94–6·06), and anxiety (11·63, 11·56–11·69).

**Interpretation** Individuals ineligible for ADHD medication trials face higher risks of adverse outcomes. This study provides the first empirical evidence for the limited generalisability of ADHD RCTs to real-world clinical populations, by applying eligibility criteria extracted from a comprehensive dataset of RCTs to a large real-world cohort. Triangulating evidence from RCTs and real-world studies is crucial to inform rigorous evidence-based treatment guidelines.

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## Introduction

Pharmacotherapy is an important component of the multimodal treatment of ADHD.[1] Randomised controlled trials (RCTs) are considered the gold standard to evaluate the efficacy and tolerability of a treatment. However, their strict inclusion and exclusion criteria might limit the generalisability of findings to clinical populations routinely seen in clinical practice. Common exclusion criteria in RCTs of ADHD medications include the presence of psychiatric or neurodevelopmental comorbidities (eg, major depressive disorder, autism spectrum disorder, psychosis, or intellectual disability) or other medical conditions (eg, cardiovascular disease).[2] These conditions frequently co-occur with ADHD,[3–7] and, as a result, a substantial percentage of individuals with ADHD would be considered ineligible for these RCTs.

Findings from one RCT in US adults with ADHD suggest that approximately 31% of individuals with ADHD presenting for routine clinical care would meet eligibility for participation in the RCT.[8] However, these findings are based on one RCT in a specific country and refer to adults only. Notably, it is unclear how the excluded real-world ADHD groups differ in their treatment pattern and outcomes compared with the relatively homogeneous RCT

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See Comment page 86

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## Research in context

### Evidence before this study

We searched PubMed, Web of Science, and PsycINFO for studies published up to April 1, 2024, using the search terms "ADHD" (and equivalents), "clinical trials", "real-world evidence", and "treatment outcomes". We included studies comparing the outcomes between randomised controlled trial (RCT)-eligible and RCT-ineligible ADHD populations. We found only one study, from the USA, based on a single RCT, showing that only approximately a third of adults with ADHD presenting for routine clinical care would meet eligibility for participation in the RCT. Therefore, evidence on the representativeness of RCTs of ADHD medications based on datasets of multiple RCTs across the world and across the lifespan is needed. Furthermore, no study comprehensively examined differences in multiple clinical and functional outcomes between RCT-eligible and RCT-ineligible populations in a large, real-world cohort.

### Added value of this study

This is the first study to assess the representativeness of RCTs on ADHD medications in a real-world large nationwide cohort (189 699 children, adolescents, and adults in Sweden) based on inclusion and exclusion criteria gathered from a comprehensive international database of 164 RCTs. We found that 53% of individuals in real-world practice (approximately 74% of adults, 35% of adolescents, and 21% of children) would be ineligible for these RCTs. Our study also highlights different treatment patterns and less favourable clinical and functional outcomes in ineligible individuals. Overall, our study offers empirical evidence for the limited generalisability of ADHD RCTs to broader, real-world ADHD populations.

### Implications of all the available evidence

Our findings, combined with previous evidence, highlight the pressing need to triangulate evidence from standard RCTs and studies specifically targeting typically excluded populations, and to combine data from RCTs with findings from real-world studies. Future guidelines should consider evidence from both RCTs and real-world studies to provide more comprehensive, applicable treatment recommendations for diverse ADHD populations.

samples. Therefore, it is crucial to gain additional insight, based on multiple datasets of RCTs across the world and across the lifespan, on the representativeness of RCTs on ADHD medications, and to identify potential differences in treatment patterns and clinical and functional outcomes between individuals who would be eligible for RCTs and those who would not.

The aims of this study were: first, quantify the percentage of individuals with ADHD initiating ADHD medications in the real world who would be ineligible for RCT ADHD medication efficacy trials; second, to evaluate differences in medication switching and medication discontinuation within 1 year between eligible and ineligible groups; and third, to explore whether important clinical and functional outcomes, such as inpatient psychiatric hospitalisations, injuries and accidents, and the number of specialist care visits related to substance use disorder, depression, and anxiety disorder, differ between eligible and ineligible individuals over a 12-month observation period. We hypothesised that compared with hypothetically RCT-eligible individuals, those ineligible for RCTs would show higher rates of medication discontinuation and switching, reflecting greater clinical complexity and a potentially poorer treatment response, and higher rates of adverse clinical and functional outcomes, most likely indicating a greater underlying clinical severity and comorbidity burden.

## Methods

### Study population

This cohort study used data from multiple Swedish national registries including the National Patient Register, Prescribed Drug Register (initiated in July, 2005), and the Cause of Death Register. These registries contain data on all specialised inpatient and outpatient care centres with diagnoses recorded according to the ICD system, as well as pharmacy-dispensed medications based on the Anatomical Therapeutic Chemical classification, for the total population living in Sweden.

We identified all individuals with a registered ICD-10 diagnosis code for ADHD (F90) between Jan 1, 2007, and Dec 31, 2019, who were at least 4 years of age at the age of diagnosis. To focus on individuals receiving pharmacotherapy, the cohort was restricted to those with at least one dispensed prescription for an ADHD medication during this period. This restriction ensured that our study population consisted of individuals with a confirmed ADHD diagnosis who were receiving pharmacological treatment for this condition, thereby excluding patients who might have been treated off-label with ADHD medications for other conditions.[9] We included all medications for ADHD approved in Sweden within the specified timeframe. This included stimulants (methylphenidate [N06BA04], amphetamine [N06BA01], dexamphetamine [N06BA02], and lisdexamphetamine [N06BA12]) and non-stimulants (atomoxetine [N06BA09] and guanfacine [C02AC02]). Jan 1, 2007, was chosen as the start date to allow a washout period of at least 18 months before the first ADHD medication dispensation date to establish ADHD medication status,[10] which was defined as no ADHD drug dispensations in the 18 months before treatment initiation. Informed consent is waived for register-based studies in Sweden. People with lived experience were not involved in the research and writing process. This study was approved by the

Karolinska Institute Ethical Review Board (contract numbers Dnr 2020–06540 and Dnr 2022–06204–02).

### Exposure and outcomes

Exposure was RCT eligibility versus ineligibility, which was established by systematically assessing whether individuals within the Swedish registries met common exclusion criteria from RCTs gathered from the freely accessible MED-ADHD dataset. This dataset of double-blind RCTs of ADHD medications was initially created by the European ADHD Guidelines Group to conduct the systematic review and network meta-analysis by Cortese and colleagues.[2] We used data from RCTs included in the most recent update of MED-ADHD (on Jan 22, 2024), encompassing 164 eligible RCTs. A detailed list of participants' exclusion criteria for each RCT in MED-ADHD and additional information is reported in the appendix (pp 2–34).

After analysis of each of the 164 retrieved RCTs, the most common exclusion criteria were antidepressant use (74% of RCTs), psychosis (65%), bipolar disorder (49%), substance use disorder (39%), cardiovascular disease (38%), learning disability or low intelligence quotient (36%), anxiety disorder (35%), and autism spectrum disorder (35%; table 1). Exclusion criteria for our study were defined based on the criteria present in at least 30% of the RCTs and were assessed within 1 year before the initiation of ADHD treatment to reflect current clinical status. This threshold was selected to reflect commonly applied criteria in RCTs, because it represents a frequency where a specific condition is excluded in at least one of every three RCTs. This approach balances the need to capture prevalent exclusion criteria and the need to maintain a reasonable scope for our real-world effectiveness study. By mirroring these commonly applied criteria using register diagnoses, we aimed to create cohort groups representing typical ADHD RCT-eligible and RCT-ineligible samples for comparison of real-world outcomes. Additional, less frequent RCT inclusion and exclusion criteria, such as baseline symptom severity thresholds, could not be extracted from the registers due to the unavailability of such measures. The appendix (p 35) shows the ICD-10 codes used to define eligibility status in the cohort study.

Primary outcomes for the present study were treatment switching, defined as change of any ADHD medication within 12 months after the start of pharmacological treatment, and treatment discontinuation, defined as a gap of 180 days or more between two dispensations within 12 months after treatment initiation.[11] We estimated the discontinuation date as the midpoint between the prescription date and the expected end of the medication supply (using the defined daily doses per dispensed packages). By choosing the midpoint, we minimised the maximum error in our estimation, assuming discontinuation times are uniformly distributed within the interval. This approach reduces the potential overestimation of treatment duration, providing a more conservative estimate of time to discontinuation.

| | Percentage of RCTs (N=164) |
|---|---|
| Antidepressant use | 121 (74%) |
| Psychosis | 107 (65%) |
| Bipolar disorder | 80 (49%) |
| Substance use disorder | 64 (39%) |
| Cardiovascular disease | 62 (38%) |
| Learning disability or low intelligence quotient | 59 (36%) |
| Anxiety disorder | 58 (35%) |
| Autism spectrum disorder | 58 (35%) |
| Pregnancy | 53 (32%) |
| History of seizures | 49 (30%) |
| Psychotropic medications | 44 (27%) |
| Tourette syndrome | 43 (26%) |
| Alcohol use disorder | 40 (24%) |
| Depression | 40 (24%) |
| Suicidality | 40 (24%) |

These reasons for exclusion were based on the included 164 RCTs reported in the appendix (p 35) and used as a reference in our study. RCT=randomised controlled trial.

***Table 1:*** **Most common 15 reasons for exclusion in RCTs of ADHD medications**

For the **MED-ADHD dataset** see https://med-adhd.org/

See **Online** for appendix

Secondary outcomes were the number of: inpatient psychiatric hospitalisations (ICD-10 codes F00–99); emergency department visits or hospitalisations related to accidental injuries or accidents (ICD-10 codes S00–T78 or V00–X59; appendix p 35); and specialist care encounters with an alcohol-related or drug-related diagnosis (F10–16 or F18–19), depression (F32–34), and anxiety (F40–42). All secondary outcomes were assessed at 1 year from treatment initiation.

These secondary outcomes were selected on the basis of established clinical relevance in ADHD and supporting evidence. Psychiatric hospitalisations served as a broad measure of severe psychiatric episodes requiring intensive care, reflecting overall psychiatric burden. Injuries and accidents, consistently linked to ADHD and shown to be reduced by medication,[12] provided an objective measure of functional impairment. Specialist visits for substance use disorders, depression, and anxiety were chosen due to their high comorbidity with ADHD, frequent exclusion from RCTs, and current clinical uncertainty regarding treatment approaches.[13] These outcomes allow for the investigation of treatment response in patient populations typically under-represented in clinical trials.

### Statistical analysis

The percentage of patients with ADHD meeting RCT eligibility criteria was calculated, and socioeconomic characteristics were summarised for both groups and stratified by age at treatment initiation (children [aged

<13 years], adolescents [aged 13–17 years], and adults [aged >17 years]). For the primary outcomes, Cox regression analyses evaluated differences in time to treatment switching and early discontinuation between eligible and ineligible groups. Estimates were adjusted for potential confounders, including sex, age in years (continuous), and calendar year, based on their potential influence on both eligibility status and treatment outcomes. For the main analyses (ie, treatment switching and early discontinuation), follow-up started from the first ADHD medication dispensation. The end of follow-up was established as: treatment switching or early discontinuation (depending on the outcome), death, or migration, whichever happened first by 1 year from the start of ADHD treatment or by the end of the study period (Dec 31, 2020). Analyses were stratified by age groups. Individuals were excluded from the study if they emigrated or died before the start of follow-up.

Incidence rate ratios (IRRs) with 95% CIs were calculated using quasi-Poisson[14] regression models comparing the rates of psychiatric hospitalisations, injuries or accidents, and specialty care visits related to substance use disorders, depression, and anxiety in the 1 year after starting ADHD medications between eligible and ineligible groups. The start of follow-up was defined the same way as in the main analyses, and differences in individual follow-up durations were accounted for by including the log of person-time as an offset. Quasi-Poisson regression was chosen to address violations of the equidispersion assumption, because it provides adjusted SEs when the variance exceeds the mean.[14] Models were adjusted for sex and calendar year and stratified by age group. Cluster-robust standard errors were used to account for the non-independence of observations within families. Data management and statistical analyses were performed using SAS version 9.4 and R version 4.3.2. The Strengthening the Reporting of Observational studies in Epidemiology reporting guidelines were followed (appendix pp 37–42).

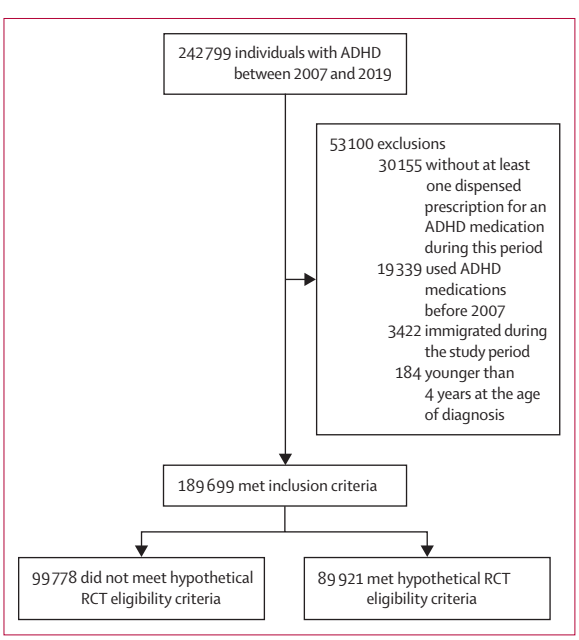


*Figure:* **Study population flow diagram**
RCT=randomised controlled trial.

### Sensitivity analyses

To assess the robustness of our findings, we conducted a series of sensitivity analyses. First, we applied a more stringent definition of treatment discontinuity, using a gap of 90 days in medication supply instead of the 180 days used in the main analysis. This approach allowed us to evaluate how different definitions of treatment adherence might affect our results. Second, we excluded individuals who discontinued treatment after the initial prescription (n=6279). This exclusion allowed us to focus on individuals who engaged with the treatment beyond the initial prescription, potentially providing a more accurate representation of treatment effects in individuals who committed to using the treatment.

Lastly, to account for variations in outcome counts potentially influenced by baseline severity, we adjusted for individual latent severity factor scores measured 1 year before ADHD treatment initiation. These latent scores, serving as a proxy for severity, were estimated using three indicators: psychiatric hospitalisations, injuries or accidents, and substance use disorders. To accommodate the high prevalence of zero counts, these indicators were modelled using zero-inflated Poisson and zero-inflated negative binomial models, selecting the best-fitting model based on the Bayesian Information Criterion (appendix p 36). The resulting individual factor scores, representing each person's estimated severity level, were then included as a covariate in sensitivity analyses to adjust for baseline severity differences between RCT-eligible and RCT-ineligible groups. Factor scores were estimated using Mplus version 8.3.

### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

The study cohort comprised 189 699 individuals (112 153 men and boys [59%] and 77 546 women and girls [41%]) with an ADHD diagnosis and initiating pharmacological treatment for ADHD, with a mean age of 21·52 years (SD 12·83; range 4–68 years) at the start of treatment. Among those, 99 778 (53%) were classified as ineligible based on common RCT exclusion criteria (ie, meeting at least one exclusion criterion; figure). When stratifying by age, ineligibility percentages were highest for adults (76 477 [74%] of 103 023), and substantially lower

for children (10 643 [21%] of 50 995) and adolescents (12 658 [35%] of 35 681). Ethnicity data were not available.

Individuals who were ineligible for the RCTs had a history of antidepressant use (67 824 [68%]), anxiety disorder (47 157 [47%]), substance use disorder (27 258 [27%]), and autism spectrum disorder (20 471 [21%]) within 1 year before the start of ADHD pharmacological treatment. Table 2 shows all exclusion criteria used to define the eligible and ineligible groups and summary statistics stratified by age.

Ineligible individuals had a higher risk of treatment switching (hazard ratio 1·14 [95% CI 1·12–1·16]) and a slightly decreased risk of medication discontinuation (0·96 [0·94–0·98]) compared with eligible individuals. Stratified analyses indicated similar risks across different age groups, except for children who had a higher risk for treatment discontinuation (1·17 [1·12–1·22]; table 3).

Within 1 year of treatment initiation, there was a significantly increased count of events for all outcomes for the ineligible group. The IRR of having any psychiatric inpatient hospitalisation within 1 year after treatment initiation in ineligible individuals compared with eligible individuals was 9·68 (95% CI 9·57–9·78); of having a specialist care visit related to substance use disorder, 14·78 (14·64–14·91); of depression-related specialist care visits, 6·00 (5·94–6·06); and of anxiety-related specialist care visits, 11·63 (11·56–11·69). When examining differences in the rate of injuries or accidents, the ineligible group showed a 31% increased rate compared with the eligible group (1·31 [1·27–1·35]). Age-stratified analyses showed that ineligible adolescents had the highest risk of psychiatric inpatient hospitalisation (11·63 [10·88–12·39]; table 4).

| | Overall | | Children (aged <13 years) | | Adolescents (aged 13–17 years) | | Adults (aged >17 years) | |
|---|---|---|---|---|---|---|---|---|
| | Eligible (n=89 921) | Ineligible (n=99 778) | Eligible (n=40 352) | Ineligible (n=10 643) | Eligible (n=23 023) | Ineligible (n=12 658) | Eligible (n=26 546) | Ineligible (n=76 477) |
| Sex | | | | | | | | |
| Male | 61 610 (69%) | 50 543 (51%) | 30 735 (76%) | 8012 (75%) | 14 255 (62%) | 5551 (44%) | 16 620 (63%) | 36 980 (48%) |
| Female | 28 311 (31%) | 49 235 (49%) | 9617 (24%) | 2631 (25%) | 8768 (38%) | 7107 (56%) | 9926 (37%) | 39 497 (52%) |
| Age at start of treatment, years | 13 (10–16) | 26 (17–37) | 9 (8–11) | 9 (8–11) | 15 (14–16) | 15 (14–16) | 20 (17–29) | 30 (23–40) |
| First ADHD medication | | | | | | | | |
| Guanfacine | 244 (<1%) | 464 (<1%) | 159 (<1%) | 136 (1%) | 44 (<1%) | 118 (1%) | 41 (<1%) | 210 (<1%) |
| Amphetamines | 9 (<1%) | 18 (<1%) | 1 (<1%) | 2 (<1%) | 1 (<1%) | 2 (<1%) | 7 (<1%) | 14 (<1%) |
| Dexamphetamine | 47 (<1%) | 183 (<1%) | 6 (<1%) | 4 (<1%) | 3 (<1%) | 3 (<1%) | 38 (<1%) | 176 (<1%) |
| Methylphenidate | 81 178 (90%) | 81 850 (82%) | 37 032 (92%) | 9364 (88%) | 20 890 (91%) | 10 991 (87%) | 23 256 (88%) | 61 495 (80%) |
| Atomoxetine | 6209 (7%) | 11 917 (12%) | 2523 (6%) | 909 (9%) | 1470 (6%) | 1039 (8%) | 2216 (8%) | 9969 (13%) |
| Lisdexamphetamine | 2234 (2%) | 5346 (5%) | 631 (2%) | 228 (2%) | 615 (3%) | 505 (4%) | 988 (4%) | 4613 (6%) |
| Treatment outcomes | | | | | | | | |
| Switching | 24 369 (27%) | 30 088 (30%) | 11 780 (29%) | 3354 (32%) | 6055 (26%) | 3980 (31%) | 6534 (25%) | 22 754 (30%) |
| Discontinuation | 27 509 (31%) | 27 057 (27%) | 10 195 (25%) | 2946 (28%) | 8754 (38%) | 4155 (33%) | 8560 (32%) | 19 956 (26%) |
| Functional outcomes, at least 1 count | | | | | | | | |
| Inpatient psychiatric hospitalisations | 1765 (2%) | 11 104 (11%) | 292 (1%) | 230 (2%) | 672 (3%) | 1060 (8%) | 801 (3%) | 9814 (13%) |
| Injuries or accidents | 9027 (10%) | 13 054 (13%) | 3285 (8%) | 858 (8%) | 2895 (13%) | 1823 (14%) | 2847 (11%) | 10 373 (14%) |
| Specialist care visits for substance use disorder | 947 (1%) | 10 573 (11%) | 4 (<1%) | 4 (<1%) | 489 (2%) | 523 (4%) | 454 (2%) | 10 046 (13%) |
| Specialist care visits for depression | 2508 (3%) | 17 940 (18%) | 254 (1%) | 214 (2%) | 992 (4%) | 2507 (20%) | 1262 (5%) | 15 219 (20%) |
| Specialist care visits for anxiety | 2529 (3%) | 23 977 (24%) | 501 (1%) | 980 (9%) | 925 (4%) | 3850 (30%) | 1103 (4%) | 19 147 (25%) |
| Conditions (exclusion criteria) | | | | | | | | |
| Bipolar disorder | 0 | 8307 (8%) | 0 | 44 (<1%) | 0 | 220 (2%) | 0 | 8043 (11%) |
| Anxiety disorder | 0 | 47 157 (47%) | 0 | 1616 (15%) | 0 | 5960 (47%) | 0 | 39 581 (52%) |
| Substance use disorder | 0 | 27 258 (27%) | 0 | 60 (1%) | 0 | 1363 (11%) | 0 | 25 835 (34%) |
| Autism spectrum disorder | 0 | 20 471 (21%) | 0 | 6675 (63%) | 0 | 3540 (28%) | 0 | 10 256 (13%) |
| Psychosis | 0 | 3694 (4%) | 0 | 16 (<1%) | 0 | 110 (1%) | 0 | 3568 (5%) |
| Intellectual disability | 0 | 4880 (5%) | 0 | 1914 (18%) | 0 | 850 (7%) | 0 | 2116 (3%) |
| Cardiovascular disease | 0 | 6434 (6%) | 0 | 464 (4%) | 0 | 351 (3%) | 0 | 5619 (7%) |
| Epilepsy | 0 | 4155 (4%) | 0 | 1268 (12%) | 0 | 622 (5%) | 0 | 2265 (3%) |
| Antidepressant use | 0 | 67 824 (68%) | 0 | 1059 (10%) | 0 | 6090 (48%) | 0 | 60 675 (79%) |

Data are n (%) or median (IQR).

***Table 2:*** **Descriptive statistics of the study cohort stratified by age and eligibility status**

Sensitivity analyses for treatment switching and discontinuation yielded consistent results across age groups. After adjusting for baseline severity scores, we observed a substantial decrease in IRRs, with results consistent with those in the primary analysis, except for injuries or accidents for children or adolescents, where estimates showed no increased rates (tables 3, 4).

## Discussion

We found that a substantial proportion of children (21%), of adolescents (35%), and most adults (74%) with ADHD would be deemed ineligible for typical RCTs on the basis of common exclusion criteria. Our study provides, for the first time, data on children. The percentage of ineligible adults aligns with that previously reported in one single RCT by Surman and colleagues,[8] who found that 61% of adults with ADHD in a community sample would be excluded due to stringent eligibility criteria. Overall, current evidence highlights a significant gap between the populations included in RCTs and those encountered in real-world clinical settings, particularly among adults.

Notably, this gap has also been observed in other psychiatric disorders. Research of RCTs on medications for schizophrenia highlights the significant disparity between the broader patient population and those who qualify for trials, primarily due to exclusion criteria that eliminate many individuals with comorbid conditions and more severe manifestations of the disorder: 79% of individuals with schizophrenia spectrum disorders would be deemed ineligible for RCTs.[15]

We also found that individuals ineligible for RCTs had a significantly higher risk of treatment switching with a slightly decreased risk of early medication discontinuation compared with eligible individuals, except in children, who showed an increased risk for treatment discontinuation. The increased risk of treatment switching among individuals who were ineligible might suggest a more complex clinical profile, requiring multiple adjustments of medication type to produce optimal outcomes. However, interpreting these patterns requires caution. Although switching might indicate greater symptom severity or an inadequate initial response, it could also reflect deliberate strategies for complex cases. For example, individuals with comorbid anxiety might start with a non-stimulant before transitioning to a stimulant, if necessary,[13] representing a planned, stepwise

| | Outcome | Overall | Children (aged <13 years) | Adolescents (aged 13–17 years) | Adults (aged >17 years) |
|---|---|---|---|---|---|
| Main analysis (N=189 699) | Treatment switch | 1·14 (1·12–1·16) | 1·10 (1·06–1·14) | 1·15 (1·11–1·20) | 1·19 (1·15–1·23) |
| Main analysis (N=189 699) | Treatment discontinuation | 0·96 (0·94–0·98) | 1·17 (1·12–1·22) | 0·86 (0·83–0·90) | 0·89 (0·86–0·92) |
| First sensitivity analysis* (N=189 699) | Treatment discontinuation | 0·90 (0·89–0·91) | 1·07 (1·04–1·10) | 0·88 (0·85–0·90) | 0·87 (0·85–0·89) |
| Second sensitivity analysis† (N=183 420) | Treatment switch | 1·15 (1·12–1·17) | 1·10 (1·06–1·14) | 1·16 (1·11–1·20) | 1·19 (1·16–1·22) |
| Second sensitivity analysis† (N=183 420) | Treatment discontinuation | 0·90 (0·88–0·92) | 1·04 (0·99–1·09) | 0·83 (0·80–0·86) | 0·85 (0·83–0·88) |

Data are hazard ratio (95% CI). All models were adjusted for sex, age, and calendar year. *Model defining treatment discontinuation as a gap of 90 days or more. †Model excluding individuals who discontinued treatment after the first prescription.

*Table 3:* **Summary of the results from Cox models stratified by age**

| | Outcome | Overall (N=189 699) | Children (aged <13 years; n=50 995) | Adolescents (aged 13–17 years; n=35 681) | Adults (aged >17 years; n=103 023) |
|---|---|---|---|---|---|
| Main analysis* | Psychiatric inpatient hospitalisation | 9·68 (9·57–9·78) | 7·21 (7·10–7·32) | 11·63 (10·88–12·39) | 8·89 (8·43–9·34) |
| Main analysis* | Injuries or accidents | 1·31 (1·27–1·35) | 1·19 (1·15–1·24) | 1·63 (1·39–1·87) | 1·65 (1·47–1·83) |
| Main analysis* | Specialist care visit for substance use disorder | 14·78 (14·64–14·91) | 8·73 (8·60–8·85) | 33·56 (32·46–34·67) | 24·34 (23·68–24·99) |
| Main analysis* | Specialist care visit for depression | 6·00 (5·94–6·06) | 5·37 (5·3–5·44) | 4·40 (4·10–4·71) | 4·49 (4·26–4·71) |
| Main analysis* | Specialist care visit for anxiety | 11·63 (11·56–11·69) | 10·27 (10·21–10·34) | 9·75 (9·33–10·17) | 9·14 (8·83–9·45) |
| Third sensitivity analysis† | Psychiatric inpatient hospitalisation | 3·76 (3·67–3·85) | 3·10 (3·00–3·19) | 3·59 (3·03–4·15) | 2·57 (2·22–2·92) |
| Third sensitivity analysis† | Injuries or accidents | 1·02 (0·98–1·07) | 0·94 (0·90–0·99) | 1·21 (0·97–1·44) | 1·24 (1·06–1·42) |
| Third sensitivity analysis† | Substance use disorder | 3·42 (3·30–3·54) | 2·53 (2·41–2·65) | 4·82 (4·05–5·60) | 3·31 (2·83–3·79) |
| Third sensitivity analysis† | Depression | 5·56 (5·50–5·62) | 5·00 (4·93–5·06) | 4·06 (3·75–4·37) | 4·20 (3·98–4·42) |
| Third sensitivity analysis† | Anxiety | 10·54 (10·48–10·61) | 9·48 (9·42–9·55) | 8·44 (8·03–8·85) | 8·15 (7·84–8·45) |

Data are incidence rate ratio (95% CI). *Model adjusted for sex and calendar year. †Model adjusted for sex, calendar year, and latent baseline severity scores.

*Table 4:* **Results from the quasi-Poisson model stratified by age**

approach rather than treatment failure. Furthermore, the higher switching rate coupled with a decreased risk of treatment discontinuation among individuals ineligible for RCTs might suggest that switching facilitates finding more effective medications, potentially mitigating discontinuation risk. This highlights a possible adaptive aspect of clinical care for complex cases. This complexity indicates the challenges in translating RCT findings to real-world practice and emphasises the need for long-term studies of treatment trajectories in diverse ADHD populations.

The increased risk of treatment discontinuation among children might be attributed to several factors. First, there are heightened concerns about medication side-effects[16] in paediatric populations, which could make clinicians and parents more cautious about treatment. This caution might lead to a lower threshold for discontinuing medication when side-effects occur or when the initial response is suboptimal. Additionally, the process of treatment switching, which could potentially lead to finding a more suitable medication, might be approached more conservatively in children due to these same concerns. This conservative approach to switching could result in fewer opportunities to find an effective medication before discontinuation is considered. Furthermore, children's developing physiology and potential difficulties in articulating treatment effects might complicate the process of finding the right medication and dose, potentially leading to premature discontinuation if optimal results are not quickly achieved. The treatment patterns we observed, particularly in children, should be considered within the broader context of multimodal ADHD management. Non-pharmacological interventions (eg, behavioural therapy, parent training, and school-based accommodations) often play a crucial role alongside medication management. The increased risk of medication discontinuation among children who were ineligible for RCTs might reflect shifts towards these non-pharmacological approaches, rather than treatment abandonment. For instance, families might opt to prioritise behavioural interventions if medication response is suboptimal or side-effects are problematic. The interplay between pharmacological and non-pharmacological treatments could influence both switching and discontinuation patterns, particularly in complex cases where behavioural interventions might provide additional support during medication adjustments or serve as alternative strategies. Lastly, the involvement of parents or guardians in treatment decisions for children adds another layer of complexity, because their perceptions and concerns can significantly influence treatment continuation or discontinuation.

Notably, we also found that the ineligible group had nearly ten times the rate of psychiatric inpatient hospitalisations within 1 year after treatment initiation, along with markedly higher rates of specialty care visits: approximately 14 times higher for substance use disorder, approximately six times higher for depression, and approximately 11 times higher for anxiety. Although the direction of these findings is not unexpected given the RCT's exclusion criteria, one strength of our study was to quantify the magnitude of these differences, which can inform public health policies. The difference in rates of injuries and accidents was smaller, with the ineligible group having a 31% higher rate of injuries or accidents. These findings might be accounted for, at least partly, by the fact that psychiatric comorbidity—a common reason for exclusion from RCTs—predicts worse outcomes in ADHD.[17] The markedly higher rates of psychiatric hospitalisations and substance use disorder visits in the ineligible group, even after adjusting for baseline severity, emphasise the clinical and public health implications of the findings. These adverse outcomes might be indicative of more severe or complex ADHD symptoms, comorbid psychiatric conditions, or other psychosocial factors that are often excluded from RCTs but prevalent in real-world clinical settings.

Overall, in line with previous evidence, our results highlight important gaps between evidence-based recommendations and guidelines and clinical reality,[18] particularly regarding the limitations of relying solely on RCT evidence to inform clinical decision making and guidelines and policies. This reliance on RCT evidence might be less problematic in paediatric populations, given the lower number of ineligible individuals in younger age groups. However, for adult ADHD populations, where ineligibility rates are higher, the limitations of RCT-based evidence become more pronounced, creating a paradox: those patients who might benefit most from evidence-based guidance are the least represented in clinical trials that are meant to inform guidance. Individuals meeting RCT eligibility criteria typically have a less complicated course of ADHD, potentially reflecting, in part, a more favourable response to medication. This selection effect in RCTs might result in a misestimation of treatment efficacy and adverse outcomes when findings are extrapolated to the broader ADHD population. For instance, drug interactions and adverse events might be more likely in excluded groups, especially those with medical multimorbidity.[19] Clinicians thus face the challenging task of not only identifying when RCT findings from relatively straightforward cases can be meaningfully extrapolated, but also recognising when the clinical complexity demands fundamentally different treatment approaches.

These considerations suggest a need for a more comprehensive approach to clinical research in ADHD. Although the narrow entry criteria in traditional RCTs provide a cost-effective approach for establishing the efficacy and safety of a medication that is useful for regulatory authorities, they limit generalisability to real-world, heterogeneous populations. To address this, a balanced research strategy is needed, considering how the results from traditional RCTs, pragmatic trials with

broader inclusion criteria, real-world observational studies, and targeted trials in typically excluded populations complement each other. The triangulation of these data would provide clinicians with a more complete understanding of medication effectiveness across diverse patient groups and clinical contexts. Furthermore, the consistent reporting of study participant selection processes in future ADHD trials (ie, participant flow) would enable a better assessment of trial generalisability and facilitate more direct comparisons with real-world populations.

Implementing a comprehensive research strategy faces challenges from multiple fronts: regulatory bodies favouring trials with strict eligibility criteria, the reluctance of funding agencies to support studies on licensed drugs in broader populations, and pharmaceutical companies' focus on individuals less likely to show safety concerns that could jeopardise regulatory approval. These issues create a gap between efficacy studies that assess treatments under ideal conditions, and effectiveness studies that evaluate real-world outcomes. Although efficacy studies are crucial for establishing a treatment's potential, effectiveness studies provide insights into the practical effect across diverse populations, including those with comorbidities often excluded from RCTs. Addressing this tension requires a shift in research priorities and funding allocation to support both types of studies, leading to more inclusive clinical guidelines and personalised treatment strategies that better serve the broader ADHD population.

Emerging methods offer promising solutions to bridge this gap. Research has focused on developing frameworks for integrating aggregate or individual patient data[20] from both randomised and observational studies to build more generalisable prediction models.[21] These approaches use two-stage network meta-analysis techniques and incorporate methods to account for differences in study design and potential biases.[21] This integration method helps to address the limitations of RCTs, such as their stringent inclusion criteria, by incorporating the broader and more diverse patient populations seen in observational studies.

Some limitations of this study should be acknowledged. The registry-based design meant we did not have detailed clinical data on ADHD severity and functioning that are typically captured in RCTs (eg, standardised ADHD rating scales, quality of life measures, and academic or occupational performance). Although our outcomes represent important real-world events that affect patient wellbeing and health-care use, we acknowledge they differ from traditional RCT outcomes. However, our chosen outcomes complement RCT findings by capturing severe events that are often too rare to be meaningfully assessed in trials, yet are crucial for clinical decision making. Future research could address this limitation by linking registry data with clinical records to capture standardised symptom assessments and developing validated proxy measures for ADHD severity that can be derived from registry data, and conducting pragmatic trials with broad eligibility criteria and outcomes other than the traditional ones.

We applied common but not universal RCT exclusion criteria; some trials might be more inclusive. Another limitation was the challenge in operationalising specific exclusion criteria within registry data. For instance, distinguishing between current and historical diagnoses—a distinction often crucial in clinical trials to assess potential interference with the study—was not feasible with our data. The generalisability of findings to countries with different health systems and access should be investigated because Sweden has a universal, publicly funded health-care system and has some of the highest rates of prescription of ADHD medication globally.[22] The pharmacological options for ADHD treatment in Sweden represent a subset of those available in countries such as the USA, potentially limiting the generalisability of our findings to other countries. For instance, viloxazine, which was approved for ADHD by the US Food and Drug Administration in 2021,[23] is not available in Sweden. Longitudinal research is warranted to confirm results and provide insights into longer term clinical trajectories of excluded ADHD subgroups over time in relation to medication treatment.

Our study showed that a substantial portion of individuals with ADHD, in particular adults, are ineligible for standard RCTs, and these individuals have higher rates of adverse clinical outcomes compared with their eligible counterparts. The findings emphasise the need for complementary evidence from pragmatic trials and observational studies to inform treatment decision making and public health policies for individuals with ADHD.

#### Contributors

MG-A, SC, SVF, and JHN designed the study. MG-A planned and performed all statistical analyses. MG-A and SC wrote the initial draft of the manuscript. HL, PL, RK-H, BMD'O, IB, and ZC contributed to data acquisition. SC and HL provided supervision and contributed to funding acquisition. All authors contributed to the interpretation of the results, and reviewing and editing of the manuscript. MG-A, HL, PL, RK-H, IB, and ZC had full access to and verified all the data in the study, and accept responsibility for the decision to submit the article for publication.

#### Declaration of interests

HL reports receiving grants from Shire/Takeda Pharmaceuticals during the conduct of the study; personal fees from and serving as a speaker for Shire/Takeda Pharmaceuticals and Evolan Pharma outside the submitted work; and sponsorship for a conference on ADHD from Shire Pharmaceuticals outside the submitted work. SC declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian ADHD Resource Alliance, the British Association of Psychopharmacology; from Healthcare Convention for educational activity on ADHD; and has received honoraria from Medice. All other authors declare no competing interests.

#### Data sharing

The Public Access to Information and Secrecy Act in Sweden prohibits us from making individual level data publicly available. Researchers who are interested in replicating our work can apply for individual level data at Statistics Sweden: www.scb.se/en/services/guidance-for-researchers-and-universities/.

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