**Evaluating ADHD Medication Trial Representativeness: A Swedish Population-Based Study Comparing Hypothetically Trial-Eligible and Ineligible Individuals**

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# Summary

**Background**

Randomised controlled trials (RCTs) evaluating attention-deficit/hyperactivity disorder (ADHD) medications often use strict eligibility criteria, potentially limiting generalisability to patients in real-world clinical settings. We aimed to 1) determine the proportion of individuals with ADHD who would be ineligible for medication RCTs and 2) evaluate differences in treatment patterns and clinical/functional outcomes between RCT-eligible and ineligible individuals.

**Methods**

We used Swedish national registries to identify individuals with ADHD, aged 4-68, initiating pharmacological treatment between January 1, 2007, and December 31, 2019, with follow-up through December 31, 2020. Hypothetical RCT ineligibility was determined 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. Poisson models compared eligible and ineligible individuals on rates of psychiatric hospitalizations, injuries/accidents, and substance misuse within 1 year of initiating ADHD medications. People with lived experience were not involved in the research and writing process. Ethnicity data were not available.

**Outcomes**

Out of 189,699 individuals (112,153 males [59%] and 77,546 [41%] females; mean age=21[range 4-68] years) initiating ADHD medication, 53% (74% of adults, 35% of adolescents, and 21% of children) would have been ineligible for RCT participation. Ineligible individuals had a higher likelihood of treatment switching (HR=1·15, 95% CI 1·12-1·17), and a decreased likelihood of medication discontinuation (HR=0·96 [0·94-0·98]) compared to eligible individuals. RCT-ineligible individuals had significantly higher rates of psychiatric hospitalizations (IRR=3·76 [3·67-3·85]) and specialist care visits related to substance misuse (IRR=3·42 [3·30-3·54]), depression (IRR=6·00 [5·94-6·06]), and anxiety (IRR=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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# Research in context

**Evidence before this study:** We searched PubMed, Web of Science, and PsycINFO for studies published up to April 1st, 2024, using the search terms "ADHD" (and equivalents), "clinical trials", "real-world evidence", and "treatment outcomes". We included studies comparing outcomes between RCT-eligible and ineligible ADHD populations. We found only one study, from the United States, based on a single randomized controlled trial (RCT), showing that only about one-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/functional outcomes between RCT-eligible and ineligible populations in a large, real-world cohort.

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

**Implications of all the available evidence:** Our findings, combined with previous evidence, highlights the pressing need to triangulate evidence from standard RCTs and those specifically targeting typically excluded populations, and to combine data from RCTs with 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.

# Introduction

Pharmacotherapy is an important component of the multimodal treatment of attention-deficit/hyperactivity disorder (ADHD).1 Randomized controlled trials (RCTs) are considered the gold standard to evaluate efficacy and tolerability of a treatment. However, their strict inclusion/exclusion criteria may limit the generalizability of findings to clinical populations routinely seen in clinical practice. Common exclusion criteria in RCTs of ADHD medications include the presence of psychiatric/neurodevelopmental comorbidities (e.g., major depressive disorder, autism spectrum disorder, psychosis, or intellectual disability) as well as other medical conditions (e.g., cardiovascular disease).2 These conditions frequently co-occur with ADHD,3–7 and, as a result, a substantial percentage of individuals with ADHD would not meet the typical inclusion criteria for these RCTs.

Indeed, findings from the only available study based on one RCT in US adults with ADHD suggests that only about 31% of individuals with ADHD presenting for routine clinical care would meet eligibility for participation the RCT.8 However, these findings are based on one RCT in a specific country and refer to adults only. Importantly, it remains unclear how excluded real-world ADHD groups differ in their treatment pattern and outcomes compared to the relatively homogeneous RCT 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 of ADHD medications, and to identify potential differences in treatment patterns and clinical/functional outcomes between individuals who would be eligible for RCTs and those who would not.

The aims of this study were to: 1) quantify the percentage of individuals with ADHD initiating ADHD medications in the real world who would be ineligible for RCT ADHD medication efficacy trials, 2) evaluate differences in medication switching and medication discontinuation within one year between eligible and ineligible groups, and 3) explore whether important clinical/functional outcomes, such as inpatient psychiatric hospitalizations, injuries/accidents, the number of specialist care visits related to substance use disorder, depression, and anxiety, differ between eligible and ineligible individuals over a 12-month observation period. We hypothesised that compared to hypothetically RCT-eligible individuals, those ineligible for RCTs would show: 1) Higher rates of medication discontinuation and switching, reflecting greater clinical complexity and potentially poorer treatment response, 2) higher rates of adverse clinical/functional outcomes, likely indicating greater underlying clinical severity and comorbidity burden.

# Methods

## Study population

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

We identified all individuals with a registered ICD-10 diagnosis code for ADHD (F90) between January 1, 2007 to December 31, 2019 who were at least 4 years old 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 may 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 lisdexamfetamine [N06BA12]), and nonstimulants (atomoxetine [N06BA09] and guanfacine [C02AC02]). January 1, 2007 was chosen as the start date to allow a washout period of at least 18 months prior to the first ADHD medication dispensation date to determine ADHD medication status,10 which was defined as no ADHD drug dispensations in the 18 months prior to 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 (Dnr 2020-06540; Dnr 2022-06204-02).

## Exposure and outcomes

Exposure was RCT eligibility versus ineligibility, which was determined by systematically assessing whether individuals within the Swedish registers would meet common inclusion/exclusion criteria from RCT 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 (EAGG) to carry out the systematic review and network meta-analysis by Cortese et al. (2018).2 We used data from RCTs included in the most recent update of MED-ADHD (January 22nd, 2024), encompassing 164 eligible RCT. A detailed list of participants’ exclusion criteria for each RCT in ADHD-MED and additional information is reported in the appendix (pp2-34).

After analysing each of the 164 retrieved RCTs, the most common exclusion criteria were history of antidepressants (73% of RCTs), psychosis (65·4%), bipolar disorder (48·5%), history of substance use disorder (39%), cardiovascular disease (38%), learning disability or low IQ (36%), anxiety disorder (35%), and autism spectrum disorder (ASD; 35%; see Table 1 for the top 15 most common exclusion criteria). Exclusion criteria for our study were defined based on criteria present in at least 30% of the RCTs and were assessed within one year prior to the initiation of ADHD treatment to reflect current clinical status. This threshold was selected to reflect commonly applied criteria in RCTs, as it represents a frequency where a certain condition is excluded in at least one out of every three RCTs. This approach balances the need to capture prevalent exclusion criteria while maintaining 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 ineligible samples for comparison of real-world outcomes. Additional less frequent RCT inclusion/criteria like baseline symptom severity thresholds could not be extracted from the registers due to unavailability of such measures. Appendix (p35) shows the ICD-10 codes used to define eligibility status in the cohort study.

Primary outcomes for the present study included 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 minimized the maximum error in our estimation, assuming discontinuation times are uniformly distributed within the interval. This approach reduces potential overestimation of treatment duration, providing a more conservative estimate of time-to-discontinuation.

Secondary outcomes included the number of 1) inpatient psychiatric hospitalization (ICD-10 codes F00-F99), 2) emergency department visits or hospitalizations related to accidental injuries/accidents (ICD-10 codes S00-T78, V00-X59; appendix p35), and 3) specialist care encounters with an alcohol/drug-related diagnosis (F10-F16, F18-F19), depression (F32-34), and anxiety (F40-F42) All secondary outcomes were assessed at 12 months from treatment initiation.

These secondary outcomes were selected based on established clinical relevance in ADHD and supporting evidence. Psychiatric hospitalizations 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 investigation of treatment response in patient populations typically underrepresented in clinical trials.

## Statistical analysis

The percentage of ADHD patients meeting RCT eligibility criteria was calculated, and socioeconomic characteristics were summarized for both groups and stratified by age at treatment initiation (children [<13], adolescents [13-17], and adults [>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 (i.e., treatment switching and early discontinuation) follow-up started from the first ADHD medication dispensation. The end of follow-up was determined as whichever happened first: treatment switching or early discontinuation (depending on the outcome), death, migration, one year from the start of ADHD treatment, or end of the study period (December 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 (IRR) with 95% confidence intervals (CIs) were calculated using quasi-Poisson14 regression models comparing the rates of psychiatric hospitalizations, injuries/accidents, and specialty care visits related to substance misuse, depression, and anxiety in the 12 months 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, as it provides adjusted standard errors 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 the non-independence of observations within families. Data management and statistical analyses were performed using SAS 9.4 and R version 4.3.2.15 The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) reporting guidelines were followed (appendix pp37-42).

## 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 impact our results. Second, we excluded single-prescription discontinuers (n=6,279). 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 committed users.

Lastly, to account for variations in outcome counts potentially influenced by baseline severity, we adjusted for individual latent severity factor scores measured one year prior to ADHD treatment initiation. These latent scores, serving as a proxy for severity, were estimated using three indicators: psychiatric hospitalizations, injuries/accidents, and substance misuse. 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 Bayesian Information Criterion (appendix p36). 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 ineligible groups. Factor scores were estimated using Mplus 8.3.16

**Results**

The study cohort included 189,699 individuals (59% men) with an ADHD diagnosis and initiating pharmacological treatment for ADHD with a mean age of 21·52 years (SD=12·83) at the start of treatment. Among those, 99,778 (53%) were classified as ineligible based on common RCT exclusion criteria (i.e., having at least one; Figure 1). When stratifying by age, ineligibility percentages were highest for adults (74%), and substantially lower for children (21%) and adolescents (35%). Ethnicity data were not available.

RCT-ineligible individuals had a prior history of antidepressants (68%), anxiety disorders (47%), substance use disorder (27%), and ASD (21%) within one 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 (HR=1·14, 95% CI 1·12-1·16) and a slightly decreased risk of medication discontinuation (HR=0·96, 95% CI 0·94-0·98) compared to eligible individuals. Stratified analyses indicated similar risks across different age groups, except for children who exhibited a higher risk for treatment discontinuity (HR=1·17 [1·12-1·22]; see Table 3).

Within 12 months of treatment initiation, there was a significant increased count of events for all outcomes for the ineligible group. Compared to the eligible group, ineligible individuals had almost ten times the rate of having any psychiatric inpatient hospitalization within one year after treatment initiation (IRR=9·68 [9·57-9·78]),14 times higher rate of having a hospital visit related to substance misuse (IRR=14·78 [14·64-14·9]), a sixfold increase in depression-related specialist care visits (IRR=6·00 [5·94-6·06]), and an elevenfold increase in anxiety-related specialist visits (IRR=11·63 [11·56-11·69]). When examining differences in the rate of injuries/accidents, the ineligible group showed a 31% increased rate compared to the eligible group (IRR=1·31 [1·27-1·35]). Age-stratified analyses showed that ineligible adolescents had the highest risk of psychiatric inpatient hospitalization (IRR=11·63 [10·88-12·39]; Table 4).

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/accidents for children or adolescents, where estimates showed no increased rates (Tables 3 and 4).

**Discussion**

We found that a substantial proportion of children (21%), adolescents (35%) and even more adults (74%) with ADHD would be deemed ineligible for typical RCTs based on common exclusion criteria. While our study provides, for the first time, data on children, the percentage of ineligible adults aligns with those previously reported in one single RCT by Surman et al.,8 reporting 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 on RCTs of 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.17 This discrepancy is starkly illustrated by the fact that, within that study, 79% of individuals with schizophrenia spectrum disorders would be deemed ineligible for RCT.

We also found that RCT-ineligible individuals had a significantly higher risk of treatment switching with a slightly decreased risk of early medication discontinuation compared to eligible individuals, except in children, who showed an increased risk for treatment discontinuation. The increased risk of treatment switching among ineligible individuals might suggest a more complex clinical profile, requiring multiple adjustments of medication type to achieve optimal outcomes. However, interpreting these patterns requires caution. While switching might indicate greater symptom severity or 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 approach rather than treatment failure. Further, the higher switching rate coupled with a decreased risk of treatment discontinuation among RCT-ineligible individuals 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 emphasizes the need for long-term studies of treatment trajectories in diverse ADHD populations.

The increased risk for treatment discontinuation among children may be attributed to several factors. Firstly, there are heightened concerns about medication side effects18 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, may 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 may complicate the process of finding the right medication and dosage, potentially leading to premature discontinuation if optimal results are not quickly achieved. Moreover, the treatment patterns we observed, particularly in children, should be considered within the broader context of multimodal ADHD management. Non-pharmacological interventions (e.g., behavioural therapy, parent training, and school-based accommodations) often play a crucial role alongside medication management. The increased risk of medication discontinuation among RCT-ineligible children might reflect shifts toward these non-pharmacological approaches, rather than treatment abandonment. For instance, families might opt to prioritize 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, as their perceptions and concerns can significantly influence treatment continuation or discontinuation.

Importantly, we also found that the ineligible group had nearly ten times the rate of psychiatric inpatient hospitalizations within one-year post-treatment initiation, along with markedly higher rates of specialty care visits: 14 times higher for substance misuse, six times higher for depression, and 11 times higher for anxiety. While the direction of these findings is not unexpected given the RCTs exclusion criteria, one strength of our study is to quantify the magnitude of these differences, which can inform public health policies. The difference in rates of injuries and accidents was comparatively smaller, albeit still noteworthy, with the ineligible group exhibiting a 31% higher rate of injuries/accidents. These findings may be accounted for, at least partially, by the fact that psychiatric comorbidity –a common reason of exclusion from RCTs– predicts worse outcomes in ADHD.19 The markedly higher rates of psychiatric hospitalizations and substance misuse events in the ineligible group, even after adjusting for baseline severity, emphasize the clinical and public health implications of the findings. These adverse outcomes may also be indicative of more severe or complex ADHD symptomatology, 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/guidelines and clinical reality,20 particularly regarding the limitations of relying solely on RCT evidence to inform clinical decision-making and guidelines/policies. This reliance on RCT evidence may be less problematic in paediatric populations, given the much 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 significant 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 exhibit a less complicated course of ADHD, potentially reflecting, in part, a more favourable response to medication. This *'selection effect*' in RCTs may 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 may be more likely in excluded groups, especially those with medical multimorbidity.21 Clinicians thus face the challenging task of not only determining when RCT findings from relatively straightforward cases can be meaningfully extrapolated, but also recognizing 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 a medications efficacy and safety that is useful for regulatory authorities, they limit generalizability 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. Further, consistent reporting of study participant selection process in future ADHD trials (i.e., participant flow) would enable better assessment of trial generalizability and facilitate more direct comparisons with real-world populations.

Implementing a comprehensive research strategy faces challenges from multiple fronts: regulatory bodies favouring narrowly defined trials, funding agencies’ reluctance to support studies on existing drugs in broader populations, and pharmaceutical companies' focus on subjects less likely to exhibit safety concerns that could jeopardize regulatory approval. This creates a gap between efficacy studies that assess treatments under ideal conditions, and effectiveness studies that evaluate real-world outcomes. While efficacy studies are crucial for establishing a treatment's potential, effectiveness studies provide insights into practical impact 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 personalized treatment strategies that better serve the broader ADHD population.

Emerging methodologies offer promising solutions to bridge this gap. Recent research has focused on developing frameworks for integrating aggregate or individual patient data22 from both randomized and observational studies to build more generalizable prediction models.23 These approaches utilize two-stage network meta-analysis techniques and incorporate methods to account for differences in study design and potential biases.23 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.

## Limitations

While this study provides valuable insights into the real-world treatment outcomes and clinical events among RCT-ineligible individuals with ADHD, some limitations should be acknowledged. The register-based design meant we lacked detailed clinical data on ADHD severity and functioning that are typically captured in RCTs (e.g., standardized ADHD rating scales, quality of life measures, academic/occupational performance). While our outcomes represent important real-world events that impact patient well-being and healthcare utilization, 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 1) linking registry data with clinical records to capture standardized symptom assessments and developing validated proxy measures for ADHD severity that can be derived from registry data, and 2) 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 may be more inclusive. Another limitation was the challenge in operationalizing certain 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. However, to address this issue, we defined 'current' diagnoses as those recorded within one year prior to the initiation of ADHD treatment. While this approach provides a standardized timeframe, it does not fully capture how comorbidity criteria are applied when enrolling patients in an RCT. The generalizability of findings to countries with different health systems and access should be investigated as Sweden has a universal, publicly funded health care system and among the highest rates of ADHD medication prescribing globally.24 Additionally, the pharmacological options for ADHD treatment in Sweden represent a subset of those available in countries like the United States, potentially limiting the generalizability of our findings. For instance, viloxazine, which was approved for ADHD by the FDA in 2021,25 is not available in Sweden. Regardless, a key strength of utilizing nationwide registries was assessing outcomes among excluded individuals who are often missing from clinic-based studies. Additional 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.

## Conclusions

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

# Author Contribution

MGA, SC, SVF, JHN designed the study

MGA planned and performed all statistical analyses.

MGA and SC wrote the initial draft of the manuscript

HL, PL, RK-H, BD’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, reviewing and editing of the manuscript.

MGA, HL, PL, RK-H, IB, and ZC had full access to all the data in the study and accept responsibility to submit the article for publication

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# Role of the Funding source

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

# Declaration of interests

Henrik Larsson reported 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 AB outside the submitted work; and sponsorship for a conference on attention-deficit/hyperactivity disorder from Shire Pharmaceuticals outside the submitted work. Prof. Cortese has declared 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, and from Healthcare Convention for educational activity on ADHD, and has received honoraria from Medice. The remaining authors declare having no conflict of interest.

# Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

# **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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# Tables

**Table 1**. Most common 15 reasons for exclusion in randomised controlled trials (RCTs) of ADHD medications.

|  |  |
| --- | --- |
| **Condition** | **Percentage of RCTs** |
| Antidepressants | 73.8 |
| Psychosis | 65.4 |
| Bipolar disorder | 48.5 |
| Substance use disorder | 39.2 |
| Cardiovascular disease | 37.7 |
| IQ and learning disabilities | 36.2 |
| Anxiety disorder | 35.4 |
| Autism Spectrum Disorder | 35.4 |
| Pregnancy and related | 32.3 |
| History of seizures | 30.0 |
| Psychotropic medications | 26.9 |
| Tourette syndrome | 26.2 |
| Alcohol use disorder | 24.6 |
| Depression | 24.6 |
| Suicidality | 24.6 |

These reasons for exclusions were based on the included 164 randomised controlled trials reported in Appendix Table 1 and used as a reference in our study.

IQ = Intelligence quotient

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

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Overall** | | **Children** | | **Adolescents** | | **Adults** | |
| **Variable** | **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%) | 8,012 (75%) | 14,255 (62%) | 5,551 (44%) | 16,620 (63%) | 36,980 (48%) |
| Female | 28,311 (31%) | 49,235 (49%) | 9,617 (24%) | 2,631 (25%) | 8,768 (38%) | 7,107 (56%) | 9,926 (37%) | 39,497 (52%) |
| Age at treatment, years (IQR) | 13 (10, 16) | 26 (17, 37) | 9·32 (7·91, 10·61) | 9·20 (7·53, 10·62) | 14·86 (13·97, 15·75) | 15·29 (14·34, 16·15) | 20 (17, 29) | 30 (23, 40) |
| *First ADHD medication* |  |  |  |  |  |  |  |  |
| Guanfacine | 244 (0·3%) | 464 (0·5%) | 159 (0·4%) | 136 (1·3%) | 44 (0·2%) | 118 (0·9%) | 41 (0·2%) | 210 (0·3%) |
| Amphetamines | 9 (<0·1%) | 18 (<0·1%) | 1 (<0·1%) | 2 (<0·1%) | 1 (<0·1%) | 2 (<0·1%) | 7 (<0·1%) | 14 (<0·1%) |
| Dexamphetamine | 47 (<0·1%) | 183 (0·2%) | 6 (<0·1%) | 4 (<0·1%) | 3 (<0·1%) | 3 (<0·1%) | 38 (0·1%) | 176 (0·2%) |
| Methylphenidate | 81,178 (90%) | 81,850 (82%) | 37,032 (92%) | 9,364 (88%) | 20,890 (91%) | 10,991 (87%) | 23,256 (88%) | 61,495 (80%) |
| Atomoxetine | 6,209 (6·9%) | 11,917 (12%) | 2,523 (6·3%) | 909 (8·5%) | 1,470 (6·4%) | 1,039 (8·2%) | 2,216 (8·3%) | 9,969 (13%) |
| Lisdexamphetamine | 2,234 (2·5%) | 5,346 (5·4%) | 631 (1·6%) | 228 (2·1%) | 615 (2·7%) | 505 (4·0%) | 988 (3·7%) | 4,613 (6·0%) |
| *Treatment outcomes* |  |  |  |  |  |  |  |  |
| Switching | 24,369 (27%) | 30,088 (30%) | 11,780 (29%) | 3,354 (32%) | 6,055 (26%) | 3,980 (31%) | 6,534 (25%) | 22,754 (30%) |
| Discontinuation | 27,509 (31%) | 27,057 (27%) | 10,195 (25%) | 2,946 (28%) | 8,754 (38%) | 4,155 (33%) | 8,560 (32%) | 19,956 (26%) |
| *Functional outcomes, % with at least 1 count* |  |  |  |  |  |  |  |  |
| Inpatient psychiatric hospitalizations | 1,765 (2·0%) | 11,104 (11%) | 292 (0·7%) | 230 (2·2%) | 672 (2·9%) | 1,060 (8·4%) | 801 (3·0%) | 9,814 (13%) |
| Injuries/accidents | 9,027 (10%) | 13,054 (13%) | 3,285 (8·1%) | 858 (8·1%) | 2,895 (13%) | 1,823 (14%) | 2,847 (11%) | 10,373 (14%) |
| Specialist care visits, substance use disorder | 947 (1·1%) | 10,573 (11%) | 4 (<0·1%) | 4 (<0·1%) | 489 (2·1%) | 523 (4·1%) | 454 (1·7%) | 10,046 (13%) |
| Specialist care visits, depression | 2,508 (2·8%) | 17,940 (18%) | 254 (0·6%) | 214 (2·0%) | 992 (4·3%) | 2,507 (20%) | 1,262 (4·8%) | 15,219 (20%) |
| Specialist care visits, anxiety | 2,529 (2·8%) | 23,977 (24%) | 501 (1·2%) | 980 (9·2%) | 925 (4·0%) | 3,850 (30%) | 1,103 (4·2%) | 19,147 (25%) |
| *Conditions* |  |  |  |  |  |  |  |  |
| Bipolar disorder | 0 (0%) | 8,307 (8·3%) | 0 (0%) | 44 (0·4%) | 0 (0%) | 220 (1·7%) | 0 (0%) | 8,043 (11%) |
| Anxiety disorder | 0 (0%) | 47,157 (47%) | 0 (0%) | 1,616 (15%) | 0 (0%) | 5,960 (47%) | 0 (0%) | 39,581 (52%) |
| Substance use disorder | 0 (0%) | 27,258 (27%) | 0 (0%) | 60 (0·6%) | 0 (0%) | 1,363 (11%) | 0 (0%) | 25,835 (34%) |
| Autism spectrum disorder | 0 (0%) | 20,471 (21%) | 0 (0%) | 6,675 (63%) | 0 (0%) | 3,540 (28%) | 0 (0%) | 10,256 (13%) |
| Psychosis | 0 (0%) | 3,694 (3·7%) | 0 (0%) | 16 (0·2%) | 0 (0%) | 110 (0·9%) | 0 (0%) | 3,568 (4·7%) |
| Intellectual disability | 0 (0%) | 4,880 (4·9%) | 0 (0%) | 1,914 (18%) | 0 (0%) | 850 (6·7%) | 0 (0%) | 2,116 (2·8%) |
| Cardiovascular disease | 0 (0%) | 6,434 (6·4%) | 0 (0%) | 464 (4·4%) | 0 (0%) | 351 (2·8%) | 0 (0%) | 5,619 (7·3%) |
| Epilepsy | 0 (0%) | 4,155 (4·2%) | 0 (0%) | 1,268 (12%) | 0 (0%) | 622 (4·9%) | 0 (0%) | 2,265 (3·0%) |
| Antidepressants | 0 (0%) | 67,824 (68%) | 0 (0%) | 1,059 (10·0%) | 0 (0%) | 6,090 (48%) | 0 (0%) | 60,675 (79%) |

IQR=interquartile range; ADHD=Attention-deficit/hyperactivity disorder

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **HR (95% CI)** | | | |
| **Analysis** | **Outcome** | **Overall** | **Children** | **Adolescents** | **Adults** |
| Main analyses  (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 analyses  (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) |
| Sensitivity 1†  (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) |
| Sensitivity 2‡ (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) |
| Sensitivity 2‡  (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) |

All models were adjusted for sex, age, and calendar year.

†Model defining treatment discontinuation as a gap of ≥90 days

‡Model excluding single-prescription discontinuers.

HR=Hazard ratio; CI=confidence interval.

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **IRR (95% CI)** | | | |
| **Analysis** | **Outcome** | **Overall**  (N=189,699) | **Children**  (N=50,995) | **Adolescents**  (N=35,681) | **Adults**  (N=103,023) |
| Main analyses† | Psychiatric inpatient hospitalization | 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 analyses† | Injuries/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 analyses† | 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 analyses† | 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 analyses† | 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) |
| Sensitivity 3‡ | Psychiatric inpatient hospitalization | 3·76 (3·67-3·85) | 3·10 (3·00-3·19) | 3·59 (3·03-4·15) | 2·57 (2·22-2·92) |
| Sensitivity 3‡ | Injuries/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) |
| Sensitivity 3‡ | 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) |
| Sensitivity 3‡ | 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) |
| Sensitivity 3‡ | 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) |

†Model adjusted for sex and calendar year.

‡Model adjusted for sex, calendar year, and latent baseline severity scores.

IRR = incidence rate ratio; CI=confidence interval.

# 

# Figures

**Figure 1**. Study population flow diagram.

A diagram of a patient's health

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