Effect of ADHD Medication on Criminality and Injuries

Quasi-Experimental Evidence for Patients on the Margin of Treatment

Tarjei Widding-Havneraas

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2023

UNIVERSITY OF BERGEN

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Date of defense: 07.11.2023

Year: 2023

Title: Effect of ADHD Medication on Criminality and Injuries

Name: Tarjei Widding-Havneraas

Print: Skipnes Kommunikasjon / University of Bergen

List of abbreviations

2SLS – Two stage least squares

ACE – Average causal effect

ACR – Average causal response

ADHD – Attention-deficit/hyperactivity disorder

ATC – Anatomical Therapetic Chemical

ATE – Average treatment effect

ATT – Average treatment effect on the treated

BCE – Before current era

CACE – Complier average causal effect

CAMHS – Child and adolescent mental health services

CD – Conduct disorder

CFA – Confirmatory factor analysis

CPR – Central Population Register

CV – Coefficient of variation

DA – Dopamine

DAG – Directed acyclic graph

DDD – Defined daily dose

DSM – Diagnostic and Statistical Manual of Mental Disorders

EF – Executive function

e.g. – exempli gratia (for example)

ER – Emergency room

EW – Emergency ward

FPCI – Fundamental problem of causal inference

FRM – Fractional response model

GLM – Generalized linear model

GST – General strain theory

i.e. – id est (that is)

ICD – International Classification of Diseases

ICE – Individual-level causal effect

ICPC – International Classification of Primary Care

IV – Instrumental variable

LATE – Local average treatment effect

LPM – Linear probability model

MR – Mendelian randomization

MoBa – The Mother, Father and Child Cohort Study

NCoDR – Norwegian Cause of Death Register

NE – norepinephrine

NPR – Norwegian Patient Registry

NNT – Number needed to treat

NorPD – Norwegian Prescription Database

OLS – Ordinary least squares

ODD – Oppositional defiant disorder

SCT – Self-control theory

SLT – Social learning theory

RCT – Randomized controlled trial

RS-DBD – Parent/Teacher Rating Scale for Disruptive Behavior Disorders

SEM – Structural equation model

SES – Socioeconomic status

SUD – Substance abuse disorder

SUTVA – Stable unit treatment value assumption

WHO – World Health Organization

Scientific environment

2015-: Competence Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital

2018-: Department of Clinical Medicine, University of Bergen

2018-: EPINOR – National Research School in Population-Based Epidemiology

2021-2022: Centre for Demography and Ecology, University of Wisconsin-Madison

2022-: Department of Special Needs Education, University of Oslo

Main supervisor:
Professor Arnstein Mykletun, DrPsychol
Co-supervisors:
Professor Henrik Daae Zachrisson, PhD
Associate Professor Anne Halmøy, MD PhD
Professor Ingvar Bjelland, MD DrMed

Preface

My motivation for this thesis developed with my interest for answering important research questions with innovative methodology and registry data. I was intrigued by the importance of effective treatment of ADHD as I learned more about the prevalence of ADHD, debates around medication, and the disorder's association to criminality and other important outcomes such as injuries through my work at the Competence Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital.

This thesis is part of the *ADHD controversy project* at the Competence Centre for Research and Education in Forensic Psychiatry. My PhD work was conducted alongside a position I started in 2015 to establish this and other registry-based projects with project investigator Arnstein Mykletun, centre leader Knut Rypdal, and the project team. I worked on ethics, funding, and data applications, as well as data wrangling and statistical analyses. This gave me the valuable experience of working on registry-based projects from the early stages of ideas to communicating results to the outside world.

My thesis is interdisciplinary in terms of methodology, collaboration, and my development as a researcher. Epidemiology serves as the disciplinary home, while the methodology draws on quasi-experimental techniques from economics, and theories of crime and injuries firmly based in the behavioral sciences. I hold a MPhil in Sociology and Bachelor in Economics which has helped navigate the methodological literature, while social scientific training in theories of human behavior and social systems have complemented my epidemiological training. I have also been lucky to collaborate with and learn from experts in causal inference, psychiatric epidemiology, economics, and sociology.

I hope this work proves relevant to others interested in pharmacological treatment of ADHD and, ultimately, that this thesis provides a small positive contribution to healthcare for people with ADHD.

Acknowledgements

First, I would like to thank all my supervisors. Arnstein Mykletun, my main supervisor, thank you for our collaborative work in establishing registry-based projects at the Competence Centre for Research and Education in Forensic Psychiatry. I am grateful for the opportunities you gave me and all I have learned from you and our work on suicide prevention programs to registry-based work in psychiatric epidemiology. Henrik Daae Zachrisson, thanks for quickly orienting me in key literature on causal inference, always seriously engaging with my written work, and cheering me on. Your kindness and mentorship have been highly appreciated. Anne Halmøy and Ingvar Bjelland, thanks for your excellent guidance. Your clinical and epidemiological expertise was crucial to my understanding of ADHD and pharmacological treatment.

Moreover, Knut Rypdal, our projects at the Competence Centre for Research and Education in Forensic Psychiatry would not have been possible without your long-term commitment. Thanks for all your support and contributions. Simen Markussen at the Ragnar Frisch Centre for Economic Research, I aspire to a fraction of your capacity to make complex issues understandable. Thanks for everything you taught me about data wrangling and statistical analysis and all your contributions to my work. Felix Elwert at University of Wisconsin-Madison, it has been a privilege to work with you and learn about methodology, writing, and being a researcher in general. My research stay at University of Wisconsin-Madison was a unique opportunity to experience an exciting academic environment and a great city.

To my wonderful co-PhD candidates, Ingvild Lyhmann and Ashmita Chaulagain, thanks for your friendship, cheerfulness, and our fun collaborative work. Elisabeth Sandtorv and Daniil Butenko; thanks for companionship and enjoyable discussions. Ang Yu, Vikas Gawai, Mar Espadafor, Shiro Furuya, and Michael Zavslavsky, thanks for making my stay in Madison fun both academically and personally.

I also want to thank the rest of my colleagues at the Competence Centre for Research and Education in Forensic Psychiatry: Mette Senneseth, thanks for fun talks and good advice; Rolf Gjestad, thanks for your contagious light humour and answering all sorts of statistics questions; Steffen Stamnes, thanks for your positive spirit; Miles Rinali, thank you for your advice and constant uplifting mood; Thomas Nag, Helge Andreas Hoff, Ragnar Urheim, Martin Mindestrømmen, Oda Brandseth Lekve, and Siri Nome, thanks for all the pleasant talks over the years. Thanks to the EPINOR research network for promoting a good environment and education for aspiring epidemiologists.

I am grateful to all the helpful people at the Norwegian Patient Registry, Norwegian Prescription Database, and Statistics Norway for kindly assisting me with all questions concerning the process of receiving and understanding the registry data in this thesis.

Thanks to Thomas Lorentzen for introducing me to statistical analyses with Norwegian registry data in the first place. I am thankful for your great supervision and for offering me the opportunity to publish my first scientific study.

Thanks to my dear friends for your support, interesting talks, and good times. Thanks in particular to Jørgen Hansen, Rene Høidal, Roy Hammer, Ivan Daniloff, Joe Chrisp and Joan Abbas. I am also thankful to the university basketball community for always offering a healthy break. To my dear mom and dad, thanks for all your love and support, and a nurturing upbringing filled with art, science, and travel. My dearest Siri, thanks for bringing me so much joy with your love and encouragement. I am glad we got to share our PhD journeys, and I am excited for our future.

Tarjei Widding-Havneraas
Bergen, June 2023

Abstract in English

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children and adolescents. Large geographical variations in diagnosis and medication for ADHD have raised concerns about under- and overtreatment. There is demand for more causal knowledge about how pharmacological treatment of ADHD impacts real-life outcomes among otherwise similar patients who receive treatment due to varying provider preference for treatment. This thesis estimates effects of pharmacological treatment of ADHD on crime and injuries and examines geographical variation in diagnoses and symptom load of ADHD based on Norwegian population-wide registry and survey data. Variation in providers' (i.e., clinicians) treatment preference for patients on the margin of treatment is used as quasi-experimental randomization to pharmacological treatment in an instrumental variable design. The treatment effects concern patients where providers differ in treatment decisions, and do not include patients with a very low or high symptom burden where there is clinical consensus.

I find protective effects of pharmacological treatment on violence- and public-order-related crimes, but not other types of crime. I do not find clear evidence for treatment effects on overall injuries. Furthermore, the geographical variation in diagnoses of ADHD is much larger than what can be explained by variation in symptom load. The thesis contributes to three areas in ADHD research: the debate on under- and overtreatment, causal inference, and long-term effects on crime and injuries.

Clinical treatment decisions are based on a holistic assessment where many outcomes are considered. This thesis shows that pharmacological treatment reduces some types of crimes, but not overall injuries, for the understudied patient group on the margin of treatment, and this expands the evidence base for clinicians' decisions for two important real-life outcomes among people with ADHD. The methodological approach illustrates how quasi-experimental designs and registry data can be combined to estimate treatment effects that cannot be obtained in randomized experiments due to ethics nor observational studies due to unobserved confounding.

Abstract in Norwegian

Attention-deficit/hyperactivity disorder (ADHD) er den vanligste nevropsykiatriske lidelsen hos barn og unge. Store geografiske variasjoner i diagnostisering og medisinering av ADHD har bidratt til bekymringer om under- og overbehandling. Det er behov for mer kausal kunnskap om hvordan farmakologisk behandling av ADHD påvirker virkelige utfall for personer med mildere symptomer som behandles eller ikke behandles avhengig av behandlers preferanser. Denne avhandlingen estimerer effekter av farmakologisk behandling av ADHD på kriminalitet og ulykker, og undersøker geografisk variasjon i diagnoser og symptombelastning for ADHD basert på norske register- og surveydata. Variasjon i klinikeres behandlingspreferanse for pasienter i «gråsonen» (eller på marginen) for behandling anvendes som en kvasieksperimentell randomisering til ADHD medisin for ellers like pasienter i et instrumentvariabeldesign. Behandlingsestimatene gjelder pasienter hvor klinikeres behandlingsbeslutninger varierer, og inkluderer ikke pasienter med lav eller høy symptombelastning der det er klinisk konsensus.

Jeg finner beskyttende effekter av farmakologisk behandling på vold- og orden- og integritetsrelatert kriminalitet, men ikke andre typer kriminalitet. Jeg finner ikke klar støtte for behandlingseffekter på ulykker. Videre er den geografiske variasjonen i ADHD-diagnoser betydelig større enn det som kan forklares av variasjon i symptombelastning. Avhandlingen bidrar til tre områder innen ADHD-forskningen: debatten om under- og overbehandling, kausal inferens, og langtidseffekter for kriminalitet og ulykker.

Kliniske behandlingsbeslutninger er basert på en helhetlig vurdering. Avhandlingen viser at farmakologisk behandling reduserer noen typer kriminalitet, men ikke ulykker, for den understuderte pasientgruppen i «gråsonen» for behandling, og utvider dermed evidensgrunnlaget til klinikers beslutninger for to viktige utfall. Samtidig vises hvordan kvasieksperimentelle design og registerdata kan kombineres for å gi effektestimater som ikke kan oppnås med randomiserte eksperimenter grunnet etikk eller observasjonsstudier grunnet uobservert konfundering.

List of publications

Study I: Tarjei Widding-Havneraas, Henrik Daae Zachrisson, Simen Markussen, Felix Elwert, Ingvild Lyhmann, Ashmita Chaulagain, Ingvar Bjelland, Anne Halmøy, Knut Rypdal, Arnstein Mykletun. Effect of Pharmacological Treatment of ADHD on Criminality. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2023. https://doi.org/10.1016/j.jaac.2023.05.025.

Study II: Tarjei Widding-Havneraas, Felix Elwert, Simen Markussen, Henrik Daae Zachrisson, Ingvild Lyhmann, Ashmita Chaulagain, Ingvar Bjelland, Anne Halmøy, Arnstein Mykletun. Effect of ADHD medication on risk of injuries: a preference-based instrumental variable analysis. *European Child & Adolescent Psychiatry*. 2023. https://doi.org/10.1007/s00787-023-02294-6.

Study III: Tarjei Widding-Havneraas, Simen Markussen, Felix Elwert, Ingvild Lyhmann, Ingvar Bjelland, Anne Halmøy, Ashmita Chaulagain, Eivind Ystrøm, Arnstein Mykletun, Henrik Daae Zachrisson. Geographical variation in ADHD: do diagnoses reflect symptom levels? *European Child & Adolescent Psychiatry*. 2023. 32: 1795-1803. https://doi.org/10.1007/s00787-022-01996-7.

Other publications not included in this thesis

Tarjei Widding-Havneraas. Young adults not in employment, education, or training: a register-based study, 1993-2009. 2016. *Norwegian Journal of Working Life Studies*, 33 (4), 360-378.

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Tarjei Widding-Havneraas, Ashmita Chaulagain, Ingvild Lyhmann, Henrik Daae Zachrisson, Felix Elwert, Simen Markussen, David McDaid, Arnstein Mykletun. Preference-based instrumental variables in health research rely on important and underreported assumptions: a systematic review. 2021. *Journal of Clinical Epidemiology,* 139, 269-278.

Tarjei Widding-Havneraas & Henrik Daae Zachrisson. A Gentle Introduction to Instrumental Variables. 2022. *Journal of Clinical Epidemiology,* 149, 203-205.

Ingvild Lyhmann, **Tarjei Widding-Havneraas**, Henrik Daae Zachrisson, Ingvar Bjelland, Ashmita Chaulagain, Arnstein Mykletun, Anne Halmøy. Variation in attitudes toward diagnosis and medication of ADHD: a survey among clinicians in the Norwegian child and adolescent mental health services. 2022. *European Child & Adolescent Psychiatry,* 1-11.

Ashmita Chaulagain, Ingvild Lyhmann, Anne Halmøy, **Tarjei Widding-Havneraas**, Olav Nyttingnes, Ingvar Bjelland, Arnstein Mykletun. A systematic meta-review of systematic reviews on Attention Deficit Hyperactivity Disorder (ADHD). In press, *European Psychiatry*.

Table of contents

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children and adolescents[1, 2] with childhood-onset characterized by age-inappropriate hyperactivity, impulsivity, and inattention that negatively impacts multiple domains such as school, work, and social settings.[3] Pharmacological treatment of ADHD is common although long-term treatment effects is debated.[4] Moreover, large between- and within-country variation in rates of diagnosis and medication of ADHD[5-7] and increased rates of diagnosis and medication among children born late in the year relative to classroom peers[8-10] have raised concerns about "medicalization".[11-13] Other view these developments as indicative of improved recognition among clinicians, where formerly undiagnosed and untreated persons are now receiving much-needed early intervention.[14, 15] The field of ADHD thus entails important and evolving debates including the diagnosis[16] and treatment of ADHD,[17-19] as well as the aetiology and conceptual understanding of the disorder itself.[3, 20]

This thesis contributes to the three following topics in the literature on pharmacological treatment of ADHD: the debate about under- and overtreatment, causal knowledge about pharmacological treatment of ADHD, and long-term effectiveness of ADHD medication on real-life outcomes.

First, there is a controversy about under- and overtreatment of ADHD. On the one hand, proponents argue for a more "restrictive" approach based on concerns for consequences of overtreatment (e.g., stigma and unnecessary side-effects of medication). On the other hand, a more "liberal" approach is advocated due to consequences of undertreatment (e.g, prevention of potential unnecessary harmful outcomes).[7] This is nevertheless a debate where some clinicians are active participants whereas others remain unaware or more normatively uninvested. All clinicians are however operating within a context with variation in treatment rates and may not know their own clinics rate relative to others. Varying views contribute to variation in local treatment cultures ranging from healthcare providers with relatively low to high treatment preferences. Such treatment variation is commonly referred to as varying "provider preference" and may encompass

individual clinicians or clinic-level treatment cultures.[7, 21] A systematic review finds evidence of both under- and overtreatment.[17] Similarly, a between-country comparison of ADHD medication usage in children and adolescents found that variation in rates of medication exceed rates of ADHD diagnosis, while there was no clear evidence concerning optimal medication rates.[6] Potential under- and overtreatment have raised concerns about treatment effects among patients with milder ADHD symptoms. A systematic review of diagnosis and treatment of ADHD concludes that there is a critical need for more information about benefits and harms of diagnosing and treating patients with milder ADHD symptoms[16]

> *Despite an abundance of research in the field of ADHD, gaps in evidence remain. In particular, high-quality studies on the long-term benefits and harms of diagnosing and treating ADHD in young people with milder symptoms are needed to inform safe and equitable practice and policy.*

Patients with milder ADHD symptoms may be subject to clinical uncertainty and treatment effects among these patients is debated.[22, 23] There is also evidence supporting varying clinical practice in treatment.[24-27] Thus, otherwise similar patients may be treated differently due to varying treatment preferences of the treating clinician.[24] Such patients are referred to as patients on the margin of treatment, and represent patients who receive or do not receive treatment due to their providers' preference (see details section 4.3.1.).[21] Causal knowledge of treatment effects in this patient group are challenging to obtain as randomized controlled trials (RCT) are unethical, whereas observational studies are hampered by unmeasured confounding. Nonetheless, such treatment effects are informative as to whether patients on the margin of treatment benefit from pharmacological treatment.

Second, by using an established but arguably underutilized quasi-experimental research design in ADHD research, I offer novel causal evidence of treatment effects for patients on the margin of treatment. Quasi-experimental designs are based on the principle that natural variation can present sources of "as good as" randomization. The key element separating RCTs from observational studies is the control of the treatment

assignment mechanism that ensures comparable treatment groups. Randomization represents an external source of treatment variation (i.e., exogenous variation). As aptly summarized by Murnane and Willett [28]

> *... applying even the most sophisticated statistical techniques to data that lack a source of exogenous treatment variation will not replicate credibly the results obtained in random-assignment experiments.*

I use an instrumental variable (IV) design which logic closely resembles an RCT. Simply put, the logic of IV methods is that the randomization indicator in an RCT is replaced by another exogenous source of treatment variation (i.e., the IV). I use variation in healthcare providers preference for pharmacological treatment of ADHD as an IV to estimate treatment effects on real-life outcomes.[21] The source of exogenous variation concerns patients in the middle of the distribution of symptom severity, where provider preference plausibly differs, whereas there is little variation in patients with either very low or high symptom severity (details in section 4).[25] The IV design is applied in Study I and II. Study III examines geographical variation in ADHD diagnoses and symptom levels, which then also assesses whether variation in ADHD symptom levels may be relevant in understanding varying provider preference.

Third, I examine the effectiveness of pharmacological treatment of ADHD on criminality and injuries which are two key real-life outcomes in ADHD.[29, 30] Long-term effectiveness of ADHD medication is a large debate[4, 18, 19] closely tied to discussions of clinical and real-life outcomes, as highlighted by Rohde [31]

> *In working with patients, we have progressively understood that significant between-group differences in scores on ADHD scales are essential, but they are not sufficient. Patients and their families are interested in real-life outcomes; they want to know how medication affects grade retention, chances of car crashes, and unplanned adolescent pregnancies, among other outcomes.*

ADHD is associated with increased rates of many adverse real-life outcomes (including injuries, low education, unemployment, and criminality) and medication may impact

several of these outcomes.[32, 33] Linked registry data is considered a valuable resource to improve knowledge[34] and this thesis is based on rich population-wide data with many years follow-up.[7] I focus on criminality and injuries which have gained attention due to higher rates of both outcomes in ADHD.[29, 30] One of the core theories of crime is based on low self-regulation, closely tied to ADHD core symptoms, which has led to suggestions that ADHD may be a key component in understanding crime.[35] Injuries, moreover, are among the worldwide leading cause of death and disability in children and adolescents[36] and persons with ADHD are considered a high-risk group that requires attention and effective intervention.[37]

In sum, we lack causal knowledge of long-term effectiveness of pharmacological treatment on real-life outcomes such as criminality and injuries for patients on the margin of treatment. This thesis contributes to these knowledge gaps. This evidence adds knowledge to two levels of prevention. Treatment effects are relevant for tertiary prevention as they are informative as to whether pharmacological treatment of ADHD can lower the impact of long-term impairment. Such treatment effects are also informative to quarternary prevention which involve the impact of potentially excessive medical treatment.[38]

In the following, I briefly outline the structure of my thesis. Three considerations should be noted. First, this thesis concern children, adolescents, and young adults, and the focus on the literature I draw upon follows suit. Second, existing research on ADHD is vast, as shown in the ADHD International Consensus Statement.[14] Extensive literature searches were carried out for this thesis, but I did not conduct a systematic review on pharmacological treatment of ADHD. However, I did lead the largest systematic review of applications of provider-preference IV designs in health to date,[21] which ensures that the most relevant studies on treatment effects are covered. This systematic review is not a formal part of this thesis but serves as an important foundation. I am also a co-author of a meta-review (systematic review of all systematic reviews) of ADHD led by my co-PhD candidate Ashmita Chaulagain (In Press, European Psychiatry), which informed included references. Third, my thesis is motivated by the IV design (Study I and II) and the assessment of validity (including

Study III). Serious causal inference warrants engagement with both subject matter knowledge and design properties, and I have prioritized space accordingly, particularly giving room for an extensive methodological section.

In the introductory section, I provide an overview of theories of ADHD and its history, prevalence and geographical variation, risk factors, prognosis and treatment including potential mechanisms, and an overview of what we know from existing IV studies, and institutional characteristics of the Norwegian healthcare system. In section 2, I summarize the main research questions of this thesis. Section 3 describes the Norwegian data registries. Section 4 describes the methodological framework. Section 5 summarizes the main findings. Finally, section 6 discusses the main findings and points toward future work.

1.1 What is ADHD?

ADHD is characterised by a clustering of the following core symptoms; hyperactivity, impulsivity, and inattention. The presence and combination of these symptoms may vary, and also overlap with other disorders, resulting in a relatively heterogeneous and complicated clinical picture.[39] Descriptions of the condition have been present throughout human history, albeit under varying terminology.[3] The current understanding of ADHD can be considered as[3]

> *... the latest stage in a long history of attempts to characterize a cluster of overlapping early onset and persistent symptoms of hyperkinesis, inattention, and impulsiveness known to harm affected individual's lives through the functional impairment they create, both in the short and long term.*

Figure 1 shows that the history of ADHD spans several centuries.[14] Descriptions of ADHD in western literature, however, may be traced back to Ancient Greece with the Greek philosopher Theophrastus (381-278 BCE) description of the “obtuse” man in his book on stereotypical characters.[40] Our conceptual understanding of ADHD is continuously evolving.[3, 20] Recent research challenge some important assumptions underlying our dominant understanding of ADHD, including findings related to adult

onset, time-varying symptom impairment, and a decreasing gender-gap in presentation of ADHD.[3]

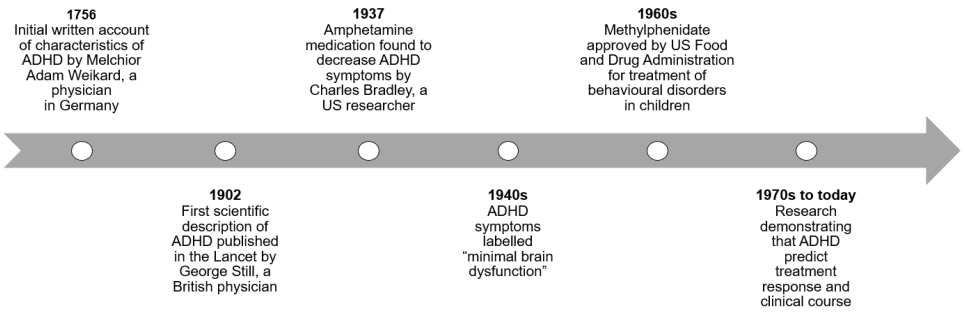

Figure 1. A brief history of attention-deficit/hyperactivity disorder.
All scientific information based on the ADHD International Consensus Statement.[14]

The etiology of ADHD is not clearly established but likely involves complex gene-environment interactions.[14] ADHD has a neurobiological basis, and persons with ADHD deviate from persons without ADHD in brain structure and function (e.g., slower development of prefrontal cortex and lower activation of attention-related areas), but there is nevertheless no definitive "ADHD pathology".[41] ADHD shares three key features with psychiatric disorders in general[42] as the diagnosis (1) must be defined by symptoms without biological markers, (2) has symptoms related to the mind rather than the body, and (3) must be contextualized with impact on the individual as well as the social expectations.[42] Differentiating boundaries of "normal" and "abnormal" is clinically challenging, and such considerations may vary by time and place.[42] Thus, the role of social context in ADHD is also important.[43]

In clinical practice, ADHD is diagnosed using either one or both of the following classification systems for mental disorders: Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)[44] or the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10).[45] ICD-11 was released in 2019 and official implementation started in 2022,[46] but is still not in use in Norway. In DSM-5, ADHD is characterized by three clinical presentations: (1) inattentiveness (or attention-deficit), (2) hyperactivity, and most commonly, (3) combined type (attention-deficit and hyperactivity). ICD-10 applies a more narrow definition of

ADHD termed hyperkinetic disorder mainly corresponding to the combined type,[41] while the ICD-11 criteria are largely the same as for DSM-5. Whereas ADHD symptoms are on a continuum without any true cut-off,[47, 48] clinicians stand before binary diagnostic and treatment choices. The heterogeneous symptom presentation often poses challenges to clinicians[41] and may contribute to varying clinical decisions.

Theories of ADHD

Multiple theories of ADHD based on neurobiological deviances have been developed. The multitude of theories may in itself indicate uncertainty.[41] In the following, I briefly present the main theories of ADHD primarily based on an overview by Bjelland and Sanne [41] with supplementary information from Willcutt [49].

Executive dysfunction

The executive dysfunction theory is the most well-known theory of ADHD. This theory suggests that ADHD symptoms stem from a primary deficit of executive functions (EF)[50], including response inhibition, working memory, mental flexibility, planning, and vigilance which, then, interfere with goal-oriented behavior. These mental abilities are important for self-regulation, and thus ADHD is considered a deficit in both EF and self-regulation.[51] The prefrontal cortex and its interactions with other regions and networks plays a key role in regulating EF.[52] Defective EF may be due to imbalances in levels of neurotransmitters (i.e., dopamine and norepinephrine) responsible in regulating cognitive and behavioral processes, including executive functions.[53] Intuitively, executive dysfunction can be considered as a "bad conductor" who have lost control of the orchestra.[41] The theory is supported by evidence showing that patients with ADHD perform worse on multiple tasks requiring EF, including tasks measuring impulsivity, attention, and planning.[50]

Dysregulation of rest- and activity networks

The theory of dysregulation of the relation between rest- and activity networks posits that the rest networks are not properly deactivated when persons with ADHD reengages in activities that require attention and engagement of the activity networks.[54] In persons without ADHD, the default ("rest") network is activated when they rest (e.g., to process experiences and prepare future activities) and subsequently deactivated while other

networks are activated when more specific activity is resumed. Disconnection in engagement of these networks may cause inattention in persons with ADHD. This may intuitively be viewed as a "switch error".[41] Evidence suggests theres is a disconnection between rest and activity networks in the brain among persons with ADHD.[54]

Delay aversion

The delay aversion theory postulates that persons with ADHD struggle with delaying gratification. This impacts choices as small immediate rewards are preferred over larger delayed rewards. Delay tolerance is linked to activity in neural circuits involving the prefrontal cortex, where dopamine plays a key role, and which ultimately affects decision-making.[49] This theory is supported by showing that persons with ADHD opt for immediate relative to delayed rewards.[55]

Dysregulation of psychophysiological condition

The theory of dysregulation of psychophysiological condition suggests that persons with ADHD struggle with proper engagement of energy levels for vigilance and activation required of cognitive processes under problem solving. Such improper regulation of energy levels then lead to either too low energy levels and subsequent attention-deficit, or too high levels resulting in hyperactivity and impulsivity.[41] A review of supporting evidence is provided by van der Meere [56].

1.2 Epidemiology of ADHD

1.2.1 Prevalence

ADHD is estimated to have a worldwide prevalence of 5.9% in youth[57] and 2.6% in adults.[58] The prevalence of childhood ADHD in Norway is estimated to 5%.[59] The diagnosis of ADHD have increased in recent decades, but ADHD as a disorder has not increased,[60] suggesting changes in clinical practice.[14, 61] Estimates of persistent ADHD from childhood to adulthood range from 30-80%,[62-64] with declines in symptoms most common for impulsivity and hyperactivity,[53, 65] and predictors for persistence including childhood severity of ADHD, comorbid conduct disorder (CD), and major depression.[66] ADHD is more common in young males compared to young females,[57]

with males typically exhibiting external symptoms (impulsivity and hyperactivity) and more internal symptoms (inattention) among females. The gender-gap may then be due to under-recognition in young females, further supported by a decreased gap with advancing age.[67] Comorbidity is high in ADHD and changes over age.[39] In childhood, oppositional defiant disorder (ODD) and CD are common.[39] ODD is characterized by recurrent negative, defiant, and hostile behavior (e.g., often losing temper, deliberately annoying people, spitefulness and vindictiveness), whereas CD is characterized by negative behavior (e.g., bullying and initiation of physical fights) and violations of age-appropriate societal norms and rules (e.g., usage of weapons, stealing, arson, forced sexual activity).[68] Substance use disorders (SUD) become more common as persons age and adulthood is characterized by several comorbidities such as antisocial personality disorder, anxiety, and somatic diseases.[39]

Between-country variation in ADHD

Country variation in the prevalence of ADHD has been a source of controversy.[1] Country-wide estimates of childhood and adolescent prevalence of ADHD vary, for example, with prevalence estimates of 10% in the US[69] to 0.3% in France.[70] International comparisons of the prevalence of ADHD is challenged by variation in diagnostic standards and methodology.[2] A meta-analysis finds no evidence of varying world region prevalence and concludes that country variation is methodological.[60] Few studies use same methodology across countries. One such study for adult ADHD finds that prevalence ranges from 1.9% in low-income countries to 4.2% in high-income countries, which is not a large variation compared to other disorders.[71] Overall, the prevalence of ADHD, particularly in Western countries, seems relatively consistent.[1] Country-wise variation in ADHD medication is considerably larger than reliable estimates of country-wise variation in diagnosis.[6] Among children and adolescents, the overall usage was 1.95% (95% CI 0.76-3.13) with national prevalence ranging from 0.27% in France to 6.69% in the US in 2010. The prevalence in ADHD medication use increased in all countries over the years they examined, with comparatively low increase in Norway. The authors argue that such variation could be due to true variation in ADHD, but as an alternative explanation they point to clinical practice. Registry-based analysis in Nordic countries also finds varying medication usage.[72]

Within-country variation in ADHD

Geographical variation in ADHD diagnosis and medication exists within countries with uniform diagnostic standards and treatment guidelines. Several studies are motivated by concerns for health inequalities related to under- and over treatment.[26, 73, 74] Studies have found within-country variation in ADHD diagnosis and medication in the US,[73] UK,[75] Denmark,[76, 77] Spain,[78] and Norway.[26, 79] Some evidence also support regional variation in genetics for ADHD in UK.[80] In this context, Study III contributes with novel evidence suggesting little geographical variation in symptoms levels of ADHD. A Norwegian study finds variation in diagnosis of ADHD but small variations in other neurological diseases (i.e., epilepsy and cerebral palsy), and concludes that clinical practice is a likely contributing factor.[26] Another Norwegian study reviews charts and finds insufficient documentation for ADHD diagnosis in 51% of all cases,[74] further supported by other studies finding varying diagnostic accuracy[15] and extent to which clinicians follow the best practice guidelines.[81] Furthermore, a Danish study finds no evidence for sociodemographic composition for large variation in prescription practices between clinics, again pointing to local treatment cultures.[77] Large between-clinics variation in prescription practice that impacts patients' treatment status has been found in the US[25] and another Danish study.[24] This is in line with the findings in Study I and II of this thesis. Varying provider preference for diagnosis and medication of ADHD is also supported by a survey led by Lyhmann *et al.* [27] in our project. This study finds support for clinicians' attitude ranging from a "restrictive" to "liberal" approach to ADHD diagnosis and medication, with an average score leaning toward the restrictive side. Clinicians' attitudes to diagnosis and medication were moderately associated and both a portion of the total variance in diagnosis and medication could be ascribed to the clinic level. A recent working paper finds that physicians are the major factor for geographic variation in provider practice in general in the US.[82] Overall, then, while several factors may contribute to varying treatment patterns, several studies point to clinical practice, which may be likely given complexities involved in diagnosing and treating ADHD. A more detailed understanding, nonetheless, also warrant a review of risk factors.

1.2.2 Risk factors

The aetiology of ADHD involves a combination of genetical, environmental, and developmental risk factors.[83-85] The ADHD International Consensus Statement[14] highlight the following risk factors: genetics, toxicants, nutrient deficiencies, pregnancy and birth related events, deprivation, stress, infection, poverty, and trauma.

Genetics

A meta-analysis shows that the heritability of ADHD is 77-80%,[85] which is similar to other severe psychiatric disorders such as bipolar disorders and schizophrenia.[86] ADHD is likely caused by multiple genes each contributing to a small extent.[87] Polygenic risk scores (PGS) (i.e., a measure of the combined effects of multiple common gene variants known to increase the risk of developing a disease) for ADHD is predictive of ADHD symptoms,[48] and those with high PGS for ADHD also tend to be diagnosed with ADHD.[88]

Environment

Pre- and perinatal factors are among the environmental factors with strongest evidence, and include maternal smoking and alcohol consumption, premature birth, low birth weight, and environmental toxins.[1] Nonetheless, most of these factors, excluding preterm birth, have shown to be driven by other unmeasured factors that run in families (e.g., genetics or how families live).[1] There are several family-related risk factors. Children in families with low socioeconomic status (SES) are on average two times more likely to have ADHD relative to peers in high SES families.[89] Increased risk of ADHD in families with low SES is also supported by quasi-experimental evidence controlling for unmeasured familial confounding.[90-92] Evidence for a reverse relationship where ADHD causes socioeconomic strain is mixed.[93, 94] A study of explanations for the link between low SES and ADHD found the following mediators most plausible: increased exposure to pre- or perinatal risk factors, family conflict in childhood, and genetical predispositions of parents. Clinical diagnostic labelling bias was not supported as children from low SES also had higher symptom load.[93] Adverse childhood experiences is more common in families with low SES,[95] and is linked to ADHD.[96] The importance of family environment and parenting is further supported in

a meta-analysis which found that poor parenting interaction (e.g., harsh discipline), maltreatment (e.g., physical abuse), and parental relationship status (i.e., divorce and single parenting) increased ADHD symptoms and diagnosis.[97]

1.2.3 Prognosis: overall, criminality, and injuries

Overall prognosis

People with ADHD have worse prognosis compared to the general population on many real-life outcomes,[14] including education, employment, drug use and disorders, antisocial behavior,[32, 98, 99] criminality,[30, 98] and injuries.[100] Studies of associations between ADHD traits and real-life outcomes rely on observational data due to inability to randomize exposure. The closest design is Mendelian randomization (MR), exploiting randomization of the genome at conception as an as-if randomization.[101] MR studies support causal relationships between ADHD liability and low education, low income,[102] substance use,[103] stroke,[104] and obesity.[105] There are, however, a lack of MR studies studying crime and injuries. Being diagnosed and treated for ADHD can impact real-life outcomes through social mechanisms. Benefits can include a sense of comfort and control and access to treatment, but also harms such as stigma and exclusion,[42, 106-109] although here, too, more research is needed on crime and injuries. All core symptoms of ADHD, and also its common comorbidities (e.g., CD/ODD) contribute to increased risk for crime and injuries.[29, 30] Evidence suggests impulsivity and hyperactivity is more linked to aggression and injuries, while inattention is related to educational and occupational outcomes.[110]

I now turn to literature and theory on ADHD and criminality and injuries, respectively, before turning to evidence of treatment effects. Given that criminality and injuries are the main real-life outcomes in this thesis, these subsections start with a brief conceptual discussion before moving to evidence and theory, drawing on both epidemiological and social scientific disciplines for an interdisciplinary understanding. Injuries and criminality closely overlap with the subfield *injury and violence epidemiology,*[111] marked by two recent advancements worth mentioning. First, epidemiologists are increasingly expanding into violent behavior, traditionally considered the domain of

psychology, sociology, and criminology. Second, the traditional separation of physical injury and psychological trauma is increasingly recognized as blurred.[111]

ADHD and criminality

What is criminality?

Legally, crime is defined as an act that violates the law.[112] Such a legal definition, however, is critized for not properly accounting for variation in laws by time and place. The French sociologist Emile Durkheim, whose work has been influential in criminology, emphasized that "crime" does not exist before we humans define it as such, and criminality thus fulfils an important societal function by showing normative and moral boundiares.[112] A more comprehensive conception consider crime as an act violating a moral rule defined as "right" or "wrong" in criminal law.[113] Such a concept merges the legal and criminological definition of crime. Furthermore, according to *Sage Dictionary of Criminology,*[114] a crime is defined by three elements: harm (injury caused and victim harmed), social consensus (level of agreement on harm), and an official societal response (existence and enforcement of criminal law).

Evidence for ADHD and criminality

Persons with childhood ADHD have an estimated two-fold risk of arrests and three-fold risk for convictions and imprisonment.[30] The prevalence of ADHD is 25% in prison,[115] with CD, SUD, and mood disorders as most common comorbidities in young prisoners. In Norway, the prevalence of ADHD in prison is 18%.[116] ADHD and crime can be associated due to a combination of ADHD symptoms, comorbidity, and other problems, and ADHD *per se* may not always be the causal link.[117] Child maltreatment, elevated in ADHD, is a predictor of crime.[30] Moreover, criminality follows an age-curve peaking in early adulthood,[118] coinciding with the life-course development of ADHD with decreasing impulsivity and hyperactivity.[39] The relationship between ADHD and criminality can be better understood by drawing on theories offering mechanisms.[119, 120]

Theories of ADHD and criminality

There are three "core" theories of crime: self-control theory (SCT), general strain theory (GST), and social learning/differential association theory (SLT).[121] These

theories focus on individual and social structural factors, with recent work integrating genetical and neurobiological perspectives.[35, 122] Criminiology has developed from thinking that crime has *one* cause towards multiple causes, and hence the following theories may act together.[112]

Self-control theory

SCT is the dominant theory of crime.[123] Self-control involves six components: impulsivity, quick and volatile behavior, risk seeking, preferring simple tasks and physical over mental tasks, and self-centeredness.[124] The core argument of SCT is that individuals' self-control is shaped early in life, with parenting considered key, and impacts individuals' propensity for criminal behavior. This can be tied to the influential taxonomy of criminal careers with adolescent-limited ("late starters") and life-course persistent antisocial behavior ("early starters") by Moffitt [125]. Late starters consists of generally normal people who commit one or few crimes during adolescence, whereas early starters consists of people with early developed problematic behavior attributed to social conditions or innate neurological conditions such as ADHD.[118] Studies show that measures of self-control is predictive of criminal behavior,[124] and the link between self-regulation and ADHD is clear as self-regulation is tied to executive functioning.[51] Researchers have argued that ADHD may be one of the main underlying explanations for crime due to core symptoms involving low self-control and the disorder's link to antisocial behavior and criminality.[35] However, critiques have been raised regarding SCT's claim to explain "all crimes at all times".[113] Other theories argue that crime is situational and to a larger extent rely on social factors (e.g., GST and SLT).

General strain theory

GST postulates that experiences of stress and strain lead people to cope through crime to end their strain.[126] Strains refer to undesirable or disliked conditions. Negative emotions are a key mediator: strains cause negative emotions such as anger, frustration, depression, and fear that pressure individuals to corrective action. Strain may also decrease ones' ability to regulate behavior and thus impact self-control. There are three main sources of strain: losing something or someone (money, friends and family, romantic partner), negative treatment (verbal/physical abuse), and inability to achieve

goals.[126] Common sources of strain include parental rejection and harsh discipline, exposure to humiliation, threats and insults, child abuse and neglect, negative peer relations, negative school experiences, and living in socioeconomically deprived areas. GST include a life-course perspective as strains can accumulate or increase in severity over time. GST, then, may explain increased criminality in ADHD in several ways: First, ADHD has a higher rate of adverse childhood experiences.[96] Second, people with ADHD have a higher risk of low education and unemployment and other related life stressors.[127] Third, social disadvantages can accumulate over time, which have been linked to both ADHD and criminality.[128, 129]

Social learning theory

SLT suggests that people learn behavior through social interaction (e.g., imitation or reinforcement).[130] Exposure to others engaged in criminal behavior will then increase one's own propensity to commit crime. The principle of "differential association" involves variation in exposure to different definitions of "right" and "wrong" forming values, attitudes, and behavior. Sources of social learning include family, peers, and other social institutions (e.g., school, prison, gangs). SLT can explain increased criminality in ADHD in multiple ways. First, ADHD is concentrated among families with lower SES which may live in more socioeconomically deprived areas with more crime. Second, risk-seeking behavior can drive selection into networks with deviant behavior. Third, persons with ADHD experience more stigma from peers and society which can lead to frustration and seeking of social acceptance with deviant peers.

ADHD and injuries

What are injuries?

An injury can be defined as physical damage to the human body as a result of either sudden or cumulative transfer of energy that exceed a threshold of the human tissue, organs, or systems; or alternatively, when the absence of a vital agent (oxygen in drowning) impacts normal physiological functioning.[131] Injuries can be unintentional or intentional due to self-harm or victimization. Intent brings in violence either toward self or others, and calls for attention to social context where power relations (e.g. intimate partner violence) and the community one resides in can play a role (e.g., social

contagion).[131] The conceptual understanding of injuries and psychological trauma are moving toward unification as injuries and violence often lie behind psychological trauma.[131]

Evidence for ADHD and injuries

Meta-analyses have found that youth with ADHD have a higher risk of injuries compared to those without ADHD.[29, 100] Severe hyperactivity and comorbid CD seem to contribute strongly to the risk of injuries.[132] While the injury risk is higher among males in the general population, females with ADHD have been found to have higher rate of injuries than men.[133] The gender-gap may be due to ADHD being more severe when detected in females in young age.[67]

Theories for ADHD and injuries

Research on injuries in youth has developed from blaming mothers for insufficient care, to individual's "injury proneness", then turning to macro conditions such as the environment and community planning, before returning to individual behavior.[134] The main mechanisms for increased risk of injury in persons with ADHD (below) tend to be individual-oriented, but the social gradient in the occurrence of ADHD and injuries suggests that environmental factors contribute.[135] Such a broad understanding of injury aligns with the dominant conceptual framework for injuries developed by William Haddon, Jr., widely considered the father of injury epidemiology. He expanded the epidemiological model of disease to injuries with the Haddon matrix which understands injuries through three elements: human, agent, and the environment.[131] The human is the person with ADHD, the agent is the source of energy inflicting injury (e.g., motor vehicle and collison), while the environment includes both physical and social factors (e.g., slippery roads and traffic laws).

A review of ADHD and injuries found that the following four mechanisms are dominant in the literature: core ADHD symptoms, comorbidity, risky driving, and the role of parents.[132] All ADHD core symptoms seem to increase the risk of injuries, while evidence of the relative role of core symptoms is uncertain. Hyperactivity and impulsivity seem to increase the risk of injuries in general, while inattention seem particularly involved in traffic-related injuries. CD stands out as the strongest

contributing comorbidity, but other comorbidities such as ODD, SUD, and antisocial personality disorder also play a role. Risky behavior, mainly in the context of traffic injuries, has been suggested as a mechanism which may also involve driving under the influence of alcohol or other substances. Parents education and their parenting style can also impact injuries.[132] Violence-related injuries (i.e., self-harm, suicidal behavior, and victimization) can be tied to several mechanisms including increased stigma, bullying, and adverse family environment.[108, 136-138] Finally, tying together theories of crime and injuries, SCT have been applied to explain how low self-control can affect both injuries (e.g., low self-control involving substance abuse and speeding) and victimization (e.g., low self-control can put people in vulnerable situations).[139] Moreover, according to GST victimization can be a source of strain causing vengeful and criminal acts.[126] Thus, effective treatment is important given the prognosis of ADHD on many real-life outcomes.

1.2.4 Treatment

Treatment guidelines for children, adolescents, and young adults

The National Institute for Health and Care Excellence (NICE) treatment guideline (NG87) for the diagnosis and treatment of ADHD recommends a holistic treatment plan encompassing psychological, behavioral, occupational or educational needs.[140] For patients aged five and older, adolescents and young people, the treatment plan involves patient and parent education about ADHD, offering additional parent-training in cases with comorbid CD and ODD, and ADHD medication given persistent ADHD symptom severity. The stimulant methylphenidate is the first-line pharmacological treatment for patients aged five and older. Nonstimulants can be offered if the patient experience adverse effects from stimulants. Cognitive behavioral therapy (CBT) can be offered if impairments continue following medication.[140] The Norwegian treatment guideline for ADHD is based on the same principles as the NICE guideline.[141] Impact of pharmacological treatment is evaluated in a trial phase of approximately four weeks continued with periodic assessments (minimum yearly) of both effect (whether the patient improves or not) and adverse effects.

The multimodal treatment of ADHD study

The multimodal treatment of ADHD study (MTA) was a comprehensive multisite trial examining pharmacological, behavioral, and combined treatment of ADHD. The first results were published in 1999 and has served as an important reference since.[142] In brief, the MTA study showed that pharmacological treatment was effective combined with psychosocial treatment *and* in itself.[143] The final results from MTA reported in 2004 further supported that combined treatment was not considerably better than medication.[144] While the MTA study is a well-known study, it is also controversial [142] as psychosocial treatment form an integral part of a holistic treatment, especially given potential non-response, side-effects, or hesitation in use of medication in patients or parents.[145]

Non-pharmacological treatment

Several non-pharmacological treatments are available for ADHD,[1] including behavioral therapies (e.g., CBT and behavioral parent therapy) for managing symptoms and social functioning,[145] psychoeducation for improved understanding of the disorder and coping strategies,[146] and group therapy (e.g., skill building, social learning, and emotional support).[147] However, evidence suggests that non-pharmacological treatments are less effective in reducing ADHD core symptoms compared to medication.[14, 145] Behavioral interventions can improve parenting and reduce childhood conduct problems,[148] whereas cognitive training can improve working memory.[149] Moreover, when studies are blinded, effects of behavioral interventions, neurofeedback, and cognitive training are limited.[145] Thus, more evidence may be needed to recommend non-pharmacological treatment as first-line treatment.[148]

Pharmacological treatment

Pharmacological treatment of ADHD is mainly based on central stimulants (methylphenidate or amphetamine) with nonstimulants (atomoxetine, guanfacine, or clonidine) as the second-line treatment.[150] Stimulants come in immediate- and extended-release formulations that acts a few hours to most of the day. There is no

[1] Space considerations only permit a brief section on non-pharmacological treatment, given the topic of this thesis.

substantial carry-over effects to subsequent days so these medications must be taken daily for sustained effects.[19] The exact mechanisms are not clearly established, but stimulant medication target the "tuning" of the neurotransmitters dopamine (DA) and norepinephrine (NE) in the prefrontal cortex to improve symptom control (reducing impulsivity, hyperactivity, and improving attention).[53] Imbalances in DA and NE impairs information processing in the prefrontal and fronto-striatal circuits and manifests in ADHD symptoms, as both too high and too low levels (inverted U-relationship) cause inefficiencies of the prefrontal cortex, thereby impacting executive functioning. DA and NE are released into the synaptic cleft between neurons, providing signal transmission from one neuron to another by binding to specific receptors on the receiver (post-synaptic) neuron. DA and NE also bind to (pre-synaptic) receptors on the sender neuron by a re-uptake mechanism, continuously assuring an optimal balance of the levels of DA and NE in the synaptic cleft. Synaptic levels of DA and NE have shown to be lower among persons with ADHD, and stimulant medication act by increasing these levels by blocking the re-uptake mechanism (and amphetamines also by increasing the release into the synaptic cleft). DA and NE also interact with other neurotransmitters in the brain, but a more complex description is beyond the scope of this introduction. Nonstimulant medication (specifically atomoxetine) works through similar mechanisms.[53]

Evidence for treatment effects

There is evidence from at least 185 RCTs to support that methylphenidate reduces ADHD symptoms for children and adolescents in the short-term, relative to placebo and no treatment.[151] Nonetheless, the mean duration of methylphenidate treatment was short (2 ½ months) and all trials were of high risk of bias. The most comprehensive overview of pharmacological treatment of ADHD to date is conducted by Cortese *et al.* [152] This review is based on 133 double-blind RCTs. Among children and for ADHD symptoms, all medications were better than placebo with strongest reduction in ADHD symptoms obtained by amphetamine followed by methylphenidate. For adults, amphetamine, methylphenidate, bupropion, and atomoxetine were better than placebo. Despite the effectiveness of amphetamine this drug had lower tolerability in children and adolescents. The review concludes that in the short-term methylphenidate should

be the first-choice among children and adolescents, whereas amphetamine should be the first-choice among adults.

Clinicians are recommended to titrate (i.e., adjusting dosage according to response) medication to optimize symptom reduction. A meta-analysis (65 RCTs) supports a dose-response efficacy of methylphenidate and amphetamines on ADHD symptom reduction.[153] Effect sizes of ADHD medication are relatively strong compared to other medications in medicine.[154] Methylphenidate is also relatively safe, as shown in a study examining 78 potential adverse effects.[155] All ADHD medications had adverse events, but the most beneficial medication was methylphenidate, while the most harmful was atomoxetine and guanfacine. Common side effects include sleep disturbance, reduced appetite, weight gain, and heightened blood pressure or heart rate.[150] Nonetheless, such side effects may be managed to reap the benefits of medication.[156] Side effects, stigma, and feeling insufficient effectiveness comprise the most common reasons for treatment discontinuation,[150] which happens in approximately half of all persons.[157] Adherence may be improved through psychoeducation and behavioral therapy.[158] Moreover, most evidence is on a group level and may conceal meaningful heterogeneity.[159] Patients' response to stimulant medication can differ due to variation in bioavailability (i.e., the amount of medication that is absorbed and used in the body),[160, 161] and may impact titration. Patients who do not respond to one stimulant is recommended to try another [162] or switch to nonstimulants.[163]

Long-term effects of pharmacological treatment

Long-term effects are among the main questions in pharmacological treatment of ADHD. "Long-term" can entail effects of taking medication over time (often one or more years)[164-167] or effects of taking medication for some time followed by discontinuation.[168] Most study the former.[2] Perspectives "for" and "against" long-term effects of stimulants has been debated in the *Journal of American Academy of Child & Adolescent Psychiatry.*[4] Coghill [18], arguing "for", emphasize that RCTs cannot be used to assess long-term effects due to ethical concerns. Randomized withdrawal designs,

[2] Nonetheless, the latter may be relevant as taking medication in critical periods in the life-course can impact trajectories (e.g., only taking medication in school may impact academic achievements and thereby later outcomes).

however, have shown continued effectiveness on ADHD symptoms at 6 months,[169] 14 months,[168] and 2 years.[170] Moreover, Scandinavian registry studies support effectiveness on real-life outcomes,[171] but comparing outcomes on vs off medication is not necessarily informative of long-term effects. The continued benefit in MTA under carefully monitoring that disappeared once the study turned observational may indicate that correctly used medication is effective in the long-term. Swanson [19], arguing "against", underscores that medication is effective in the short-term but the effectiveness vanishes over time which may be due to two mechanisms: poor treatment adherence and increased tolerance to medication. Employing maximum daily doses may suppress long-term effectiveness if the latter is true, but more research is needed to investigate this. Thus, overall, existing evidence may also be interpreted as showing no support for long-term effectiveness for treatment-as-usual. Here it can be added that in the long-term naturalistic follow-up of MTA, no support was found for an association between medication and symptom reduction, but there was support for height suppression.[172]

Effectiveness on real-life outcomes

ADHD medication has been shown to have beneficial effects for educational outcomes, mood disorders, SUD, suicidality, criminality, and injuries.[33] A review of prescription database studies found short-term protective effects of ADHD medication on injuries, motor vehicle accidents, education, and substance use disorders (estimates ranging from reductions of 9-58%).[171] Evidence of long-term effects was unclear and time-varying confounding was highlighted as an issue for within-subjects designs. Another review found that ADHD treatment (pharmacological, nonpharmacological, or multimodal) improved many long-term outcomes (e.g., education, antisocial behavior, occupation), but outcomes were not improved to normal levels.[32] More research is needed on age- and gender-related variation in effects.[173] Furthermore, as these studies are observational it remains difficult to rule out the impact of factors beyond ADHD that contribute to the heightened risk of adverse outcomes.

ADHD medication and criminality

A meta-analysis emphasizes that there is a lack of knowledge about crime protective effects of ADHD treatment.[30] Examination of long-term effects by 6 to 8 years following enrollment in the MTA study found no crime preventative effects of ADHD medication.[174] Scandinavian within-subject designs have found protective effects on violent-, drug-, and traffic-related crimes,[175, 176] but also no reductions in drug-related crimes [177] or long-term effects after treatment discontinuation.[176] There are, moreover, few high-quality studies for children and adolescents. ADHD medication may reduce criminality through improved symptom management.[175, 176] An alternative, however, is that stimulants may act "performance enhancing" by not necessarily reducing crime but making people less likely to be detected. This perspective was offered by Cohen [178] in correspondence to Lichtenstein *et al.* [176], who responded that this mechanism could not be assessed with their data, but the more credible interpretation is that medication reduces crime given what we know about treatment effects from RCTs.[179]

ADHD medication and injuries

A meta-analysis shows that ADHD medication reduce injuries in the short-term,[29] while another review shows that ADHD medication reduces the risk of injuries by 9-32%.[171] More recent within-subjects analyses found supporting evidence,[180, 181] although there are also studies showing no effects.[33] There does not appear to be variation in treatment effects on injuries across the lifespan.[132] Studies mainly attribute reductions to improved symptom control obtained with medication.

Overall, there is a need for more causal knowledge. Within-subjects designs can rule out individual fixed characteristics (e.g., genetics), but time-varying treatment-outcome confounding can drive periods on and off medication. Such designs do not use exogenous variation to identify causal effects. Despite potential strengths, quasi-experiments are not widely used in mental health research.[182] In the next section I briefly present quasi-experimental evidence for ADHD medication. Relevant methodology is presented in section 4.

1.3 Quasi-experimental evidence for treatment effects

The increased use of quasi-experimental research designs in the social sciences have commonly been referred to as a "credibility revolution".[183] Such designs have become influential in economics and health policy.[184] The main designs are IV, differences-in-differences (DiD), and regression discontinuity (RDD).[185] Only a handful studies have applied IV and DiD, and no studies have used RDD, to estimate effects of ADHD medication. These designs estimate treatment effects for different populations. I start by summarizing studies estimating the average treatment effect among all treated (ATT) then turn to IV studies estimating treatment effects for patients on the margin of treatment. The presentation of IV designs are based on a systematic review first-authored by me.[21] To the best of my knowledge, no preference-based IV studies for effects of ADHD medication has been published since.

Two Danish registry-based DiD designs finds that ADHD medication reduces injuries. [24, 37] Both studies examine the effect of ADHD medication defined as filled ADHD prescriptions corresponding to ≥182 defined daily doses (DDD) within one year post diagnosis. Dalsgaard *et al.* [24] found that ADHD medication reduced the probability of one or more contacts with a general hospital or emergency wards. In line with these findings, Dalsgaard *et al.* [37] found that ADHD medication reduced injuries and emergency ward visits. No DiD designs examine effects on criminality. Other quasi-experimental designs address other outcomes. A Canadian survey-based DiD study based on an insurance coverage expansion in Quebec (no other regions) found some support for negative effects of ADHD medication on emotional and academic outcomes.[186] A Danish registry-based study leveraged medical nonresponse as an exogenous source and found negative effects of ADHD medication discontinuation on student's grade point average.[187] A Swedish registry-based study using cohorts pre- and post-introduction of ADHD stimulant medication found no support for decreased height.[188]

Three studies have used provider preference as IV to estimate effects of ADHD medication on real-life outcomes for patients on the margin of treatment. Two studies

by the same authors are based on South Carolina Medicaid claims. All studies find large variation in provider preference that predicts patients' treatment status. One of these studies is published in a peer-reviewed journal,[25] while the other is part of a completed PhD dissertation,[189] and not published in a peer-reviewed journal. Chorniy and Kitashima [25] find that ADHD medication reduces the probability of sexual transmitted diseases, teen pregnancy, substance abuse disorders, and injuries as well as injury-related Medicaid costs. In the other (unpublished) study by Kitashima and Chorniy [189], they find that ADHD medication increases both the probability of grade repetition and decreases test performance. The institutional setting in US vary from universal healthcare systems. Importantly, then, the third IV study is based on Danish registry data.[24] Dalsgaard *et al.* [24] finds protective effects of ADHD medication on hospital contacts (any reason), emergency ward visits, and criminality. However, they measured crime as contacts with police and the data on charges was only relevant for a small part of their sample. Dalsgaard *et al.* [24] is an important contribution to the literature and the closest analysis to this thesis. Similarities and differences have been thoroughly commented in Study I-II and I return to this in the discussion. Overall, then, there is evidence for both beneficial and harmful effects of ADHD medication for patients on the margin of treatment. Moreover, there is little knowledge about treatment effects among these patients given increases in diagnosis and medication rates of ADHD. More knowledge about treatment effects in patients with milder symptoms is considered a critical evidence gap.[16]

1.4 Norwegian context and healthcare system

Causal inference from quasi-experimental designs relies on institutional knowledge, hence I describe relevant characteristics of the Norwegian context. Norway is a small open social democratic economy with a knowledge-intensive labour market, universal welfare and healthcare system, and a population of approximately 5,3 million.[190-192] Norway consistently ranks toward the top of several socioeconomic indicators, such as life satisfaction, employment, and social inequality.[190] Comparative analyses show that the Scandinavian welfare system is beneficial for health outcomes relative to other

welfare systems.[193] Nonetheless, there are social challenges, too; Norway, like other Western welfare states, have seen increases in social exclusion and socioeconomic inequalities.[194, 195]

The Norwegian healthcare system has universal coverage with automatic enrollment. The coverage includes primary care, ambulatory care, specialized somatic and mental health services, including hospital care and outpatient clinics, with 10 percent of the population using a supplementary private insurance.[196] Primary healthcare is organized by municipalties, while specialized healthcare is organized by the national government based on a system with state-owned regional health authorities.[196] Primary mental health care is provided by GPs, psychologists, psychiatric nurses, and social workers, with full coverage for persons under 18 years. GPs can refer patients to specialized care in child and adolescent mental health services (CAMHS) clinics that provide both inpatient and outpatient services.[196] Patients are automatically assigned clinics by their place of residence. Clinicians work in teams at clinics. Assessment of diagnoses such as ADHD is based on the national treatment guideline with a holistic, often multidisciplinary, systematic assessment. However, diagnostic decisions and decisions related to initiation of pharmacological treatment of ADHD lies with the psychiatrist. After patients are diagnosed with ADHD and have gone through a trial phase with ADHD medication, GPs take over follow-up with regular check-ins with the psychiatrist. In summary, the quasi-experimental design draws on the following factors that together make provider preference a credible IV in the Norwegian institutional setting: considerable variation in clinicians attitude to ADHD medication, large geographical variation in ADHD prescription rates, no clear evidence of geographical variation in ADHD symptom load, a universal healthcare system with free access and coverage of ADHD prescriptions to rule out concerns of socioeconomic selection, and residence-based assignment to clinics with varying treatment preference.

2. Aims of the thesis

The overarching aim of this thesis was to provide novel knowledge of effects of ADHD medication on criminality and injuries by combining a quasi-experimental instrumental variables (IV) design with nationwide registry data (Study I and II). Assessment of the crucial assumptions these designs rely on for credible causal inference was an important part of my thesis, and motivated Study III. The treatment effects in IV analyses concern patients on the margin of treatment. This thesis illustrates how IV designs offer causal evidence for treatment effects challenging to address with RCTs or observational studies. I examined the following three research questions:

1. What is the effect of pharmacological treatment of ADHD on criminality? (Study I)
2. What is the effect of pharmacological treatment of ADHD on injuries? (Study II)
3. Is the geographical variation in ADHD diagnoses mainly due to geographical variation in symptom levels of ADHD? (Study III)

3. Materials

3.1 Norwegian registry data

Norway and other Nordic countries have many population-wide registry data sources covering health, socioeconomic, and demographic information with linkage enabled through personal identity numbers. Such data is highly valuable to examine many research questions of international interest through large-scale analyses with long complete follow-up.[197] Much registry data is developed for administrative purposes with increased emphasis on research, and thus use of such data requires knowledge of institutional systems to understand data generating mechanisms.[198]

Data acquisition, data wrangling, and analyses of registry data is known to involve a substantial workload.[199, 200] This especially holds true for the current project that included a total of nine population-wide registry data sources with three data owners (the Health Directorate, Norwegian Institute of Public Health, and Statistics Norway), and one nationwide survey used in Study III (overview Table 1). Thus, this formed a large part of my thesis and my position devoted to assistance in obtaining ethics, funding, and data starting late 2015. This not only involved time-consuming formal processes and communication with registers, but also considerable work on design and data requirements which I eagerly took on with good support from others in the project.

Access and use of individual-level registry data is subject to strict ethics and data protection regulations (section 3.8). Sensitivity of combined data is important, where in this project particularly psychiatric and criminal information for young persons was emphasized and required much attention to data minimization (according to the "need-to-know" principle), including pseudonymization of geography, a seven-categorized version of crimes, country of birth by world region, and the use of monthly instead of daily-based dates. The Norwegian Prescription Database harmonized all pseudonimization of personal identity numbers across files. Files were stored and analysed on a secure server in Helse Bergen with limited access requiring ethics approval.

Nationwide data	Applied variables	Application
Norwegian Patient Registry	ADHD diagnosis, comorbidity, contact date, waiting list date, gender, age, clinic, injuries at emergency wards (type, severity), injuries pre-diagnosis	Patient sample for Study I and II, outcome (Study II), covariates
Norwegian Prescription Registry	Filled prescriptions for ADHD, prescription date, daily defined doses	Treatment (Study I-II), instrumental variable
Central Penal and Police Register	Criminal charges, date of crime, crime pre-diagnosis	Outcome (Study I)
Norwegian Control and Payment of Health Reimbursements Database	Injuries at emergency rooms, injury date, injuries pre-diagnosis	Outcome (Study II)
Central Population Register	Parents' civil status, country of birth, emigration, clinic-area population size, percent of youth non-norwegians, married mothers	Comparison sample from general population (Study I-II), covariates
Income, Tax, and Wealth register	Parents' labor income when child was 6 years old, clinic-area average level of parental income	Covariates
Norwegian Education Database	Parents' highest education level when child was 6 years old, clinic-area average level of parental education and high school dropout	Covariates
Municipality-State-Reporting	Child protection services pre-diagnosis	Covariates
Norwegian Cause of Death Register	Death date	Covariates
Norwegian Mother, Father, and Child Cohort Study	ADHD symptoms (insert name)	Study sample and treatment (Study III)

Table 1. Norwegian registry data and survey data used in Study I-III.

Norwegian Patient Registry

The Norwegian Patient Registry (NPR) includes data on all persons referred to and treated in specialist health services, including time and place of treatment, demographic information, and medical information with diagnosis codes based on ICD-10.[201] NPR was established as an individual-based registry in 2008, and administrative personell and clinicians are mandated by law to report data. The main aim of NPR is administration and quality assurance of specialist health care, as well as health-related research.[201] NPR also contains data on injuries in specialist care, i.e., emergency wards (EW) at hospitals.

Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) includes data on all prescriptions filled at pharmacies from 2004 onwards. The aim of NorPD includes the description of patterns in drug use, temporal trends, promotion of research of safety and effectiveness of drugs, and ensuring quality in prescribing practices.[202] NorPD includes information about type of prescription using the Anatomical Therapeutical Chemical (ATC) classification system and defined daily doses (DDD) for prescriptions in line with the World Health Organization (WHO).[203]

Central Penal and Police Register

The Central Penal and Police Register is mandated by law as the national register of convictions. The register contains all registered convictions and all information related to the police's work involved in the investigation and clearance of criminality.[204] A new criminal law was enacted in 2015 impacting registration of some crimes, but Statistics Norway provided a harmonized version for this project.

Norwegian Control and Payment of Health Reimbursements Database

The Norwegian Control and Payment of Health Reimbursements Database includes reimbursed bills for patients from health services in primary care with data from 2006 onwards.[205] All contacts with primary care, i.e., general practitioners and emergency rooms, are coded according to the International Classification of Primary Care, 2nd edition (ICPC-2).

Central Population Register

The Central Population Register (CPR) includes data on the full population with personal identified data back to 1946.[206] CPR includes data on all persons who either live or have lived in Norway, including citizenship, changes to civil status, movements in and out and within the country, births and death.[207]

Income, Tax, and Wealth Register

The Income, Tax, and Wealth Register includes information from multiple sources including tax records from the Norwegian Tax Administration, welfare benefits and services from the Norwegian Labour and Welfare Administration, *Lånekassen* (bank and part of welfare state supporting access to education for all Norwegian citizens), and household income from Statistics Norway.[208]

Norwegian Education Database

The Norwegian Education Database contains individual-level data on education dating back to 1970. All education data from primary school to PhD-level is included.[209]

Municipality-State-Reporting

The Municipality-State-Reporting register dates back to 1995 and includes information about municipality activities including data on economics, schools, health, and social services such as child protection services.[210]

Norwegian Cause of Death Register

The Norwegian Cause of Death Register (NCoDR) contains information about the time and cause of death for all persons who at the time of death registered residents in Norway and is based on death certificates.[211]

Norwegian Mother, Father, and Child Cohort Study

The Norwegian Mother, Father, and Child Cohort Study (MoBa) is a population-based pregnancy cohort study carried out by the Norwegian Institute of Public Health and encompasses participants from all regions in Norway between 1999 to 2008. The cohort has a consent rate of 41% of all pregnancies and contains 114,500 children,

95,200 mothers and 75,200 fathers.[212] Study III used version 12 of the quality-assured data files made available for research in January 2019.

Municipality-level data set

A data set with municipality-level health and sociodemographic variables was made from openly available aggregate data from several registers in Statistics Norway and the Norwegian Institute of Public Health and made linkable to the other registries through harmonized pseudonymized municipality codes by NPR.

3.2 Outcomes

Criminal charges

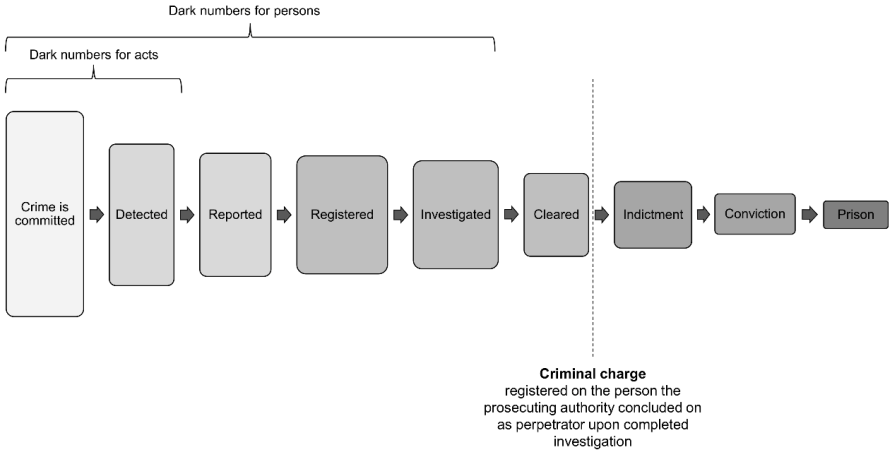

Figure 2. The criminal justice chain and registration of criminal charges.
Based on illustration and information by Lomell.[213]

In Study I, crime was measured by using all criminal charges that led to a prosecutor's determination to indict, impose fine, refer to juvenile mediation, grant conditional discharge, or dismiss due to non-criminal responsibility (such as mental illness or age). The interest lies in criminal acts. Figure 2 shows how the measurement of crime with crime statistics involves a trade-off between reported crimes with low quality for many

persons or convictions with high quality for few persons,[213] and thus, criminal charges present a balance between quantity and quality. More details on clearance rates by types of crimes is provided in the supplementary of Study I.

A global indicator for any crime and indicator variables for each of the following crime categories was defined: violence and abuse (henceforth violence), order and integrity (henceforth public-order), sexual, drug, traffic, property theft and other (the latter containing either property damage or other crimes of acquisition such as deception, and other crimes including environment). These indicators were defined separately for one to four years of follow-up as binary variables taking value one for one or more charge and otherwise zero. Four years of follow-up were chosen based on the strength of the IV being sufficiently strong for four years. Descriptive analyses additionally assessed crime up to eight years using the same binary indicator definition. In supplementary analyses, the general severity of criminal charges was assessed using a four-level severity indicator developed by Statistics Norway corresponding to imprisonment for one year or less, one to three years, three to ten years and over ten years.

Injuries

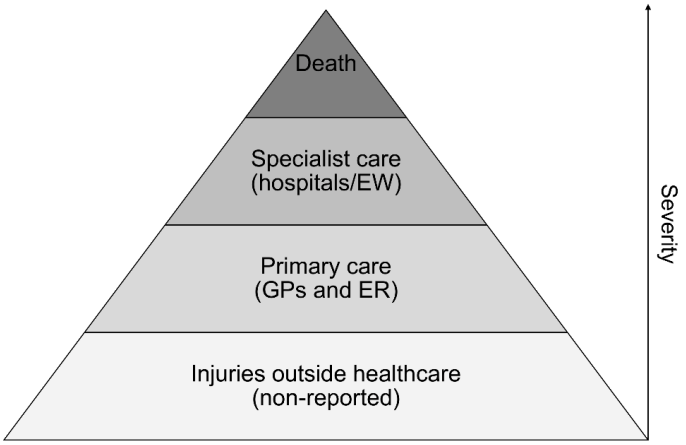

Figure 3. The injury pyramid with increasing severity towards the top.
Based on illustration by Norwegian Institute of Public Health.[214]

In Study II, Injuries was measured as any injury-related contact with primary care emergency rooms (ER) or specialist care emergency wards (EW) at hospitals. Three binary indicators were defined for one to four years follow-up. The first variable took value one if having an injury-related contact in either ER or EW, zero otherwise. The second and third variable were defined likewise, but separately for ER and EW. For further information a set of binary indicators were defined for type of injury. In ER, the following injuries were defined based on categorization of ICPC-2 codes (in parenthesis) developed by the Norwegian Institute of Public Health: head (N79, N80), fracture (L72-L76), sprain (L77-L81, L96), penetration (S13, S18), poison (A84, A86), burn (S14), eye (F75, F76, F79), ear (H76-H79), other (S12, S15-S19, A80. A81, A88, B76, B77, D79, D80, N81, R87, R88, U80, X82, Y80), as well suicide-related contacts (P77). In EW, indicators were additionally coded for self-harm and victimization. While NCoDR contained data on death due to injury, there was very few events.

Incidence of ADHD diagnosis

In Study III, the cumulative incidence proportion of ADHD diagnosis rate was defined as all new patients aged 0-18 registered with ADHD diagnosis (ICD-10 F90.0) in 2011-2016, divided by the mid-value of the population aged 0-18 in 2011-2016.[215] This measure was defined at municipality- and clinic-level.

3.3 Treatment

Pharmacological treatment

In Study I and II, pharmacological treatment was based on all filled ADHD prescriptions for the patient population. Stimulants included Metylphenidate (N06BA04), Dexamphetamine (N06BA02), Lisdexamfetamine (N06BA12), Amphetamine (N06BA01). Nonstimulants included Atomoxetine (N06BA09). Pharmacological treatment was operationalized as the cumulative sum of defined daily doses (DDD) filled for all ADHD prescriptions separately for one to four years following diagnosis of ADHD. The same approach was used for defining stimulant and

nonstimulant treatment used in supplementary analyses. Details are presented in the methodology section (section 4.3.5.).

ADHD symptom load

In Study III, Individual-level data from MoBa was used to measure ADHD symptom load. MoBa measures ADHD symptoms with The Parent/Teacher Rating Scale for Disruptive Behavior Disorders (RS-DBD) which is used in clinical practice with evidence supporting good reliability and validity.[216, 217] RS-DBD measures inattention with nine items and hyperactivity and impulsivity is measured with nine other items, all on a four-level response scale (1 = Never/Rarely, 2 = Sometimes, 3 = Often, 4 = Very often) (overview of items in Supplementary to Study III). Data was collected when children were aged 8, in line with an estimate of the average age of diagnosis in Norway.[218] The continuous latent construct of ADHD symptoms was measured with confirmatory factor analysis then used to define two population-level measures: the proportion of individuals in the catchment area of each clinic with ADHD symptoms at or above the 95th percentile aligning with a countrywide prevalence of 5% among children and adolescents.[59] In sensitivity analysis, the 90th percentile was used to encompass potentially large variation. Proportions of children with elevated levels of ADHD symptom levels were defined as the number of persons surpassing the percentile cut-offs divided by the total participants in MoBa for each clinic catchment area.

3.4 Clinics catchment area

The determination of clinics' catchment area was made in collaboration with NPR, utilizing data on all patient contacts at all clinics and patients' residence municipality in 2009. Clinics serve one or more municipalities, as well as city districts in the four largest cities (Oslo, Bergen, Trondheim, Stavanger) which collectively constitute the catchment area. The clinic assignment to a municipality was identified based on the highest number of patient contacts originating from that municipality. To illustrate, if a clinic in western Norway had 15 patients residing in a municipality in northern Norway and 700 patients residing in a municipality in western Norway, the latter

municipality was considered the municipality served by that clinic. Notably, no substantial changes in municipality codes occurred throughout the study period.

3.5 Provider preference

The latent construct of provider preference was computed as the mean number of DDD for filled ADHD medication among patients diagnosed with ADHD at the clinic level. Provider preference was defined separately for stimulant and nonstimulant medication in supplementary analyses. Detailed considerations of provider preference are provided in the methodology (section 4.3.1.).

3.6 Covariates

Study I and II used an adjustment set containing variables on patients, family, and catchment area characteristics. The following patient-level variables were included: age, gender, presence of comorbid diagnoses at the time of ADHD diagnosis, country of birth (Norway, Europe, outside Europe), year of clinic contact, history of crime (Study I) or injuries (Study II) prior to ADHD diagnosis, previous involvement with child protection services. Family covariates included parents' marital status (married, unmarried, or other including widowed, divorced, separated), income and educational attainment when the child was aged 6 (primary school, high school, short and long university education). Catchment area covariates encompassed population size, high school dropout rates, and aggregated measures derived from the general population sample, including parents' income, percentage of youth immigrants, parents' educational level, and mothers' marriage rate. Covariates for patients and family characteristics were measured at baseline, while catchment area characteristics were measured during 2009-2011. Together, this adjustment set is meant to account for clinics' patient mix.

3.7 Study samples

Study I and II uses a patient population sample defined by NPR based on all contacts for any reason for persons aged 5 to 18 when in contact with CAMHS in 2009-2011. While NPR was established as an individual-based registry in 2008, some data quality issues concerning relevant diagnostic information in 2008 led us to start the cohort 2009 with inclusion up to 2011 to ensure a large cohort for statistical power and long follow-up with data up to 2021. A comparison sample was defined by Statistics Norway in collaboration with NPR consisting of the general population without contact with CAMHS in 2009-2011. This cohort was a randomly drawn sample of somewhat larger size to the patient sample matched on sex, age, and geography, with same follow-up as the patient sample. The patient cohort was used to define the samples for main analyses which consist of persons who were registered with ADHD diagnoses for the first time between 2009 and 2011. Study I focus on criminality measured by criminal charges which is rare in children, hence the sample was restricted to patients aged 10 to 18 when diagnosed with ADHD. Study II focus on injuries which is considerably more common among children, and thus the sample included all patients aged 5 to 18 when diagnosed with ADHD. The general population cohort was restricted by age accordingly.

In Study I, the patient sample contains all persons aged 10 to 18 with their first registered ADHD diagnosis (ICD-10 Hyperkinetic disorder, F90.0 (80.5%), F90.1 (11.0%), F90.8 (7.4%), and F90.9 (1.1%) as primary diagnosis in NPR between 2009 and 2011 (n=5,624). The general population sample consisted of a matched random sample aged 10-18 with a randomly generated inclusion date in 2009-2011 (n=50,271).

In Study II, the patient sample consisted of all persons aged 5 to 18 who received their first registered ADHD diagnosis (ICD-10: F90.0 (81.3%), F90.1 (11.3%), F90.8 (6.2%), and F90.9 (1.1%) as primary diagnosis in NPR in 2009 to 2011. The general population sample contained all aged 5-18 in 2009-2011 with a randomly generated inclusion data (n=75,184).

In Study III, complete municipality-level data for diagnosis data from NPR for 2011-2016 was used (n=422). This was combined with individual-level data from MoBa, where data on all persons with ADHD symptoms was pooled for 2011-2016 (n=39,850). The main analyses were based on clinic-level data (n=63), with cities represented by one clinic due to lack of city-level data reducing the number of clinics from a total of 73.

3.8 Ethics

Study I-III was approved by the Regional Research Ethics Committee of Norway (2017/2150) and Study III additionally under (2017/2205). These approvals are given based on considerations of the projects' fulfilment of criteria specified in the Act on medical and health research ("the Health Research Act") and the Act of treatment of personal information ("the Person Protection Act"), and is in accordance with the General Data Protection Regulation (GDPR), and the Data Protection Impact Assessment (DPIA) was approved by the data protection officer in Helse Bergen HF. Informed consent was not required as all data analyses were anonoymized. The project was exempted from this requirement as it was assessed as important for society and protective of the welfare and integrity of participants.[7]

4. Methods

The methodological challenge of this thesis centres around drawing causal inference from observational data. The methodological framework draws on three complementary strands in modern causal inference that together form a unified approach to causal questions: (1) the potential outcomes framework for causal effects, (2) instrumental variables for quasi-experimental identification of causal effects, and (3) causal graphs to ground the designs in substantive knowledge.[219, 220]

The potential outcomes framework offers a principled and transparent approach to causal inference with an emphasis on necessary assumptions. This has become the dominant approach in sociology, economics, epidemiology, and statistics.[220] Using *counterfactuals* to answer *what if* questions lie at the core. The following question is often used to introduce this style of thinking: what happens if you take an aspirin due to a headache? You stand before two *potential outcomes*: your headache with and without aspirin. The causal effect is the contrast between the *realized* and *unrealized* (or *counterfactual*) outcome.[220] The simple contrast between factual and counterfactual outcomes under treatment states forms the basis from which this framework extends to multiple applications. A control group serve as the counterfactual to the treatment group. Being able to control – or otherwise know – the treatment assignment mechanism is thus fundamental to counterfactual thinking, and is also why RCT with investigator-led randomization is the ideal design.[221]

IV designs can be viewed as a way of "reconstructing" an RCT in observational data. A "naturally" occurring variation – the IV – is used as the treatment assignment mechanism and then defended to be "as good as" randomization. Thus, a valid IV represent the treatment assignment mechanism and enables estimation of unbiased treatment effects under strict assumptions. Multiple candidate IVs have been applied, including genetics for diseases (MR) and examiner discretion (e.g., judges, case workers, and clinicians), where the logic is that some persons are as good as randomly assigned to a treatment due to their examiner's preference.[222] This thesis relies on variation in provider preference for pharmacological treatment of ADHD as an IV.

Provider preference IVs are increasingly applied in health research as shown in the most comprehensive systematic review on provider preference IVs to date,[21] conducted as groundwork for the IV analyses in this thesis. This review showed that necessary IV assumptions were underreported. My work aspired to seriously engage with these assumptions. This necessitated a causal model to ground the IV designs in.

A causal model of how the world works is *sine qua non* for finding and defending credible IVs. Causal graphs, or directed acyclic graphs (DAG), represent a compelling, graphically intuitive way of thinking through IV designs and formed an important foundation for Study I-III. The causal model the IV analysis in this thesis rely on was developed in exemplary fashion.[223, 224] Felix Elwert led this effort in collaboration with the clinical expertise on our project. I assisted by examining potential challenges posed by various considerations using the graphical criteria of DAGs.

Structure for this section

For a broader view on the methodological approach in this thesis, I start by briefly placing potential outcomes in a wider philosophical, historical, and methodological context. I start with the distinction between philosophy of causality and causal inference in statistics. I then describe how causal effects are defined in potential outcomes and how causal graphs are helpful to assess assumptions. Then I present the main intuition of IV methods and how provider preference is applied as a candidate IV, followed by considerations of the IV assumptions. I then move on to present the main causal graph and generalizations of IV used. Lastly, I discuss estimation and other methodological considerations in Study I-III.

4.1. Causality and causal inference

Causation has been central to science since its early beginnings.[225] Causality covers general, philosophical questions dating back at least to the ancient Greeks.[226] Causal inference, on the other hand, emerged as approaches to questions of causality in philosophy in the 18th and 19th century, and statistics in the 20th century.[221, 227, 228] The philosophy of causation is vast.[229, 230] I only touch briefly on the roots of counterfactual

causation which forms the foundation for potential outcomes. While I focus on potential outcomes, I sympathize with the view that every methodology has limits, and a pluralist stance can be helpful.[231-233]

Philosophy of counterfactuals

Counterfactual reasoning in philosophy can be traced to the Scottish philosopher David Hume.[234, 235] The definition of "cause" was problematized by the fact that all we ever can do is *observe*. We never truly *see* that one thing "causes" another, thus causal effects are nonidentifiable.[234, 236, 237] The English philosopher John Stuart Mill may be the first to explicitly define a causal effect as the contrast between realized and unobserved outcomes.[238, 239] Mill developed three criteria for causal effects: the cause must (1) precede the effect, be associated with the effect, credibly present the only explanation for the effect.[240] While philosophers developed the concept of counterfactual thinking, the *mathematical* formalization first came with the advent of randomized experiments in the 20th century.

Statistical approaches to causal inference

The most important early contributions to the potential outcomes framework was by the statisticians Jerzy Neyman and Ronald Fisher. Neyman[241] developed the notation for randomized experiments, while Fisher[242] established randomization as the "reasoned basis" for causal inference,[221, 242] meaning that randomization was a logical, justifiable foundation for drawing causal inference as it ensured "comparable" groups (section 4.3). The potential outcomes framework was expanded to observational studies by Donald B. Rubin in the 1970s.[243, 244] The experimental ideal had by then been firmly established in many disciplines.[245-247] Throughout the 1980s and 1990s, the computer scientist Judea Pearl developed DAGs which can be tied to potential outcomes through graphical criteria.[248] IV methods originate around the same time as randomized experiments. IV methods were likely originally proposed by the economist Phillip G. Wright to identify causal effects in the context of price equilibriums.[249-251] The name "instrumental variable" was coined by the economist Olav Reiersøl [252]. An instrumental variable is an *instrument* or *tool* that can be used to isolate causal effects between two other variables (see also, Morgan and Winship [219]). Work on estimators

followed (e.g., Theil [253]). Through a series of key papers, economists Joshua Angrist and Guido Imbens with Rubin expanded IV to allow for heterogeneous effects and simultaneously merged IV to potential outcomes.[254-256]

Mode of inference

Assumption-free causal inference is impossible. Identification of causal effects in the potential outcomes framework depend on a set of *identification* assumptions[220] covered in section 4.3.3, whereas the separate topic of *estimation* is covered in section 4.3.6. Under these assumptions, potential outcomes follow a *deductive* form of logic where associations have causal interpretation if the premises are true. In practice, nonetheless, researchers usually do not know if all assumptions hold and still rely on *inductive* inference[233] in line with much epidemiological research.[257]

4.2 Potential outcomes and causal graphs

4.2.1 Definition of causal effects

Individual-level causal effect

In the following, I use a simple running example of the effect of stimulant medication on injuries, which can be tied to Study I and II (the former by switching outcome to crime).[3] Suppose a person with ADHD often unintentionally hurts herself by clumsiness such as tripping over her own feet and bumping into objects. She takes stimulant medication and experiences fewer injuries. To frame this as an individual-level causal effect (ICE) in potential outcomes notation for person i, we have the multi-valued outcome injury, $Y_i \in (0, 1, 2, \dots, J)$ and a binary treatment indicator for stimulant medication, $D_i \in (0,1)$, taking value one for stimulant medication and zero otherwise. The person then has two potential outcomes: the outcome under medication, denoted Y_i^1, and under no medication, Y_i^0. ICE, δ_i, of stimulant medication on injuries is simply the difference between the two potential outcomes

[3] I follow the convention in presenting potential outcomes by starting with the simplest scenario of causal effects under the scenario of a binary treatment. I expand on generalizations to multi-valued treatment with covariates used in Study I-II.

$$\delta_i = Y_i^1 - Y_i^0 \qquad \text{(eq. 1)}$$

Because we only ever observe one realized outcome, ICE can never be estimated directly.[239] This is the *fundamental problem of causal inference* (FPCI),[258] and also why causal analysis often is considered a *missing data problem.*[221, 259]

Average causal effects

As ICE is not identifiable, attention is on aggregated causal effects such as the average causal effect (ACE) in a population represented by a random sample. This shift to the population-level also includes a shift to expected values, where $E[.]$ refers to the expectation operator from probability theory.[219] For simplicity, individual-level notation is now dropped. To assess effects of stimulant medication on injuries, we define the causal contrast of interest, $E[\delta]$, as the group-level difference in injuries between patients with and without stimulant medication, e.g., over one year follow-up after being diagnosed with ADHD. ACE is defined as

$$E[\delta] = E[Y^1] - E[Y^0] \qquad \text{(eq. 2)}$$

where $E[Y^1]$ is mean number of injuries among patients who took stimulants, and $E[Y^0]$ is mean number of injuries among patients who did not take stimulants. Again, ACE can be estimated but not directly calculated as we do not observe persons' outcomes under both treatment states.[239] In sum, counterfactual outcomes represented by close substitutes can be used to "solve" the missing data problem.[259] This requires "comparable" treatment and control groups. *Randomization* and *statistical adjustment* are the most common approaches.[259] Randomization ensure comparability by design, while statistical adjustment rely on no unobserved confounding. The quasi-experimental IV design use provider preference as a source of "as good as" randomization for comparable groups among patients on the margin of treatment. IV must meet *identification* assumptions for any estimate to have causal interpretation. "Comparable groups" (unconfoundedness) is considered most important[220] and serve as an intuitive segway from randomized experiments to IV analysis (remaining assumptions, section 4.3.3).

4.2.2 Obtaining comparable groups

In the context of effects of pharmacological treatment of ADHD on injuries, unconfoundedness imply that stimulant medication was assigned to an individual patient *completely unrelated* to how treatment affects injuries

$$(Y^1, Y^0) \perp\!\!\!\perp D \qquad \text{(eq. 3)}$$

The potential outcomes are then independent of treatment. This is counterintuitive outside RCTs as clinicians assign medication *specifically* considering outcomes. Cunningham [239] aptly point out that dependence between potential outcomes and treatment is "likely the rule for all sorts of human-based sorting". The main challenge is to circumvent this issue. RCTs are so highly valued because the investigator-led randomization makes unconfoundedness very plausible. In a *perfect* RCT (i.e., no attrition, blind assignment, complete adherence)[260], randomization is the only variable affecting treatment status. Without randomization researchers must control for the assignment mechanism through adjusting for all confounding, C, and defend *conditional unconfoundedness*

$$(Y^1, Y^0) \perp\!\!\!\perp D \mid C \qquad \text{(eq. 4)}$$

This essentially requires assuming a *conditionally* random experiment with observational data.[220] It is unrealistic to preclude any *unobservable confounding.* The control group then is a less credible counterfactual and results in an estimate of ACE *plus* selection bias.[185] Quasi-experimental designs are thus often considered a more credible strategy to identify causal effects.

4.2.3 Using causal graphs for research designs

Study I-III are based on considerations founded in DAGs. DAG present a way to examine the potential for causal *identification* before considering *estimation*. Identification may involve adjustment for variables as well as *not* adjusting for variables (for an introduction, see Elwert [261]). I briefly present a DAG for statistical adjustment, RCTs, and then instrumental variables, drawing on Steiner *et al.* [262] Figure 4 is a graphical presentation of the key common-cause confounding problem the IV

designs in this thesis seeks to circumvent. The effect of stimulant medication, D, on injuries, Y, among patients with ADHD, is biased by unobserved confounding, C, representing ADHD symptom severity and other unobserved variables.

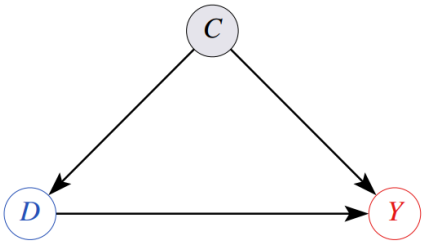

Figure 4. Causal graph for effect of ADHD medication in observational study.
This and following causal graphs made in causalfusion.net.

Variables are presented as *nodes* connected by unidirectional *arrows* implying direction of causation. C represents a noncausal "backdoor path" between D and Y. The "backdoor criterion" states that we can meet conditional unconfoundedness by "closing" the backdoor path through conditioning on C, i.e., $D \leftarrow \boxed{C} \rightarrow Y$, and thus obtain the causal effect of D on Y. In absence of data on C, the back-door cannot be closed and treatment effects remains biased.

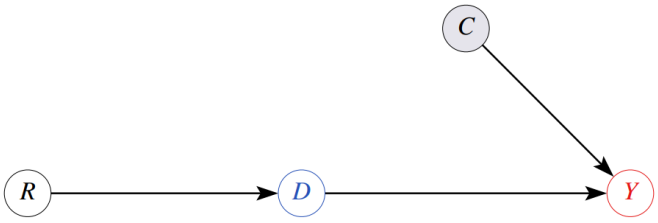

Figure 5. Causal graph for effect of ADHD medication in RCT.
Graph based on causal graphs for randomized experiments in Steiner *et al.* [262]

Figure 5 show how a perfectly implemented RCT breaks the confounding backdoor $D \leftarrow C \rightarrow Y$ by design through randomization, R, to assign treatment, D. Because only R affects D here, there is no longer a path between C and D. In RCTs with noncompliance, however, the backdoor path $D \leftarrow C \rightarrow Y$ re-enters the picture, and require researchers to adjust for C.[263] In practice, this can be circumvented by focusing

on the intention to treat (ITT) estimand (i.e., $R \rightarrow Y$).[4] Alternatively, and of key importance here, R can be used as an instrumental variable as illustrated in Figure 6. This then obtains the complier average causal effect (CACE), that is, the average causal effect of treatment among those who take treatment due to randomization.[264] The randomization indicator in RCTs is often presented as the ideal IV as it meets IV assumptions by design (section 4.3.3). CACE is the same estimand we retrieve with IV methods in observational data. I return to, and expand upon, the comparison of RCTs and the candidate IV provider preference in the next section.

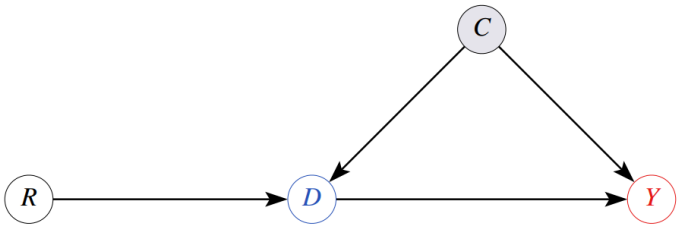

Figure 6. Causal graph for effect of ADHD medication in IV design.

4.3 Instrumental variables

When the interest lies in the effect of a treatment on an outcome, a third variable – the IV – can be used to estimate the causal effect of treatment, even in the presence of unobserved confounding.[265] In RCTs, the randomization indicator is used as an IV to correct for non-compliance and estimate CACE, more commonly referred to as the local average treatment effect (LATE).[264] The IV thus represents "the *assignment* to treatment instead of *receipt* of treatment" and can be used to obtain causal effects of treatment receipt.[221] In quasi-experiments, researchers rely on a source of variation that works "as good as" randomization. Study I and II uses provider preference for pharmacological treatment of ADHD as an IV to estimate effects of ADHD medication on crime and injury. In this section I present the intuition of provider preference as an instrumental variable, identification assumptions for IV and the causal estimand of

[4] The estimand is the target parameter of interest (e.g., treatment effect), while the estimator is the method used to obtain an estimate of the estimand.

interest, the underlying causal model, extensions of LATE to multi-valued treatment and IV and inclusion of covariates, and finally estimation.

4.3.1 Provider preference as an instrumental variable

Figure 7 illustrates how a provider preference IV design can be compared to an RCT. Varying provider preference for ADHD medication may be considered a source that is "as good as" randomization for some patients, i.e., the patients on margin of treatment (section 4.3.2). Between-clinician agreement is likely high for ADHD patients with highly severe symptoms who may benefit from medication, and patients who are effectively ineligible for ADHD medication (e.g., comorbidity or other characteristics). Thus, provider preference serves as a plausible as-if randomization only for patients on the margin of treatment.

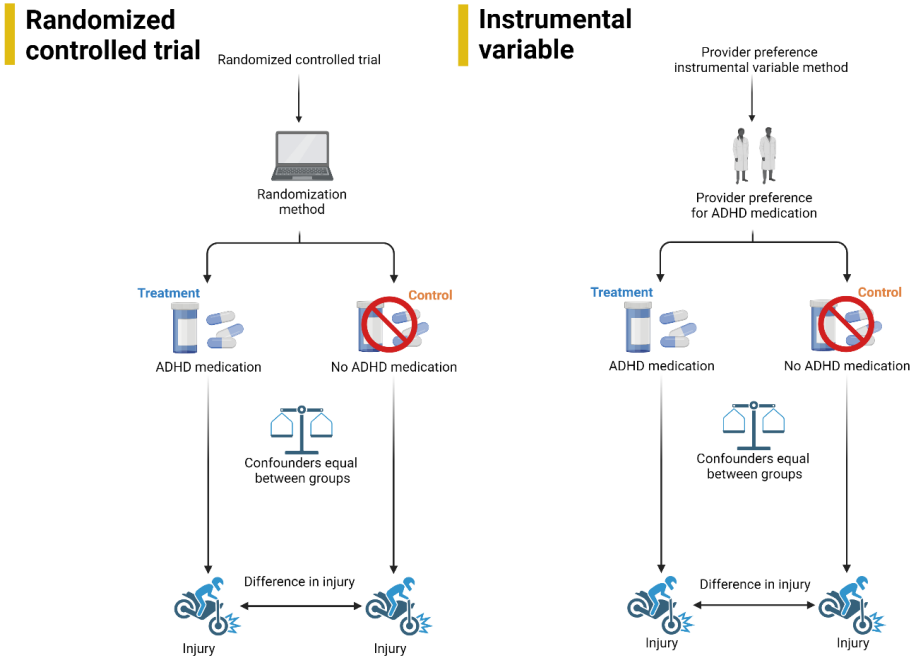

Figure 7. Comparison of RCT and IV method.
Illustration inspired by presentation of IV methods in Smith and Ebrahim [266].
Figure made in Biorender.

4.3.2 Patients on the margin of treatment

Patients on the margin of treatment are illustrated in Figure 8, which is a modified version of the theoretical model presented in the project's protocol article.[7] To simplify, let there be two clinicians: one with a high preference ("liberal") for ADHD medication, and one with a low preference ("restrictive") for ADHD medication. For patients with mild symptom severity (left in Figure 8) or high symptom severity (right in Figure 8), both clinicians agree in their treatment decision, and hence, there is no variation. The exogenous variation in treatment concerns patients in the middle of the symptom severity distribution, where the clinician with a high treatment preference prescribes ADHD medication whereas the other does not. Thus, for two patients with similar symptoms severity, one receives treatment while the other does not solely due to being assessed by a provider with higher preference for ADHD medication.[24, 25] Provider preference, then, randomizes patients on the margin of treatment to pharmacological treatment. Credible causal inference with this IV design relies on the assumptions I turn to next.

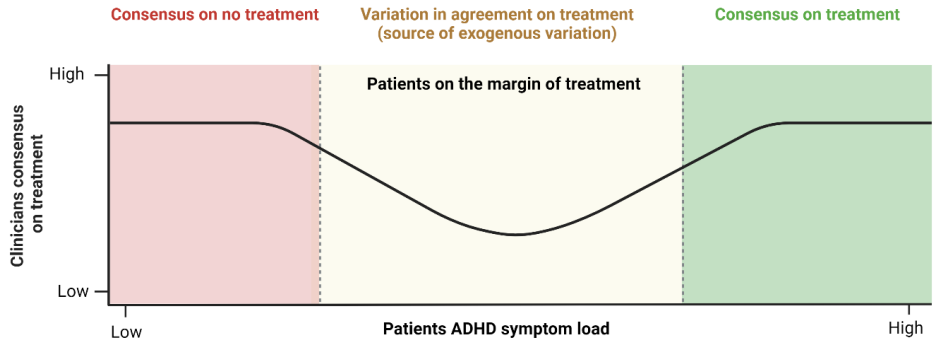

Figure 8. Theoretical model of clinicians' treatment consensus including patients on the margin of treatment in the middle of the distribution of patient's symptom load.
Clinicians' consensus for pharmacological treatment of ADHD by symptom severity among referred patients. Figure made in Biorender.

4.3.3 Identification assumptions for instrumental variables

IV methods rely on the identification assumptions of the potential outcomes framework (unconfoundedness, stable unit treatment value assumption, and positivity) and

additional IV assumptions (relevance, exclusion, and monotonicity). Relevance can be tested, but remaining assumptions must be justified by subject-matter expertise and supporting empirical analysis.[267] I base the presentation and notation of IV assumptions on Felton and Stewart [268], adopted to provider preference as an IV. I lay out the assumptions and return to results in section 5.4. For brevity, notation is based on the running example with a binary treatment and instrument.

The IV is denoted Z_i, with patient i being assessed at a provider with high ($Z_i = 1$) or low ($Z_i = 0$) preference for pharmacological treatment of ADHD. The treatment is denoted D_i, with patient i receiving pharmacological treatment for ADHD ($D_i = 1$) or not ($D_i = 0$). The outcome is denoted Y_i, whether patient i got injured one year following diagnosis. A set of controls are included, denoted X_i. The outcome is represented by $Y_i(D_i = 1)$ if the patient, potentially counter-to-fact, were assigned treatment. If the patient was assigned to control, $Y_i(D_i = 1)$ becomes an unobserved counterfactual outcome. The treatment effect for patient i is then the difference $Y_i(D_i = 1) - Y_i(D_i = 0)$, where only one potential outcome is realized (i.e., the fundamental problem of causal inference). The potential treatment patient i would receive had the patient been randomly assigned to a provider with high instead of low medication preference is denoted $D_i(Z_i = 1)$, and may, again, be counterfactual. Finally, let $Y_i(D_i = 1, Z_i = 1)$ represent the potential outcome observed for patient i had the patient both been exposed to a provider with high medication preference and taken medication.

Assumption 1: Relevance

$$E[D_i(Z_i = 1) - D_i(Z_i = 0)] \neq 0 \qquad \text{(eq. 5)}$$

Provider preference must affect treatment for some patients. Treatment status for patient i if assigned the instrument differs from treatment status for patient i if not assigned the instrument for some patients. This assumption can be empirically verified, most commonly by testing the *F*-statistic of the IV on treatment in the first stage

including all potential controls. Values above 10 have conventionally been considered sufficient for a strong IV,[269] with recent work suggesting 104.7.[270]

Assumption 2: Unconfounded instrument

$$Y_i(d, z) \perp\!\!\!\perp Z_i \text{ for all } d, z \qquad \text{(eq. 6)}$$

The instrument, provider preference, is randomized to patients. Provider preference share no unmeasured common causes with neither the outcome nor the treatment. The potential outcomes, regardless of treatment (d) or provider preference level (z), are independent of the distribution of provider preference for all values of treatment and provider preference. Concretely, suppose some providers have patients with generally more severe ADHD symptoms. Such patients would have a higher risk of injuries and provider preference would be associated with the patients' ADHD symptoms severity, which is also related to injuries. Thus, provider preference is no longer independent of the potential outcomes under different treatment levels. This violation makes it difficult to separate the effect of ADHD medication from the effect of patients' symptom severity. The main contribution of Study III in this context was to assess this assumption. Clinics' patient-mix may affect provider preference for pharmacological treatment and outcomes (injury or crime), represented by controls, X_i. Hence, we rely on a *conditionally* unconfounded provider preference instrument

$$Y_i(d, z) \perp\!\!\!\perp Z_i \mid X_i \text{ for all } d, z \qquad \text{(eq. 7)}$$

which means that unconfoundedness holds given adjustment for controls. No unobserved instrument-outcome confounding may be challenging to assume, but the rich set of controls in Study I and II is a strength. Unconfoundedness was assessed through balance tests, examining whether provider preference varied by covariates.

Assumption 3: Exclusion

$$Y_i(d, z) = Y_i(d, z') = Y_i(d) \text{ for all } z, z', d, i \qquad \text{(eq. 8)}$$

Provider preference do not affect the outcome except through pharmacological treatment. The outcome for patient i we would observe if the patients were assigned pharmacological treatment level d is the same regardless of the instrument (z, z') assigned, and this holds across all patients and all levels of provider preference and pharmacological treatment. Exclusion is violated if there is a direct effect of provider preference on the outcome. Exclusion was empirically evaluated by examining reduced form estimates of effect of provider preference for ADHD medication *among the general population sample*. The logic was that if provider preference only affected outcomes through ADHD medication, there should be no associations here.

Assumption 4: Monotonicity

		Low provider preference $Z_i = 0$	
		Doesn't take drug $D_i = 0$	Takes drug $D_i = 1$
High provider preference $Z_i = 1$	Doesn't take drug $D_i = 0$	Never-takers	Defiers
	Takes drug $D_i = 1$	Compliers	Always-takers

Table 2. Compliance classes in IV analysis.
Version adopted to provider preference based on Angrist *et al.* [254] and Angrist [271].

Monotonicity is generally introduced by presenting the four "compliance classes" of the population with a binary treatment and instrument (Table 2). *Compliers* only take medication if assigned to a provider with high preference for medication. *Defiers*, on the other hand, only take medication if assigned to a provider with low preference for medication and are assumed away. *Always-takers* take, while *never-takers* do not take, medication independently of provider preference. Always-takers are likely patients with severe ADHD symptoms that clinicians always prescribe medication. Never-takers likely do not have as severe ADHD symptoms or other traits making clinicians refrain from medication. Thus, compliers are the only patient group whose treatment status is affected by provider preference. This patient group likely comprise patients

where there is clinical uncertainty regarding treatment effects. Patients' membership in compliance classes is not directly observable because it depends on the patient's latent response to being assigned a provider with high or low medication preference.[222] This is an important point for clinical implications of LATE estimates, which I return to in the discussion. Monotonicity assumes *no defiers* which imply that the treatment status for patient i if the patient were assigned to a provider with high preference for pharmacological treatment is equal or larger than the treatment status if patient i were assigned a provider with a lower preference for pharmacological treatment

$$D_i(Z_i = 1) \geq D_i(Z_i = 0) \text{ for all } i \qquad \text{(eq. 9)}$$

Then, as summarized by Angrist *et al.* [254], by *exclusion*, the effect of provider preference on always- and never-takers (represented diagonally in Table 2) is zero. By *monotonicity*, defiers (upper right hand in Table 2) do not exist, and by *relevance*, the proportion of compliers in the sample is non-zero and represent the patients we obtain a treatment effect for. The existence of defiers would bias any LATE estimate. Moreover, monotonicity is the most underreported assumption in preference-based IV designs in health.[21] As Swanson and Hernan [272] note, monotonicity may be violated when using preference-based IV due to the specific weighting of risks and benefits that may end up contradicting provider preferences.[272] While monotonicity cannot be empirically verified, it can be indirectly assessed through examining the relationship between treatment status and provider preference.

Assumption 5 and 6: SUTVA and positivity

The stable unit treatment value assumption (SUTVA) implies that there is only one version of the treatment ("consistency") and that there is no interference between patients ("no interference").

$$\text{If } Z_i = z \text{ then } D_i = D_i(z). \qquad \text{(eq. 10)}$$

$$\text{If } Z_i = z \text{ then } D_i = D_i(d),$$
$$\text{then } Y_i = Y_i(d, z)$$

SUTVA means that the effect of pharmacological treatment on the outcome is the same for all individuals who receive the treatment. This may be supported by the dose-response relationship of ADHD medication.[153] A potential violation of SUTVA could be if patients who receive ADHD medication from providers with high preference have different outcomes compared to those who receive ADHD medication from providers with lower preference, even if they take the same amount of medication. This could be driven by an unobserved preference for psychosocial treatment affecting quality and usage of medication. Another violation may occur if the treatment received by one patient impacts the outcomes of other patients. Given familial aggregation of ADHD, treatment receipt in one sibling could affect another. We did not have data to assess this. Nonetheless, IV analyses were conducted by stimulant vs. non-stimulant medication to assess whether treatment effects could vary by medication type. Positivity implies that, across values of confounders, at least some patients receive a nonzero value of provider preference.

$$0 < \Pr(Z_i = 1 \mid X_i) < 1 \qquad \text{(eq. 11)}$$

Violations of positivity means that some individuals have no chance of receiving one of the treatment levels, given their level of the instrument. When positivity does not hold, IV estimators may not be consistent so convergence to the true treatment value in increasing sample size does not necessarily hold. The direction and magnitude of the bias in the IV estimator depend on the degree of the violation and the relationship between treatment, IV, and outcome. Positivity was assessed by descriptively examining provider preference values across confounders. Given assumptions 1-6, LATE has a causal interpretation.

The main IV assumptions and key violations are illustrated in Figure 9 which shows that *relevance* holds with $Z \rightarrow D$. The IV is *randomized* as no nodes cause Z. *Exclusion* holds if there are no open paths between Z and Y except through D. Assumptions 5 and 6 are not easily illustrated.[260]

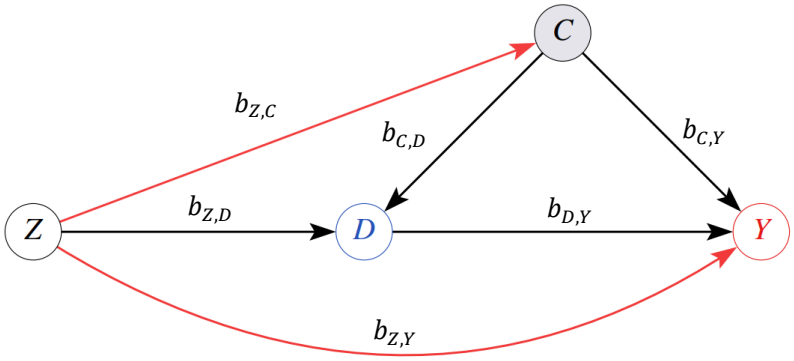

Figure 9. Instrumental variable assumptions.
An IV, Z, for the effect of treatment, D, on outcome, Y, with unobserved treatment-outcome confounding, C. Covariation denoted b_{X_1,X_2}, where X_n refers to either D, Y, C, or Z. Biasing paths that violate IV are red. A valid Z must predict D and have no open paths to Y except through D.Figure based on Mills, Barban, and Tropf.[101]

LATE that can be defined by the IV-estimator,[254] i.e., the ratio of the sample covariances between the outcome and instrument (*reduced form*) and treatment and instrument (*first stage*)

$$\beta_{IV} = \frac{b_{Z,Y}}{b_{Z,D}} = \frac{Cov(Y,Z)}{Cov(D,Z)} \qquad \text{(eq. 12)}$$

With binary treatment and instrument, as the running example, the Wald-estimator [273] can be used

$$\beta_{IV} = \frac{E[Y|Z=1] - E[Y|Z=0]}{E[Y|D=1] - E[Y|D=0]} \qquad \text{(eq. 13)}$$

In medical terms, IV is a ratio between two established RCT effects[274]

$$\beta_{IV} = \frac{Intention\ to\ treat\ effect}{Encouragement\ effect} \qquad \text{(eq. 14)}$$

which adopted to provider preference IV becomes

$$\beta_{IV} = \frac{Provider\ preference\ effect\ on\ injury}{Provider\ preference\ effect\ on\ treatment} \quad \text{(eq. 15)}$$

Although the intuition and interpretation hold, estimation becomes more complicated when adding covariates and using multi-valued treatments and instruments, which I return to in section 4.3.5.

4.3.4 Causal graph for preference-based instrumental variables

Figure 10 presents the main DAG for identification of effects of pharmacological treatment of ADHD on the outcome of interest, which here is crime (Study I) and injury (Study II). The DAG is valid for both outcomes.

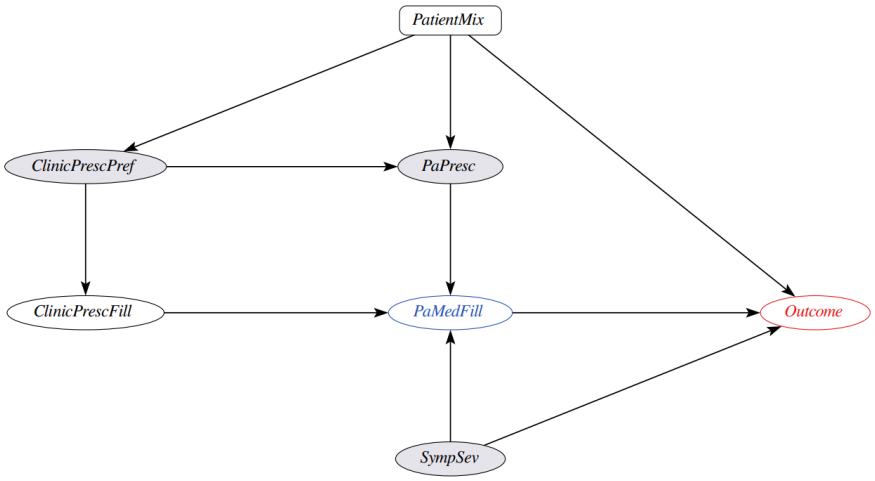

Figure 10. Causal graph for effect of ADHD medication with preference-based IV.
Figure made in causalfusion.net.

The treatment is patient's take-up of ADHD medication, represented by the latent node $PaPresc$ and measured as patient's filled prescriptions for ADHD medication, represented by the observed node $PaMedFill$. The outcome, crime (Study I) and injury (Study II), is represented by the outcome node, $Outcome$. The main source of common-cause treatment-outcome confounding is symptom severity, represented by the unobserved node, $SympSev$. The IV is provider preference for ADHD medication, represented by the latent node $ClinicPrescPref$ measured as the average amount of

filled ADHD prescriptions for patients at each clinic, $ClinicPrescFill$. For $ClinicPrescFill$ to be a valid IV, there must be no *open* pathways between $ClinicPrescFill$ and $Outcome$. The patient's own symptom severity should not affect the clinics' prescription preference as clinics are assigned by residence. Clinics' patient mix represent a source of instrument-outcome confounding. This path is closed by conditioning on patient mix, represented by the boxed node $\boxed{PatientMix}$ to indicate that it is conditioned on. Other paths are blocked by non-adjusted colliders, i.e., nodes on a pathway with two or more arrows toward them. The following path is blocked at treatment: $ClinicPrescFill \leftarrow ClinicPrescPref \rightarrow PaPresc \rightarrow PaMedFill \leftarrow SympSev \rightarrow Outcome$. According to the causal model in this DAG, $ClinicPrescFill$ is a valid IV conditional on $PatientMix$. This is the approach used in Study I and II.

4.3.5 Generalized local average treatment effects

The IV analyses in Study I and II rely on two main generalizations of LATE: (1) continuous treatment (dose-response) and IV, and (2) inclusion of covariates. In both cases, the IV estimate is a weighted average of treatment effects for patients who take treatment due to provider preference.[275] Moreover, with covariates, 2SLS retrieves an estimate that is the average across all covariate-specific LATE estimates.[275] Finally, with a variable treatment intensity, the treatment effect is a weighted average derivate.[275] Figure 11 illustrates how the logic of IV with binary treatment extends to multi-valued treatments.

Study I and II define treatment as the cumulative number of DDD for ADHD-prescriptions filled cumulatively for one, two, three, and four years following diagnosis of ADHD. Four years was chosen as the max number of years follow-up for IV analyses due to the decreasing strength of the first stage regression (see *Relevance*, above). The treatment variable was scaled so a one-unit increase represents a transition from no pharmacological treatment to full-time pharmacological treatment throughout the follow-up period. For example, by one year follow-up a one-unit increase corresponds to an increase of 365 DDD. This was obtained by dividing the sum of DDDs over follow-up by 365*years follow-up.

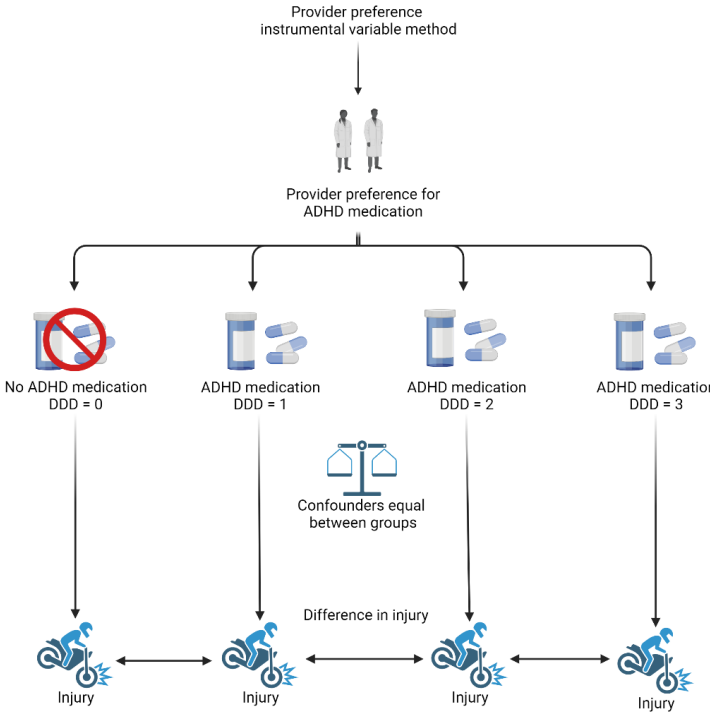

Figure 11. Effect of multivalued ADHD medication in IV design.
Example with one year follow-up post being diagnosed with ADHD Treatment is multi-valued with defined daily doses corresponding to no medication (DDD = 0), one year (DDD = 1), two years (DDD = 2), and three years (DDD = 3). Figure made in Biorender.

Treatment is multi-valued taking value $D \in (0, 1, 2, \dots, J)$ where J represents maximum. Exceptionally few patients exceed 3 times more DDDs than their year(-s) follow-up (e.g., DDD > 1095 by one year). The IV is measured as the average clinic-level number of filled DDD for ADHD prescriptions for other patients than patient i, to exclude the possible effect of patient i on her own assigned IV value. The IV is also scaled the same way as treatment and can be considered multi-valued, $Z \in (0, 1, 2, \dots, J)$. The estimand is the average causal response (ACR) which still is rooted in LATE.[275] Specifically, then, the IV analyses estimate the effect of increasing treatment for ADHD prescriptions corresponding to full-time follow-up. Because outcomes are binary, 2SLS estimates are interpreted as the percentage point change in the probability of the outcome with a one-unit increase in treatment.

4.3.6 Estimation

Instrumental variables estimators are consistent in large samples and characterized by high variance and mean bias in small samples.[274] *Consistency* imply that estimated effects become closer to the true effect as $n \to \infty$. *High variance* means low precision in estimates, i.e., values widely spread around true value. *Mean bias* imply that the expected value systematically differs from the true value. High variance and mean bias are aided by larger sample size and a strong, exogenous IV. Thus meeting IV assumptions is important for both identification and statistical inference. At its simplest, estimates from IV can be obtained with the standard IV-estimator (eq. 12) or Wald-estimator (eq. 13). In practice, the most commonly used estimator is *two-stage least squares* (2SLS). This is the main estimator in Study I and II. For robustness analyses, the maximum-likelihood based IV Probit estimator have been used, too. Here, I describe how the models are set up with 2SLS and, briefly, IV Probit.

Two stage least squares

2SLS performs IV analysis in two regressions.[265] In the first regression, known as *first stage*, treatment is regressed on the provider preference instrument and covariates. Explained treatment values from the first stage are then used in the *second stage* regression alongside the same covariates to retrieve the causal effects of ADHD medication on the outcome. The first stage regression uses ordinary least squares (OLS) with treatment, D, regressed on the IV, Z, and covariates, X, where β are regression coefficients and υ is the error term

$$D = \beta_0 + \beta_1 Z + \beta_2 X + \upsilon \qquad \text{(eq. 16)}$$

We then take the predicted treatment values, $\widehat{D}$, and include them as the treatment in the second stage regression. In the *second stage*, we use OLS with the outcome of interest, Y, regressed on predicted treatment values, $\widehat{D}$, and the same covariates, X, where δ are regression coefficients and ϵ is the error term

$$Y = \delta_0 + \delta_1 \widehat{D} + \delta_2 X + \epsilon \qquad \text{(eq. 17)}$$

The first stage essentially isolates unconfounded variation in treatment, and this variation is then used to obtain causal effects of treatment in the second stage.

Standard errors

While eq. 16 and eq. 17 give correct coefficients, standard errors must be corrected for the use of the estimated instead of measured treatment in the second stage. This adjustment is automatically conducted in standard packages that also solve the first and second stage simultaneously, such as `ivregress 2sls` in Stata, which I used. Standard errors were clustered at clinic-level to account for potential within-cluster correlations, e.g., patients could be more similar within rather than between clinics. Without accounting for this, standard errors could be artificially decreased increasing the rate of false positive findings.[276]

Modelling binary outcomes: Linear probability models and Probit

2SLS obtains LATE whether the outcome is binary or continuous. Moreover, 2SLS provides LATE estimates directly while more complex modelling requires an additional step to obtain marginal effects. Arguments for 2SLS with binary outcomes rely on same arguments as that between linear probability models (LPM) and probit (or logit) models.[275] The key potential issue with using LPM is that fitted values for predicted probability of the outcome can exceed $[0, 1]$.[275, 277] Probit models, on the other hand, are more complex and computationally more intensive. They nonetheless bound probabilities between zero and one. Hence, IV Probit may be more suitable.[278] Thus, as robustness analyses, the main IV analyses in Study I and II were conducted using both 2SLS and IV probit to ensure robust estimates. Results in both papers were similar regardless of whether 2SLS or IV Probit were used to estimate LATE.

Supplementary analyses

Study I and II also examine whether pharmacological treatment of ADHD is *associated* with probability of criminal charges/injuries. Here, too, LPM and Probit was used. The estimand in these analyses is the average treatment effect on the treated (ATT). However, causal interpretation relies on the strong and unrealistic assumption of unconfoundedness, which there is no reason to believe holds true. However, the

direction of selection bias is likely known. Patients with severe ADHD symptoms positively select into treatment and outcome, contributing to underestimated treatment effects (i.e., biased upwards). Furthermore, based on substantive considerations (section 1), treatment effects in the following subgroup analyses were conducted: sex, medication type, ADHD without comorbid CD/ODD (F90.1), "young" and "old". Robustness analyses were conducted by taking out patients who had filled any ADHD prescription prior to the evaluation of treatment effects. Finally, Study I and II also examine the risk ratio of criminal charges/injuries in patients with ADHD relative to the general population. These models were based on generalized linear models (GLM) with a log-link function and the binomial family.

Missing data

Given high completeness of data and complex modelling, complete case analysis was used in Study I-II (89% and 91% completeness, respectively). While imputation models could be a viable alternative such methods may induce bias if the imputation model is misspecificed[279] which becomes particularly relevant with complex modelling used in Study I-II, whereas most other methods are considered inferior to complete case.[280]

4.4 Examining geographical variation in ADHD

Study III combined several methods. Geographical variation and clustering of ADHD diagnosis was examined with spatial analysis through map visualization. CFA was used to measure the latent construct of ADHD symptoms based on symptom scores in RS-DBD. The extent to which variation in ADHD diagnosis and ADHD symptom load could be ascribed to the clinic-level was investigated with intra-class correlations from variance-component models. The degree to which variation in ADHD diagnosis and symptom load levels exceeded chance variation was examined with bootstrapped confidence intervals. Proportions outside bootstrapped confidence intervals were considered larger than chance variation. The coefficient of variation (CV), a measure of variability relative to the mean, was used to measure variation in ADHD diagnosis and symptom levels. To determine the likelihood of observing the CV by chance,

bootstrapping was used to obtain the full expected distribution of CV under H_0 with equal probability of diagnoses or symptom levels across clinics. Association between symptom levels and diagnosis was estimated with fractional regression models (FRM). Two analyses were conducted, separately using the 95th and 90th percentile cut-offs of ADHD symptom levels as predictors for ADHD diagnosis, with heteroskedasticity-robust standard errors and models weighted by MoBa respondents. Average marginal effects were reported, i.e., the percentage point change in ADHD diagnosis with one percentage point increase in ADHD symptom levels.

Two metrics was used to investigate the amount of unexplained variation in ADHD diagnoses: the CV for the residual and the r^2 for the observed and predicted values. A formal test was conducted to determine if the unexplained variation in ADHD diagnoses, accounting for ADHD symptom levels, surpassed chance variation. This involved comparing the observed CV to the distribution of expected CVs under the null distribution. To address statistical uncertainty, here, too, a bootstrap approach was used based on predicted values from FRM. Study III was based on aggregated data on municipality- and clinic-level with complete information thus complete cases analyses was used. All data wrangling and reported statistical analyses for Study I-III was conducted in Stata[281] with additional analyses in R.[282]

5. Results

This thesis examined the effects of pharmacological treatment of ADHD on criminality (Study I) and injuries (Study II), as well as the geographic variation in diagnoses and symptoms of ADHD (Study III) among children, adolescents, and young adults. All studies used Norwegian population-wide registry data and linkage of multiple data sources, including nationwide survey data on symptoms of ADHD (Study III). Study I and II used a provider preference IV design to estimate effects of pharmacological treatment of ADHD on criminality and injuries for patients on the margin of treatment, while Study III used several methods to examine geographical variation in ADHD. In the following I present results from Study I-III with emphasis on the main findings.

5.1 Effect of ADHD medication on criminality

In Study I, I examined effects of pharmacological treatment of ADHD on later criminality in persons aged 10 to 18 at the time of diagnosis in 2009 to 2011 (n=5,624). I found evidence of considerable variation in provider preference for ADHD medication with support for the main IV assumptions. IV analyses showed that pharmacological treatment reduced the probability of criminal charges related to violence for all persons on the margin of treatment with 7.3 percentage points (pp.) (95% CI: 13.3-1.2) by two years follow-up, with somewhat stronger effects in females and patients without comorbid CD/ODD (i.e., excluding F90.1). Among patients without comorbid CD/ODD, pharmacological treatment reduced the probability of public-order criminal charges by 12.3 pp. (95% CI: 21.4-3.1) by three years and 15.4 pp. (95% CI: 29.7-1.1) by four years follow-up. There was no evidence on other types of crimes such as property-, sexual-, or drug-related crimes.

Analyses by medication type showed that stimulants, which most patients took, is driving the effects, and there was no support for effects of nonstimulants (although these estimates were relatively imprecise). Effect estimates were somewhat stronger when leaving out patients without comorbid CD/ODD, but analyses of only those with these comorbidities were uninformative due to low sample size. Effects were somewhat

stronger in older patients, but these estimates were also more imprecise. There was not clear evidence of sex-differences in treatment effects, and estimates for females were generally more uncertain due to lower sample size and a weaker IV, especially for the third and fourth year. To make effect sizes more clinically intuitive, we presented numbers needed to treat (NNT) which says how many additional persons would have to be treated over the same time to prevent one event. The effect sizes correspond to a NNT of 14, 8 and 7, respectively. There was no evidence of reductions in drug-, traffic-, sexual-, or property-related charges. Sex-differences was challenging to examine in IV analyses due to a relatively small proportion of females and a weaker IV resulting in more imprecise estimates. Linear probability models (LPM) showed negative associations between ADHD medication and any crime, violence-, public-order-, traffic-, drug-, and property-related charges, but also a positive association with sexual-related charges. These estimates concern all treated and are likely biased upwards due to selection into both treatment and outcome which we correct for in IV analyses.

Moreover, persons with ADHD had higher risk of all types of crimes compared to the general population, with the highest risk ratios for violence-, sexual-, other-, property-, drug-, public-order, and traffic- charges, respectively. Females with ADHD had a higher relative risk than males with ADHD for most types of crime, except traffic- and property-related, as well as sexual-related crimes which was very rare among females. Persons with ADHD and comorbid CD/ODD (i.e., F90.1) had a higher proportion of any crime compared to persons with ADHD without these comorbidities (not reported in Study II). Severity of most criminal charges corresponded to under one year prison sentence. The overall severity of crimes was generally higher among persons with ADHD with one third involving prison sentences exceeding one year compared to one fourth in the general population. Violence-related crimes was relatively more severe with approximately half of all crimes corresponding to one year or more imprisonment for both people with ADHD and the general population.

5.2 Effect of ADHD medication on injuries

In Study II, I investigated effects of pharmacological treatment of ADHD on injuries in primary care emergency rooms (ER) and specialist care emergency wards (EW) among persons aged 5 to 18 at the time of diagnosis in 2009 to 2011 (n=8,051). There was substantial variation in provider preference for pharmacological treatment of ADHD. The main assumptions of the IV design were supported.

I found no clear evidence of causal effects of pharmacological treatment on overall injuries for patients on the margin of treatment. While there was no statistical support for protective effects on any injuries not ER-related injuries, there was weak evidence for protective effects on EW-related injuries by three years overall (-15.1 pp., 95% CI: CI: -29.1 to -1.1; NNT: 7) and for females (-21.5 pp., 95% CI: -37.8 to -5.3; NNT: 5), and four years overall (-21.6 pp., 95% CI: -39.5 to -3.7; NNT: 5), and for females (-38.2 pp., 95% CI: -62.3 to -14.0; NNT: 3). Results from LPM, which are likely biased due to unmeasured confounding, showed no support for associations for any injuries nor ER-related injuries, and a weak negative association between ADHD medication and EW-related injuries. Nevertheless, the main IV estimates were imprecise especially for females, and given that we conducted multiple tests and had no strong a priori theory to expect effects in EW- but not ER-related injuries, we erred on the side of caution by interpreting the overall findings as not providing clear evidence of treatment effects.

Persons with ADHD had a higher risk of all injuries, ER-related injuries, and EW-related injuries, and the risk was higher in females compared to males, compared to the general population. Analyses by type of ER-related injuries showed increased risk of head, fracture, sprain, penetration, poisoning, but not eye and burn, injuries, with the same general pattern of higher risks in females than males. Persons with ADHD also had a considerably higher risk of suicide-related contacts at ER and self-harm-related contacts at EW, while only females with ADHD also had a higher risk of victimization-related contacts at EW. Some of these outcomes, however, were still relatively rare despite our relatively large sample size making some estimates imprecise. The

proportion of any injury were higher among persons with comorbid CD/ODD (i.e., F90.1). In terms of severity, the presentation in either ER or EW is indicative. Approximately one fourth of persons with ADHD had one or more ER contacts during follow-up compared to one fifth without ADHD, whereas around 7 percent of people with ADHD had one or more injury-related EW-contact by four-years follow-up.

5.3 Geographical variation in ADHD

In Study III, I found that geographic variation in rates of ADHD diagnoses rates was much larger than what could be explained by geographic variation in levels of ADHD symptom load, suggesting that factors beyond health care access and unequal symptom levels contribute to observed variation. The variation of incidence of ADHD diagnoses between the clinics with the lowest to the highest levels varied by a factor of nearly 10 (0.4% to 3.9%), whereas the average incidence of ADHD diagnosis rate was 1.6% from 2011-2016. The confirmatory factor analyses for ADHD symptoms had relatively good measures of fit. ADHD symptom levels for the whole population of 8-year-olds followed a distribution with most toward the low end of the spectrum up to a tail end with few having high scores. Graphical depiction of diagnoses rates at municipality level showed clear patterns of clustering. Half of the municipality-level variation in ADHD diagnosis and below one percent of the variation in ADHD symptom levels ≥95% could be ascribed to the clinic-level. Moreover, the coefficient of variation (CV), measuring how much variation there is relative to the mean, was 46% for ADHD diagnosis and exceeded chance variation, whereas it was 18% for ADHD symptom levels ≥95% and did not exceed chance variation. There was support for a weak and imprecise association of 0.26 pp. (95% CI: 0.09 to 0.42) between ADHD diagnosis rate and symptom levels ≥95%. Analyses examining between-clinics variation in ADHD diagnosis rate and symptom levels ≥95% showed that the variation in ADHD diagnosis rate was much larger than what could be explained by symptom levels ≥95%.

5.4 Assessment of instrumental variable assumptions

Relevance was empirically verified with *F*-statistics for provider preference in first stage regressions showing that the IV was strong compared to conventional thresholds for strong IVs [269] and, for many analyses, a recent suggestion of a considerably higher threshold.[270] *Exclusion* as examined through reduced form analyses (associations between provider preference and outcome in general population) showed generally no support for associations. For crime, there was no association between provider preference and violence-related charges in any years of follow-up nor public-order-related charges in year three and four of follow-up, although there was a weak positive association in year one and two of follow-up. Thus, reduced form analyses supported exclusion the years that there was evidence of treatment effects. *Unconfoundedness*, as supported in the DAG (Figure 10) given adjustment for patient-mix was additionally supported by balance tests. Overall, these tests showed balance of covariates over values of provider preference, additionally supported by low joint *F*-test values. There was, however, a small positive association between father's having primary school as highest education level (relative to long university education) and provider preference in Study I and II. The strength with Study III is that it contributes with empirical evidence suggesting that there is no large variation in ADHD symptom load. *Monotonicity* was supported by analyses showing a monotonic positive association between provider preference and patient's treatment value. *Positivity* was supported by all patients being exposed to the provider preference of their clinic. Finally, *SUTVA* was examined by analyses by medication type, suggesting that stimulants are effective whereas nonstimulants may not be.

6. Discussion

6.1 Summary of results and contributions

This thesis estimates effects of pharmacological treatment of ADHD on criminality and injuries for patients on the margin of treatment using a quasi-experimental instrumental variable (IV) design and examines geographical variation in diagnoses and symptom load of ADHD based on Norwegian population-wide registry and survey data. Overall, I find effects of pharmacological treatment on crimes related to violence and public-order, but not other types of crime. I do not find clear evidence for treatment effects on injuries. I find that the geographical variation in diagnoses of ADHD is much larger than what can be explained by variation in symptom load. The thesis contributes to three areas in ADHD research: concerns about under- and overtreatment, causal knowledge about pharmacological treatment of ADHD, and long-term effectiveness on criminality and injuries.

First, the causal estimates concern patients on the margin of treatment which is informative to the debate of under- and overtreatment and calls for more knowledge on treatment effects among patients with milder symptoms. These patients are particularly relevant for clinical decision-making as they represent cases where there may be uncertainty about pharmacological treatment. In line with concerns of under- and overtreatment, analyses of the extent to which geographical variation in diagnoses of ADHD was explained by symptom load revealed that factors outside symptom load and health care access play a contributing role. This knowledge is not only relevant to support the IV analyses, but also contributes to an evidence base for equitable healthcare.

Second, I used a methodological approach that is relatively novel in ADHD research.[21] A valid IV design corrects for unobserved confounding which is a stubborn methodological challenge in the literature on effects of ADHD medication on real-life outcomes in general.[283] The validity of the IV design was supported by numerous analyses in Study I-III. There are a few within-subjects designs for criminality and

injuries but these studies cannot rule out time-varying unmeasured confounding such as symptom severity impacting periods on and off medication[284] and are additionally ill-suited for long-run effects.[19] Similarly, while difference-in-difference designs have been used to examine effects of ADHD medication on injuries, these studies have not used detailed data on types of injuries and treatment effects concern all treated. Credible treatment effect estimates for patients on the margin of treatment are not attainable in other experimental or quasi-experimental designs.

Third, the focus on criminality and injuries heeds the call for more knowledge about real-life outcomes. Clinical outcomes such as changes in symptoms is fundamental, but information about what really happens in the lives of persons who receive medication may be just as important for patients, their families, and society. The combination of comprehensive nationwide data on types of crimes and injuries is relatively rare, especially for samples consisting of children and adolescents. The long-term follow-up of four years also make the causal estimates relevant to debates on long-term effectiveness of ADHD medication.[18, 19]

In the following, I discuss the main results of Study I-III in context of existing knowledge. Then I turn to strengths and limitations which discusses the overall validity of the IV design based on findings from Study I-III and other relevant aspects. I end with some concluding remarks and suggestions for future research.

6.2 Findings in context

6.2.1 Effect of ADHD medication on criminality

Persons with ADHD had a higher risk of all types of crimes compared to the general population, corroborating existing knowledge. In line with dominant criminological theories (section 1.2.3), the elevated risk of criminality can be ascribed to a combination of lower self-control, higher levels of social strain, and selection into environments with deviant social learning, and thus involves both biological and social mechanisms.

Females with ADHD had a higher relative risk for most crimes compared to males with ADHD, which may be due to stronger symptom severity when ADHD is diagnosed in females in young age.[67] This "early detection" selection would also explain these findings in light of the general tendency for females to score higher on self-control.[285] The use of registered ADHD diagnosis in the Norwegian setting where only specialists can set diagnoses likely contributes to a sample with overall higher symptom severity compared to other survey-based samples. Males with ADHD relative to females with ADHD, however, had higher risk of sexual- and property-related crimes. Sex-differences in sexual offending may be related to atypical sexual interests, a history of sexual abuse, social isolation, and emotional problems, however, more research is needed on this topic.[286] Moreover, property crimes such as theft and robbery have been presented as masculine crimes,[287] where traditional gender roles and the ideal of the male breadwinner may play in. However, more research is required to explore these sex-differences. Persons with comorbid CD/ODD (F90.1) also had higher levels of crime compared to those without these comorbidities, in line with existing research.[30]

The main IV analyses showed that pharmacological treatment had protective effects on violence- and public-order related charges, whereas there was not support for effect on other outcomes for patients on the margin of treatment. Results from linear probability models, concerning all treated and likely affected by unmeasured confounding, also suggested negative associations for these outcomes. Supplementary analyses suggested that stimulants were effective while nonstimulants were not, corroborating existing knowledge on the general superiority of stimulants regarding effectiveness of ADHD medication.[152]

Violence and public-order crimes involve antisocial behavior such as violent and aggressive assaults, physical abuse, threats, harassment, and disregard for other's rights, boundaries, and property.[288] Low-self control can increase aggressive and antisocial behavior.[289] As ADHD medication improves symptom control, including impulsivity, it is credible that pharmacological treatment reduces these outcomes through improved executive functioning. While persons with ADHD experience more social strain commonly contributing to more criminal behavior, improvement of

symptom control may reduce impulsivity and channel coping strategies away from criminal acts. The improvement of symptom control, as part of a broader treatment approach, may also lead to reassessments of deviant attitudes, values, and perceptions, picked up from family or peers through social learning. Such an interpretation could also see the medication effects as part of a more holistic treatment approach which may include the patient's motivation to shifts one's conditions. An alternative interpretation is that ADHD medication simply makes persons better at avoiding crime detection.[178] Given the inherent aggressive and antisocial character in many violence- and public-order related crimes, it is somewhat contraintuitive that the main mechanism would be that ADHD medication reduces the detection of such crimes. Thus, while it certainly cannot be ruled out, it does not present a strikingly compelling explanation relative to the symptom reduction mechanism countered by Lichtenstein and Larsson [179], which could also be grounded in theories of self-control, social strain, and social learning.

Moreover, ADHD medication reduced public-order-related crimes among patients without comorbid CD/ODD, which suggests that patients with these additional behavioral impairments are more difficult to treat effectively, and hence, medication does not represent a "quick fix". This interpretation aligns with literature showing that ADHD with comorbid CD is a combination resulting in highly antisocial behavior even described as "fledging psychopathy".[35, 290] In sum, then, multiple interacting theoretical mechanisms may drive these treatment effects.

The NNT estimates (14 for violence over two years; 8 and 7 for patients excluding F90.1 over two and three years, respectively) are relevant to guide clinicians' considerations of treatment decisions. No other study has provided similar estimates. NNT estimates for stimulant medication for all treated may serve as relevant contextualization, although any comparison of NNT estimates across settings warrants caution given varying population, outcomes, and follow-up duration. A study on ADHD medication for children and young adults combined data from three studies including an RCT and found an NNT of 3 to prevent grade repetition or development of CD/ODD, an NNT of 4 to prevent an injury (in a driving simulation), and an NNT of 10 to prevent development of a substance use disorder.[291] Based on these estimates,

the authors concluded that ADHD medication had strong protective effects. The strength of NNT in ADHD medication can also be contextualized by comparison to other medications. Statins for heart disease have been estimated to have an NNT of 83 for mortality and 39 for non-fatal heart attack over 5 years,[292-295] while aspirin have an NNT of 42 for major heart attack over 1 month.[296, 297] Overall, the NNT estimates seem to align with meta-analytic evidence showing that ADHD medication have relatively strong effect sizes compared to other medications in medicine.[154]

Protective effects of ADHD medication on crime for patients on the margin of treatment is in line with the only other IV study on this topic.[24] Comparisons of estimates for patients on the margin of treatment and all treated are not directly comparable as the latter likely include patients with stronger symptom severity with clear consensus on treatment. However, results from IV analyses are in line with negative associations between ADHD medication and criminality in other large-scale Scandinavian registry studies.[175, 176] Study I improve our knowledge of treatment effects among patients on the margin of treatment in multiple ways. I contribute with causal estimates for types of crimes, showing relevant heterogeneity, and importantly establishing that specifically violence- and public-order crimes are reduced. Dalsgaard *et al.* [24] had data on police contacts and charges (for any reason) that was only relevant for a small subsample. Moreover, the overall sample was larger in Study I compared to that study. Multiple subgroup analyses contribute with novel information about sex-, age-, medication-, and comorbidity-related information. Treatment is defined continuously instead of binary, thus avoiding imposing an artificial dicotomization and several area-level covariates are included to account for potential area-level characteristics that could influence provider preference and outcomes. Finally, Study I examine effects of medication up to four years post diagnosis and hence provide long-term treatment effect estimates.

In Norway and internationally, there is a debate about whether ADHD medication is protective against criminality. An opinion piece from Norwegian psychiatrists emphasized that many people with ADHD would have avoided prison with timely diagnosis and treatment and hence ADHD is undertreated.[298] They point to Study III

in this thesis to illustrate how there may be practice variation in ADHD that can include not only *overtreatment* but also *undertreatment*.[5] In a counterarguing opinion piece, a doctor and psychiatrist argue that "[e]ven if medication for ADHD had reduced the risk of crime, it is a questionable argument for increased medication of children and young people" (own translation)[299] and caution against following US in medicating as a preventative measure. This debate is highly relevant for my findings, but it is important to underscore that Study I-III concern positive findings and I do not offer value judgements.[300] My findings, moreover, concern pharmacological treatment for patients on the margin of treatment and do not necessarily imply that increasing medication rates is beneficial *in general*. Ultimately, treatment decisions rely on balancing many benefits and harms, and criminality is one of many considerations in such a holistic clinical assessment.

6.2.2 Effect of ADHD medication on injuries

People with ADHD had a heightened risk for all types of injuries, including self-harm and victimization-related injuries in both primary (ER) and secondary care (EW), including all types of injuries and violence-related injuries such as self-harm, victimization, and suicide-related contacts, corroborating existing knowledge.[29, 132] Females with ADHD had higher risk of injuries compared to males with ADHD, which like criminality, may be related to stronger symptom severity when young females are diagnosed with ADHD.[67] These findings may be better understood by considering that injuries involve the Haddon Matrix of humans, agents, and environment,[111] with the following core mechanisms in the literature: ADHD core symptoms, comorbidity (particularly CD/ODD), risky driving, and the role of parents' education and parenting style.[132] Furthermore, self-harm and victimization could be understood in light of stigma, more adverse childhood experiences, and comorbid anxiety and depression.[96, 136]

The ADHD core symptoms can increase injuries through impulsivity and inattention (e.g., not looking for traffic when crossing streets) and hyperactivity with its general

[5] Note that the introduction of Study III emphasizes that geographical variation in the diagnosis of ADHD which do not coincide with ADHD symptom load may reflect both under- and overtreatment.

increased level of activity (e.g., tripping over or bumping into objects). Acting impulsively without properly considering consequences may also put persons in unfavorable situations including school fights raising the risk of sustaining injuries. Such behavior would also be more likely with additional behavioral problems, which was further supported through the higher proportion of injuries among persons with comorbid CD/ODD. While I did not have data specifying if injuries were traffic-related, risky driving is a credible mechanism and there were more traffic-related crimes among persons with ADHD in Study I. Finally, in terms of environmental factors, persons with ADHD did have parents with lower levels of education in line with existing research.[132] Many injuries happen at home and under the care of parents, indicating that the home environment and parents are important factors.[301] Parenting style may influence injury risk through attempts at learning children self-control, which has been linked to injury risk.[139] Moreover, higher levels of child protection service involvements in persons with ADHD indicate more adverse childhood experiences which is associated with higher risk of self-harm and suicidal behavior.[302]

The main IV analysis shows no clear evidence of protective effects of ADHD medication on injuries among patients on the margin of treatment. These findings may be due to several factors. First, the effectiveness of ADHD medication may be smaller among this patient group as they likely consist of patients with lower sympom severity. Second, despite a relatively large sample and a strong IV, the treatment effects were imprecise. Thus, it may be that there in fact are treatment effects, but that they are smaller than what could be detected. Hence it is important to underline that the absence of evidence of effects does not necessarily mean that there are no effects.[303]

Only two other studies have used IV to estimate effects of ADHD medication on injuries and both studies find protective effects.[24, 25] However, one of these studies was conducted in the setting of US and based on South Carolina Medicaid claims with selective eligibility criteria, using injury-related claims and associated costs as outcomes.[25] The other study was conducted in the setting of the universal healthcare system of Denmark, using nationwide registry data and contacts with hospitals and emergency ward as outcomes.[24] That study finds large effects and the authors state that

this warrants cautious interpretation. Those findings and the interpretation align with the relatively large, imprecise findings suggesting protective effects of medication on EW-related injuries with NNT estimates ranging from 3 to 7 in Study II. Moreover, while Dalsgaard *et al.* [24] offers causal estimates of ADHD medication on injuries, Study II importantly expand our knowledge by using detailed data on types of injuries and examines long-term treatment effectiveness. To contextualize the findings with existent knowledge of treatment effects among all treated, most studies suggest that ADHD medication reduces the risk of injuries,[29] although most of the literature concerns all treated and have issues with unmeasured confounding. In sum, the overall lack of compelling evidence for protective effects of ADHD medication on injuries among patients on the margin of treatment suggests that injury reduction alone should not motivate the treatment decision for this patient group.

6.2.3 Geographical variation in ADHD

Despite a free universal healthcare system, relatively low social inequality, and a national treatment guideline for ADHD, there was considerable geographical variation in ADHD diagnoses that far exceeded geographical variation in high levels of ADHD symptom levels. This is the first study combining detailed geo-coded data on ADHD symptoms and ADHD diagnosis to examine covariation. The findings of within-country variation in ADHD diagnoses are in line with other studies,[26, 73, 75-79] but Study III contributes with novel information about the role of symptom load. If levels of symptoms level would be a strong factor, observed variation in ADHD diagnoses would likely be more warranted and less concerning regarding the debate of potential under- and overtreatment.[304] Considerable geographical variation in diagnoses of ADHD that do not coincide with symptom levels contribute to concerns of potential under- and overtreatment. These findings, then, also raises concerns from a health policy perspective as such variation challenges the principle of equal healthcare regardless of geographical location. Varying clinical practice patterns have been presented as a likely explanation to geographical variation in ADHD diagnosis and treatment.[26, 74] The survey study on clinicians attitudes toward ADHD conducted in the ADHD controversy project showed that there was variation in clinicians' attitudes,[27] and similar findings have been found in other survey studies.[305] Study III adds to this

evidence base by showing that factors beyond ADHD symptom load and health care access are important. Study I and II further shows clear variation in provider preference for pharmacological treatment of ADHD that strongly affects patients' treatment status. Moreover, to which I return to when considering the overall validity of the IV strategy in the next section, it was crucial to empirically examine whether geographical variation in ADHD could be attributed mostly to varying symptom load, as this could challenge the concept of provider preference as an important contributing factor.

6.3 Strengths and limitations

Strengths

The main strengths of this thesis lie in the use of an IV design to circumvent unmeasured confounding combined with comprehensive nationwide registry data including detailed data on criminality and injuries and relevant covariates with several years follow-up. An important strength with the Norwegian context is that residence-based assignment to clinics reduces concerns of self-selection ("patient-shopping") to clinics based on provider preferences. Such causal effects can only be estimated by using a quasi-experimental provider preference IV design as both RCTs and observational studies are either unethical, unfeasible, or challenged by unmeasured confounding. The rare combination of geo-coded data on symptom levels and diagnoses of ADHD is a strength further supported by the institutional setting with free healthcare access that reduces concerns of selection bias. Moreover, study hypotheses was preregistered (ISRCTN: 11891971) and protocolled[7] with the intention of publishing results regardless of findings.

The methodological framework of this thesis is firmly based in the potential outcomes framework that is a principled approach to causal inference based on counterfactuals with transparent critical assumptions. The design was developed by using directed acyclic graphs, an effort led by methodological expertise and substantive experts. The IV design and common methodological strengths and issues was assessed through a systematic review of applications in health research prior to conducting IV analyses.[21]

The analyses were conducted in line with calls for careful assessment and transparent reporting of assumptions required for causal inference.[21, 268, 306]

The overall validity of IV designs can be considered on a continuum from low to high credibility based on the extent to which the critical assumptions are met.[307] The key assumption in this thesis is that assignment to treatment is as good as random for patients on the margin of pharmacological treatment with the use of provider preference for treatment. The validity of this assumption, again, requires that the IV meets the conditions outlined in section 4 examined through supplementary analyses in Study I-II and findings from Study III. Overall, these analyses support the IV assumptions. Nonetheless, only one of these assumptions can be empirically verified whereas the others rely on arguments based on clinical knowledge.

Limitations

The two main concerns of the IV design are the assumption of provider preference representing a source of as good as random assignment, and whether patients' treatment status only vary by medication dosage. First, while there are several supportive findings from analyses of IV assumptions, these analyses do not verify these assumptions, which ultimately rely on substantive knowledge. IV analyses can solve treatment-outcome confounding, but instrument-outcome confounding may be another concern.[222, 308] Analyses carefully adjusted for many covariates to capture patient-mix, but all common causes of the instrument and outcome cannot be completely ruled out.

Second, there could be multiple versions of treatment and the analyses cannot rule out that there are varying preferences for psychosocial treatment that plays a part. I did not have data to examine whether there also was varying provider preference in psychosocial treatment. Moreover, familial aggregation of ADHD[309] could lead to treatment interference where receipt of treatment among one sibling affects treatment of other siblings. This could have been further explored with sibling data which I did not have access to.

Third, while joint *F*-test values for balance tests were low, suggesting a relatively random distribution of provider preference, *F*-test values were not zero which indicated some non-randomness, but the overall influence on provider preference was small.

Fourth, patients that defy provider preference have been argued to pose a potential issue in provider preference IV as clinicians typically balance several harms and benefits in treatment decisions.[222, 310, 311] Monotonicity was supported, but the existence of defiers cannot be ruled out. Nonetheless, while there may be patients that could defy provider preference, any bias induced by such patients rely on the prevalence of patients with such co-existing preference-violating conditions and may not pose a critical concern.

Fifth, concerning data, the use of filled ADHD prescription data may involve measurement error in treatment and provider preference. Data on crime are also challenged by the issue of detection to be registered. Detection rates, again, likely vary by type of crime, where for example minor thefts from grocery stores are harder to detect compared to homicide. In terms of measuring crime in ADHD research, multiple measurements have been used, including "contacts with police", arrests, charges, convictions and imprisonment. In criminology, there is a discussion of how these measurements capture crime in society. The larger categories (e.g., contacts with police and arrests) may be more reflective of crime in the population but also include a considerable amount of "false positives". The more restricted category of convictions will likely contain fewer "false positives" but also underestimate the true prevalence of crime. Criminal charges can present a balance of quality and quantity.[213] Data on injuries, like crime, are challenged by the need for the injury to be detected to be registered, and hence the burden of injuries is likely often underestimated, especially regarding milder injuries[312] but more severe interpersonal injuries including partner violence may go unregistered as well. Moreover, as with registry data more generally, not all relevant information is available, and more documentation of data quality would be informative.[198] There is also a debate around how representative ADHD diagnosis in registry data are.[283] No study has investigated the validity of ADHD diagnosis in NPR, but in the similar Danish healthcare system, a study suggests a positive predictive value of 0.87.[313] The differentiation between prevalent and incident cases is also known

to be challenging due to truncation at start of follow-up,[198] however, results were robust to multiple sample specifications.

Sixth, the data was relatively complete for Study I-II and complete for Study III motivating complete case analyses. While the proportion of missing data was around the proportion considered reasonable for complete case analyses (10%), this rule of thumb like many others, have been critized.[314] The missing proportion is likely not missing completely at random and may induce some issues. Nevertheless, the application of multiple imputation models, too, come with risk of introducing bias through misspecified models which becomes especially relevant with complex models.[279, 280]

Seventh, there is a debate on the usefulness of LATE. A cornerstone in this debate is that it is not possible to point out *who* the patients on the margin are.[222] Others have criticized IV analyses as a way to provide precise answers to wrong questions, with the quasi-experimental turn leading researchers astray on an endless search for potential quasi-experiments to answer niché research questions instead of core research questions that need to be answered to move the field.[315] These critiques, however, concern the use of IV generally, and must be contextualized by underscoring that IV has been used in many settings, including scenarios with dubious validity.[316] In contrast, IV has the advantage of high internal validity and sometimes LATE may be exactly what we are interested in.[317] In preference-based IV in health research, for example, it is highly relevant to know the effects of treating patients on the margin. Nonetheless, it remains true that compliers cannot be identified[222] which poses a challenge to the already complex translation process from research to practice.[318] However, it is possible to identify overall characteristics of patients on the margin relative to the overall patient sample, although these analyses have mostly been developed for strict settings (e.g., binary IV and treatment)[319] which could not be utilized in my thesis. Moreover, the key reason as to why IV analyses provide LATE and not ATE is the assumption of no effect heterogeneity. A recent study suggests that this assumption may sometimes be relaxed.[320] If so, this would open IV analyses for credible estimates of ATE which could prove helpful for many causal questions.

Eight, the IV estimates had large standard errors and were somewhat imprecise. Moreover, the treatment effects are based on a cohort defined in 2009 to 2011. Given increasing medication trends in Norway more patients may receive medication today, which is relevant to consider as there could be diminishing returns to medicating more persons.[24]

Finally, concerning Study III, the analyses were based on an ecological design precluding individual-level inference that were not drawn. Data on symptoms were measured when the child was 8 years, while diagnosis data was on persons aged 0-18 years, where the symptom levels among the latter population could vary from 8-year-olds. Confounding bias could also impact the observed association between ADHD symptom levels and ADHD diagnoses, although the focus of this study nevertheless was the unconditional and conditional on ADHD symptom levels variation in ADHD diagnosis. The use of MoBa data could also pose some issues with selection as participants have a somewhat higher socioeconomic status and higher proportion of Norwegian natives compared to the general population.[321, 322]

6.4 Implications

Clinicians faced with patients where there is considerable uncertainty now have more evidence to inform their decisions. The findings from this thesis are especially important as patients on the margin of treatment is an understudied patient group whose treatment is determined by varying treatment preferences. Moreover, the study population is young and early intervention is important in prevention of potential criminal careers[323] and life-long disability sustained through injuries.[324] This, nonetheless, does not imply that medication should or should not be used preventative for these outcomes, but the evidence for criminality and injuries could form part of clinicians' treatment decisions. I have focused on bringing positive empirical evidence to the debate on under- and overtreatment, and normative statements are outside the scope of my thesis. The clinical implications, however, may be affected by clinicians' own attitude (i.e., "restrictive" or "liberal").[7, 27] Restrictive clinicans may emphasize the pros and cons of the NNT to prevent one crime and the lack of clear evidence of

treatment effects on injuries. Liberal clinicians could underscore the protective effects on harmful crimes and emphasize that there is at least not evidence for harmful effects on injuries. Nevertheless, while criminality and injuries are two important real-life outcomes in ADHD, treatment decisions rely on a holistic assessment balancing multiple benefits and harms.

Not only is the variation in ADHD relevant as a source for causal identification of treatment effects, but this thesis also shows that there is considerable clinic-wise variation in rates of diagnosis and pharmacological treatment of ADHD with unparalleled variation in symptom levels of ADHD, which could indicate unwarranted variation. Findings can inform further efforts to investigate the magnitude, trends, and consequences of such variation for treatment policies. Furthermore, this thesis shows that persons with ADHD have higher levels of criminality and injuries, emphasizing the need for early detection, appropriate intervention, and policies to ensure high-quality care. The implications of the evidence in this thesis should be considered within the Norwegian context (section 1.4), which may vary from other institutional and cultural settings. The novel knowledge in this thesis gives clinicians, patients and their family, and policymakers a broader evidence base to make better-informed decisions for the long-term success for persons with ADHD.

6.5 Conclusions and future research

In summary, I find effects of pharmacological treatment on crimes related to impulsivity, but not other types of crime for patients on the margin of treatment. I do not find convincing evidence for treatment effects on injuries among the same patient group. I find that the geographical variation in diagnoses of ADHD is much larger than what can be explained by variation in symptom load. While clinical treatment decisions rely on a holistic consideration, this thesis provide evidence for treatment effects on two key real-life outcomes for persons with ADHD.

This thesis contributes to three areas in ADHD research. First, the causal estimates and investigation of geographical variation are informative to the debate on under- and

overtreatment of ADHD. Second, the thesis improves our causal understanding of pharmacological treatment of ADHD. Third, estimates concern patients on the margin of treatment and offers evidence of long-term effects on criminality and injuries. This introduction, then, has contributed with an overview of the evidence base, theories, and debates that have motivated Study I-III. A considerable part of this introduction has expanded upon the methodological framework underlying this thesis with an emphasis on strengths and limitations of such designs in psychiatric epidemiology. Moreover, this thesis shows how combining quasi-experimental research designs based on credible sources of exogenous variation with high-quality register data can be used to answer research questions challenging to address with RCTs or observational studies.

There are several venues for future work. First, it is important to examine treatment effects for other real-life outcomes among patients on the margin of treatment for a more comprehensive understanding of treatment in this patient group. Second, replications in other settings would be valuable in itself and through the international comparisons it would enable. Third, studies exploring mechanisms could enrich our contextual understanding. For example, mixed-methods studies could use qualitative work to explore experiences of patients on the margin of treatment and clinicans' considerations of treatment for this patient group. Fourth, other causal designs could be informative and as methods for causal inference are constantly evolving, this will be a promising direction for future research. Considering the high prevalence of ADHD and its impact on many real-life outcomes, further research combining high-quality data and innovative methodological designs is needed to support the best treatment practices to reduce the impairments of ADHD for patients, their families, and society.

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Study I

Effect of Pharmacological Treatment of Attention-Deficit/Hyperactivity Disorder on Criminality

RH = ADHD Medication and Criminality

Tarjei Widding-Havneraas, MPhil, Henrik Daae Zachrisson, PhD, Simen Markussen, PhD, Felix Elwert, PhD, Ingvild Lyhmann, CandPsychol, Ashmita Chaulagain, MPH, Ingvar Bjelland, MD, PhD, Anne Halmøy, MD, PhD, Knut Rypdal, CandJur, Arnstein Mykletun, PhD

Editorial
Supplemental Material

Accepted June 20, 2023

Messrs. Widding-Havneraas and Rypdal, Mss. Lyhmann and Chaulagain, Profs. Bjelland and Mykletun, and Dr. Halmøy are with Haukeland University Hospital, Bergen, Norway. Mr. Widding-Havneraas, Mss. Lyhmann and Chaulagain, Profs. Bjelland and Mykletun, and Dr. Halmøy are with University of Bergen, Bergen, Norway. Prof. Mykletun is also with Norwegian Institute of Public Health, Oslo, Norway; University of Tromsø, Tromsø, Norway; and Nordland Hospital, Bodø, Norway. Prof. Zachrisson is with the University of Oslo, Oslo, Norway. Dr. Markussen is with Ragnar Frisch Centre for Economic Research, Oslo, Norway. Prof. Elwert is with the University of Wisconsin-Madison, Madison, Wisconsin.

TW is supported by funding from the Western Norway Regional Health Authority (912197), Research Council Norway (288585/IAR), and Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital. HZ, SM, FE, IL, and AC were supported by Research Council Norway (288585/IAR). AM is supported by Research Council Norway (288585/IAR) and Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital. HZ is also supported by funding from the European Research Council Consolidator Grant ERC-CoG-2018 EQOP [grant number 818425].

The research was performed with permission from the Regional Committees for Medical and Health Research Ethics.

This work has been prospectively registered: https://www.isrctn.com/ISRCTN11891971.

Statistical experts for this research: Dr. Markussen is an econometrician. Prof. Elwert is a sociologist and statistician. Prof. Zachrisson is a methodologist with expertise in causal inference.

Author Contributions
TW: Conceptualization, methodology, data curation, formal analysis, visualization, funding acquisition, project administration, writing-original draft, writing-review & editing. HZ: Conceptualization, supervision, methodology, writing-review & editing. SM: Conceptualization, supervision, methodology, writing-review & editing. FE: Conceptualization, methodology, writing-review & editing. IL: writing-review & editing. AC: writing-review & editing. IB: Conceptualization, supervision, writing-review & editing. AH: Conceptualization, supervision, writing-review & editing. KR: Conceptualization,

writing-review & editing. AM: Conceptualization, funding acquisition, methodology, supervision, project administration, writing-review & editing.

ORCID
Simen Markussen: 0000-0003-0899-9579

Disclosure: Prof. Zachrisson, Dr. Markussen, Profs. Elwert and Bjelland, Dr. Halmøy, Prof. Mykletun, Mr. Widding-Havneraas, Mss. Lyhmann and Chaulagain, and Mr. Rypdal have reported no biomedical financial interests or potential conflicts of interest.

Correspondence to Tarjei Widding-Havneraas, MPhil, Haukeland University Hospital, Sandviksleitet 1, 5036 Bergen; e-mail: tarjei.widding-havneras@helse-bergen.no

Abstract

Objective: Criminality rates are higher among persons with ADHD and evidence that medication reduces crime is limited. Medication rates between clinics vary widely even within universal healthcare systems, partly due to providers' treatment preferences. We used this variation to estimate causal effects of pharmacological treatment of ADHD on four-years criminal outcomes.

Method: We used Norwegian population-level registry data to identify all unique patients aged 10 to 18 diagnosed with ADHD between 2009 and 2011 (n=5,624), their use of ADHD medication, and subsequent criminal charges. An instrumental variable design, exploiting variation in provider preference for ADHD medication between clinics, was used to identify causal effects of ADHD medication on crime among patients on the margin of treatment, i.e., patients who receive treatment due to their provider's preference.

Results: Criminality was higher in patients with ADHD relative to the general population. Medication preference varied between clinics and strongly affected patients' treatment. Instrumental variable analyses supported a protective effect of pharmacological treatment on violence- and public-order-related charges with numbers needed to treat of 14 and 8, respectively. There was no evidence for effects on drug-, traffic-, sexual-, or property-related charges.

Conclusion: This is the first study to demonstrate causal effects of pharmacological treatment of ADHD on some types of crimes in a population-based natural experiment. Pharmacological treatment of ADHD reduced crime related to impulsive-reactive behavior in patients with ADHD on the margin of treatment. No effects were found in crimes requiring criminal intent, conspiracy, and planning.

Study preregistration information: The ADHD controversy project: Long-term effects of ADHD medication; https://www.isrctn.com/; 11891971.

Key words: ADHD; pharmacological treatment; quasi-experiment

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is associated with criminality.[1-5] While the prevalence of ADHD is estimated to 5.9% in youth, and 2.5% in adults,[6] it is 25% among prisoners.[7] Potential mechanisms for this over-representation include increased risky behavior among persons with ADHD,[8] and exposure to compounding family risks and deviant peers.[1,9] Early detection and appropriate treatment is called for to prevent crime and reduce social costs in this patient group.[6,10,11]

Pharmacological treatment of ADHD is common,[6] and randomized controlled trials (RCT) show reduced short-term symptoms while evidence of effectiveness on funtional outcomes such as crime remains uncertain.[12] A systematic review of research on ADHD and crime concludes that knowledge about treatment effects on crime is limited and that small samples in past research may contribute to inconclusive findings.[1,13] A comprehensive RCT finds no crime protective effects of ADHD medication relative to other treatments after eight years.[14] Scandinavian registry-based within-subjects studies comparing crime in periods on and off medication report mixed results, including reductions in violence-, drug-, and traffic-related crimes[2,15] or no reduction.[16] Notably, within-subjects designs cannot rule out all unmeasured confounding, such as time-varying symptom severity, that may affect both treatment and criminality.[17] Overall, the question of whether pharmacological treatment of ADHD reduces crime remains unanswered.

This study estimates causal effects of pharmacological treatment of ADHD on crime using a quasi-experimental provider-preference based instrumental variables (IV) design. Our approach circumvents unmeasured confounding that may otherwise bias treatment effects as symptom severity is positively associated with crime[18] and pharmacological treatment. IV mimics RCTs by exploiting a source of "as good as" random variation in treatment instead of investigator-led randomization. We use variation in provider preference for pharmacological treatment as an IV.[19] Patients with moderate symptom severity may receive pharmacological treatment in one clinic but not another and patients cannot choose providers based on desired outcomes in our institutional setting (i.e., the Norwegian universal healthcare system) as their

provider is assigned by residence municipality. Our IV analysis estimates the average treatment effect of pharmacological treatment of ADHD for patients "on the margin of treatment," i.e., patients who would vs. would not receive treatment depending on their provider's medication preference. Thus, the estimate may not generalize to children who would receive medication regardless of which provider they attend.

The main aim of this study is to estimate the effect of pharmacological treatment of ADHD on crime for patients on the margin of treatment. We also provide population-based evidence on rates of crime in ADHD compared to the general population.

Method

Sample

Our patient sample includes all individuals born 1991-2001 who received their first ADHD diagnosis from the Norwegian child and adolescent mental health services (CAMHS) between 2009 and 2011 (age 10 through 18), as registered in the Norwegian patient registry (N=5,624). ADHD diagnoses are defined as all ICD-10 Hyperkinetic disorder codes, i.e., F90.0 (80.5%), F90.1 (11.0%), F90.8 (7.4%), and F90.9 (1.1%). ICD-10 hyperkinetic disorder corresponds mainly to DSM-IV ADHD combined type and DSM-V ADHD combined clinical presentation[20]. In ICD-10, co-occurring hyperkinetic disorder and ODD or CD is coded as F90.1 hyperkinetic conduct disorder. Younger birth cohorts (2002-2006) were excluded as they have a very low risk of crime during follow-up (Figure S1, available online). We also analyze a general population sample comprising a random sample of persons aged 10 to 18 without contact with CAMHS in 2009-2011 matched on age, sex, and geography given a random inclusion date instead of date of diagnosis in 2009-2011 (N=50,271).

Criminal charges

Crime was measured by using all criminal charges that resulted in a prosecutor's decision to indict, fine, conditionally discharge, dismiss on grounds of not being criminally responsible (e.g., due to mental illness or age), or referral to juvenile mediation, as registered in the Central Penal and Police Registry (criminal charges by decision, Table S1, available online, and clearance rate for crimes, Table S2, available online).

We defined a global crime indicator as having been charged for any of the seven Statistics Norway crime categories: property theft, violence and abuse (henceforth violence), sexual, drug, public order and integrity violations (henceforth public-order), traffic, and other. Other includes property damage, other crimes (e.g., environmental), and other crimes of acquisition (e.g., deception). Persons of all ages can be charged for crimes while the minimum age is 15 for criminal prosecution.[21] We coded cumulative binary indicators taking value one for one or more charges and zero otherwise for each year of follow-up.

ADHD medication

We used all filled prescriptions in the Norwegian Prescription Database for ADHD medication as defined by the Norwegian Institute of Public Health (percent of total ADHD prescriptions over follow-up in parenthesis). Stimulants: Metylphenidate (N06BA04, 89.8%), Dexamphetamine (N06BA02, 0.6%), Lisdexamfetamine (N06BA12, 0.06%), Amphetamine (N06BA01, 0.06%). Non-stimulants: Atomoxetine (N06BA09, 9.5%). Pharmacological treatment is defined as the cumulative number of daily defined doses (DDD) filled for any ADHD prescriptions over years following ADHD diagnosis. For ease of interpretation, the treatment variable was scaled so a one unit increase in the treatment variable represent an increase from 0 to full-time medication in the entire follow-up period. For example, pharmacological treatment for the first year of follow-up is measured as the cumulative number of DDD for ADHD prescriptions divided by 365. Hence, the treatment variable equal 1 if the patient filled prescriptions corresponding to 365 days of pharmacological treatment.

Covariates

We used patient, family, and clinic area covariates to adjust for patient mix (overview of data sources, Table S3, available online). Patient and family covariates were measured prior to or at the time of ADHD diagnosis, while catchment area characteristics were measured during 2009-2011 to prevent post-treatment bias. We included: age, sex, year of contact with clinic, psychiatric comorbidity at time of diagnosis, country of birth (Norway, Europe, Outside Europe), charges before ADHD diagnosis, parents' marital status (married, unmarried, other (widowed, divorced, separated)), parent's highest education when the child was 6 years (primary school, high school, short- and long university education), and parent's labor income when the child was 6 years. Covariates on catchment area characteristics were included to account for potential area-level common causes of provider preference and crime. We included municipality-level population size and high school dropout rates, and the following aggregated measures from the random sample of the general population: municipality-level labor income of parents and clinic-level percent of youth crime, youth immigrants, mothers' marriage rate, and parents' education level.

Statistical analyses

Risk ratios for any crime and types of crimes at 8 years follow-up for patients with ADHD relative to the matched sample were calculated using generalized linear models with the binomial family and log link-function. Models were stratified by sex and age-adjusted.

Linear probability models (LPM) was used to estimate associations between pharmacological treatment and criminal charges.[22] Analyses were conducted on multiple samples: all patients, all patients excluding F90.1, i.e., patients with additional behavioral challenges, stratified by sex due to potentially important differences in ADHD and criminality, by stimulants/non-stimulants as effectiveness may differ, and patients aged 14-18 at time of diagnosis. Analyses were also conducted using Probit models as robustness checks. Causal interpretation of LPM estimates requires that the exposure is assumed to be conditionally random

given covariates.[23] This is unlikely and motivates our IV design. LPM models are nonetheless included for comparison purposes to IV results in line with the common convention in IV analysis.[19,24]

The IV design used the observed variation in pharmacological treatment between clinics as quasi-randomization to pharmacological treatment accounting for patient-mix. In Norway, only psychiatrists are licensed to initiate pharmacological treatment, but they work in teams with other professions. Broadly, provider preferences are measured as the clinic-level average number of DDDs for filled ADHD prescriptions among patients with ADHD, cumulatively and separately for one to four years. Four years were chosen for IV analysis as the IV was sufficiently strong for this duration only. Specifically, the leave-one-out average was used to measure provider preference for all patients other than patient *i*, thereby eliminating potential influence of patient *i* on the provider preference relevant to him/her. For ease of interpretation, IVs are scaled the same way as treatment. IV analyses are conducted for the same samples as LPM. The estimand is the local average treatment effect (LATE): the average causal effect of pharmacological treatment for patients on the margin of pharmacological treatment.[22]

A valid provider preference IV requires the following assumptions (see Supplement 1 for details, available online): relevance, exclusion, independence, monotonicity, and the stable unit treatment value assumption.[22] Relevance is empirically tested with the IV's F-statistic in first stage regressions of treatment on IV and covariates. Exclusion is evaluated by reduced form estimates in the general population sample where provider preference should not affect crime. Independence is tested by examining covariate balance for the IV. Monotonicity is tested by examining residuals from first stage regressions against values of the IV. The LATE was estimated with two-stage least squares (2SLS) and, as robustness checks, IV Probit models.[25] All models clustered standard errors at the clinic-level and were conducted in Stata 17,[26] using coefplot for data visualization.[27] Reporting guidelines for IV analysis[28] were followed and hypotheses preregistered (ISRCTN: 11891971) and protocolled.[29]

Results

Descriptive statistics

[Table 1 here]

Table 1. Baseline characteristics for patients with ADHD and the general population, aged 10 to 18 in 2009-2011 (N = 55,896) Note: ADHD diagnosis when in contact with CAMHS 2009-11, and matched general population excluding those in contact with CAMHS 2009-11. Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CAMHS = child and adolescent mental health services; no. = number; NOK = Norwegian kroner; SD = standard deviation; USD = US dollar; yrs. = years. [a]Plus-minus values are mean ± SD. Age at diagnosis corresponds to age at inclusion for the general population. [b]Yearly with USD/NOK exchange rate average for 2010 (USD 1/NOK 6.0453).

Table 1 shows baseline characteristics of the ADHD patient sample and the matched general population sample. The ADHD sample was somewhat younger with more male persons, Norwegian background, and criminal charges before inclusion. Parents of patients with ADHD had lower income, education, and were less likely to be married. Catchment area characteristics were relatively similar. Table 2 shows considerably higher rates of charges among patients with ADHD compared to the matched general population, and large sex differences, over 8 years follow-up. The highest risk ratios were for violence and sex-related charges. Risk ratios were relatively similar by 4 years follow-up (see Table S4 and S5, available online).

[Table 2 here]

Table 2. ADHD, general population, and risk of criminal charges over 8 years follow-up after 2009-11 (N=54,198) Note: Patients diagnosed with ADHD in 2009-2011 and general population excluding those in contact with CAMHS in 2009-2011 aged 10 to 18 at time of inclusion followed for 8 years, excluding those who either died (n=95) or emigrated (n=1,603). Age-adjusted risk ratios. Abbreviations: 95 % CI = 95 % confidence interval; ADHD = attention-deficit/hyperactivity disorder; CAMHS = child and adolescent mental health services; no. = number; RR = risk ratio.

Assessment of the instrumental variable

[Figure 1 here]

Overall, 79% of all patients had filled ≥1 ADHD prescription the first year after diagnosis, while 87% had filled ≥1 prescription by four years. The average percent of patients who had filled ≥1 ADHD prescription varied from 42% to 100% between clinics by four years follow-up (Figure S2, available online). Clinics had a median of 52 (interquartile range (IQR): 66) patients who were diagnosed with ADHD in 2009-2011.

Figure 1A shows the distribution of provider preference for ADHD medication. The median provider preference decreased from prescribing .72 DDD (IQR: .24) over the first year of follow-up to .64 DDD (IQR: 12). The relationship between treatment values and provider preference were positively increasing, lending support to monotonicity (Figure S3, available online).

Figure 1B further shows that the largest variation in provider preference occurs in the first year followed by a convergence across clinics in subsequent years. Nonetheless, clinics with the highest prescription practice continue prescribing more medication in later years. Instrument relevance is supported by strong first stage F-statistics for the IVs across the first years with all values considerably above conventional thresholds for strong IVs (Figure S4A, available online).[30] There was relatively strong balance of potential

instrument-outcome confounding variables as shown by low joint F-statistic values (Figure S4B, available online). There was no evidence for effects of provider preference on crime in the general population for the main IV results which supports exclusion (Figure S5, available online).

Results for linear probability models and instrumental variable analyses

[Figure 2 here]

Figure 2 presents estimated associations between pharmacological treatment and the probability of being charged with a crime from LPMs for 1-4 years follow-up after ADHD diagnosis for all patients, patients excluding F90.1, and by sex. Among all patients, patients excluding F90.1., and male patients, pharmacological treatment was negatively associated with the probability of charges for any crime, drug, violence, traffic, public-order, and property. The strength of associations among all patients varied from the strongest percentage points (pp.) reduction in drug-related charges (-1.9 pp., 95% CI: -2.9, -0.8) to a small positive increase in sex-related charges by four years (1 pp., 95% CI: 0.05, 1.5). There was no association between pharmacological treatment and criminal charges for female patients which is a small group with few events compared to the other groups (e.g., zero sexual-related charges), and hence estimates are more uncertain. Estimates with large uncertainty are not reported. Probit models provided similar results (Figure S6, available online). As our main results are the IV models, remaining LPM results are presented in Supplement 2 and Figures S7-S10, available online.

[Figure 3 here]

Figure 3 presents estimated LATEs from 2SLS IV models for all patients, patients excluding F90.1, and by sex. Pharmacological treatment reduces the probability of violence-related charges among all patients, patients excluding F90.1 and female patients over two years follow-up. Among all patients, pharmacological treatment reduces violence-related charges by 7.3 pp. (95% CI: 13.3, 1.2). This corresponds to a number

needed to treat (NNT) estimate of 14, indicating that treatment intensity would have to be increased from 0 to two years DDDs for 14 patients to avoid one violence-related criminal charge. NNT estimates are similar for violence-related charges among patients excluding F90.1 (NNT: 13) and female patients (NNT: 10). IV results also support an effect of pharmacological treatment on public-order charges among patients excluding F90.1 at three- and four-years follow-up. Here pharmacological treatment reduces public-order charges by 12.3 pp. (95% CI: 21.4, 3.1) at three years and 15.4 pp. (95% CI: 29.7, 1.1) at four years follow-up. This corresponds to NNT estimates of 8 and 7, respectively. Standard errors were large. First stage was weak for female patients at year three and not supported in year four, thus, these estimates are not reported.

Estimated LATEs from IV Probit models gave very similar effect estimates (Figure S11, available online). These models additionally supported the following effects of pharmacological treatment: any crime for all patients at three years follow-up (-.18.5 pp., 95% CI: -.35.6, -1.3; NNT: 5); violence at first year follow up for all patients (-2.8 pp, 95% CI: -5.4, -0.2; NNT: 36), all patients excluding F90.1 (-3.1 pp., 95% CI: -5.5, -0.6; NNT: 33), and male patients (-4.1 pp., 95% CI: -8.0, -0.1; NNT: 25); public-order charges for all patients at three years follow-up (-9.2 pp., 95% CI: -16.7, -1.8; NNT: 11); traffic-related charges for all patients at three years follow-up (-7.1 pp., 95% CI: -13.3, -0.1; NNT: 14); property-related charges for female patients (-12.3 pp., 95% CI: -23.0, -1.7; NNT: 8) at two years follow-up, and all excluding F90.1 (-8.8 pp., 95% CI: -17.2,-0.3; NNT: 11) at three years follow-up.

IV analysis by medication type showed support for reduced violence (-6.3 pp., 95% CI: -12.3, -0.3; NNT: 16) over two years (Figure S12, available online), while estimates for non-stimulants were imprecise (Figure S13, available online). In patients aged 14 to 18 at time of diagnosis, there was support for reduction in violence (-20.9 pp., 95% CI: -38.0, -3.6; NNT: 5) at two years follow-up (Figure S14, available online). There was no support for effects in patients with only F90.1, but standard errors were large (Figure S15, available online). Most violence- and public-order charges were either of low or moderate severity corresponding to under 1 or 1-3 years of prison, with more severe violence-related charges (Table S6, available online).

Discussion

In this study, we examined the effects of pharmacological treatment of ADHD on criminality using a quasi-experimental provider-preference instrumental variable design combined with nationwide registry data. Provider preference for pharmacological treatment varied considerably between clinics and strongly affected patients' treatment status. All categories of crime were elevated in children and adolescents with ADHD compared to the general population. IV analyses suggests that pharmacological treatment can have protective effects on violence- and public-order related crimes among patients on the margin of pharmacological treatment.

Violence and public-order crimes are often caused by reactive-impulsive behavior which is more common in ADHD,[1] and often related to social context.[31] There is no consensus on effects of pharmacological treatment of ADHD on criminality.[1,13-16] Our results are consistent with several Scandinavian studies that suggest protective effects.[2,15] A major strength to our design, relative to existing research, is that IV methods can correct for all types of unobserved confounding. Our study thus adds credible causal estimates to the evidence showing that pharmacological treatment of ADHD can reduce criminality.

Comparing estimates across studies is challenged by varying, and often not clearly stated, estimands. We presented associational estimates (using LP regressions) alongside causal estimates of the local average treatment effect (LATE).[19] Results from these two analyses differed, but so do their estimands and assumptions for causal inference. Our associational estimates are likely biased upwards as patients with severe ADHD symptoms select positively into both treatment and crime. IV analysis accounts for this selection bias, and the estimated treatment effects were considerably larger. IV estimates, strictly speaking, only refer to patients on the margin of treatment, not to the average patient. Moreover, IV also corrects for potential measurement error which otherwise attenuate LP regression estimates.

The IV estimates have large standard errors which make it difficult to detect small treatment effects and may therefore explain why the effects for which we find statistically significant evidence are substantively large. Less precision is expected as IV only uses treatment variation induced by provider preference whereas LPM uses all treatment variation. Treatments effects also became less precise over follow-up as the first stage weakens.

To our knowledge, only one other study estimates LATE for pharmacological treatment of ADHD on crime using nationwide registry data. That study found fewer contacts with police but no reduction in charges following treatment, but their sample size was relatively low for the latter analyses.[32]

This study has several strengths. Norway has a universal publicly funded healthcare system. In Norway, as in the US,[33] large geographical variation in ADHD diagnoses and medication[29,34] as well as clinicians' attitudes to ADHD diagnoses and medication[35] suggest practice variations. Since patients are assigned to clinics based on their place of residence and cannot choose their provider due to a negligible private sector, provider preferences are plausibly random with respect to patient outcomes, especially after adjusting for patient-mix, which we address with a rich set of covariates.

The use of a quasi-experimental IV design combined with rich nationwide data provides credible estimates of causal treatment effects. IV assumptions are extensively examined and supported by subject knowledge and statistical tests. Results were similar across models using LPM and 2SLS and Probit and IV Probit.[36] Treatment effects from the IV analyses are highly relevant to clinical practice. We provide evidence on whether it is beneficial to increase pharmacological treatment among patients where there likely is clinical uncertainty. Examining treatment and crime over the same time window also circumvents issues of artificial cut-offs for treatment and outcome windows.

There are also limitations to consider. First, the two overarching uncertainties regarding the IV design are whether variation in provider preference for medication truly is effectively random for patients (exogenous), and if the treatment patients receive between clinics truly differ only by medication dosage. Provider preference is arguably as good as random for patients accounting for patient-mix within our

institutional setting. However, we cannot entirely preclude provider-related common causes of the instrument and outcome.[37] Substantial geographical variation in ADHD symptom load has been ruled out.[34] Second, we cannot preclude clinic-wise variation in preference for psychosocial treatment. Receiving pharmacological treatment probably implies more contact with CAMHS. This introduces uncertainty in whether the effects are due to pharmacological treatment alone. We could not adjust for psychosocial treatment as this is not recorded in our registry data. Nonetheless, treatment effect variation by medication type showed varying effectiveness suggesting that more contact with CAMHS is an unlikely explanation. Third, ADHD is highly heritable causing familial aggregation[38] and may cause interference. Detection of ADHD and treatment of one child may cause parents to suspect ADHD and medication benefits in siblings. We did not have access to sibling data. However, this would have to be a strong mechanism to cause concern, and to our knowledge there is no strong evidence of this. Fourth, monotonicity in provider-preference IV designs have been challenged as defiers may exist due to clinicians' varying balancing of risks and benefits.[39] Analyses, however, supported a monotonic relationship between patient's treatment and providers' preference. Fifth, there may be measurement error related to using filled prescriptions from pharmacies for treatment and provider preference. Moreover, the general problem of underreported crimes, whether due to non-detection or non-reporting, cannot be addressed with our register data. These data are typically more reliable for some crimes (e.g., drugs) than others (e.g., theft that may be prevalent in persons with ADHD). However, Norwegian register data on consumed prescriptions do not exist and data on criminal charges are often considered to more accurately reflect societal crime relative to convictions.[40]

Reducing crime in ADHD populations is an important priority for society and in the interest of the individual patients and their immediate family. The observed variation in rates of pharmacological treatment of ADHD is likely partly caused by variation in provider preferences, that is variation in clinicians' attitudes to medication in patients with ADHD,[34,35] and the clinical implication of this study may be affected by clinicians' position on the ADHD controversy. Clinicians with a liberal attitude to ADHD medication are typically concerned about adverse long-term outcomes in untreated ADHD, including for example elevated

risk of criminality. They are optimistic that pharmacological treatment may reduce such adverse outcomes. These findings may be taken as empirical support of the liberal position on pharmacological treatment in ADHD. On the contrary, clinicians with a restrictive position on pharmacological treatment are concerned about over-treatment, medicalization, and unnecessary side effects. They may question if pharmacological treatment in an additional 8 to 14 children with ADHD is justified to prevent a public-order or violence-related criminal charge among one of these children. Most public-order and violence-related charges were of low to moderate severity (Table S6, available online), which is of relevance in treatment decisions. The lack of support for protective effects of medication in the remaining categories of crime may be read as supporting the restrictive position. Nonetheless, clinical decision-making for pharmacological treatment of ADHD relies on many considerations, of which crime reduction is one.

In conclusion, this is the first study to demonstrate causal effects of pharmacological treatment of ADHD on some types of crimes in a population-based natural experiment. Pharmacological treatment of ADHD reduced crime related to impulsive-reactive behavior in patients with ADHD on the margin of treatment, while no effects were found in crimes requiring criminal intent, conspiracy, and planning.

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	ADHD diagnosis (n = 5,624)		General population (n = 50,271)	
Individual characteristics				
Age at diagnosis, mean ± SD[a]	13.5	± 2.5	14.0	± 2.6
Male persons, no. (%)	3,714	(66.0)	24,705	(51.1)
Country of birth, no. (%)				
Norway	4,405	(78.3)	35,601	(70.8)
Europe	767	(13.6)	7,340	(14.6)
Outside Europe	452	(8.0)	7,330	(14.6)
Crime before diagnosis, no. (%)	417	(7.4)	888	(1.8)
Psychiatric comorbidity, no. (%)	1,515	(27.0)	-	-
Family characteristics				
Parents' labor income (USD), mean ± SD[b]				
Labor income, father	49,746	± 36,020	60,496	± 55,342
Labor income, mother	24,912	± 22,150	29,658	± 24,432
Parents' highest education, no. (%)				
University long, father	213	(3.8)	4,856	(9.7)
University short, father	644	(11.5)	9,855	(19.6)
High school, father	2,699	(48.0)	22,753	(45.3)
Primary school, father	1,827	(32.5)	9,812	(19.5)
University long, mother	119	(2.1)	2,837	(5.6)
University short, mother	1,062	(18.9)	14,304	(28.5)
High school, mother	2,449	(43.6)	19,732	(39.3)
Primary school, mother	1,900	(33.8)	10,916	(21.7)
Parents' civil status, no. (%)				
Unmarried, father	1,412	(25.5)	8,463	(16.8)
Married, father	2,698	(48.0)	31,252	(62.2)
Other, father	1,154	(20.5)	7,112	(14.2)
Unmarried, mother	1,560	(27.7)	9,155	(18.2)
Married, mother	2,706	(48.1)	31,242	(62.2)
Other, mother	1,248	(22.2)	7,824	(15.6)
Catchment area characteristics				
Youth crime (≥1 charge), % ± SD	3.0	± 0.7	3.0	± 0.7
Youth immigrants, % ± SD	24.9	± 10.6	27.8	± 13.0
Parents' primary school education, % ± SD	8.0	± 4.7	8.8	± 5.9
Parents' married, % ± SD	61.5	± 6.4	62.9	± 6.3
Parents' labor income (USD), mean ± SD	50,663	± 8,527	52,375	± 11,337
High school dropout, % ± SD	25.6	± 5.1	24.9	± 5.5
Population (0-65+ yrs.), mean ± SD	33,060	± 38,126	36,600	± 38,413

Table 1. Baseline characteristics for patients with ADHD and the general population, aged 10 to 18 in 2009-2011 (N = 55,896)

Note: Attention-deficit/hyperactivity disorder (ADHD) diagnosis when in contact with CAMHS 2009-11, and matched general population excluding those in contact with CAMHS 2009-11. CAMHS = child and adolescent mental health services; no. = number; NOK = Norwegian kroner; SD = standard deviation; USD = US dollar; yrs. = years.

[a]Plus-minus values are mean ± SD. Age at diagnosis corresponds to age at inclusion for the general population.

[b]Yearly with USD/NOK exchange rate average for 2010 (USD 1/NOK 6.0453).

	ADHD diagnosis, no. (%)						Matched general population, no. (%)						Risk ratios comparing ADHD to general population					
	Male persons (n=3,664)		Female persons (n=1,867)		Total persons (n=5,531)		Male persons (n=24,994)		Female persons (n=23,673)		Total persons (n=48,667)		Male persons		Female persons		Total persons	
Crime													RR	95 % CI	RR	95 % CI	RR	95 % CI
Any crime	1,410	(38.48)	343	(18.37)	1,753	(31.69)	4,714	(18.86)	1,300	(5.49)	6,014	(12.36)	2.28	[2.18, 2.39]	3.35	[3.00, 3.73]	2.71	[2.60, 2.84]
Drug	603	(16.46)	149	(7.98)	752	(13.60)	1,648	(6.59)	325	(1.37)	1,973	(4.05)	2.96	[2.72, 3.23]	5.78	[4.79, 6.97]	3.69	[3.41, 3.99]
Violence	497	(13.56)	74	(3.96)	571	(10.32)	770	(3.08)	118	(0.50)	888	(1.82)	4.99	[4.48, 5.56]	7.90	[5.93, 10.52]	6.05	[5.46, 6.69]
Traffic	593	(16.18)	79	(4.23)	672	(12.15)	1,985	(7.94)	350	(1.48)	2,335	(4.80)	2.39	[2.20, 2.60]	2.85	[2.24, 3.62]	2.77	[2.56, 3.01]
Public-order	516	(14.08)	74	(3.96)	590	(10.67)	1,368	(5.47)	257	(1.09)	1,625	(3.35)	3.14	[2.86, 3.45]	3.62	[2.81, 4.66]	3.57	[3.26, 3.90]
Property	367	(10.02)	114	(6.11)	481	(8.70)	635	(2.54)	442	(1.87)	1,090	(2.24)	4.04	[3.56, 4.58]	3.28	[2.68, 4.00]	3.89	[3.50, 4.32]
Sexual	115	(3.14)	1	(0.05)	116	(2.10)	132	(0.53)	8	(0.03)	140	(0.29)	5.80	[4.51, 7.45]	1.60	[.20, 12.79]	7.11	[5.56, 9.09]
Other	361	(9.85)	31	(1.66)	392	(7.09)	630	(2.52)	88	(0.37)	718	(1.48)	4.26	[3.75, 4.83]	4.43	[2.95, 6.64]	5.05	[4.48, 5.70]

Table 2. Attention-Deficit/Hyperactivity Disorder (ADHD), General Population, and Risk of Criminal Charges Over 8 years Follow-up After 2009-11 (N=54,198)

Note: Patients diagnosed with ADHD in 2009-2011 and general population excluding those in contact with CAMHS in 2009-2011 aged 10 to 18 at time of inclusion followed for 8 years, excluding those who either died (n=95) or emigrated (n=1,603). Age-adjusted risk ratios. CAMHS = child and adolescent mental health services; no. = number; RR = risk ratio.

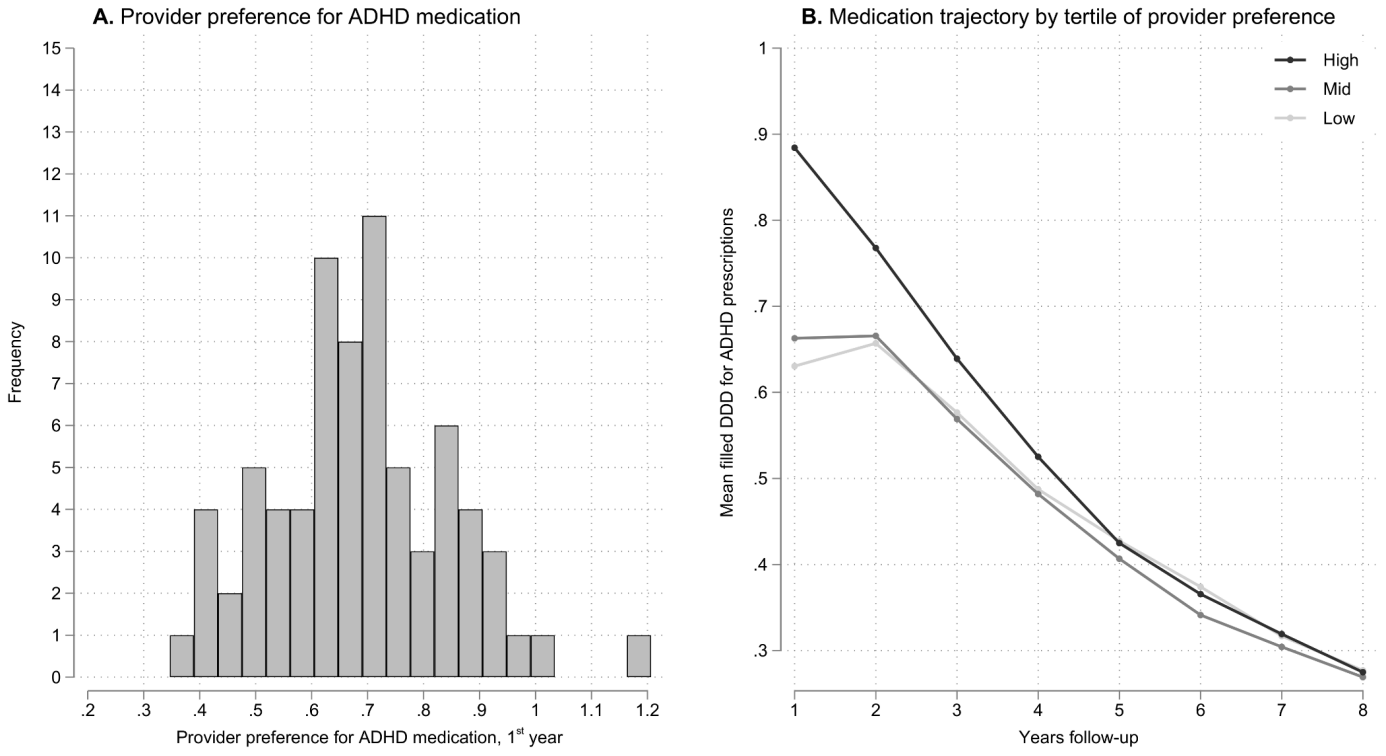

Figure 1. Variation Between Clinics in Attention-Deficit/Hyperactivity Disorder (ADHD) Medication Among Patients Diagnosed With ADHD

Note: A: Provider preference for ADHD medication at clinic level as mean defined daily doses for ADHD medication first year after ADHD diagnosis among patients on *x*-axis. Provider preference is scaled so value one equals 365 DDD. B: Medication trajectories. Yearly mean filled ADHD medication after diagnosis by tertiles of clinics' medication preference. Abbreviations: ADHD = attention-deficit/hyperactivity disorder; DDD = daily defined doses.

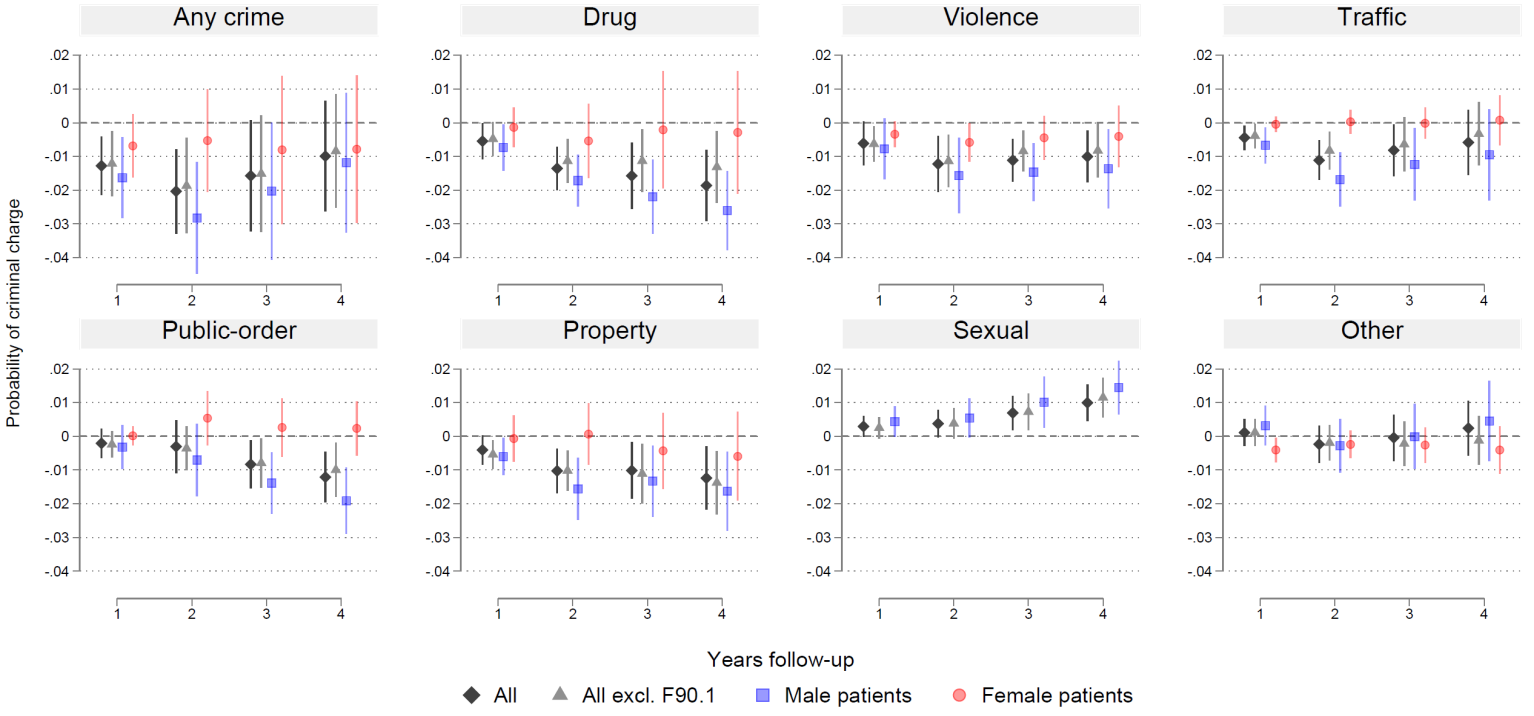

Figure 2. Associations Between Attention-Deficit/Hyperactivity Disorder (ADHD) Medication and Criminal Charges From Linear Probability Models

Note: Patients with ADHD diagnosis in Norway 2009-2011 aged 10 to 18 at time of diagnosis. Coefficient plots for regressions with 95% confidence intervals from LPM adjusted for patient mix. Abbreviations: ADHD = attention-deficit/hyperactivity disorder; excl. = excluding; LPM = linear probability model.

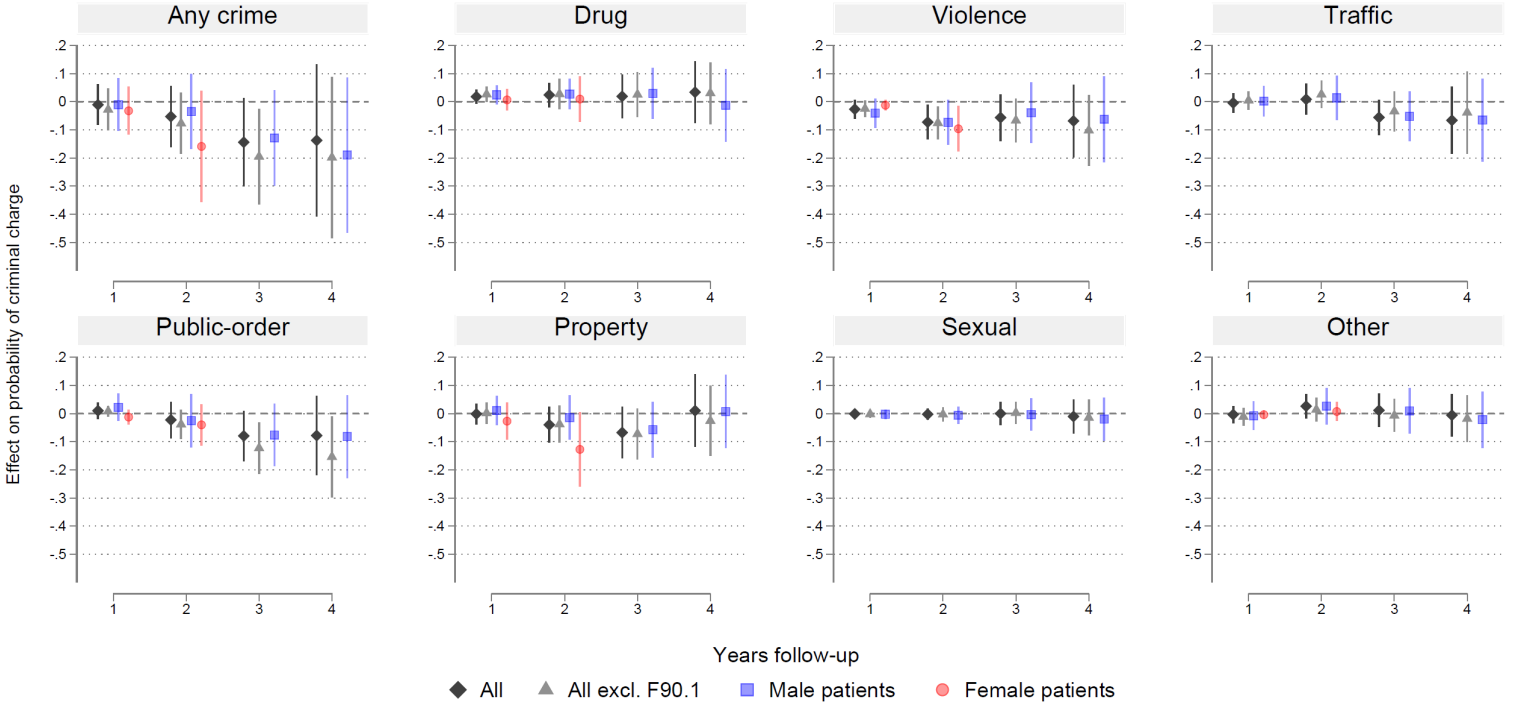

Figure 3. Effect Estimates of Attention-Deficit/Hyperactivity Disorder (ADHD) Medication on Criminal Charges From Instrumental Variable Analyses

Note: Patients diagnosed with ADHD in Norway 2009-2011 aged 10 to 18 at time of diagnosis. Coefficient plots for regressions with 95% confidence intervals. Two stage least squares (2SLS) estimates adjusted for patient mix. Abbreviations: ADHD = attention-deficit/hyperactivity disorder; excl. = excluding.

Study I
Supplementary

Online supplementary to

Effect of Pharmacological Treatment of ADHD on Criminality

Data

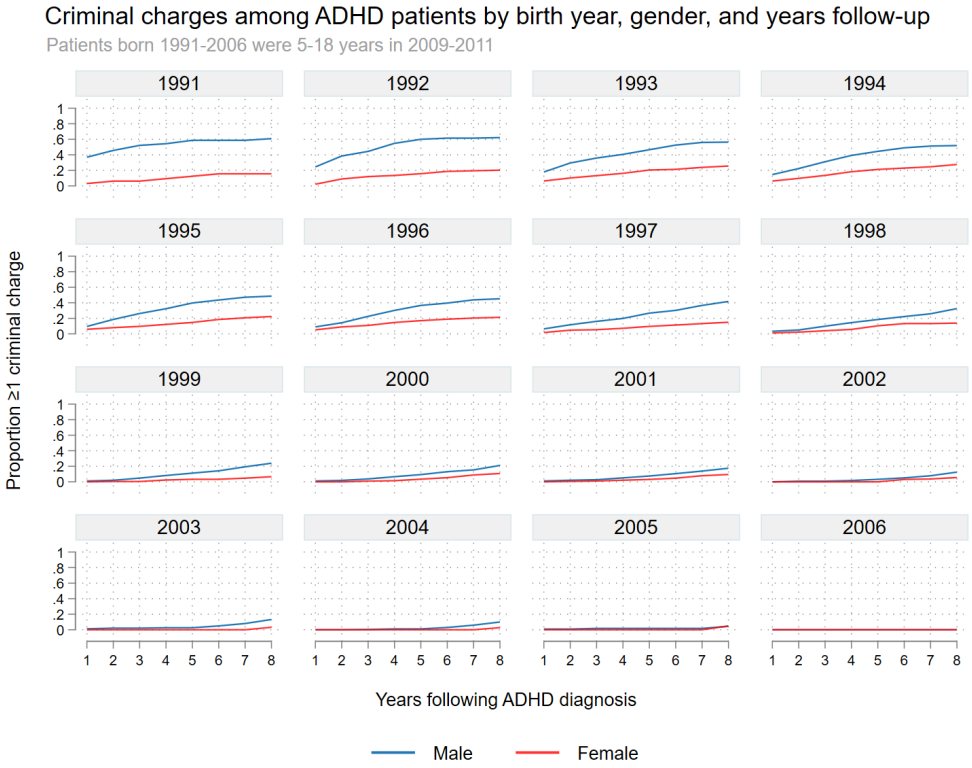

Figure S1. Criminal charges by birth cohorts, gender, and years follow-up.

	5-14 years	15-17 years	18-20 years	21-24 years
All decisions	2 391	4 740	9 815	11 220
Dismissed, not criminally responsible	2 391	27	64	99
Transferred to juvenile mediation	0	920	347	212
Conditional discharge	0	1 077	327	179
Fine	0	1 544	6 018	6 855
Indictment	0	640	2 402	3 013

Table S1. Criminal charges by decision and age group, 2012. Data from Statistics Norway Table 09420: Charged persons, by the police's decision (https://www.ssb.no/statbank/table/09420). Juvenile mediation in Norwegian is organized by The National Mediation Service (NMS) (https://konfliktraadet.no/en/about-us/). Persons under age 15 will be charged but their charge will be dismissed as persons under age 15 are considered not criminally responsible by Norwegian law. Indictment/fines combined comprise the main category: 46% in 15-17 years, 86% in 18-20 years, and 88% in 21-24 years.

	All decisions (no.)	Solved (no.)	Clearance rate (%)
Any crime	359 803	170 416	47.4
Drug	49 813	43 144	86.6
Traffic	48 641	38 921	80.0
Public-order	36 153	26 109	72.2
Violence	31 887	16 939	53.1
Sexual	4 211	2 242	53.2
Other	45 463	18 774	41.3
Property	143 635	24 287	16.9

Table S2. Clearance rate by type of crime, 2012. Charges included in solved cases. "Other" includes Statistics Norway categories "property damage", "other crimes" (e.g., nature and environmental), and "other crimes of acquisition" (e.g., deception, fraud, embezzlement). Data from Statistics Norway Table 09405: All investigated crimes (https://www.ssb.no/statbank/table/09405). Additional information on Statistics Norway classification of crimes can be found at: https://www.ssb.no/klass/klassifikasjoner/146/koder.

Covariates	Data source
Patients	
Age	Norwegian Patient Registry
Sex	Norwegian Patient Registry
Year of contact	Norwegian Patient Registry
Comorbidity	Norwegian Patient Registry
Country of origin	Central Population Registry
Crime before diagnosis/include	Central Penal and Police Registry
Emigration	Central Population Registry
Death	Norwegian Cause of Death Registry
Family	
Parents labor income	Income, Tax, and Wealth Registry
Parents education level	Norwegian Education Database
Parents marital status	Central Population Registry
Catchment area	
Youth crime	Central Penal and Police Registry
Youth immigration	Central Population Registry
Parents labor income	Income, Tax, and Wealth Registry
Parents education level	Norwegian Education Database
Parents marital status	Central Population Registry
High school dropout rate	Statistics Norway
Population	Statistics Norway

Table S3. Data sources for covariates.

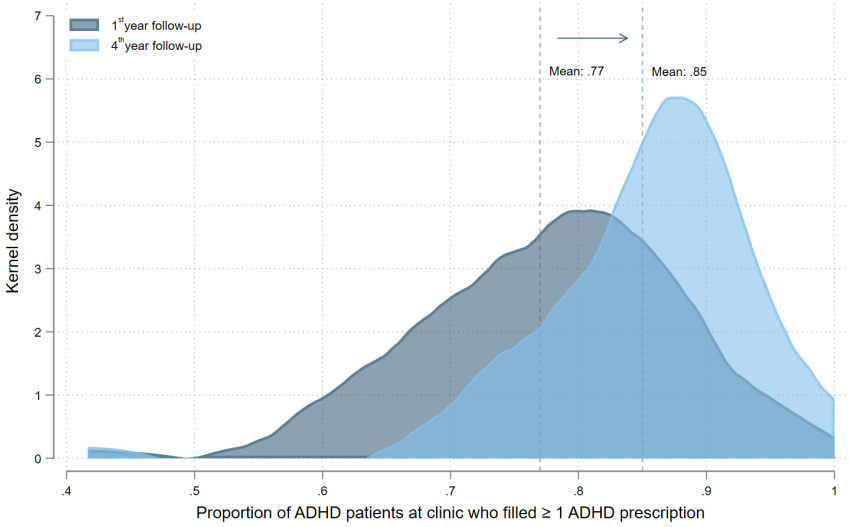

Figure S2. Provider variation in proportion of patients who filled ≥ 1 ADHD prescription the first and fourth year of follow-up, clinic-level (n=73).

Supplement 1: Instrumental variable analysis

A valid provider preference IV needs to (1) predict treatment (relevance), (2) only affect crime through treatment (exclusion), (3) be effectively randomized to patients (independence), (4) only affect patient's treatment in one direction (monotonicity). Also, the stable unit treatment value assumption (SUTVA) require (i) no interference (patient's treatment status do not affect other patients' potential outcomes) and (ii) no treatment variation.[1, 2] Relevance can be empirically verified, while the remaining assumptions must be justified by substantive knowledge and falsification tests. Relevance is tested with the IV's F-statistic in a first stage regression between treatment and the IV. F-statistic values above 10 are typically considered strong, although recent literature points to a threshold of 104.[3] *Exclusion* is met as there are no strong plausible pathways between provider preference and crime except through treatment and is empirically tested by reduced form estimates in the general population sample where provider preference should not affect crime. *Independence* is met net of patient-mix and is empirically tested by examining covariate balance for the IV. *Monotonicity* is plausibly met as no strong reasons imply many "defiers" (i.e. patients who received more medication in providers with low medication preference who simultaneously would receive less medication among providers with high medication preference) and is tested by examining the relationship between treatment and the IV.[4]

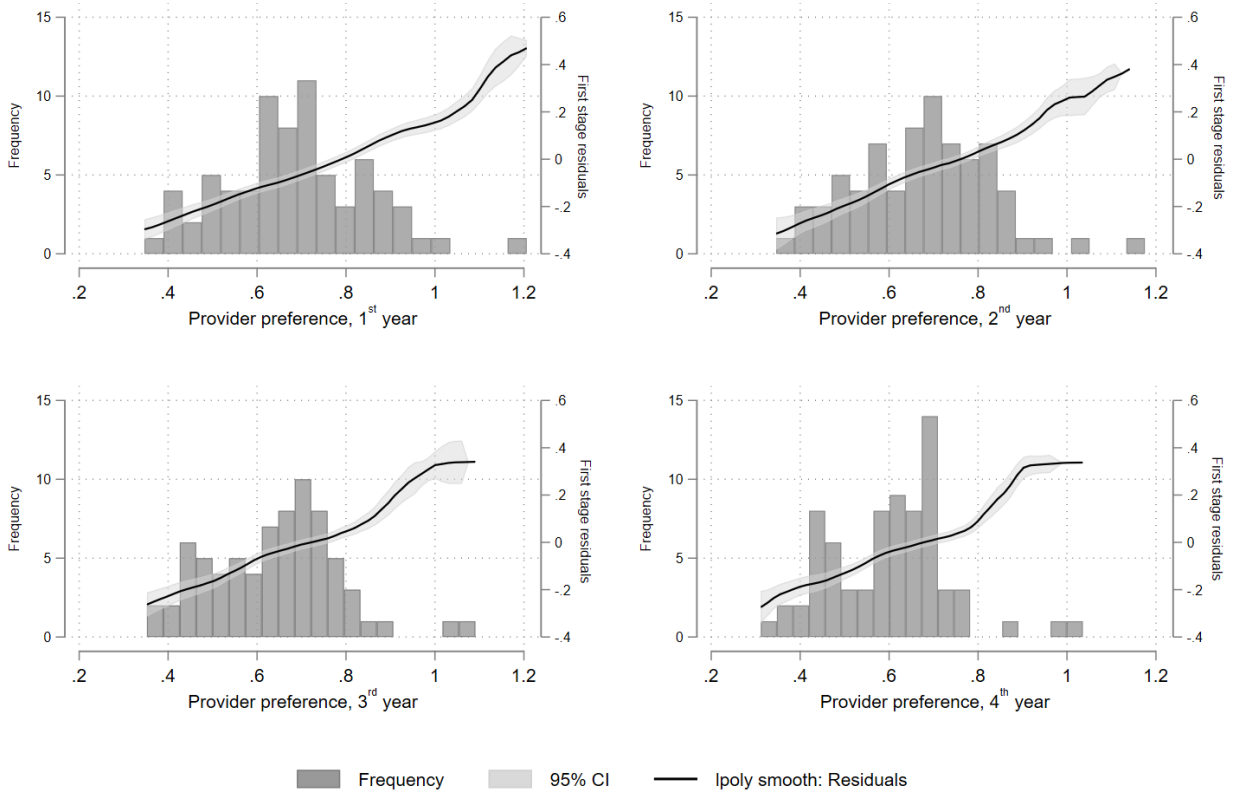

Figure S3. Variation between clinics in ADHD medication among patients diagnosed with ADHD for the first to fourth year following ADHD diagnosis. Provider preference for ADHD medication at clinic level as mean defined daily dosages for ADHD medication by years after ADHD diagnosis among patients on *x*-axis. Residuals from first stage regressions of treatment on IV plotted against values of IV with local polynomial regression line and residual values on right side *y*-axis.

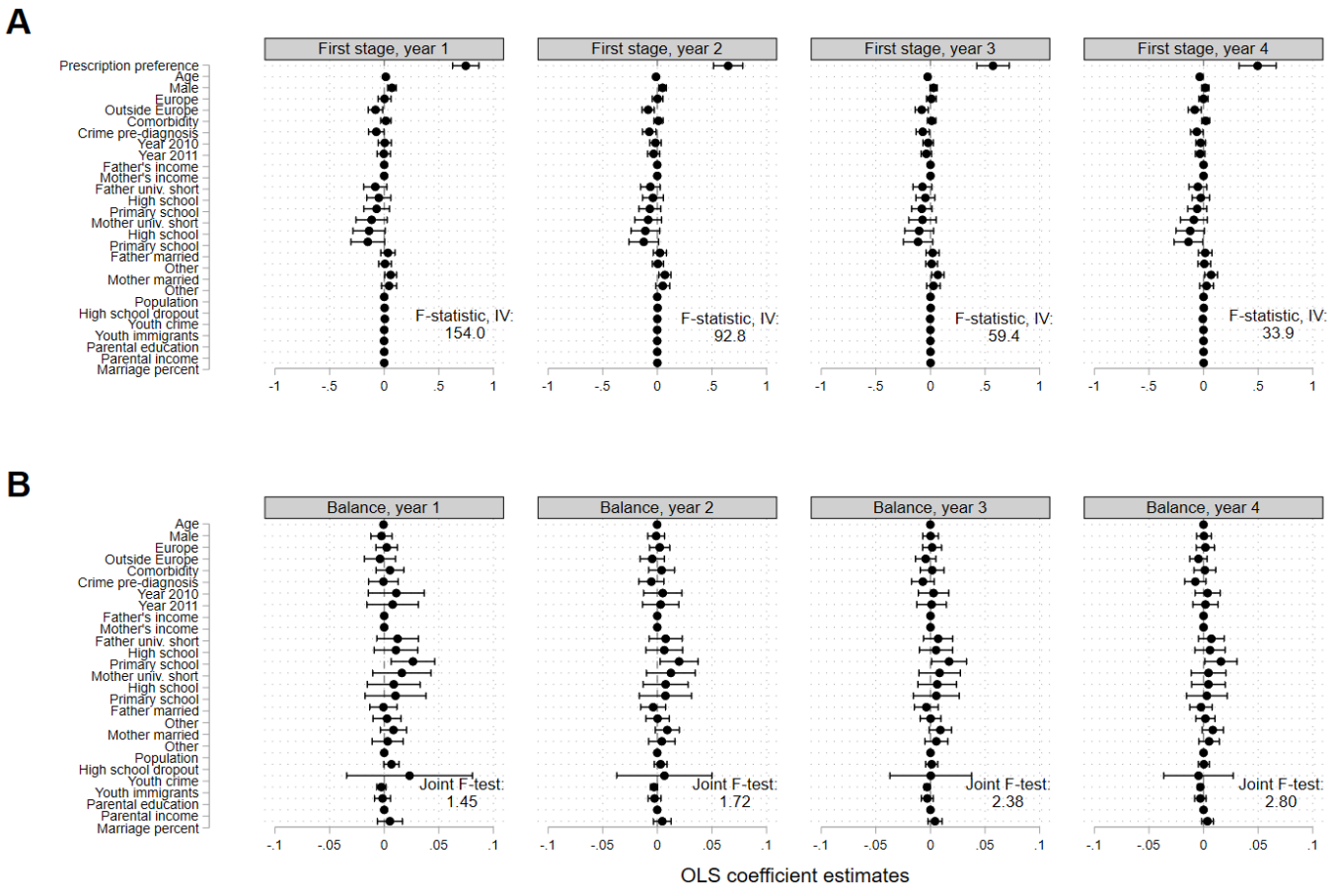

Figure S4. First stage and balance. Coefficient plots from linear regressions with standard errors clustered at clinics. First stage F-statistic for instrumental variable and joint F-test reported.

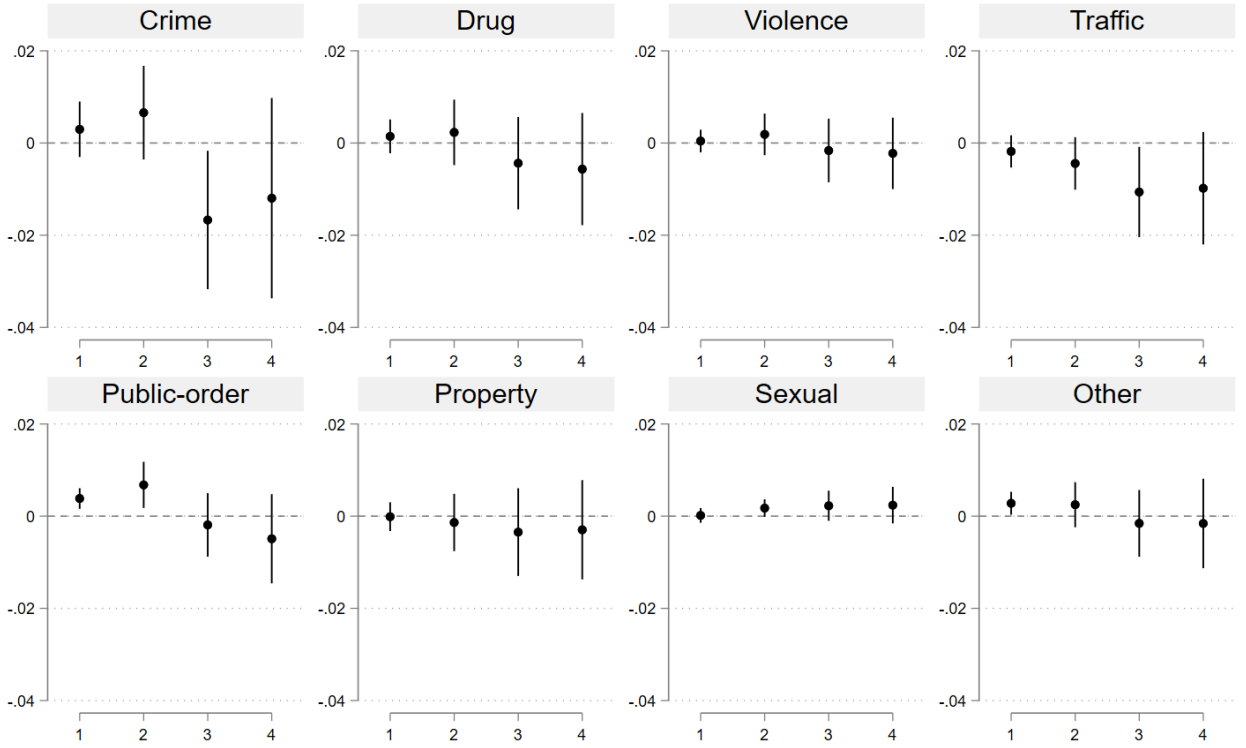

Figure S5. Reduced form estimates. Associations between provider preference for ADHD medication and crime in the general population sample. Coefficient plots with 95% confidence intervals based on linear probability models.

Crime and risk ratios at four years follow-up

	1st year			2nd year			3rd year			4th year		
	Male (n=3707)	Female (n=1908)	Total (n=5415)	Male (n=3700)	Female (n=1904)	Total (n=5604)	Male (n=3697)	Female (n=1901)	Total (n=5598)	Male (n=3691)	Female (n=1896)	Total (n=5587)
Any crime	279 (7.53)	67 (3.51)	346 (6.16)	458 (12,38)	118 (6,20)	576 (10.28)	652 (17.64)	156 (8.21)	808 (14,43)	840 (22.76)	204 (10.76)	1044 (18.69)
Drug	58 (1.56)	19 (1.00)	77 (1.37)	127 (3,43)	38 (2,00)	165 (2.94)	202 (5.46)	56 (2.95)	258 (4,61)	289 (7.83)	78 (4.11)	367 (6.57)
Violence	98 (2.64)	13 (0.68)	111 (1.98)	158 (4,27)	32 (1,68)	190 (3.39)	221 (5.98)	36 (1.89)	257 (4,59)	281 (7.61)	51 (2.69)	332 (5.94)
Traffic	43 (1.16)	5 (0.26)	48 (0.85)	102 (2,76)	10 (0,53)	112 (2.00)	168 (4.54)	17 (0.89)	185 (3,30)	240 (6.50)	30 (1.58)	270 (4.83)
Public-order	64 (1.73)	8 (0.42)	72 (1.28)	122 (3,30)	19 (1,00)	141 (2.52)	192 (5.19)	29 (1.53)	221 (3,95)	267 (7.23)	32 (1.69)	299 (5.35)
Property	78 (2.10)	31 (1.62)	109 (1.94)	134 (3,62)	48 (2,52)	182 (3.25)	192 (5.19)	65 (3.42)	257 (4,59)	241 (6.53)	79 (4.17)	320 (5.73)
Sexual	15 (0.40)	0 (100)	15 (0.27)	25 (0,68)	0 (100)	25 (0.45)	40 (1.08)	0 (100)	40 (0,71)	61 (1.65)	0 (100)	61 (1.09)
Other	73 (1.97)	6 (0.31)	79 (1.41)	127 (3,43)	8 (0,42)	135 (2.41)	172 (4.65)	12 (0.63)	184 (3,29)	215 (5.82)	16 (0.84)	231 (4.13)

Table S4. Criminal charges by type of crime, sex, and years follow-up for patients aged 10 to 18 years at time of ADHD diagnosis (n, %).

Type of crime	Risk ratio [95% CI]	
Any crime	3.21	[3.02, 3.42]
Drug	4.43	[3.95, 4.97]
Violence	7.10	[6.19, 8.15]
Traffic	2.95	[2.59, 3.36]
Public-order	3.92	[3.45, 4.45]
Property	4.10	[3.60, 4.67]
Sexual	8.32	[5.89, 11.75]
Other	5.45	[4.65, 6.40]

Table S5. Risk ratio with 95% confidence intervals for crime in ADHD patients (n=5,587) vs. general population (n=49,547) ages 10 to 18 after 4 year follow-up.

Supplement 2: Subgroup analyses in LPM models

Increased pharmacological treatment was associated with reductions in any charges for all patients, patients excluding F90.1, and males. Pharmacological treatment was also associated with reductions in charges related to drugs, violence, traffic, public-order, and property, whereas there was support for positive associations with sexual-related charges. These findings were consistent across all patients, patients excluding F90.1, and males, but not females. Analyses by medication type revealed the same overall findings for stimulant medication (Figure S8), whereas non-stimulant medication had more positive associations (Figure S9). Results from analysis by age group 14 to 18 at time of diagnosis (Figure S10) and only patients with F90.1 (Figure S7) was also relatively consistent with the overall findings.

Probit models

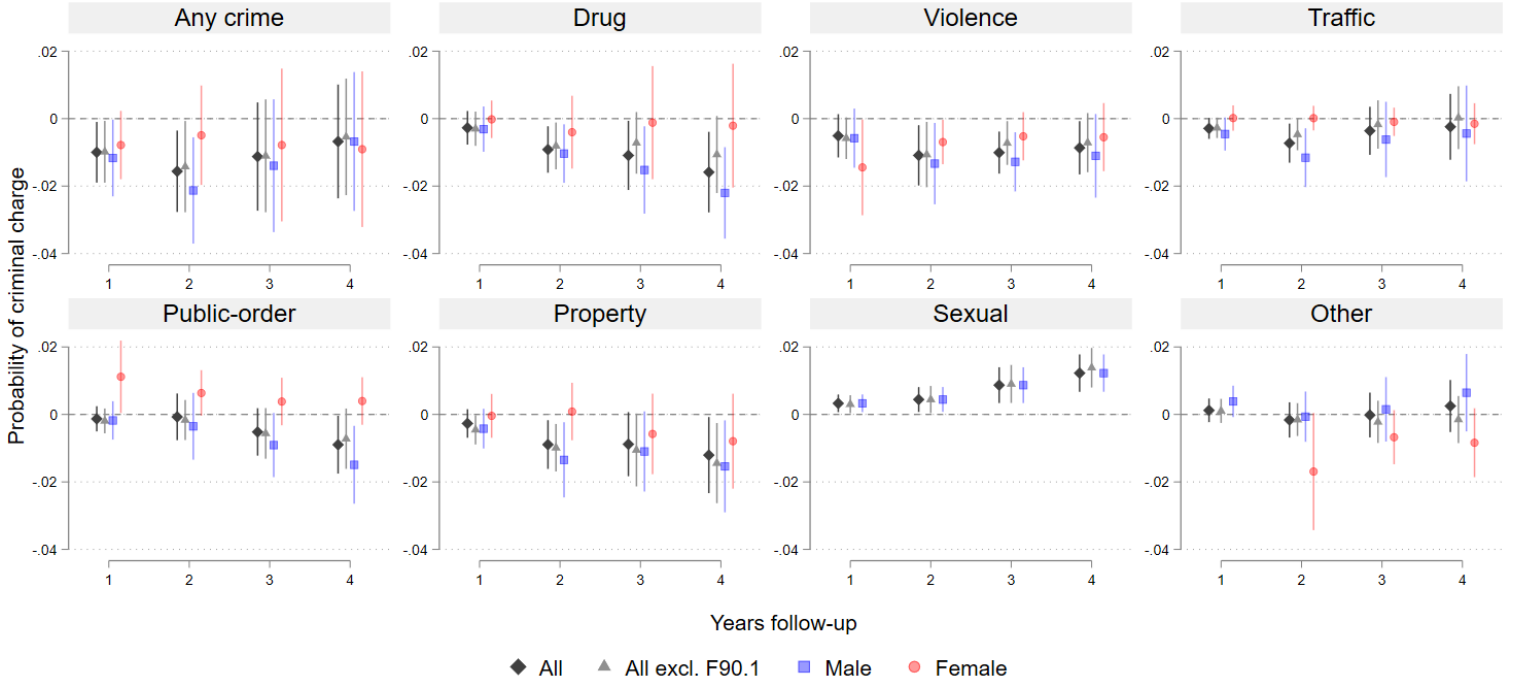

Figure S6. Probit models for associations between pharmacological treatment of ADHD and crime.

LPM subgroup analyses

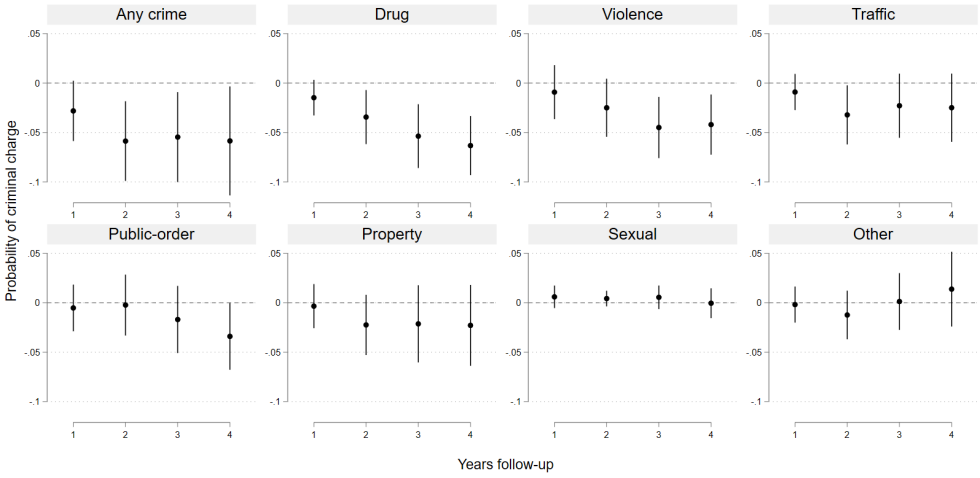

Figure S7. LPM patients with only F90.1.

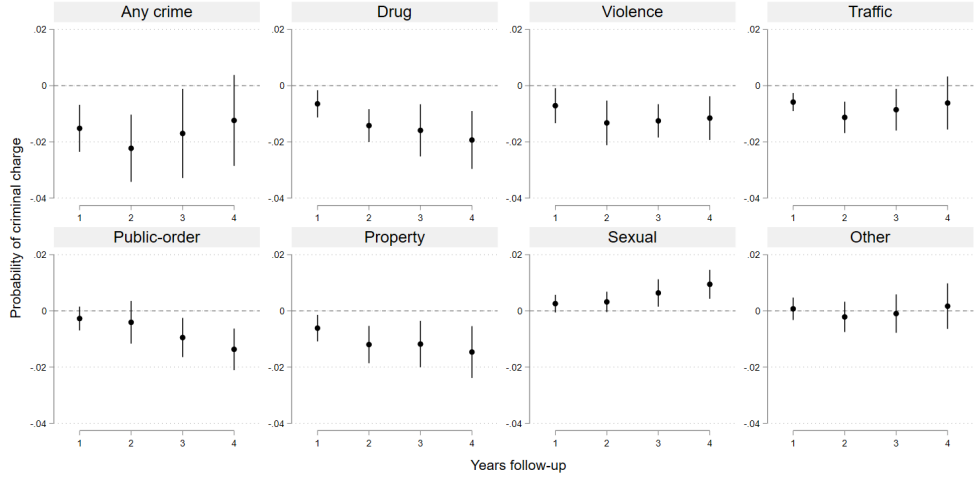

Figure S8. LPM stimulant medication.

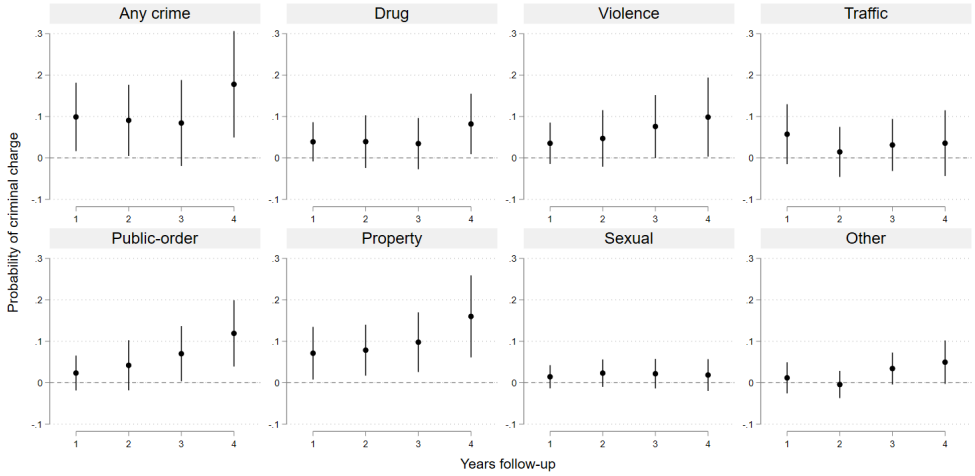

Figure S9. LPM non-stimulant medication.

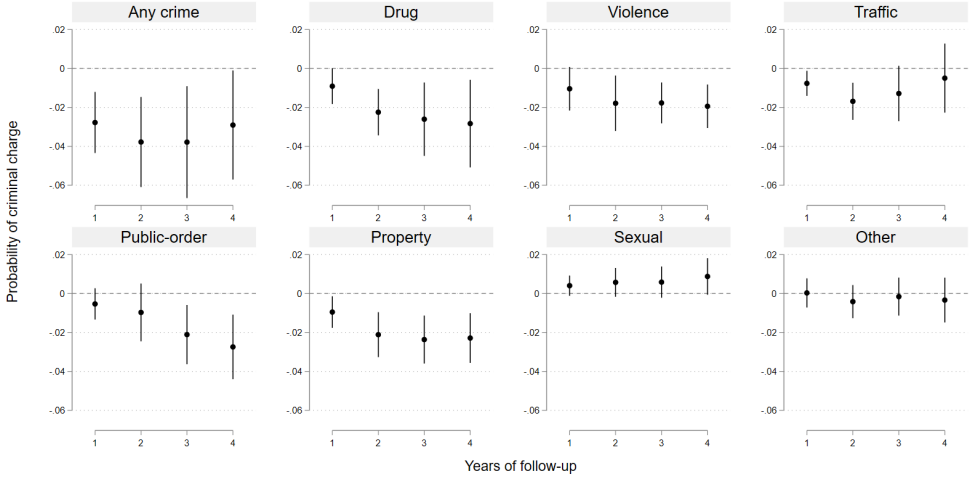

Figure S10. LPM ages 14 to 18.

IV Probit models

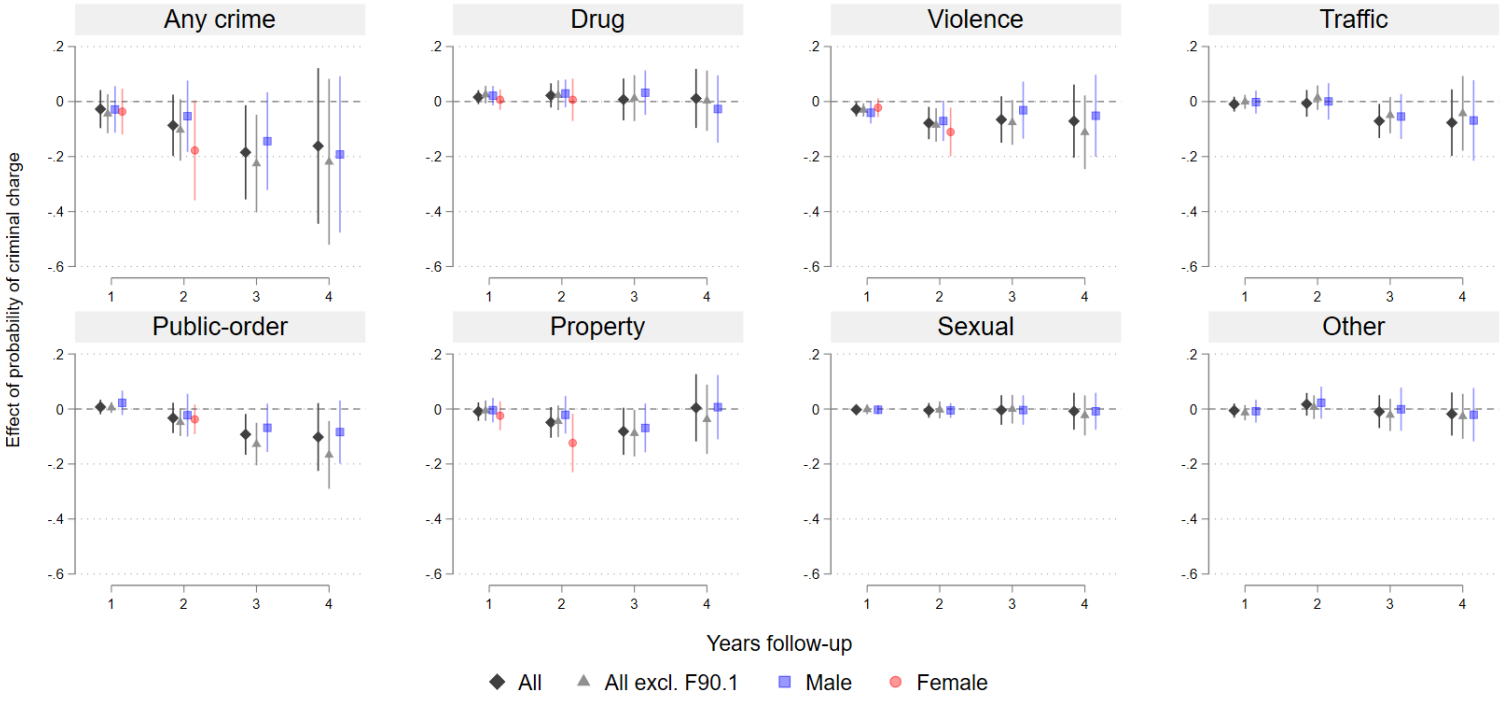

Figure S11. IV Probit models for effects of pharmacological treatment of ADHD on the probability of crime.

2SLS subgroup analysis

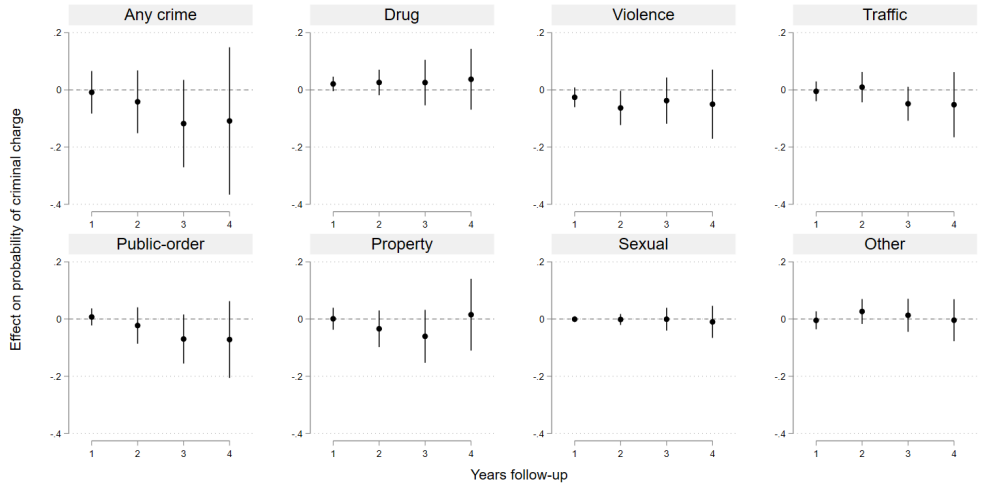

Figure S12. 2SLS Stimulant medication.

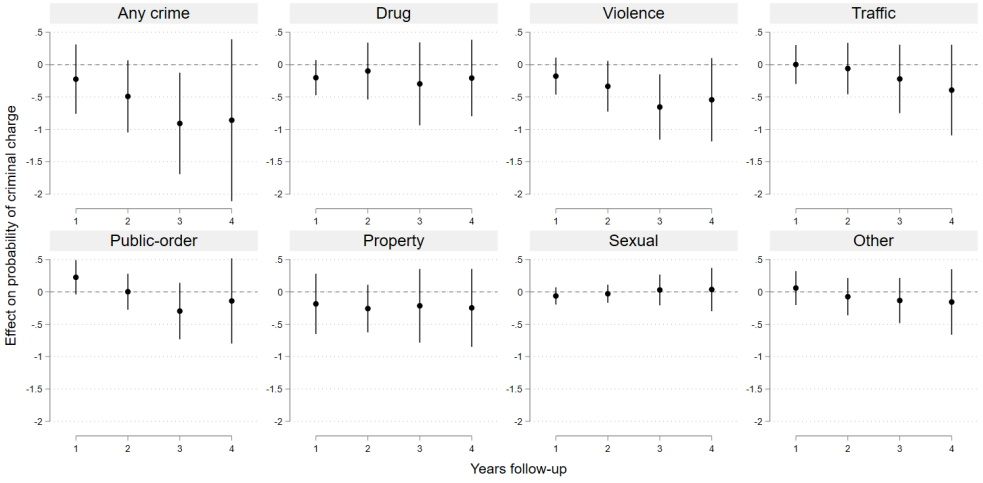

Figure S13. 2SLS Non-stimulant medication.

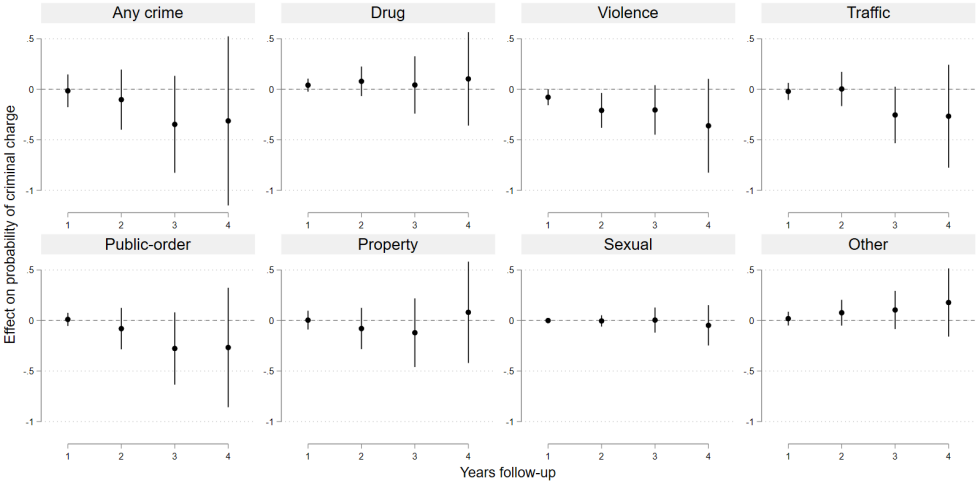

Figure S14. 2SLS aged 14 to 18.

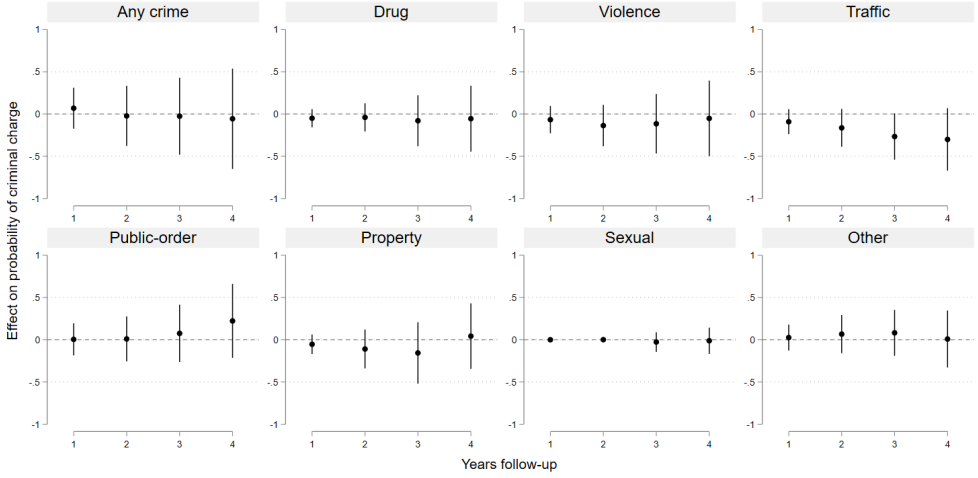

Figure S15. 2SLS only F90.1.

Severity of criminal charges

	Any crime	Violence	Public-order
Group: ADHD			
Under 1 year	66.1	48.7	73.4
Over 1 year	26.3	36.6	25.1
Over 3 years	6.4	13.6	1.5
Over 10 years	1.2	1.1	0.1
Mean (SD)		1.4 (0.7)	
Group: General population			
Under 1 year	75.9	51.6	85.7
Over 1 year	19.1	26.4	13.4
Over 3 years	4.1	20.1	1.0
Over 10 years	1.0	1.8	0
Mean (SD)		1.3 (0.6)	

Table S6. Severity of crime by Statistics Norway's four categories of severity based on maximum prison sentences (i.e., punishment for crimes after convictions following a criminal procedure), where value 1 is least severe and value 4 is most severe. Category "over 3 years" and above are considered serious crimes.

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Study II

Effect of ADHD Medication on Risk of Injuries:

The ADHD Controversy Project

Tarjei Widding-Havneraas[1,2*], Felix Elwert[3,4], Simen Markussen[5], Henrik Daae Zachrisson[6],

Ingvild Lyhmann[1,2], Ashmita Chaulagain[1,2], Ingvar Bjelland[2,7], Anne Halmøy[2,7],

Knut Rypdal,[1] Arnstein Mykletun[1,8,9,10]

Affiliations:

[1] Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital, Bergen, Norway

[2] Department of Clinical Medicine, University of Bergen, Bergen, Norway

[3] Department of Sociology, University of Wisconsin-Madison, Madison, WI, USA

[4] Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison, Madison, WI, USA

[5] Ragnar Frisch Centre for Economic Research, Oslo, Norway

[6] Department of Special Needs Education, University of Oslo, Oslo, Norway

[7] Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

[8] Division of Health Services, Norwegian Institute of Public Health, Oslo, Norway

[9] Department of Community Medicine, University of Tromsø, Tromsø, Norway

[10] Centre for Work and Mental Health, Nordland Hospital, Bodø, Norway

[*] Corresponding author: Tarjei Widding-Havneraas (tarjei.widding-havneras@uib.no)

For: *American Journal of Epidemiology*

Word count: 3594

CRediT

TW: Conceptualization, methodology, data curation, formal analysis, visualization, funding acquisition, project administration, writing-original draft. FE: Conceptualization, methodology, writing-review & editing. SM: Conceptualization, supervision, methodology, writing-review & editing. HZ: Conceptualization, supervision, methodology, writing-review & editing. IL: writing-review & editing. AC: writing-review & editing. IB: Conceptualization, supervision, writing-review & editing. AH: Conceptualization, supervision, writing-review & editing. KR: funding acquisition, project administration, writing-review & editing. AM: Conceptualization, funding acquisition, methodology, supervision, project administration, writing-review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

TW is supported by funding from the Western Norway Regional Health Authority (912197), Research Council Norway (288585/IAR), and Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital. HZ, SM, FE, IL, AC, IB, AH was supported by Research Council Norway (288585/IAR). AM supported by Research Council Norway (288585/IAR), and Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital. HZ also supported by funding from the European Research Council Consolidator Grant ERC-CoG-2018 EQOP [grant number 818425].

Abstract

ADHD is associated with an increased risk of injury. Causal evidence for effects of pharmacological treatment on injuries is scarce. We estimated effects of ADHD medication on injuries using variation in provider preference as an instrumental variable (IV). Using Norwegian registry data, we followed 8,051 patients who were diagnosed with ADHD aged 5 to 18 between 2009 and 2011 and recorded their ADHD medication and injuries treated in emergency rooms and emergency wards up to four years after diagnosis. Persons with ADHD had an increased risk of injuries compared to the general population (RR 1.35; 95% CI: 1.30-1.39), with higher risk in females (RR 1.47; 95% CI: 1.38-1.56) than males (RR 1.23; 95% CI: 1.18-1.28). There was considerable variation in provider's preference for ADHD medication between clinics, with the 90th percentile having a 1.79 times higher prescription rate than the 10th percentile. Provider preference strongly influenced patients' treatment status. Overall, there was no clear causal evidence for protective effects of pharmacological treatment on injuries among patients on the margin of treatment.

Key words: ADHD, pharmacological treatment, injury, quasi-experiment, instrumental variable

Introduction

Injuries are the worldwide leading cause of death and disability among children and adolescents.[1] Meta-analyses have found that youth with attention-deficit/hyperactivity disorder (ADHD) have a higher risk of injuries compared to those without ADHD.[2, 3] Additionally, people with ADHD have a heightened risk of suicide attempts [4], suicide, and injury-related death.[5, 6] The increased injury risk in ADHD have been attributed to the core ADHD symptoms of impulsivity, hyperactivity, inattention, and common comorbid disorders such as conduct disorder (CD) and oppositional defiant disorder (ODD).[2] Consequently, injury prevention is especially important for this high-risk group.

Randomized controlled trials (RCT) show that ADHD medication reduces short-term ADHD symptoms,[7] but no similar results exist from RCTs for reduction in injuries. Meta-analytic evidence suggests that ADHD medication can reduce injuries.[2, 8, 9] ADHD medication is associated with reductions in emergency room visits,[10] traumatic brain injuries,[11] burn injuries,[12] bone fractures,[13] transport accidents,[14] all-cause mortality,[15] with mixed evidence for suicide attempts.[16] There is less knowledge about treatment effects in children and adolescents.[17] Moreover, geographical variation in diagnosis and treatment of ADHD have led to concerns about under- and overtreatment caused by clinical practice variation.[18-21] There are calls for more knowledge about treatment effects among persons who may receive treatment due to varying clinical practice which likely concerns patients with milder symptoms.[22] Such knowledge can be obtained by using a quasi-experimental provider preference IV design combined with population-wide data with several years follow-up.

We use idiosyncratic variation in provider preference for pharmacological treatment across clinics as an instrumental variable (IV) to identify causal effects of pharmacological treatment of ADHD on the risk of injuries among patients on the margin of treatment. Between-clinics variation in provider preference represent a source of "as good as" randomization to treatment for these patients and we thus circumvent unmeasured confounding and obtain treatment effects for a clinically relevant population. Only two other

studies have used provider preference as an IV for effects of ADHD medication on injuries. A Danish study finds protective effects of medication on hospital visits that may be driven by a reduction in injuries, although estimates are imprecise.[23] Similarly, a US Medicaid claims-based study finds that ADHD medication reduces the yearly incidence of injuries and injury spending.[24] Thus, more causal knowledge is needed about treatment effects on long-term functional outcomes, such as injuries, and in particular among persons who may be treated differently due to varying clinical practice.[22, 25-27]

The main aim of this study is to estimate the effect of pharmacological treatment of ADHD on injuries for patients on the margin of treatment by use of such a design. We use registry data for the entire Norwegian population to estimate the causal effect of ADHD medication injuries up to four years following diagnosis through a provider preference IV design.

Methods

Sample

Our ADHD patient sample includes all patients who were diagnosed with ADHD for the first time between the ages of 5 and 18 in 2009-2011 (n=8,051) by the Norwegian Child and Adolescent Mental health Services (CAMHS), as registered in the Norwegian patient registry (NPR). The ADHD patient sample consists of persons diagnosed with ICD-10 Hyperkinetic disorder, i.e., F90.0 (81.3%), F90.1 (11.3%), F90.8 (6.2%), and F90.9 (1.1%). Additionally, we constituted a general population sample aged 5-18 without contact with CAMHS in 2009-2011 that were matched on age, sex, and geography, and a randomly generated inclusion date in 2009-2011 (n=75,184).

Injuries

Injuries include intentional and unintentional accidental or self-inflicted physical damage caused by sudden or cumulative transfers of energy.[28] We used data on all contacts for injuries treated at emergency rooms

(ER) in primary care (mainly outpatient clinics) registered in the Norwegian Control and Payment of Health Reimbursements Database (KUHR) and emergency wards (EW) in secondary care (i.e., hospitals) registered in the Norwegian Patient Register (NPR). Contacts at ER are coded according to the International Classification of Primary Care, 2nd edition (ICPC-2). We defined cumulative indicators for any injury-related contact at ER or EW taking value one if registered with an injury code, and zero otherwise, separately for each of the first four years following diagnosis. We defined three primary outcomes: any injuries at either ER or EW, only ER, and only EW. For ER-related contacts, we also defined a set of indicators for types of injuries by body part based on a categorization developed by the Norwegian Institute of Public Health: head, fracture, sprain, burn, poison, penetration, ear, eye, other (ICPC-2 codes in Table S1), also including suicide-related contacts. EW-related contacts included contacts for injuries, self-harm, or violence/assault.

ADHD medication

We used data for filled ADHD prescriptions from the Norwegian Prescription Database for ADHD medications as defined by the Norwegian Institute of Public Health (percent of total ADHD prescriptions in parenthesis). Stimulants included Metylphenidate (N06BA04, 87.5%), Dexamphetamine (N06BA02, 0.8%), Lisdexamfetamine (N06BA12, 0.06%), Amphetamine (N06BA01, 0.04%), while non-stimulants included Atomoxetine (N06BA09, 11.54%). Pharmacological treatment was defined as the cumulative number of daily defined doses (DDD) filled for any ADHD prescription over one to four years after being diagnosed with ADHD. Treatment was scaled to make one unit increase correspond to an increase from 0 to full-time pharmacological treatment over follow-up.

Covariates

We included covariates for patients, their families, and the clinics' catchment area to adjust analyses for patient mix and catchment area characteristics. Patient covariates was measured at baseline and catchment

area covariates was measured between 2009 and 2011. The following variables were adjusted for: age, sex, comorbid diagnosis at time of diagnosis, country of birth (Norway, Europe, Outside Europe), year of contact with clinic, injuries prior to ADHD diagnosis, child protection service intervention prior to ADHD diagnosis, and parents' labor income and highest education when the child was 6 years (primary school, high school, short- and long university education) and marital status (married, unmarried, other (widowed, divorced, separated)). Catchment area characteristics included population size, high school dropout rates and, using aggregated measures from the general population sample: percent of youth immigrants, parents' labor income, parents' education level, mother's marriage rate (overview of data sources, Table S2).

Statistical analyses

We computed risk ratios for any injury and types of injuries at four-years follow-up for patients with ADHD relative to the matched sample with generalized linear models. Linear probability models (LPM) were used to estimate associations between pharmacological treatment and injuries.[29] The estimand is the average treatment effect on the treated (ATT). Causal interpretation of LPM estimates requires that the exposure is assumed to be conditionally random given covariates.[30] This is unlikely and motivates our IV design. Analyses were conducted on multiple samples: all patients and stratified by sex due to potentially important differences in ADHD and injury, by stimulants/non-stimulants as effectiveness may differ, and in patients aged 5-12 and 13-18 at time of diagnosis (median-split).

The IV design used the observed variation in pharmacological treatment between clinics as quasi-randomization to pharmacological treatment net of patient-mix.[31] Consider two similar patients at two clinics with varying treatment preference: one patient is not treated while the other is treated due to a stronger treatment preference. Treatment effects, then, concern patients on the margin of treatment, leaving out patients where there is strong clinical consensus on treatment. The estimand is the local average treatment effect (LATE), which is the average treatment effect among patients on the margin for pharmacological treatment who receive treatment due to their provider's preference.[29]

In the Norwegian healthcare system, pharmacological treatment initiation is within the discretion of psychiatrists who collaborate in teams at clinics. To measure provider preference, we calculate the average number of defined daily doses (DDD) for filled ADHD prescriptions for patients with ADHD at clinic level. We selected a four-year time frame as the IV was sufficiently strong only during these years. We show medication over a 8-year period in Figure 2B to illustrate the long-term development. Provider preference was measured as a leave-one-out average to exclude any potential impact an individual patient may have on the preference they are exposed to. The IV was scaled in the same manner as the treatment. IV analyses were conducted on the same samples as LPM. IV rely on the important assumptions.[31, 32] Relevance is tested with the *F*-statistic from the first stage. Exclusion is examined by reduced form analyses based on the general population sample. Independence is examined with tests of covariate balance over values of the IV. Monotonicity is investigated by examining the association between treatment and provider preference (more details, Supplementary section 1.2). Estimation of LATE was based on two-stage least squares (2SLS). As robustness checks, we estimated models using Probit.[33] We also examined robustness of results by excluding a subset of patients who had filled prescriptions prior to their sample inclusion date. Standard errors were clustered by clinics. All analyses were done in Stata 17[34] and coefficient plots was made with *coefplot*.[35] We followed reporting guidelines for IV analyses[36] and preregistered (ISRCTN: blinded) and protocolled our analyses (reference blinded).

Results

Descriptive statistics

	ADHD diagnosis when in contact with CAMHS 2009-11 (n = 8,051)	General population, excluding those in contact with CAMHS 2009-11 (n = 75,184)
Patient characteristics		
Age at diagnosis, mean ± SD[1]	11.7 ± 3.4	11.6 ± 4
Male, no. (%)	5,566 (69.1)	38,505 (51.2)
Country of birth, no. (%)		
Norway	6,263 (77.8)	52,618 (70.0)
Europe	1,080 (13.4)	11,204 (14.9)
Outside Europe	707 (8.8)	11,362 (15.1)
Injury before diagnosis, no. (%)	4,768 (58.2)	34,469 (45.9)
Child protection service before diagnosis, no. (%)	1,379 (17.13)	1,614 (2.2)
Comorbidity, no. (%)	2,003 (24.9)	-
Family characteristics		
Parents' labor income (USD), mean ± SD[2]		
Labor income, father	54,900 ± 40,410	69,311 ± 66,870
Labor income, mother	28,374 ± 24,879	35,929 ± 29,999
Parents' highest education, no. (%)		
University long, father	316 (3.9)	8,143 (10.8)
University short, father	994 (12.4)	15,859 (21.1)
High school, father	3,849 (47.8)	33,673 (44.8)
Primary school, father	2,561 (31.8)	14,028 (18.7)
University long, mother	221 (2.8)	5,398 (7.2)
University short, mother	1,629 (20.2)	23,549 (31.3)
High school, mother	3,437 (42.7)	28,264 (37.6)
Primary school, mother	2,640 (32.8)	15,031 (20.0)
Parents' civil status, no. (%)		
Unmarried, father	2,356 (29.3)	15,432 (20.5)
Married, father	3,767 (46.8)	46,622 (62.0)
Other, father	1,474 (18.3)	9,050 (12.0)
Unmarried, mother	2,526 (31.4)	16,503 (22.0)
Married, mother	3,785 (47.0)	46,549 (61.9)
Other, mother	1,604 (19.9)	9,829 (13.1)
Catchment area characteristics		
Youth immigrants, % ± SD	26.8 ± 10.5	30.0 ± 13.0
Parents' primary school education, % ± SD	7.9 ± 4.6	9.0 ± 6.0
Parents' married, % ± SD	60.4 ± 6.3	61.6 ± 6.0
Parents' labor income (USD), mean ± SD	48,019 ± 7,192	49,858 ± 9,726
High school dropout, % ± SD	25.6 ± 4.1	24.8 ± 4.3
Population (0-65+ yrs.), mean ± SD	32,913 ± 26,765	37,696 ± 30,506

Table 1. Baseline characteristics for patients with ADHD and the general population, aged 5 to 18 in 2009-2011 (n=83,235) Note: [1]Plus-minus values are mean ± SD. [2]USD/NOK exchange rate average for 2010 (USD 1/NOK 6.0453).

Table 1 shows baseline characteristics of the ADHD patient sample and the general population sample. The ADHD sample was had more males, Norwegian background, and injuries before inclusion. Parents of patients with ADHD had lower income, education, and marriage rate. Catchment area characteristics were relatively similar.

Figure 1 shows higher rates of any injury and injury contacts at ER, but not EW, for both male and female patients with ADHD compared to the general population over 4 years follow-up. The highest risk ratios were for injuries treated at ER. Patients with ADHD and comorbid CD/ODD had somewhat higher prevalence of any injuries (37.2%) at four-years follow-up. In terms of specific types of injuries, persons with ADHD had higher risk of all types of injuries with the ER, except for burn injuries (Figure S1). The highest increased risk was for suicide-related contacts with ER, followed by self-harm and victimization-related contacts with EW (Figure S2). Outside violence-related injuries, the increased risk was highest for penetration-, poison-, and ear-related injuries. There was, however, relatively few events related to self-harm-, victimization-, poison- and ear-injuries.

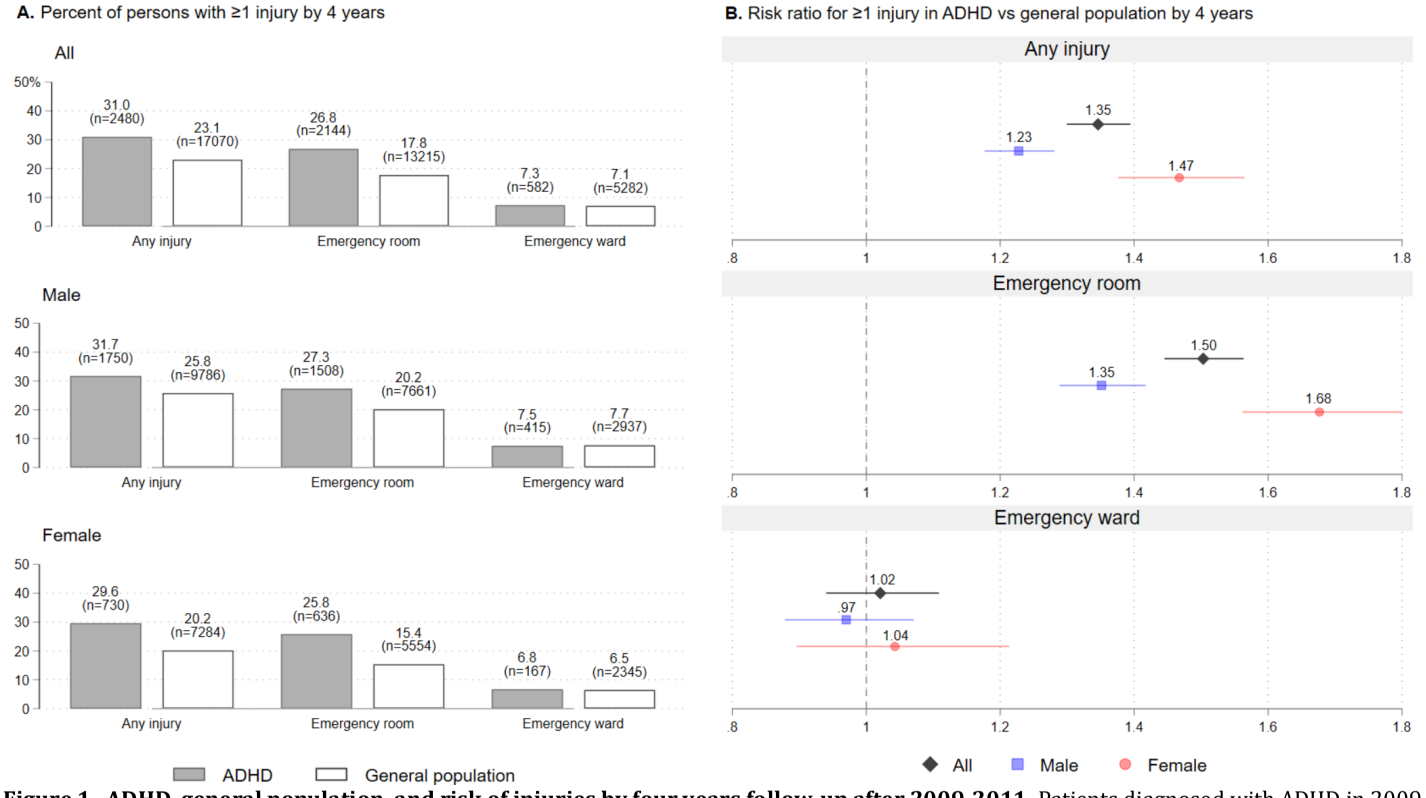

Figure 1. ADHD, general population, and risk of injuries by four years follow-up after 2009-2011. Patients diagnosed with ADHD in 2009-2011 and general population excluding those in contact with child and adolescent mental health services in 2009-2011 aged 5 to 18 at time of inclusion (unique n=83,235) excluding those who either died (n=48) or emigrated (n=1,091), and percentage reported for each bar.

Evaluation of instrumental variable

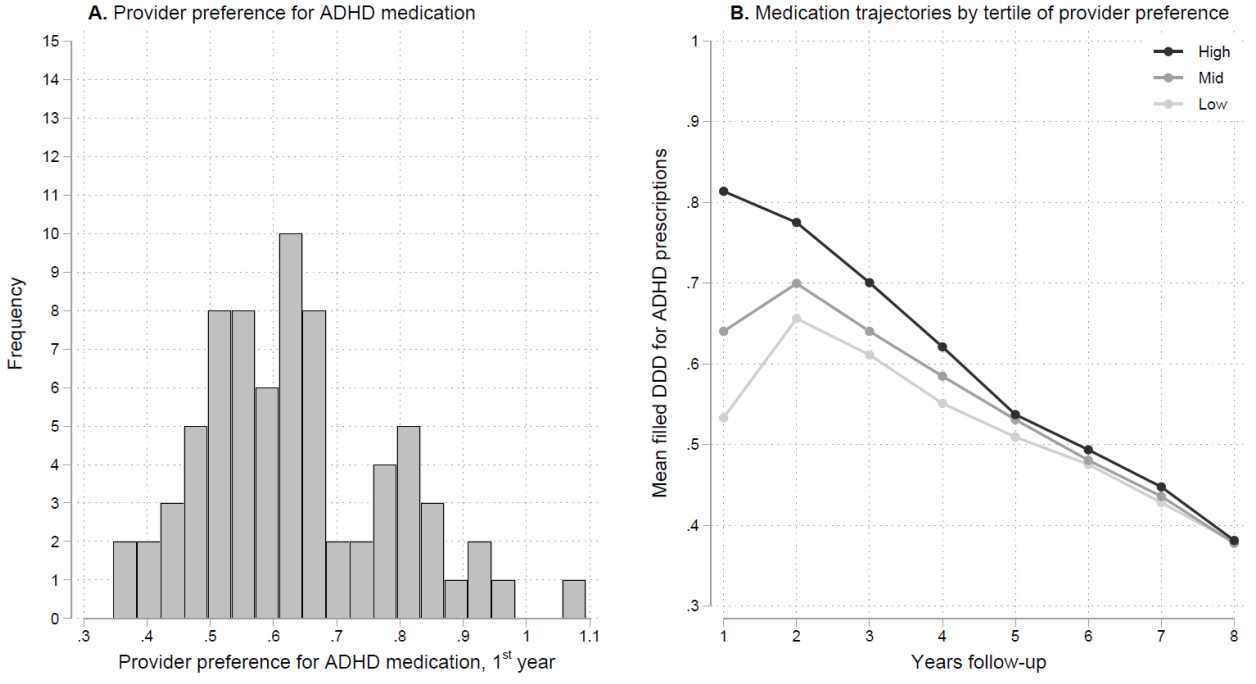

Figure 2. Variation between clinics in pharmacological treatment of ADHD among patients diagnosed with ADHD. A: Provider preference for pharmacological treatment at clinic level as mean defined daily dosages (DDD) for ADHD medication first year after patients' ADHD diagnosis on *x*-axis. B: Providers' pharmacological treatment trajectories. Yearly mean filled DDD for ADHD prescriptions after diagnosis scaled so 1 equal 365 DDD and divided into tertiles (high, mid, low) of clinics first year prescription preference.

Figure 2A shows the distribution of provider preference measured as DDD for filled ADHD prescriptions scaled by 365 (i.e., a value of 1 corresponds to 365 DDD). Median DDD was .65 (interquartile range: .25; coefficient of variation: .22). Clinics had a median of 77 patients (interquartile range: 90). 78.1% of all patients with ADHD had filled ≥1 ADHD prescription the first year after diagnosis, 87.5% by four years, and 89.9% by eight years follow-up. Figure 2B shows that variation in provider preference varies from .53 in the lowest to .81 in the highest tertile in the first year of follow-up, and subsequently converges to .55 to .62 by four years follow-up, and .38 in both tertiles by 8 years follow-up. Prescription rates remained consistently highest and lowest in the upper and lower tertile, and converged to similar values by five years. The P90/P10 ratio was 1.79 the first year and 1.65 by four years follow-up. Relevance is supported by strong first stage *F*-statistics above the conventional threshold of 10, with year one to three above the recent suggested threshold of 104.7.[37] The *F*-statistic for year one to four was 460.3, 217.3, 139.4, and 88.7 (Figure S3). The balance of covariates across the IV was relatively strong as shown by low joint *F*-statistic values (Figure S4). Provider preference was not associated with injury in the general population, supporting exclusion (Figure S5), and had a monotonic relationship with medication (Figure S6).

Figure 3 presents associations between pharmacological treatment and the probability of any injuries, injuries in ER and EW from LPMs for 1-4 years follow-up after ADHD diagnosis for all patients and by sex. There was no evidence of associations between pharmacological treatment and any injuries nor injuries treated at ERs. There was support for negative association between treatment and injuries at EWs at three-years follow-up overall (-1.0 percentage point (pp.), 95% CI -1.8 to -0.3) and for females (-1.4 pp., 95% CI -2.8 to 0.04) and four-years follow-up overall (-1.3 pp., 95% -2.4 to -0.3) and for females (-1.7 pp., 95% CI -3.8 to -0.04). Probit models provided similar results (Figure S6). There were also similar results in subgroups of persons aged below and above the median age of 12 (Figure S7). Analyses of associations by medication type showed support for the same negative association between medication and EW, while there was no support for any associations for nonstimulant medication (Figure S8). Injury-specific LPM results are reported in the supplementary (Figure S9).

Results for linear probability models and instrumental variable analyses

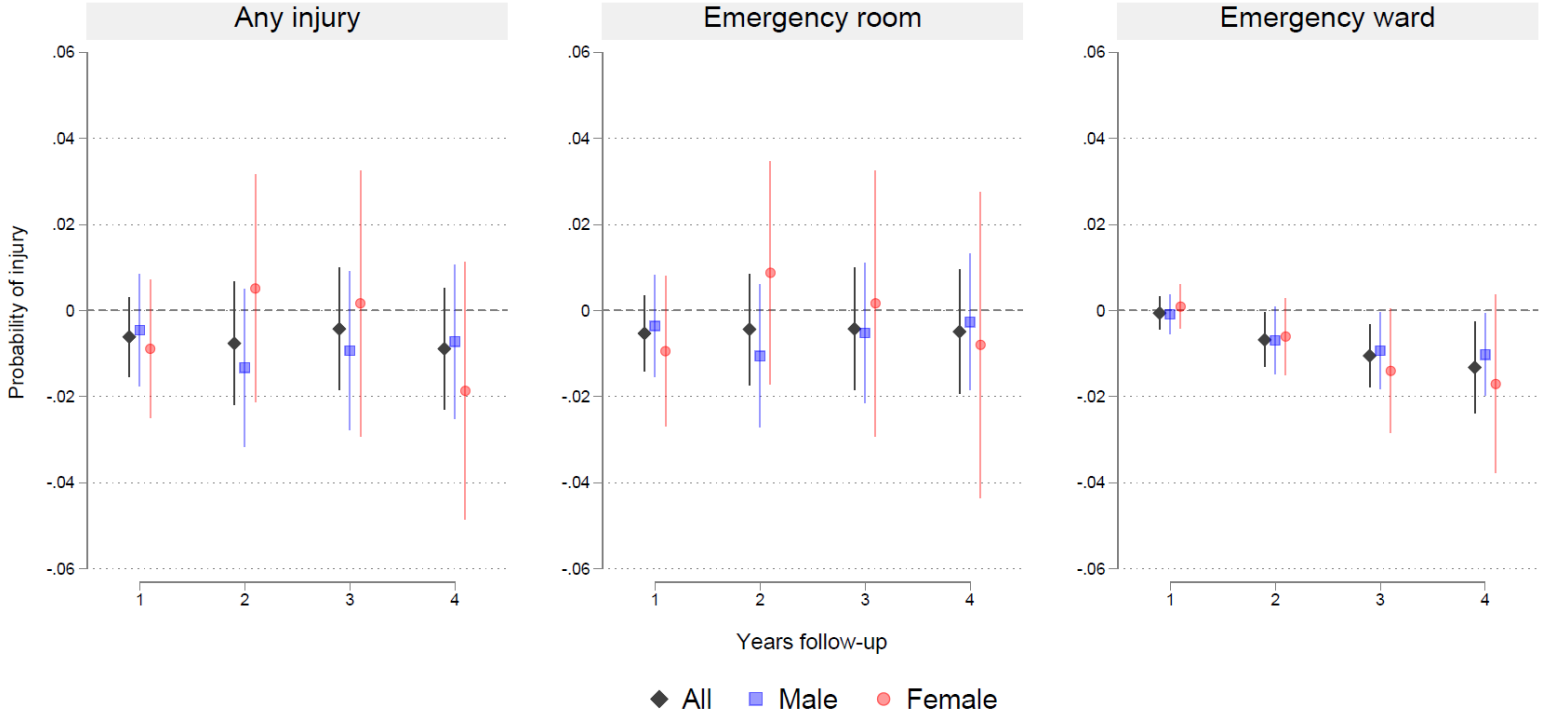

Figure 3. Associations between ADHD medication and injuries from linear probability models. Patients with ADHD diagnosis in Norway 2009-2011 aged 5 to 18 at time of diagnosis. Coefficient plots for regressions with 95% confidence intervals from LPM adjusted for patient mix.

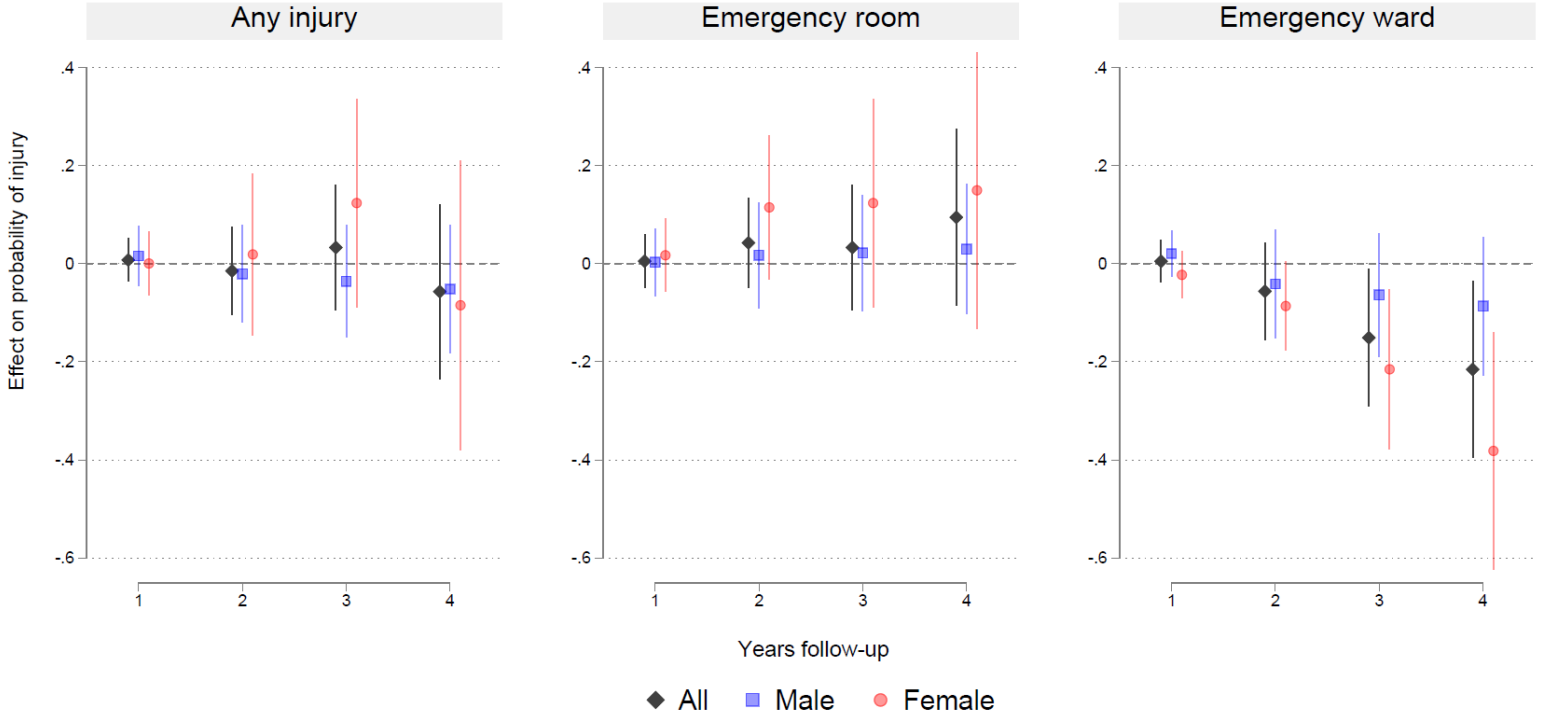

Figure 4. Effect estimates of ADHD medication on injuries from instrumental variable analyses. Patients with ADHD diagnosis in Norway 2009-2011 aged 5 to 18 at time of diagnosis. Coefficient plots for regressions with 95% confidence intervals. Two stage least squares estimates adjusted for patient mix.

Figure 4 presents estimates of LATEs from 2SLS IV models for all patients and by sex. Treatment effects were relatively imprecise with wide 95% confidence intervals. The estimated treatment effects showed no evidence of pharmacological treatment on any injuries or injuries treated in in ERs. There was support for pharmacological treatment reducing the probability of injuries in EW at three-years follow-up for all (-15.1 pp., 95% CI: -29.1 to -1.1) and at four-years follow-up for all (-21.6 pp., 95% CI: -39.5 to -3.7), which equals a number needed to treat (NNT) of 7 and 5, respectively. There was support for protective effects of medication on EW for females at three-years follow-up (-21.5 pp., 95% CI: -37.8 to -5.3; NNT: 5) and four-years follow-up (-38.2 pp., 95% CI: -62.3 to -14.0; NNT: 3). Robustness checks showed similar results, including models based on IV Probit estimation (Figure S10) and robustness analysis excluding patients who had filled one or more prescription prior to diagnosis (Figure S11).

There was no evidence of age-related variation in treatment effects (Figure S12). Results for IV analyses for stimulant medication were similar to the main IV analyses, while there was no support for any effects for nonstimulant medication (Figure S13). IV analyses for specific types of injuries indicated that pharmacological treatment reduced ER-related burn-injuries all at two- (-2.6 pp., 95% CI: -4.1 to -1.1; NNT: 38) and three-years (-3.0 pp., 95% CI: -5.3 to -0.7; NNT: 33) follow-up, and for males at two- (-3.0 pp., 95% CI: -5.1 to -0.9; NNT: 33), three- (-3.8 pp., 95% CI: -6.8 to -0.9; NNT: 26), and four-years (-4.4 pp., 95% CI: -7.8 to -0-9; NNT: 23) follow-up. There was no evidence for protective effects on other ER-related injury types (Figure S14).

Discussion

Main findings

This study estimated effects of pharmacological treatment of ADHD on injuries based on a preference-based IV design and population-wide registry data. While persons with ADHD had higher risk of injuries compared to the general population, we did not find clear evidence to support negative associations between pharmacological treatment and injuries in LP-regressions, although there was some support for EW-related injuries. Nonetheless, these results are likely affected by unmeasured confounding which we correct for in IV analysis. There was large between-clinics variation in rates of pharmacological treatment which affected patients' treatment and support for the main underlying IV assumptions. Overall, IV analyses showed no evidence for protective effects of pharmacological treatment on injuries for patients on the margin of treatment.

Findings in context

Our findings support research showing that patients with ADHD are more prone to injuries than the general population. The overall RR of 1.35 (95% CI: 1.30-1.39) for any injury in persons with vs. without ADHD is similar to meta-analytic evidence.[2] The highest incidence of injuries were in males relative to females in line with existing knowledge.[38] However, females with ADHD had a higher risk of injuries than males with ADHD, which also supports existing research[39] and a potential reason may be that ADHD is more severe when detected among females in young age.[40] We contribute with analysis showing that people with ADHD have an increased risk of multiple types of injuries in both primary and secondary care, including suicide-related contacts, self-harm, and victimization. The findings that both self-harm and victimization is overrepresented in ADHD contributes to a topic with scarce high-quality data concerning a small but clinically important subgroup. There was no clear evidence of treatment effects in estimates of the average

treatment effect on the treated (ATT) from LP-regressions. These estimates are likely biased upwards as patients with severe ADHD symptoms may be more likely to select positively into both treatment and injury.

We present novel causal evidence of effects of pharmacological treatment of ADHD on injuries in both primary and secondary care for patients on the margin of treatment. The overall lack of a preventative effects of pharmacological treatment of ADHD on injuries can be attributed to several factors. First, patients on the margin of treatment are those where there is uncertainty about whether they will benefit from medication who could credibly experience lower effectiveness of medication. Hence, the treatment effects concern a specific subgroup of patients who likely differ from the overall ADHD patient population. However, effect estimates for this patient group is relevant to clinical practice as they are informative for decision-making for patients where clinicians may come to varying conclusions about treatment. These patients, nevertheless, may be difficult to identify for the individual clinician in practice.[41] Second, the treatment effects were imprecise although we used a large nationwide sample, and we had a strong IV with support for the main underlying assumptions. Due to the imprecise estimates, however, we cannot rule out that smaller treatment effects are not detected.

Our findings for EW-related injuries align with the Danish IV analysis of medication effects in ADHD which, in line with our results, found large and imprecise protective effects warranting cautious interpretation. Moreover, the findings are also consistent with the US-based study,[24] but institutional differences may play a factor. Continuous access to Medicaid requires fulfilment of eligibility requirements, whereas we have the full population. Thus, there may be differences in the socioeconomic composition of these populations. The protective effects for EW-related injuries are at best weak evidence and should be contextualized with many tests with few statistically significant findings and no trend in overall injuries. A potential mechanism behind support for injuries at EW and not ER may be that EW-related injuries are more severe, and medication may have differential impact on these incidents. However, more knowledge is needed to support such a mechanism and we err on the side of caution by interpreting these findings in line with the other null findings.

Strengths and limitations

There are several strengths to this study. The combination of quasi-experimental IV design, extensive scrutiny of IV assumptions with statistical tests and subject matter knowledge, and comprehensive nationwide data produces treatment effects with a credible causal interpretation. The findings from the IV analysis have relevance for clinical practice as they provide evidence on long term pharmacological treatment effects for patients with clinical uncertainty.

Our study is situated within the context of the Norwegian universal healthcare system, which assigns patients to clinics based on their place of residence and has a negligible private sector. As in the United States,[42] considerable geographical variation in ADHD diagnoses and medication[19, 27] and clinicians' attitudes toward ADHD[20] suggest practice variation. Prescription preference is a more plausible IV after adjusting for patient mix, which we address with a rich set of covariates. To our knowledge, only one other study has combined a provider preference IV design with nationwide registry data to estimate the effects of pharmacological treatment for ADHD on health-related outcomes, namely any hospital contact and EW contacts.[23]

There are limitations that should be considered. First, there are uncertainties tied to the IV design. Variation in provider preference needs to be random (conditional on covariates) for patients and the variation needs to only concern variation in pharmacological treatment, which may still be uncertain. We adjusted for many variables but cannot rule all potential instrument-outcome confounding.[43] Geographical variation in ADHD symptom load is likely not a concern.[19] Second, clinics' preference for psychosocial treatment may vary which means that there could be more than one treatment. This we could not rule out due to lack of appropriate data. However, receipt of pharmacological treatment may simultaneously indicate closer follow-up with clinics. Third, due to lack of sibling data and the high heritability of ADHD,[44] we could not rule out siblings as a potential source of interference. Fourth, clinicians weigh risks and benefits in their treatment decisions and hence monotonicity may be violated in some settings.[45] However, our results supported a monotonic association between treatment and provider preference. Fifth, our sample is too small to detect

precise treatment effects. Sixth, the use of filled prescriptions may include measurement error. Seventh, we cannot check whether persons in the sample filled prescriptions prior to 2009. Finally, data on injuries may also be underreported as the data we use require persons to seek help for their injuries.[46] Due to how Norwegian injury data are registered, there is no definitive way of ensuring that the same injury may be treated in both ER and EW, where the most common injuries include severe fractures, poisonings and head injuries.[46] As well, the largest EW units in the capital (Oslo) had higher registration quality the first years of the registry. However, any geographical bias would then affect both persons with and without ADHD.

Potential implications

Our study not only highlights that persons with ADHD are a high-risk group for injuries, but also underscores the need to alleviate the burden of injury among these persons. The lack of convincing evidence for protective effects of pharmacological treatment of ADHD on injuries in this study indicates that a protective effect on injuries should not be used as an argument for pharmacological treatment of ADHD in patients on the margin on treatment. However, such treatment may have other beneficial or harmful long-term outcomes among these patients. More similar studies adressing other real-life outcomes should be conducted to improve our evidence base for treatment effects.

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Study II
Supplementary

Online supplementary to

Effect of ADHD Medication on Risk of Injuries:

The ADHD Controversy Project

1.1 Data

Category	ICPC-2 codes
Head	N79, N80
Fracture	L72, L73, L74, L75, L76
Sprain	L77, L78, L79, L80, L81, L96
Burn	S14
Poison	A84, A86
Penetration	S13, S18
Ear	H76, H77, H78, H79
Eye	F75, F76, F79
Other	S12, S15, S16, S17, S19, A80, A81, A88, B76, B77, D79, D80, N81, R87, R88, U80, X82, Y80
Suicide	P77

Table S1. Categories of injury with ICPC-2 codes. The category "Other" combines "other" and "other surface injuries".

Covariates	Data source
Patients	
Age	Norwegian Patient Registry
Sex	Norwegian Patient Registry
Year of contact	Norwegian Patient Registry
Comorbidity	Norwegian Patient Registry
Country of birth	Central Population Registry
Injury before diagnosis/inclusion	Central Reimbursement and Norwegian Patient Registry
Emigration	Central Population Registry
Death	Norwegian Cause of Death Registry
Family	
Parents labor income	Income, Tax, and Wealth Registry
Parents education level	Norwegian Education Database
Parents marital status	Central Population Registry
Catchment area	
Youth immigration	Central Population Registry
Parents labor income	Income, Tax, and Wealth Registry
Parents education level	Norwegian Education Database
Parents marital status	Central Population Registry
High school dropout rate	Statistics Norway
Population	Statistics Norway

Table S2. Data sources for covariates.

1.2 Instrumental variable analysis

Provider preference need to meet the following requirements to be considered a valid IV.[1-3] First, provider preference must predict treatment (relevance). This is tested with the F-statistic of the IV in first stage regressions. Second, provider preference can only impact injuries by its effect on treatment (exclusion). This was assessed by reduced form analyses in the general population. Third, provider preference must be as good as random for patients (independence), which we account for by including covariates for patient mix. Fourth, provider preference can only impact patients' treatment either positively or negatively (monotonicity), which is examined by analyses of the relationship between provider preference and medication. Fifth, there should be no interference nor treatment variation (stable unit treatment value assumption) which we assess through analyses of medication type.

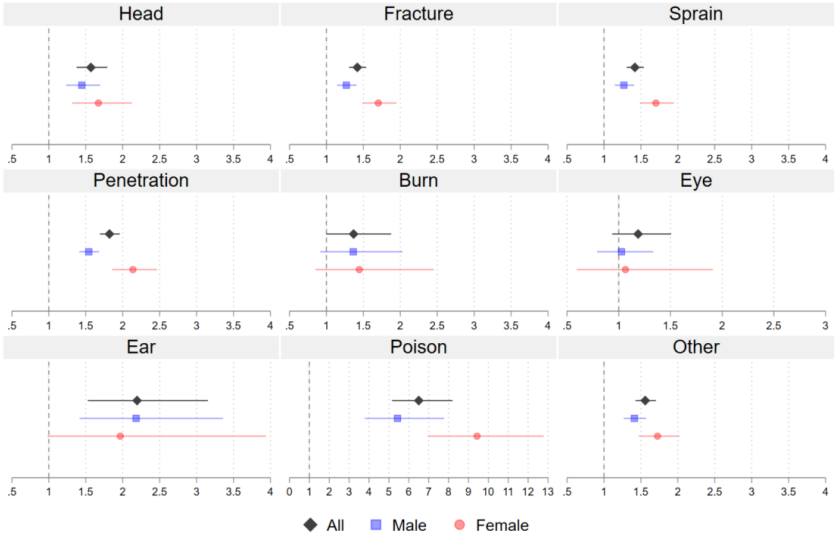

Figure S1. **Risk ratios for specific types of injuries at emergency room in persons with ADHD vs general population by 4 years follow-up.** *x*-axis differs for poison due to large estimates (but also low frequency of events).

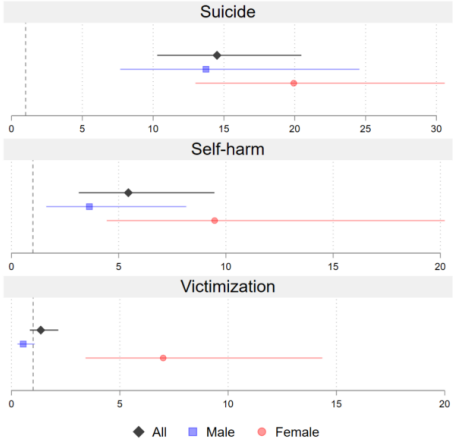

Figure S2. Suicide, self-harm, victimization. Suicide-related contacts at ER and self-harm- and victimication-related contacts at EW.

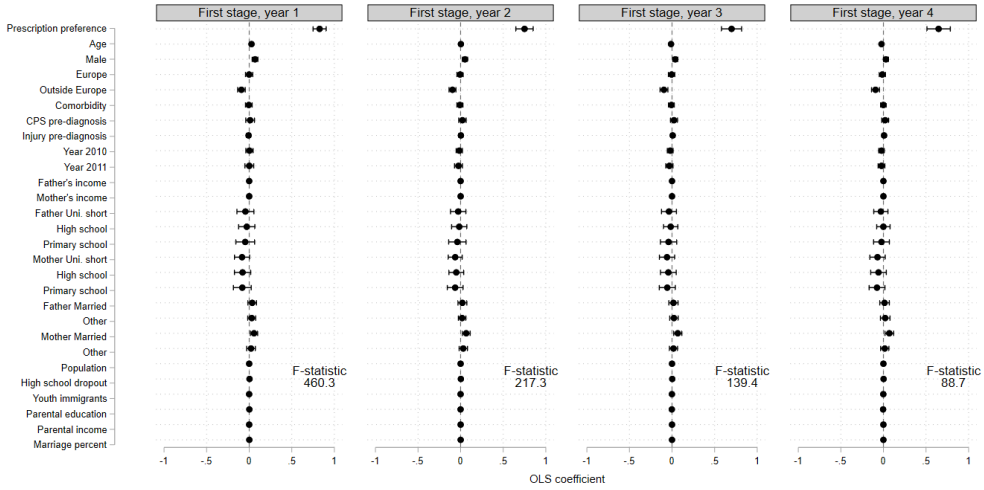

Figure S3. Coefficient plot for first stage results with *F*-statistics for the IV.

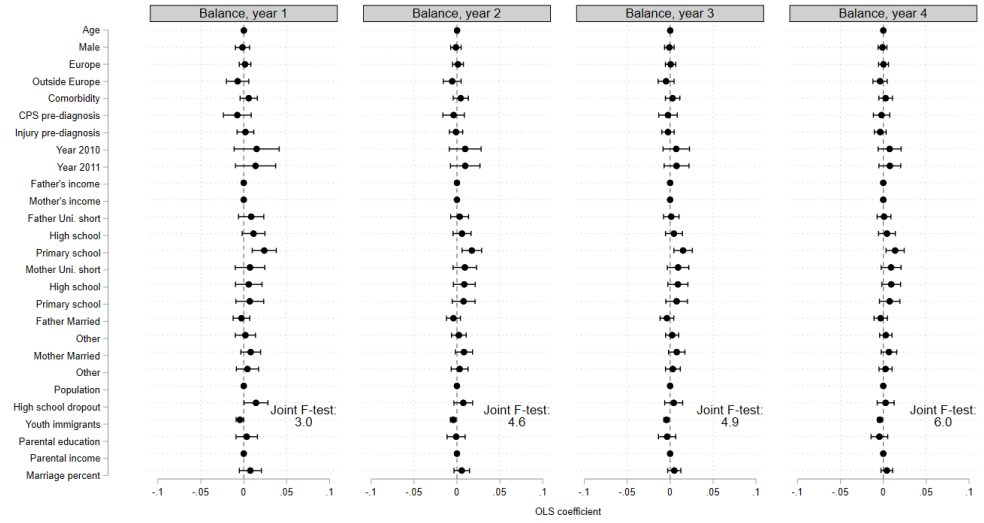

Figure S4. Coefficient plot examining balance of covariates for the IV with the joint F-test.

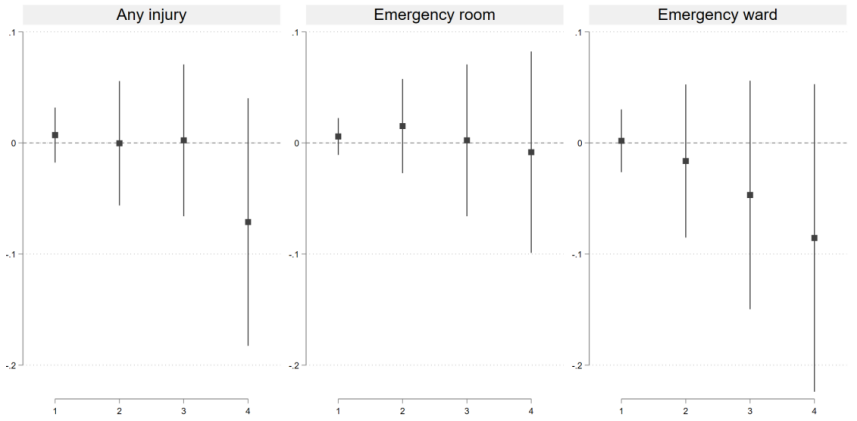

Figure S5. Reduced form. Associations between provider preference for ADHD medication and injuries in the general population sample. Coefficient plots with 95% confidence intervals based on linear probability models.

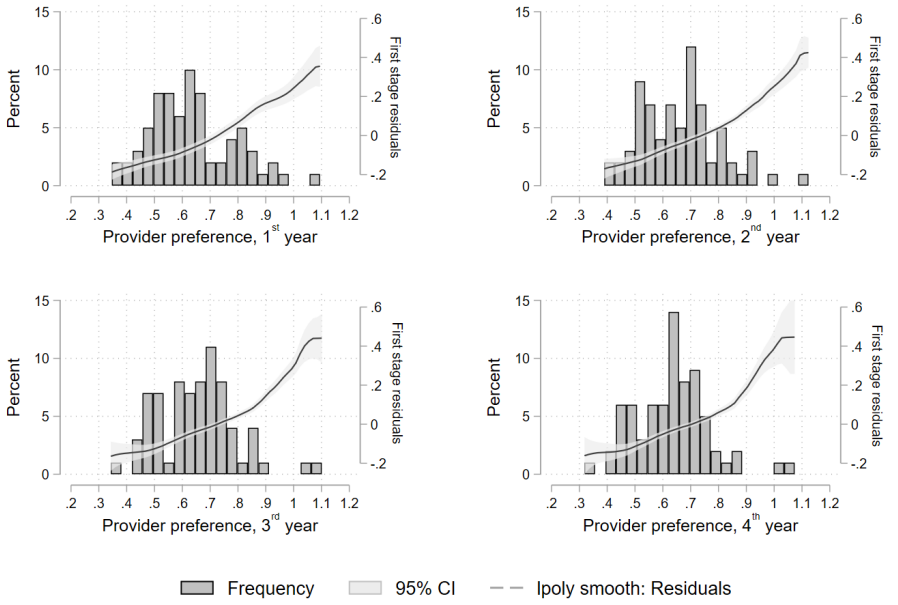

Figure S6. Variation between clinics in ADHD medication among patients diagnosed with ADHD for the first to fourth year following ADHD diagnosis. Provider preference for ADHD medication at clinic level as mean defined daily dosages for ADHD medication by years after ADHD diagnosis among patients on *x*-axis. Residuals from first stage regressions of treatment on IV plotted against values of IV with local polynomial regression line and residual values on right side *y*-axis.

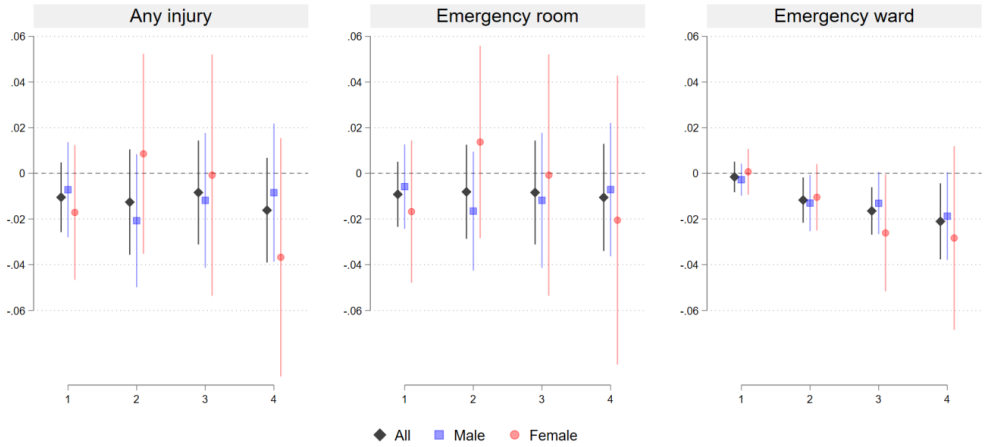

Figure S6. Probit results for association between ADHD medication and injuries.

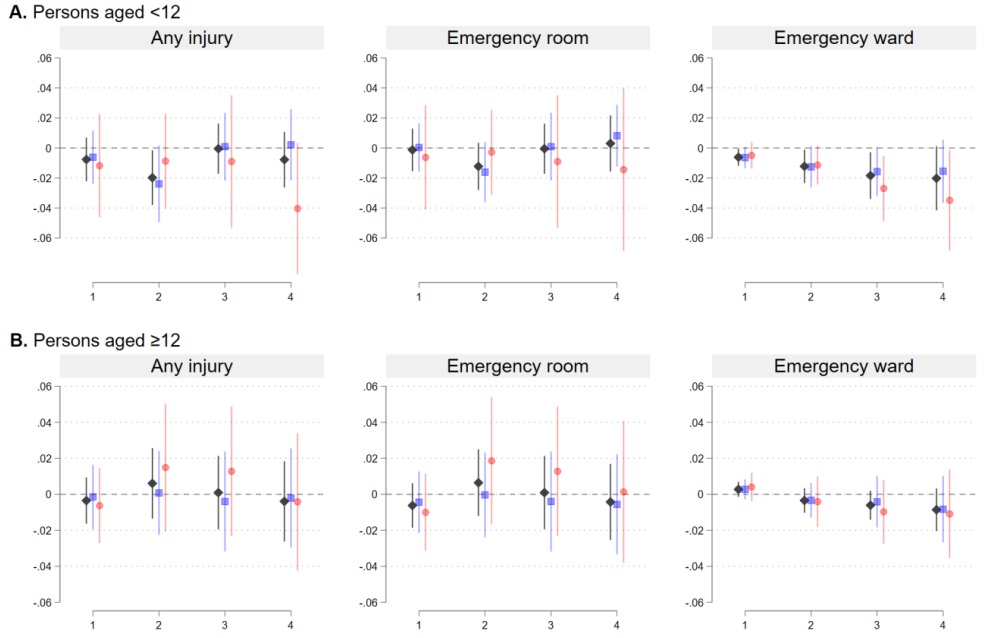

Figure S7. Linear probability model results for association between ADHD medication and injuries in patients aged below and above 12 years.

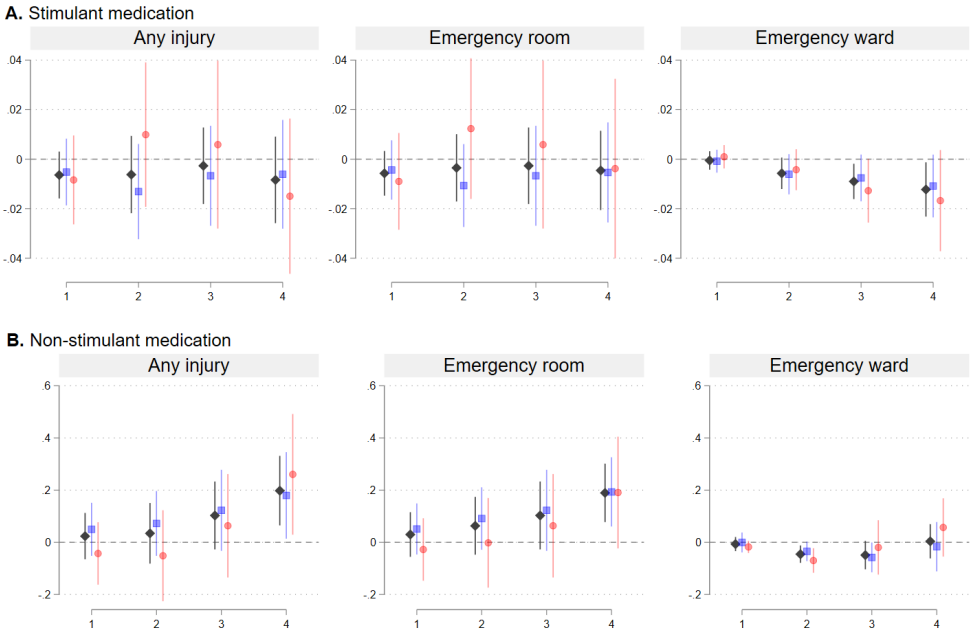

Figure S8. Linear probability model results for associations between ADHD medication and injury by type of medication.

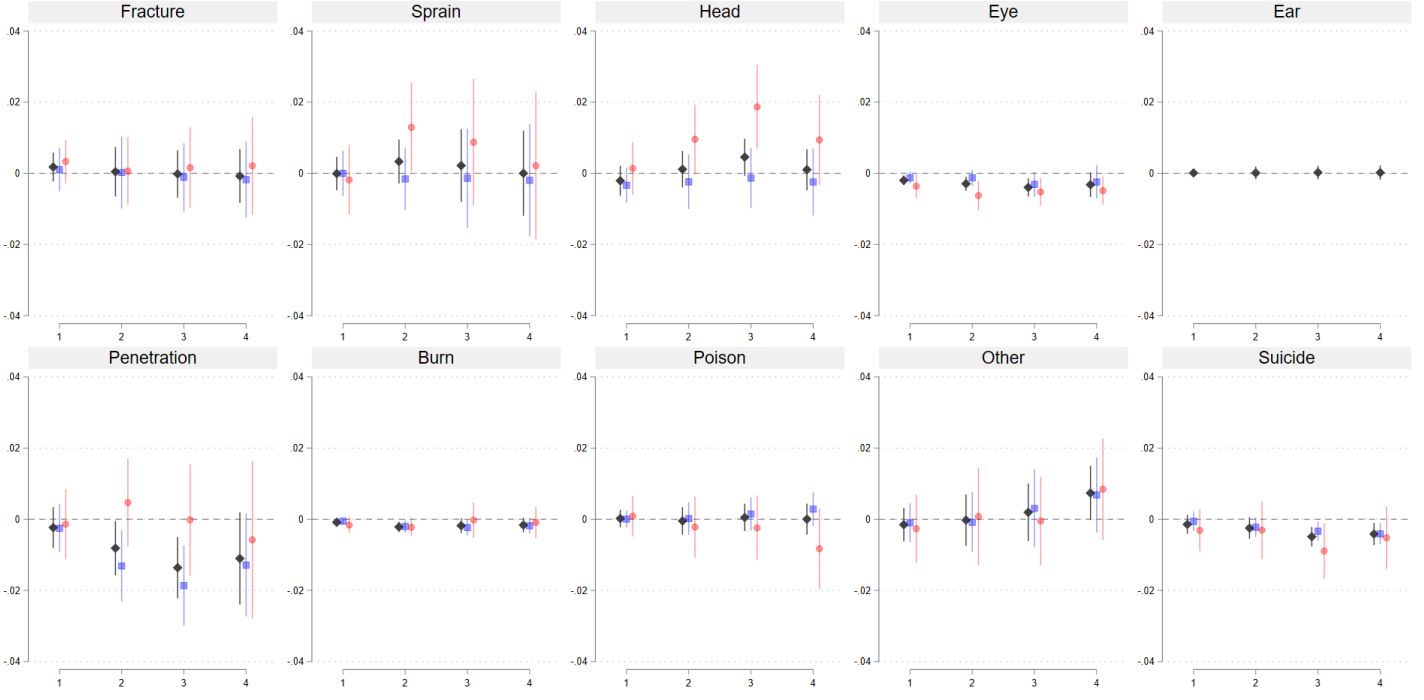

Figure S9. Linear probability model results for the association between ADHD medication and types of injuries.

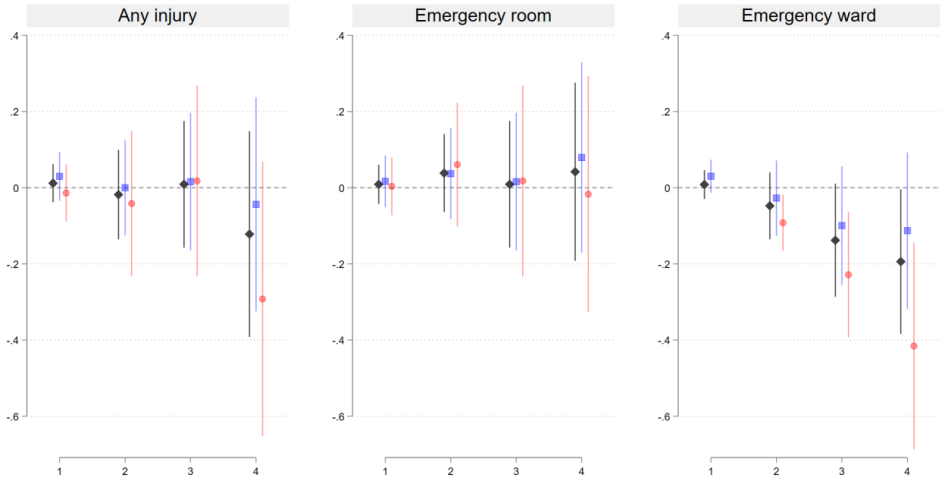

Figure S10. IV Probit results for the effect of ADHD medication on the probability of injury.

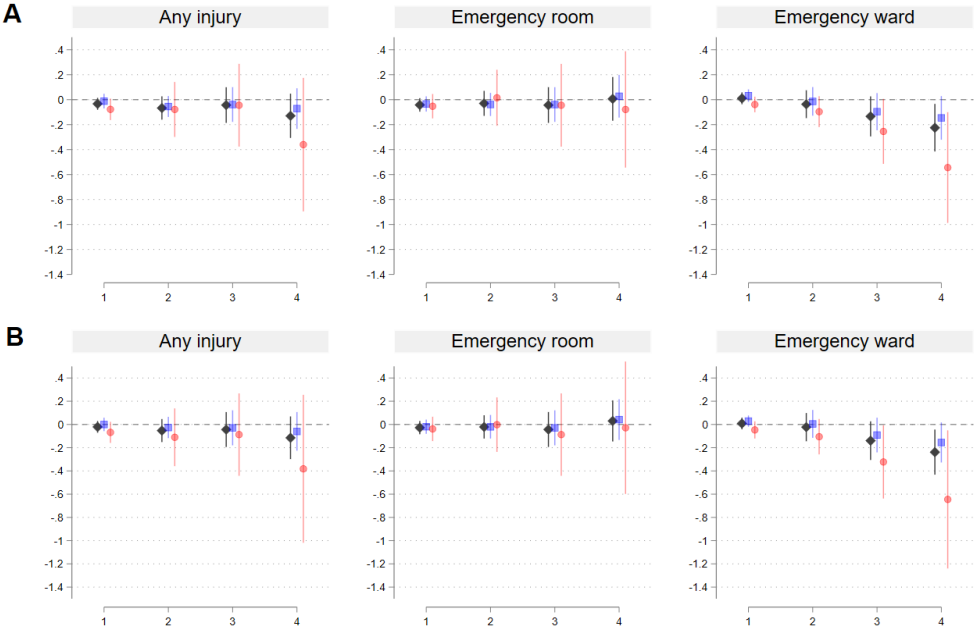

Figure S11. 2SLS results for the effect of ADHD medication on the probability of injury excluding patients who had one or more prescription prior to diagnosis. Panel A exclude patients with prescriptions prior to waitlist end date (sample n=6942). Panel B exclude patients with prescriptions prior to diagnosis (sample n=6,528).

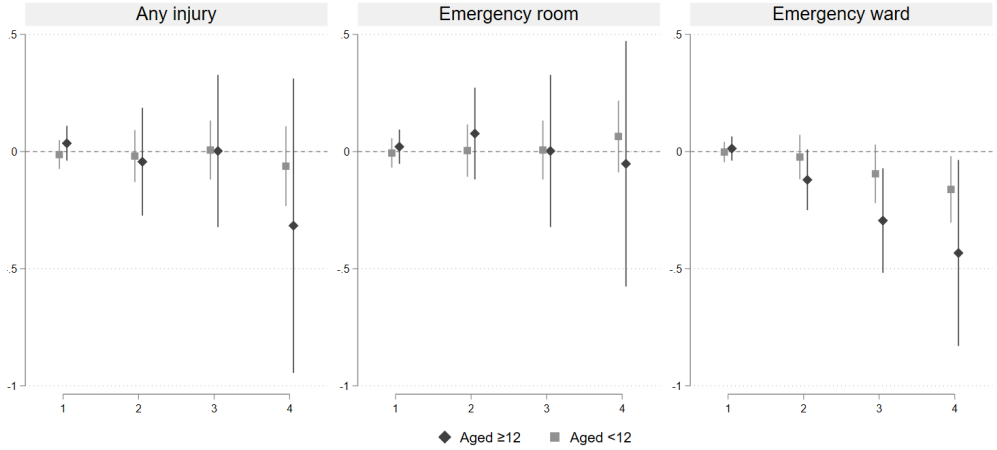

Figure S12. 2SLS results for the effect of ADHD medication on the probability of injury in patients aged below and above 12 years.

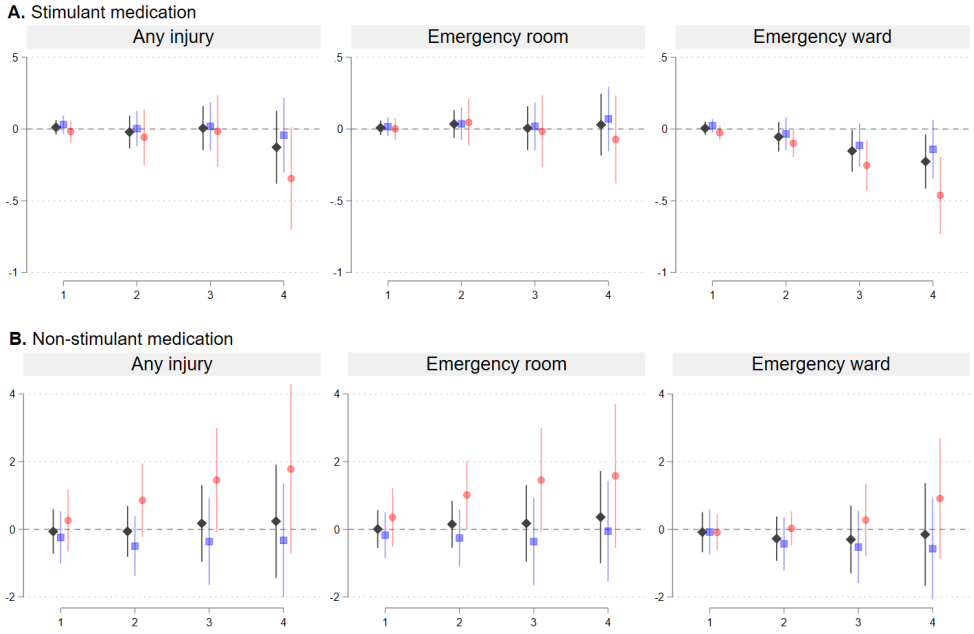

Figure S13. 2SLS results for the effect of ADHD medication on the probability of injury by type of medication.

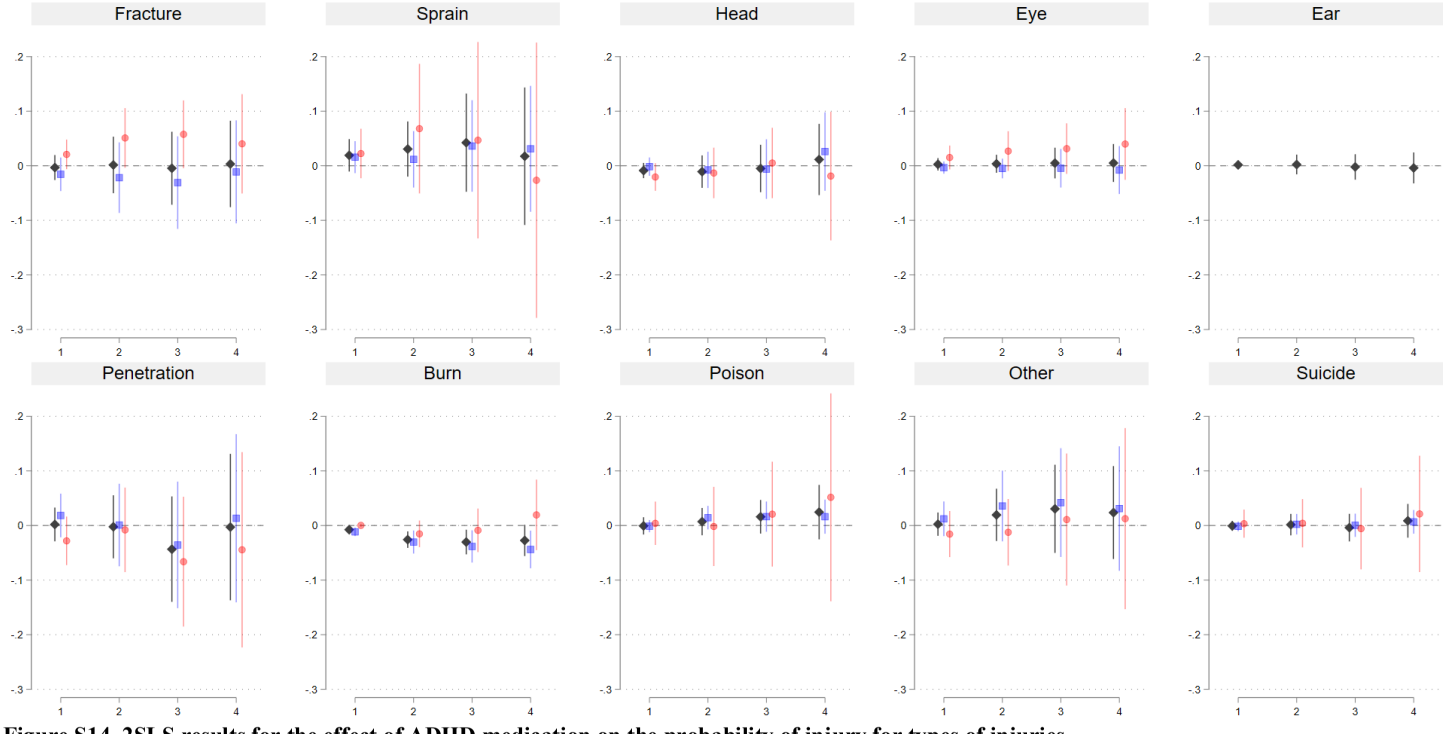

Figure S14. 2SLS results for the effect of ADHD medication on the probability of injury for types of injuries.

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Study III

European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-022-01996-7

ORIGINAL CONTRIBUTION

Geographical variation in ADHD: do diagnoses reflect symptom levels?

Tarjei Widding-Havneraas[1,2] · Simen Markussen[3] · Felix Elwert[4] · Ingvild Lyhmann[1,2] · Ingvar Bjelland[1,5] · Anne Halmøy[1,5] · Ashmita Chaulagain[1,2] · Eivind Ystrom[6,7] · Arnstein Mykletun[2,8,9,10] · Henrik Daae Zachrisson[11]

Received: 5 April 2022 / Accepted: 23 April 2022

Abstract
Rates of ADHD diagnosis vary across regions in many countries. However, no prior study has investigated how much within-country geographic variation in ADHD diagnoses is explained by variation in ADHD symptom levels. We examine whether ADHD symptom levels explain variation in ADHD diagnoses among children and adolescents using nationwide survey and register data in Norway. Geographical variation in incidence of ADHD diagnosis was measured using Norwegian registry data from the child and adolescent mental health services for 2011–2016. Geographical variation in ADHD symptom levels in clinics' catchment areas was measured using data from the Norwegian mother, father and child cohort study for 2011–2016 ($n = 39{,}850$). Cross-sectional associations between ADHD symptom levels and the incidence of ADHD diagnoses were assessed with fractional response models. Geographical variation in ADHD diagnosis rates is much larger than what can be explained by geographical variation in ADHD symptoms levels. Treatment in the Norwegian child and adolescent mental health services is free, universally available upon referral, and practically without competition from the private sector. Factors beyond health care access and unequal symptom levels seem responsible for the geographical variation in ADHD diagnosis.

Keywords Health services · Psychiatry · Child health · Adolescent · Norwegian mother, father and child cohort study · MoBa · Norwegian patient registry · ADHD · Symptoms

Introduction

Diagnosis rates of attention-deficit/hyperactivity disorder (ADHD) vary across many countries [1]. International comparisons suffer validity problems due to differing diagnostic standards and methodology (Fig. 1A) [1]. Similar geographic variation in diagnostic prevalence, however, exists within countries with a uniform diagnostic standard, for example, Norway (Fig. 1B) [2–6].

Although ADHD symptoms are fundamental in diagnosing ADHD, no prior research investigates the extent to which geographical variation in ADHD symptoms explain geographical variation in ADHD diagnoses. ADHD diagnosis is a precondition for ADHD treatment, especially

✉ Tarjei Widding-Havneraas
tarjei.widding-havneras@uib.no

1 Department of Clinical Medicine, University of Bergen, Jonas Lies Vei 87, 5021 Bergen, Norway

2 Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital, Bergen, Norway

3 Ragnar Frisch Centre for Economic Research, Oslo, Norway

4 Department of Sociology, University of Wisconsin-Madison, Madison, WI, USA

5 Division of Psychiatry, Haukeland University Hospital, Bergen, Norway

6 Promenta Research Center, Department of Psychology, University of Oslo, Oslo, Norway

7 Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway

8 Division of Health Services, Norwegian Institute of Public Health, Oslo, Norway

9 Department of Community Medicine, University of Tromsø, Tromsø, Norway

10 Centre for Work and Mental Health, Nordland Hospital, Bodø, Norway

11 Department of Special Needs Education, University of Oslo, Oslo, Norway

Published online: 18 May 2022

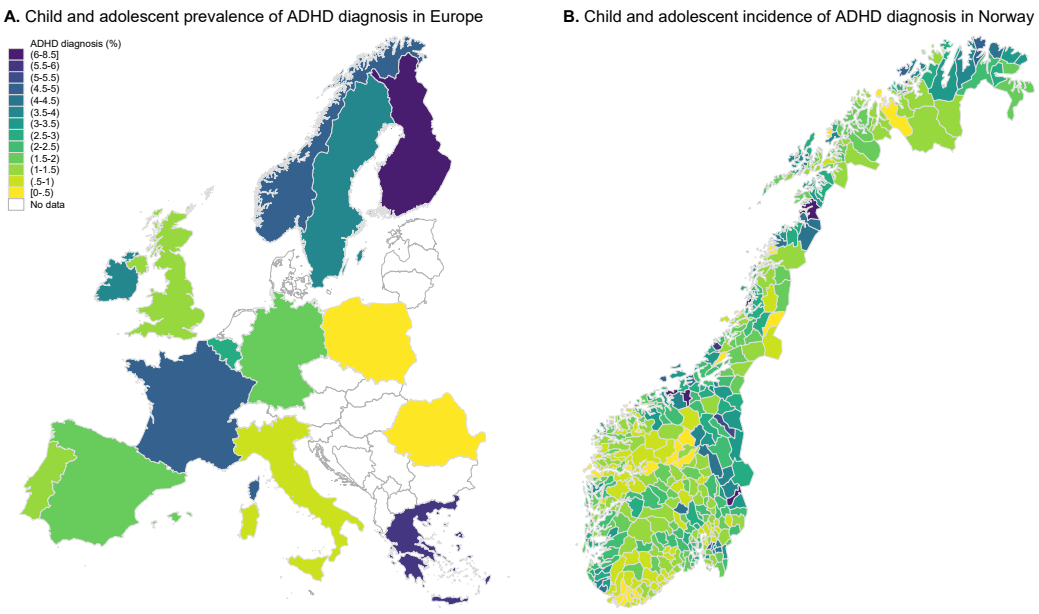

Fig. 1 Geographical variation in ADHD diagnosis in Europe and Norway. Panel **A** Prevalence rate of ADHD diagnosis in children and adolescents across European countries. Panel **B** Incidence rate of ADHD diagnosis in Norway, 0–18 years, 2011–2016. ADHD diagnoses registered in the Norwegian Patient Registry by municipality ($n = 428$)

pharmacological treatment. Geographical variation in ADHD diagnoses that does not correlate with variation in symptoms would thus raise concerns about over- and undertreatment of ADHD [7–10].

We study the extent to which geographic variation in ADHD symptoms explains geographic variation in ADHD diagnosis in Norway, where 5% of children and adolescents are diagnosed with ADHD [11]. Studying Norway has three distinct advantages. First, the availability of comprehensive, nationwide, and geo-coded data on ADHD symptoms and diagnosis. Specifically, we combine nationwide survey data on ADHD symptoms from the Norwegian mother, father and child cohort study (MoBa) with nationwide register data on the incidence of ADHD diagnosis from the Norwegian Patient Registry (NPR). Second, Norway's universal and free health care system (with a marginal private sector) largely rules out variation in healthcare access as an explanation for variation in ADHD diagnosis. Third, nationwide diagnostic standards largely rule out another explanation for geographical variation in ADHD diagnosis. Norwegian child and adolescent mental health services (CAMHS) are organized by clinics serving catchment areas comprised of one or more municipalities/city districts, where only specialists diagnose patients with ADHD and initiate treatment using national treatment guidelines [12].

The aim of this study is to examine whether ADHD symptom levels explain variation in ADHD diagnoses among children and adolescents. We explore three research questions: (1) Does between-clinics variation in the incidence rate of ADHD diagnosis exceed chance variation? (2) Does between-clinics variation in symptom levels of ADHD exceed chance variation? (3) Does between-clinics variation in the incidence rate of ADHD diagnosis, conditional on symptoms levels of ADHD, exceed chance variation?

Methods

ADHD symptoms

We measured ADHD symptoms levels for the general population using mother-reported data from MoBa for 2011–2016. We used two measures of ADHD symptoms: (1) The proportion of the population in a clinics' catchment area with ADHD symptoms equals to or above the 95th percentile, in line with a country prevalence of 5% among children and adolescents [11]. (2) As a sensitivity measure, we used a 90th percentile cut-off as some clinics may be more prone

to diagnose ADHD than others. Proportions of children with high ADHD symptom levels were calculated with individuals who scored above the thresholds as the numerator and the total participants as the denominator.

Data were reported when the child was 8 years old, corresponding to the average age of diagnosis in Norway [13]. The Parent/Teacher Rating Scale for Disruptive Behavior Disorders (RS-DBD) was used, which has good instrument validity and reliability [14, 15], and corresponds with rating scales used in the Norwegian CAMHS. RS-DBD measures inattention, hyperactivity, and impulsivity on 18 items with the same response options: (1) Never/Rarely, (2) Sometimes, (3) Often, (4) Very often (Table S1) [12]. We pooled data on ADHD symptoms for 2011–2016; birth years 2003–2008 ($n = 39{,}850$). 323 individuals in MoBa were dropped as they did not have data on municipality.

MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999 to 2008. Women consented to participation in 41% of the pregnancies. The cohort includes 114,500 children, 95,200 mothers and 75,200 fathers [16]. MoBa was established with a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics (REK), and is now regulated by the Norwegian Health Registry Act. We use version 12 of the quality-assured data files released for research in January 2019, where geo-linkage was available for cohorts from 2002. This study was approved by REK (2017/2205).

ADHD diagnosis

We used municipality-level data on all new patients registered with ADHD diagnosis in NPR (ICD-10, F90.0) between 2011 and 2016. We calculated the cumulative incidence proportion of ADHD among individuals aged 0–18 years, defined as the number of new ADHD diagnoses ($n = 19{,}342$) divided by the number of all individuals in that population using population data from Statistics Norway [17, 18]. For that purpose, we used the population mid-value for 2011–2016, conventionally defined for even numbers as the mean of the two mid-values ($n = 1{,}189{,}496$).

Clinics' catchment areas

Clinics are our unit of analysis because decision-making on diagnosis and potential treatment cultures manifest at clinic level. Clinics' catchment area was inferred in collaboration with NPR using data on patient contacts at clinics by patients' residence municipality in 2009. CAMHS are organized with clinics serving one or more municipalities (and/or city districts in Norway's four largest cities) which comprise the clinics' catchment area. The clinic a municipality is served by was defined as the clinic with the highest number of patient contacts from that municipality. For example, if a clinic in northern Norway is registered with 25 contacts from patients residing in a municipality in western Norway, and 800 contacts from patients residing in a municipality in northern Norway, the latter was defined as the main municipality the clinic serves. There were no major changes in municipality codes during the period of this study. Cities are represented by one clinic as we only have municipality-level data, reducing number of clinics from 73 to 63. The clinics catchment area list was quality-assessed by examining clinics' own descriptions of catchment areas. When combining data from MoBa and NPR, six municipalities were not merged as these were not represented in MoBa in 2011–2016, giving a total of 416 municipalities. We use geographical data on latitude and longitude collected by Fiva et al. [19] to map and examine clusters of ADHD diagnosis. NPR data follow municipality classification per 2018 ($n = 422$) while the map data follow the municipality classification prior to 2018 ($n = 428$). For the map data, we adjusted for five municipality mergers providing six additional municipalities ($n = 428$) given same value as the municipality they were merged to. NPR is a health registry with information on all individuals who have received or are awaiting treatment in specialist healthcare services since 2008 [20]. (Figure 1A) is based on prevalence data on studies from the UK [21], Sweden [22], Finland [23], Greece [24], Ireland [25], and Norway [11], with the remaining countries covered in a comparative study [26].

Statistical analyses

Confirmatory factor analysis (CFA) was applied to measure the latent ADHD symptoms construct from the symptoms score items in RS-DBD [27]. Goodness-of-fit statistics for the CFA used to measure ADHD symptoms aligns with commonly accepted values (CFI = 0.93, RMSEA = 0.07, SRMR = 0.05, $p > \chi^2 = < 0.0001$; full model in Supplement). Data on symptoms and diagnosis of ADHD on the individual- and municipality-levels were aggregated to the clinic-level to examine between-clinics variation and associations between ADHD symptoms levels and ADHD diagnosis.

We examined the extent to which ADHD diagnosis and ADHD symptoms varied at clinic level by comparing observed proportions to expected values under H_0 of equal probability of diagnosis/symptoms across clinics. Confidence intervals under H_0 were bootstrapped using 10,000 draws from the binomial distribution with probabilities equal the grand mean. Observed proportions outside of the bootstrapped 95% CI were considered larger than chance variation.

Variance-components models were used to partition the variance in ADHD symptoms and ADHD diagnosis with

municipality-level data nested within clinics. We examined variation in ADHD diagnosis and symptoms levels using the coefficient of variation (CV), a variability measure for the extent of variation relative to the mean calculated as the variable's standard deviation (SD) divided by its mean value. Bootstrapping was used to derive the expected distribution of CV under H_0 of equal probability of symptoms/diagnosis across clinics. The observed CV was compared to the null distribution to examine the probability of observing the CV by chance under H_0.

We used fractional response regression models (FRM) [28] to test whether ADHD diagnosis is associated with ADHD symptoms. The mean incidence proportion of ADHD diagnosis was predicted by ADHD symptom levels in two separate models: one with 95th percentile cut-off and one with 90th percentile cut-off as the predictor. Heteroskedasticity-consistent standard errors were used. The model was weighted by number of MoBa-respondents within catchment areas. Average marginal effects (AME) were reported.

We examined the extent of unexplained variation in incidence of ADHD diagnosis by CV for the residual and for the squared correlation coefficient between the observed and the predicted values. To formally test whether the unexplained variation in ADHD diagnosis conditional on ADHD symptoms was larger than expected by chance, we compared the observed CV to the distribution of expected CVs under H_0, where H_0 was given by the predicted values from the FRM model. Since this prediction also contains statistical uncertainty, we conducted this analysis using a bootstrap approach.

Results

The cumulative incidence of ADHD diagnosis was 0.016 (SD: 0.007, min–max: 0.004–0.039, IQR: 0.01–0.02) in 2011–2016. The proportion of children scoring over the 95th percentile on ADHD symptoms was 0.05 (SD: 01, min–max: 0–0.14, IQR: 0.045–0.053). For children scoring over the 90th percentile, the proportion was 0.1 (SD: 0.14, min–max: 0–0.14, IQR: 0.09–0.11). Two clinics had no MoBa-respondents scoring ≥ 95%, while one clinic had no participants scoring over ≥ 90%. There was nearly a tenfold difference in the incidence of ADHD diagnosis proportion from the clinic with the lowest to the highest level. (Figure 1) presents municipality-level geographical variation in the incidence rate of ADHD diagnosis showing clustering of areas with higher and lower levels of incidence of ADHD diagnosis. The intra-class correlation (ICC) from variance-components models for the incidence of ADHD diagnosis was 50.2% [CI 95%: 39 to 61] indicating that half of the total variance was attributed to the clinic level. The ICC for ADHD symptoms is < 0.01% for proportions of children with symptom scores ≥ 95% and 0.15% [CI 95%: 0.03 to 0.9] for proportions of children with symptom scores ≥ 90%.

In (Fig. 2), the upper graph in Panel A presents ADHD diagnosis proportions by clinics. The vertical line is the grand mean of observed population-weighted ADHD diagnosis with 95% CI for chance variation from 10,000 draws, whereas observed proportions (blue circles) outside 95% CI were larger than expected by chance. The observed coefficient of variation (CV) for the incidence of ADHD diagnosis proportions across clinics was 45.6% ($p = 0$).

The lower graph of Panel A presents the null distribution for CV with the excess variation in ADHD diagnosis compared to the mean of the null distribution measured in percentage difference. Similarly, the upper graph in Panel B presents proportions of children scoring ≥ 95th percentile for ADHD symptoms. Here, few observed proportions were outside 95% CI. The CV was 18% ($p = 0.23$), thus there was not support for more than chance variation as the observed CV was well within the null distribution (lower graph Panel B). In Panel C, there are more observed proportions of children scoring ≥ 90th percentile for ADHD symptoms compared to Panel B. The CV was 15% ($p = 0.025$), and there is evidence for more than chance variation.

From fractional response regression models (FRM) at the clinic level with the incidence of ADHD diagnosis as the outcome, the average marginal effect (AME) shows that the proportion of ADHD diagnosis increases 0.26 percentage points (95% CI: [0.09 to 0.42], $p = 0.002$) when the proportion of children and adolescents with ADHD symptoms ≥ 95% increase with one percentage point. We did not find support for an association between ADHD symptoms ≥ 90% and ADHD diagnosis (AME: 0.09, 95% CI: [− 0.06 to 0.24], $p = 0.25$) (Supplementary, Table S3).

Predicted values from FRMs were used for analyses of unexplained variation (Fig. 3). The 95% CI were centered at 0 for no differences between observed and predicted values. There was large between-clinics variation in residuals, with few observed residuals in the 95% CI for chance variation for both models with proportions of ADHD symptoms ≥ 95% (Fig. 3A, upper graph) and ≥ 90% (Fig. 3B, upper graph) as predictors. Moreover, the observed CV for the residuals was considerably higher than the distribution of CVs under the null distribution for both models (Fig. 3A, B, lower graphs), which was supported by formal tests (Table 1). Overall, the residuals were still large after adjusting for ADHD symptoms ≥ 95% (or ADHD symptoms ≥ 90%), indicating that other factors are influential in explaining the remaining difference between observed and predicted proportions of ADHD diagnoses.

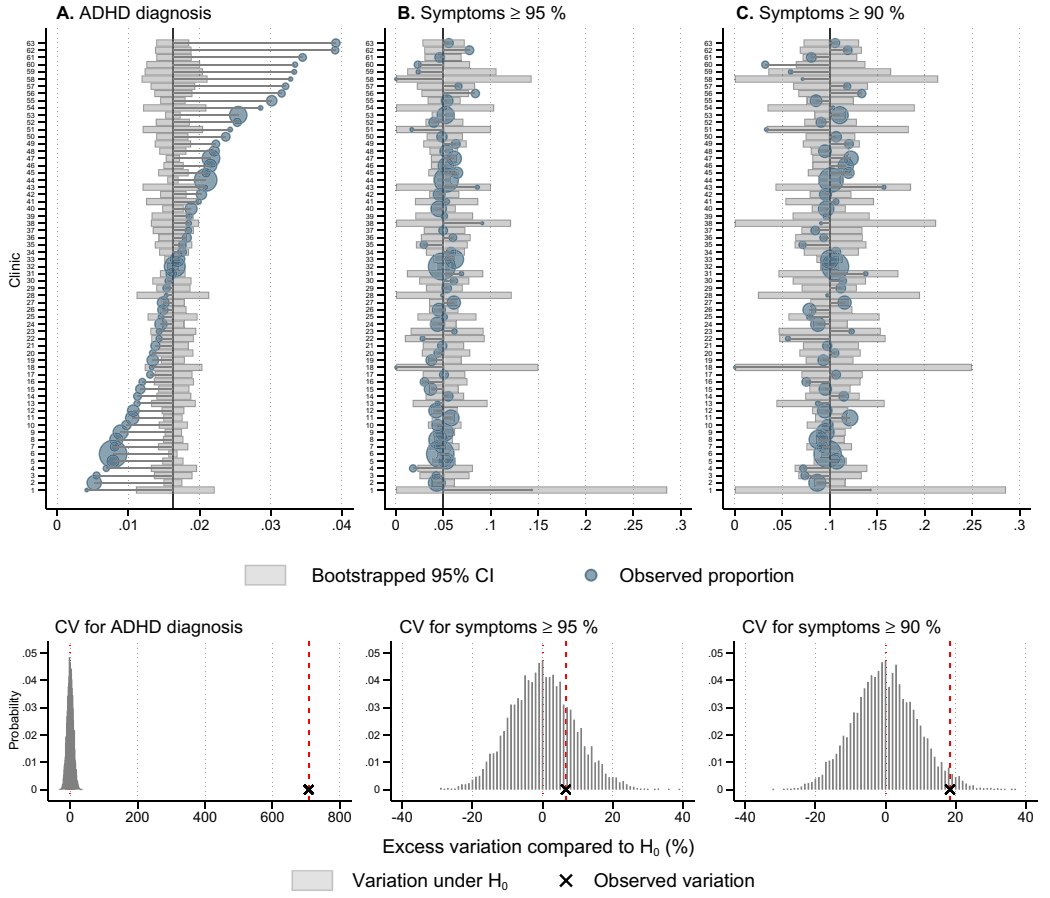

Fig. 2 ADHD diagnosis incidence rate, ADHD symptoms ≥ 95% and ≥ 90% by clinics ($n = 63$), 2011–2016. Upper graphs in Panel (**A**–**C**) present bootstrapped 95% confidence intervals (CI) for chance variation around the population-weighted grand mean (black vertical line) for diagnosis, and sample-weighted grand mean for symptoms. Observed proportions (blue circles) outside 95% CI are larger than expected by chance. The lower graphs in Panel (**A**–**C**) present the observed coefficient of variation (CV) and the expected values of CV, under the null hypothesis that *the CV does not exceed chance variation*, based on 10,000 draws. The *x*-axis is the excess variation in CV compared to $E(CV \mid H_0)$

Discussion

Summary of findings

We found support for large between-clinics variation in the incidence rate of ADHD diagnosis and considerably less variation in high levels of ADHD symptoms at the ≥ 90 percent level. There was no evidence for more than chance variation in symptoms at the ≥ 95 percent level. Municipalities clustered into areas with higher and lower levels of ADHD diagnostic incidence, where half of this variance could be ascribed to the clinic level. While there was evidence for a positive association between the incidence rate of ADHD diagnosis and high levels of ADHD symptoms, the explained variance in the incidence rate of ADHD diagnosis after controlling for ADHD symptoms was low.

Strengths and limitations

There are two considerable strengths to this study. First, the analyses are based on a unique combination of nationwide geo-coded data on both symptoms and diagnosis of ADHD.

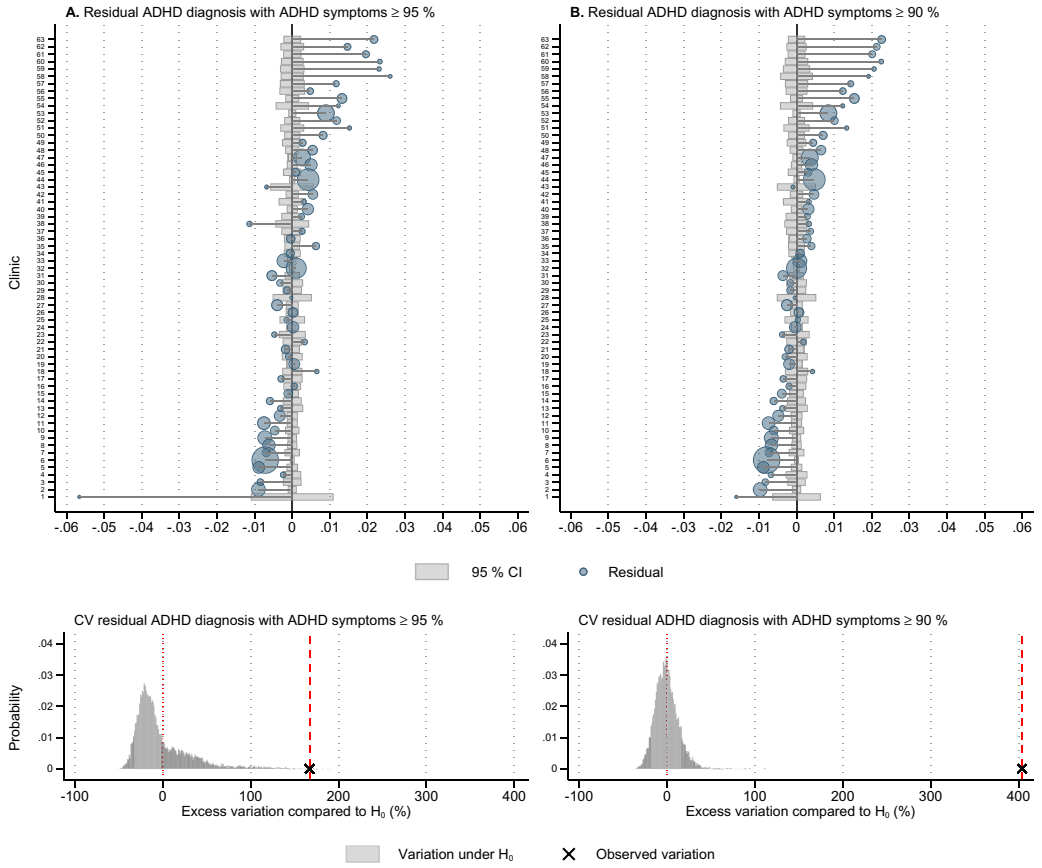

Fig. 3 Differences in observed and predicted incidence rate of ADHD diagnosis by clinics ($n = 63$), 2011–2016. Upper graphs in panel **A** and **B** show residuals for the incidence of ADHD diagnosis after controlling for ADHD symptoms ≥ 95 and ≥ 90%, respectively. Clinics are sorted in ascending order by the incidence of ADHD diagnosis, with circles proportional to the population in catchment areas. 95% CI for residual centred at 0 for no difference between observed and predicted values. Observations outside 95% CI present differences not explained by ADHD symptoms in clinics' catchment area. Lower graphs of panel **A** and **B** shows how much unexplained variation remains in ADHD diagnosis after controlling for ADHD symptoms. The extent of residual variation after controlling for ADHD symptoms is presented as a percentage difference from the expected value of CV, under the null hypothesis of *no remaining unexplained variation*, and is based on 10,000 draws

We are not aware of other similar data sources that can be used to examine the research questions in this study, nor have we discovered any study on within-country variation in ADHD diagnosis that includes data on ADHD symptoms. Second, the Norwegian context is ideal due to the single provider healthcare system with only a small portion of patients using private sector healthcare reducing concerns of selection biases into healthcare.

There are limitations to consider. First, ecological bias may be a concern as both symptoms and diagnosis of ADHD are individual-level data aggregated to clinic-level variables. However, we examined clinic-level variation and associations and did not draw inferences for the individual level [29]. Second, statistical bias could be introduced by the modifiable areal unit problem since several units of observation can be used [29]. Clinics are arguably more relevant compared to other area definitions as patients are diagnosed at clinics and there may be local treatment cultures [30]. Third, the association between symptoms and diagnosis of ADHD may be subject to confounding bias either toward or away from the null. The proportion of individuals with high levels of ADHD symptoms includes treated and untreated

Table 1 Between-clinics variation in incidence rate for ADHD diagnosis, high levels of ADHD symptoms, and unexplained variation in ADHD diagnosis after controlling for ADHD symptom levels

Model	(1) ADHD diagnosis, unconditional	(2) ADHD symptoms ≥ 95%, unconditional	(3) ADHD symptoms ≥ 90%, unconditional	(4) Residuals:ADHD diagnosis, conditional on symptoms ≥ 95%	(5) Residuals:ADHD diagnosis, conditional on symptoms ≥ 90%
Coefficient of variation (CV)					
Observed CV	.46	.18	.14	.45	.44
Mean CV under H_0	.06	.17	.12	.17	.09
[Min, Max]	[.04–.08]	[.12–.24]	[.08–.16]	[.08–.54]	[.05–.18]
Test statistic: Percent deviation between observed CV and mean CV under H_0	713.9	7.6	19.4	192.3	414.0
p-value	0	.23	.06	0	0
R^2	–	–	–	.13	.04

The coefficient of variation (CV) shows how much variation there is relative to the mean and is calculated as the variable's standard deviation divided by its mean value. H_0 for CV is that variation does not exceed chance variation. *p* value is proportion of expected values under H_0 with values equal to, or above, observed value from 10,000 trials. Models 4 and 5 are weighted by participants in MoBa. R^2 from fractional regression models with diagnosis as response and symptom levels as explanatory variable

ADHD, where the former reduces symptoms and the association between symptoms and diagnosis. As well, population composition and other potential confounders may vary between clinics. Moreover, ADHD is highly heritable (88%) [31]. Siblings live in the same catchment area which may inflate familial risk factors for ADHD. However, the focus of this study is the unconditional, and conditional on ADHD symptoms, between-clinics variation in ADHD diagnosis. Fourth, areas with high levels of ADHD diagnosis may raise awareness and increase parent- and teacher reporting of ADHD symptoms and referral rates to specialist health services, causing a reverse causal path between rates of diagnosis and ADHD symptoms. There is currently no strong empirical evidence supporting this concern. Fifth, there are at least two potential sources of selection bias. MoBa may be affected by sampling bias with overrepresentation of individuals with high SES [32], and underrepresentation of non-Norwegians, young females, single households, mothers with > 2 births or previous stillbirths, and smokers [33]. NPR only includes patients in the specialist health services and lower SES predicts more health services use [34]. Both selection mechanisms can affect observed variations and associations between symptoms and diagnosis of ADHD. Sixth, a concern may be chance findings, e.g., due to sample size, statistical power, or researcher degrees of freedom. While the Type 1 error rate is constant in increasing sample size, the Type II error rate decreases. Thus, if this study is underpowered, there is no way of knowing whether failing to reject the null hypothesis is due to insufficient sample size or a real lack of effect. As the sample consists of clinics in Norway, we could only increase the sample size using city–district codes for the four largest cities, which we did not have access to. Sixth, our measure of ADHD symptoms is only restricted to children when they are 8 years old. While this corresponds with the mean age at diagnosis, it may not perfectly reflect symptom levels for the children and adolescents from 0 to 18 years whom we have diagnosis data on.

Contribution and interpretation

This is the first study to combine nationwide data on both symptoms and diagnosis of ADHD to examine the extent to which within-country variation in ADHD diagnosis is explained by ADHD symptoms. We find considerable between-clinics variation in ADHD diagnosis despite free access to healthcare, a comprehensive welfare state, and comparatively low social inequality, which reduces the potential impact of socioeconomic conditions. This finding is in line with existing research on within-country variation in ADHD diagnosis, where clusters of municipalities with high and low incidence of ADHD diagnosis have been identified [4–6]. Regional differences in diagnostic practice have been presented as the most plausible explanation in another Norwegian study on geographic variation in ADHD diagnosis [6]. A survey supports that clinician's policy toward ADHD treatment varies [35]. The main question from a health policy perspective is whether the observed variation is unwarranted or fully explained by patient and provider characteristics [30]. The high remaining residual variation in ADHD diagnosis after controlling for ADHD symptoms suggests that other factors are important drivers of between-clinics variation in ADHD diagnosis.

Implications

ADHD symptoms should arguably explain a considerable part of between-clinics variation in ADHD diagnosis since the diagnosis is based on the assessment of symptoms, functional impairment, and differential diagnosis. The inherent puzzle clinicians are faced with in diagnosing patients with symptoms around the threshold for diagnosis may introduce a random component in being diagnosed with ADHD based on the patient's geographical residence. Accordingly, for some patients, being diagnosed with ADHD and receiving ADHD medication may ultimately come down to residing in one catchment area rather than another. From a health policy perspective, this is worrisome as it challenges the principle of equal healthcare regardless of geography. From a research perspective, the between-clinics variation in ADHD diagnosis presents a potential quasi-experiment that can inform clinical practice on effects of ADHD diagnosis and treatment [5, 36]. Future research may consider a quasi-experimental approach that exploits geographical variation in diagnosis or medication rates to fill knowledge gaps that are challenging to address with randomized experiments.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00787-022-01996-7.

Acknowledgements The Norwegian mother, father and child cohort study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study. The study was supported by funding from Research Council of Norway (288585/IAR) and Western Norway Regional Health Authority (912197). HDZ and EY was supported by funding from the European Research Council Consolidator Grant ERC-CoG-2018 EQOP [grant number 818425].

Author contribution TW-H: conceptualization, data curation, methodology, formal analysis, visualization, writing–original draft, project administration. SM: conceptualization, data curation, methodology, formal analysis, visualization, writing–original draft. FE: conceptualization, writing–original draft. IL: conceptualization, project administration. AC: conceptualization. IB: writing–original draft. AH: writing–original draft. EY: writing–original draft, resources. AM: conceptualization, supervision, methodology, writing–original draft, resources, project administration. HDZ: conceptualization, supervision, data curation, methodology, formal analysis, visualization, writing–original draft, resources, project administration.

Funding Open access funding provided by University of Bergen (incl Haukeland University Hospital).

Data availability Data cannot be publicly shared due to strict data privacy laws. Data from the Norwegian mother, father and child cohort study (MoBa) and the Norwegian Patient Registry can be made available by application to the data owners.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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Study III
Supplementary

Supplementary

1. Data used in confirmatory factor analysis for ADHD symptoms

Variable	Item		Factor
NN119	1	Fails to give close attention to details or makes careless mistakes in schoolwork	Attention-deficit
NN120	2	Has difficulty sustaining attention in tasks or play activities	
NN121	3	Does not seem to listen when spoken to directly	
NN122	4	Does not follow through on instructions and fails to finish school work, chores or duties (not due to oppositional behaviour or failure to understand instructions)	
NN123	5	Has difficulty organizing tasks and activities	
NN124	6	Avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)	
NN125	7	Loses things necessary for tasks or activities (pencils, books, toys)	
NN126	8	Is easily distracted	
NN127	9	Is forgetful in daily activities	
NN128	10	Fidgets with hands or feet or squirms in seat (sits uneasily)	Hyperactivity/ impulsivity
NN129	11	Leaves seat in classroom or in other situations in which remaining seated is expected (e.g. at the table or in group gathering)	
NN130	12	Runs about or climbs excessively in situations in which it is inappropriate	
NN131	13	Has difficulty playing or engaging in leisure activities quietly	
NN132	14	Is "on the go" or acts as if "driven by a motor"	
NN133	15	Talks excessively	
NN134	16	Blurts out answers before questions have been completed	
NN135	17	Has difficulty awaiting turn	
NN136	18	Interrupts or intrudes on others, such as in conversation or play	

Table S1. MoBa data on ADHD symptoms. Response options (all items): 1 = Never/rarely; 2 = Sometimes; 3 = Often; 4 = Very often.

2. Additional information on statistical analyses

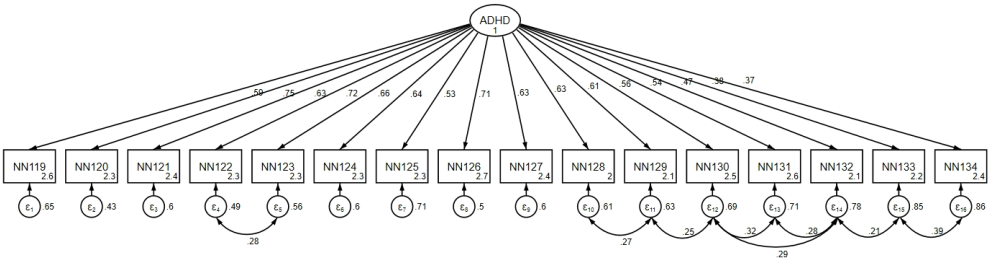

Figure S1. Confirmatory factor analysis. Standardized. Based on NN119-NN136 for years 2011-2016 (*n* = 39,850).

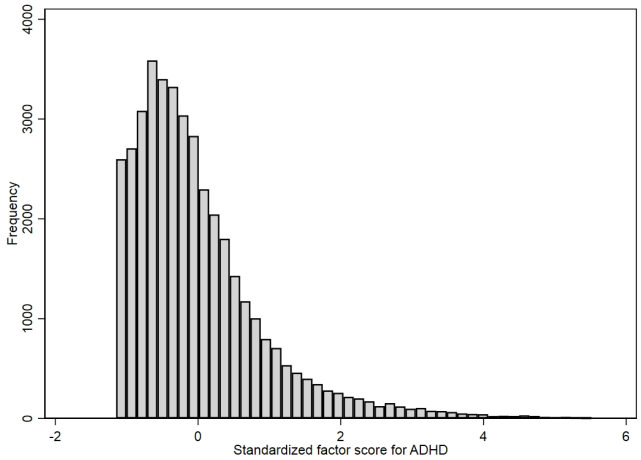

Figure S2. Histogram of factor score for ADHD symptoms.

Fit statistic	**Value**
Likelihood ratio	
χ^2 ms, model vs. saturated	18620.4
$p > \chi^2$	< 0.001
χ^2 ms, baseline vs. saturated	246434.6
$p > \chi^2$	< 0.001
RMSEA	0.07
CFI	.93
SRMR	.05

Table S2. Goodness of fit for confirmatory factor analysis of ADHD symptoms.

Model	(1)	(2)	(3)	(4)
Incidence of ADHD diagnosis	Symptoms ≥ 90 %	Symptoms ≥ 95 %	Symptoms ≥ 90 %	Symptoms ≥ 95 %
AME	.01	.06	.09	.26
95% CI	[-.08, .1]	[-.09, .21]	[-.06, .24]	[.09, .42]
Delta SE	.04	.08	.08	.08
Z	.23	.74	1.15	3.05
P > | *z* |	.82	.46	.25	.002
Weights	No	No	Yes	Yes

Table S3. Average marginal effects from fractional response models. Incidence of ADHD diagnosis regressed on proportion with high levels of ADHD symptoms at clinic level. Models are weighted by number of participants in MoBa in clinics' catchment area. Abbreviations: AME = average marginal effect, Delta SE = delta method standard error, CI = confidence interval.

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230844335 (print)
9788230841266 (PDF)