

From the Department of Global Public Health
Karolinska Institutet, Stockholm, Sweden

AUTISM-EDUCATIONAL OUTCOMES AND SELF-HARM IN ADOLESCENTS AND YOUNG ADULTS

Isidora Stark



**Karolinska
Institutet**

Stockholm 2022

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet.

Printed by Universitetservice US-AB, 2022

© Isidora Stark, 2022

ISBN 978-91-8016-843-4

AUTISM – EDUCATIONAL OUTCOMES AND SELF-HARM IN ADOLESCENTS AND YOUNG ADULTS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Isidora Stark

The thesis will be defended in public at room Atrium, Karolinska Institutet Stockholm, Friday the 16th of December 2022, at 09:00h.

Principal Supervisor:

Professor Cecilia Magnusson
Karolinska Institutet
Department of Global Public Health

Opponent:

Associate Professor Fotis Papadopoulos
Uppsala University
Department of Medical Sciences

Co-supervisor(s):

Dr. Selma Idring Nordström
Karolinska Institutet
Department of Clinical Neuroscience

Examination Board:

Associate Professor Johan Reutfors
Karolinska Institutet
Department of Medicine, Solna

Associate Professor Dheeraj Rai
Bristol Medical School
Department of Population Health Sciences
Division of Clinical Epidemiology and Public Health

Associate Professor Lorena Fernandez de la Cruz
Karolinska Institutet
Department of Clinical Neuroscience

Professor Lise Renata Pettersson Roll
Stockholms University
Department of Special Education

To my sister Aleksandra for unfailing love.

POPULAR SCIENCE SUMMARY OF THE THESIS

Autism is an umbrella term for conditions different in their origins and manifestations. Autistic individuals show common characteristics such as difficulties related to social communication and interaction paired with restricted and repetitive behaviours and interests. There are more than 52 million autistic people in the world today. While previously considered to be rare, it is nowadays recognized to be one of the most prevalent neurodevelopmental conditions. During the last eighty years, since the term autism was introduced to the scientific and clinical practice, our understanding of autism has evolved substantially. The concept and the definition of the condition, as well as the way we talk and deal with challenges that autistic people face has changed. The differences and difficulties of autistic people may influence educational performance, and overall wellbeing. However, educational outcomes and psychiatric problems in the autistic population today are not well characterized. Many autistic students with normal intellectual ability attend mainstream schools worldwide, and a clear understanding of their outcomes is needed to implement adequate support. Self-harm is common, potentially fatal, and may have specific features and determinants in autistic individuals. However, autism is not widely recognized as a group at risk for suicide that should receive full attention when seeking medical help.

This thesis utilized the rich data derived from a range of national and regional registers in Sweden to investigate two critical outcomes in early adulthood in autistic individuals. We explored and evaluated today's educational practice by objectively measured indicators of educational attainment at the end of the first two milestones in the educational pathway, compulsory/primary and lower secondary (Study I) and secondary education (Study III) in regular schools in Stockholm. In the studies II and IV we investigated self-harm in autistic individuals and if and how these behaviours compare to those who harm themselves in the non-autistic population. Study IV investigated the role that self-harm may play for its most fatal consequence, suicide death in autistic individuals.

In the studies I and III autistic students were more likely to demonstrate substantially lower educational outcomes than their non-autistic peers in both qualification for (study I) and completion of (study III) secondary mainstream school in Stockholm. In study II we found the likelihood of engaging in self-harm in autistic individuals to be as high as in individuals with depression, anxiety disorder and attention deficit hyperactivity disorder, all acknowledged to be groups at high risk of self-harm. In study IV, we confirmed previous findings of strong association between self-harm and suicide death. We also found a markedly higher risks of suicide after self-harm in autistic compared to non-autistic self-harmers.

Overall, the results of the studies in this thesis, suggest that autistic individuals are at risk of adverse outcomes, including difficulties in achieving formal educational requirements for further schooling and work, self-harm, and suicide in early adulthood. The thesis increases our understanding of today's practice of education of autistic students without intellectual

disability, points out that students are not owners of the problem, and that society must invest in sufficient adaptations to meet the specific educational needs of autistic students to strengthen the inclusive agenda. The thesis also emphasizes the necessity of increased public health interventions, clinical awareness and medical care in respect to autistic adolescents and young individuals who seek medical help for self-harm.

ABSTRACT

Autism is one of the most prevalent neurodevelopmental conditions worldwide, and autistic individuals face challenges in daily functioning related to differences and difficulties in social interaction and communication along with intense interests and behaviours. In the past, this heterogenous and common condition was considered to be rare. Outcomes in education and mental ill-health are not fully understood in the more recent cohorts.

This thesis investigates two domains of outcomes in young autistic individuals: educational performance, focusing on compulsory/primary and upper secondary mainstream schooling in autistic students without intellectual disability in study I and study III; and self-harm behaviours including their characteristics and link with suicide in studies II and IV.

All four studies in this thesis are observational, prospective, register-based total-population cohort studies. Studies I-III utilize rich data collected in Stockholm Youth Cohort, a total population cohort of children aged 0 – 17 years resident in Stockholm County in Sweden, from 2001 to 2011 (N = 736,180). A range of national and regional records were linked using personal identification numbers that are assigned to every Swedish resident. In Study IV we linked the Total Population Register to four longitudinal, nationwide, registers in Sweden: The Multi-Generation Register, The Longitudinal Integration Database for Occupational research, and The Cause-of-Death Register, and identified study population of adolescents and younger adults born between 1984-2009. We follow-up this population (N = 2,822,789) until December 31st, 2021, when the oldest study participants were aged 37 years.

In Study I we observed a significantly lower proportion of autistic students (57 %; $p < 0.05$) meeting eligibility criteria for upper secondary education as compared to their non-autistic peers (86 %; $p < 0.05$). At the end of secondary mainstream school (Study III) autistic students were almost three times less likely to complete the school (OR 2.9 [95 % CI 2.70; 3.15]) compared to their non-autistic peers. In both studies females and students with co-occurring attention deficit hyperactivity disorder were at particularly high risks of adverse outcomes. Study II observed discrepancies between self-harm, sufficiently severe to lead to hospitalization: nearly 3 % of autistic individuals had been hospitalized at least once for self-harm between the ages of 10 and 27 years, compared with 0.8 % of their non-autistic peers. In study IV, autistic individuals with a record of self-harm were found to be at substantially higher risk of suicide (HR 22.9 95 % CI [19.5 - 26.9]) than both non-autistic self-harmers HR 16.2 95 % CI [14.9 - 17.5] and autistic individuals who did not engage in self-harm (HR 1.8 95 % CI [1.5 - 2.1]), as compared to non-autistic individuals without a record of self-harm.

The findings of this thesis suggest that autistic students without intellectual disability attending mainstream education in Stockholm (compulsory and upper secondary) are at a higher risk of low educational attainment in terms of formal requirements for continuation of schooling or work. Autistic females and students with co-occurring attention deficit hyperactivity disorder are particularly sensitive to this underachievement.

Autism was associated with increased risk of self-harm independently of comorbid ADHD, depression and anxiety disorders, and the likelihood of self-harm in autism was as high as in these conditions. Choice of methods used to self-harm by autistic, may be more lethal than those used by non-autistic individuals. Self-harm in autistic individuals conveys particularly increased risk of consecutive suicide, even more so than in non-autistic peers. Together, these findings indicate that self-harm which is an important predictor of suicide in the general population, should be a matter of great clinical concern if present in young autistic individuals, and that the needs of autistic self-harmers should be included in clinical guidelines and risk assessment processes.

LIST OF SCIENTIFIC PAPERS

- I. Stark, I., Liao, P., Magnusson, C., Lundberg¹, M., Rai, D., Lager, A., & Idring Nordström, S. (2021). Qualification for upper secondary education in individuals with autism without intellectual disability: Total population study, Stockholm, Sweden. *Autism*, 25(4), 1036-1046.
doi:10.1177/1362361320975929
- II. Stark, I., Rai, D., Lundberg, M., Culpin, I., Nordström, S. I., Ohlis, A., & Magnusson, C. (2022). Autism and self-harm: A population-based and discordant sibling study of young individuals. *Acta Psychiatr Scand*.
doi:10.1111/acps.13479
- III. Stark, I., Döring, N., Lundberg, M., Rai, D., Ohlis A., Idring Nordström, S., Magnusson, C., (submitted manuscript) Completion of upper secondary mainstream school in autistic students without intellectual disability: A Total Population Register Study in Stockholm County. Submitted to *Autism International Journal of Research and Practice*.
- IV. Stark, I., Lundberg, M., Ahlqvist, V.H., Rai, D., Idring Nordström, S., Ohlis, A., Hadlaczky, G., Magnusson, C. (manuscript) Self-harm and suicide in young autistic individuals – a total population study in Sweden

CONTENTS

1	INTRODUCTION.....	1
1.1	What terminology should we use when talking about autism: “autistic person” or “person with autism”?	1
2	LITERATURE REVIEW	3
2.1	Autism.....	3
2.2	Outcomes in autism	3
2.2.1	Education.....	4
2.2.2	Self-harm	4
2.2.3	Suicide	5
2.2.4	Education and autism	5
2.2.5	Autism and self-harm.....	6
2.2.6	Knowledge gaps	7
2.3	Key concepts in epidemiology.....	9
2.3.1	Bias	9
2.3.2	Confounding.....	9
2.3.3	Collider bias	10
2.3.4	Interaction.....	10
2.3.5	Measures of association	11
2.3.6	Sibling design- informative genetic approach.....	11
3	RESEARCH AIMS	13
3.1	Overarching aim	13
3.2	Specific aims.....	13
3.2.1	Study I.....	13
3.2.2	Study II	13
3.2.3	Study III.....	13
3.2.4	Study IV.....	13
4	MATERIALS AND METHODS	15
4.1	Data sources.....	15
4.2	Measures	18
4.2.1	Exposure	18
4.2.2	Outcomes.....	18
4.2.3	Covariates	18
4.3	Study design	19
4.4	Statistical analyses.....	19
4.4.1	Poisson regression	19
4.4.2	Logistic regression	20
4.4.3	Cox regression.....	20
5	RESULTS.....	21
5.1	Educational outcomes in primary and secondary education	21
5.1.1	Study I.....	21

5.1.2	Study III.....	22
5.2	Self-harm and suicide.....	23
5.2.1	Study II.....	23
5.2.2	Study IV	23
6	DISCUSSION	25
6.1	Summary of the main findings.....	25
6.2	Findings in the context of previous research	25
6.2.1	School outcomes	25
6.2.2	Self-harm and suicide.....	26
6.3	Methodological considerations	27
6.3.1	Data sources	27
6.3.2	Psychiatric epidemiology – what is a psychiatric disorder?	28
6.3.3	Selection bias.....	28
6.3.4	Confounding.....	28
6.3.5	Problem of comorbidities in autism and collider bias.....	29
7	ETHICAL CONSIDERATIONS	30
7.1	Register studies.....	30
7.2	Autism and aspects of stigma.....	30
8	CONCLUSIONS.....	33
9	FUTURE PERSPECTIVES.....	33
9.1	Clinical implications.....	34
10	ACKNOWLEDGEMENTS.....	37
11	REFERENCES.....	41

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
CI	Confidence Interval
DAGs	Direct Acyclic Graphs
DALYs	Disability - Adjusted Life - Years
DSM	Diagnostic and Statistical Manual
HR	Hazard Ratio
ICD	International Classification of Diseases
ID	Intellectual Disorder
IQ	Intelligence quotient
NSSI	Non-suicidal self-injury
RCT	Randomized Clinical Trials
RERI	Relative Excess Risk Due to Interaction
SYC	Stockholm Youth Cohort
WHO	World Health Organization

1 INTRODUCTION

The focus of this thesis is to determine two critical outcomes in the growing population of individuals diagnosed with autism in Sweden. In recent decades, the number of individuals diagnosed with autism has increased worldwide^{1 2}. While the causes of this increase are not fully understood, it co-occurs with comprehensive societal changes following the shift to an information-based economy, including rising demands on socioemotional and cognitive functions in the labour market. This increasing demand is also mirrored by a changed educational policy, that now advocate inclusion of children with disabilities, including those with neurodevelopmental conditions such as autism, in mainstream schooling. In this setting, it is crucial to clarify to what extent educational attainments and suicidal behaviour, two closely interlinked outcomes that are essential determinants of future life chances and health, differ between autistic individuals and their typically developing peers. Overall, my thesis, aims to inform the debate on a possible over-diagnosis of autism as an explanation of the sharp rise of this diagnosis, and more importantly, on whether there is a need for policy reforms to strengthen educational and health care support for children and young people on the autistic spectrum.

1.1 WHAT TERMINOLOGY SHOULD WE USE WHEN TALKING ABOUT AUTISM: “AUTISTIC PERSON” OR “PERSON WITH AUTISM”?

Since the first time the autistic condition was presented by Grunya Sukhareva³ 1920s as a unique concept we know today as “autistic pathological avoidant psychopathy”, and two decades later when this condition was acknowledged in the scientific writings of Leo Kanner⁴ and Hans Asperger⁵, the way we refer to autism has evolved both in the scientific/clinical and more broadly in the public debates⁶. The official clinical and research authorities have during this period recategorized autism six times, and concurrently with this development the disability rights movement (and neurodiversity movement) shifted the public perspective and discussion focus from disability and impairment to the more inclusive concept of neurodiversity. This was a part of the struggle for human rights and against the inequalities and stigma faced by autistic people and their families. Some autistic advocates point out that autism is “essential” to the way they are and not “something bad” that should be divided from the person him / herself⁷. Indeed, how we use language may maintain and induce stigma and ableism (i.e. the assumption that disabled people are inferior to nondisabled people)⁸; The way the terminology is used in the scientific writing has, thus changed over the years and the suggestion to use “person first language “ shifted to using what is “appropriate given the context, such as the preference of participants themselves”⁹.

In this thesis, the ongoing debate about terminology regarded autism is acknowledged, and also the preference of many, although not all, autistic individuals and their families⁹, by using the “identity-first language”. Therefore “autistic person” and “autistic people” are used instead of “person/people with autism” throughout this thesis.

Studies I and III investigate the formal, educational attainment of autistic students without intellectual disability in mainstream school in Sweden. We acknowledge the complexity of phenomena and meanings of terms such “mainstream” education, “inclusive (full and partial) education”, “inclusion”, but since explicit aim of this thesis is not the discourse, history or definitions in this field, these terms are used interchangeably.

This literature review details the background and state of the art of the four studies founding this thesis, respectively focusing on compulsory (primary) and upper secondary school outcomes (study I and III), self-harm (study II) and the link between self-harm and suicide (study IV) in autism.

The original papers are named in roman numbers I-IV throughout the text and are appended in the end of the comprehensive summary after the references.

2 LITERATURE REVIEW

2.1 AUTISM

Autism is a spectrum of heterogeneous, complex, behaviourally defined neurodevelopmental conditions characterized by atypical sociability and restricted/repetitive patterns of behaviours and interests¹⁰. Clinical presentations vary from mild to severe autistic symptoms, and according to co-occurring neurodevelopmental, psychiatric, and medical conditions^{2 11 12}. Autism encompasses individuals presenting a spectrum of intellectual abilities, from profound mental retardation to exceptionally high ability. Recent estimates indicate that 30 % of the autistic population has co-occurring intellectual disability (ID)². Autism is considered to account for substantial health loss across the life span, and globally accounted for 92 DALYs (disability-adjusted life-years) per 100 000 population in 2019¹³. Although estimates vary over the existing research, most studies report high rates of co-morbid psychiatric disorders in autistic individuals, for example life-time depression (47 %), anxiety (54 %) and attention deficit hyperactivity disorder (ADHD, 65 %), according to a recent systematic review¹⁴. Heightened prevalence of other psychiatric conditions may be both due to shared genetics but may as well be the consequence of challenges autistic individuals deal with due to core problems of autism¹⁵. Medical treatment for autistic core problems is not available, and they impact on individuals and their families over the life-course who often need societal support⁶.

2.2 OUTCOMES IN AUTISM

Successful social, educational, residential, and vocational outcomes are milestones that when not achieved may lead to social exclusion, low self-esteem, sense of inferiority, mental health problems and suicidal ideation and potentially suicidal acts^{16 17}. Studies on outcomes have ability to increase our understanding of prognosis and potentially help us act in order to mitigate adverse consequences of conditions such as autism. Moreover, increasing concerns about long-term outcomes due to economic costs¹⁸ strengthen the need for outcome research. Findings on outcomes may profoundly affect how we view autism and its boundaries and shift societal perspective from "deficiency of hopeless prognosis and institutionalization as the outcome"¹⁹ to acknowledge the potential of autistic individuals as resource. Furthermore, autistic communities have expressed preferences regarding priorities in research of autism and have called for research that address day-to-day living, services, and support²⁰. Instead of research focusing on prevention of potential future cases, their primary concern was how the millions of existing autistic people may be further supported to overcome challenges. Previous research has attempted to pursue these objectives²¹⁻²⁷. However, the criteria used to identify outcomes of interest were in the early studies "vague and unreliable"²⁴ and do not mirror the population diagnosed today. More recent studies face the persisting problem of defining outcome measures for understanding unique features and needs of autistic individuals to improve feasible adjustments in educational and mental health care settings²⁸. The approach in this work was to elucidate formal educational attainment in the first two

steps of student's educational path. Regarding mental-health challenges self-harm and suicide may both serve as undeniable proxy of adverse outcomes and were identified as domain of great importance in this thesis.

2.2.1 Education

In the life of any individual, education is a critical step, and there is ample evidence that scholastic achievement sets the stage for future life chances and outcomes^{29 30}. Educational achievement is consequently associated with a range of health as well as socio-economic outcomes^{31 32}. This is true also for psychiatric outcomes, and studies on the general population have demonstrated that poor academic performance at the end of compulsory education predicts adverse consequences such as depression³³ and suicidal behaviours^{34 35 36} in the adulthood. Hence the investigation of educational outcomes in relation to autism is of utter public health relevance.

2.2.2 Self-harm

There is not any existing, precise, and universally accepted and implemented classification system of suicidal behaviour. Suicidologists have suggested that inclusion of a new category of *suicidal behaviour disorder* should be introduced in DSM 6 (Diagnostic and Statistical manual), since heterogenous nomenclature has hampered interpretation, and comparison of the studies over the past³⁷. Generally, suicidal behaviours include multiple phenotypes that may result in ending one's own life, and some authors discuss this as "the suicidal spectrum"³⁴. The terminology of suicidal behaviors commonly used includes 1. suicidal *ideation* (any thoughts of ending one's life), 2. suicidal *planning* (having a clear plan of ending one's life), 3. *suicide attempt* (self-injurious, non-fatal behaviours with inferred or actual intent to die), and 4. *suicide* (the event when a person purposefully ends his or her own life)³⁸.

Authors from North America have proposed distinction between *suicidal behaviours* and *non-suicidal self-injury (NSSI)* arguing that there is a qualitative difference that needs different approaches in support/planning. *NSSI* are acts of self-injury with the *intent to harm* oneself but without any *intent to die*³⁸⁻⁴⁰.

The type of *NSSI* that tend to be highly repetitive are *self-injurious behaviours or self-mutilation* (deliberate, direct destruction or alteration of one's body tissue without conscious suicidal intent), and encompass cutting, bruising, burning, head banging or biting⁴¹. These are reported in non-autistic populations to be motivated by achieving relief from negative mood states or distress, or attraction of care/attention from other people. Although not considered suicidal in their intention originally, there is a strong link between self-injurious behavior and consecutive suicide in non-autistic populations³⁷.

Surprisingly, self-injurious behaviours in autism have, historically been attributed to the diagnosis of autism itself, potentially underestimating additional psychopathology (overshadowing psychiatric morbidity or/and suicidal intent) in individuals on the autistic spectrum.

The point of departure of this thesis, according to European research tradition, is the broader umbrella term of *self-harm* as an overarching concept. Self-harm is defined as intentional self-poisoning or self-injury, regardless of the motive or suicidal intent, and includes a continuum of behaviours from non-suicidal self-injury to completed suicide. Although different forms of suicidal behavior have unique characteristics and need specific strategies to be assessed and treated, they share key-features and are closely entwined. Here I address the outcome of hospitalization for self-harm in autism, regardless of intent any self-harm severe enough to lead to such secondary care is an event of great relevance. In-depth knowledge on risk factors, as well its association to suicide, of this outcome is crucial for treatment and prevention.

2.2.3 Suicide

Self-harm (as defined above) and its most catastrophic form, suicide, is one of the main public health concerns worldwide⁴². Suicide is fourth most common cause of death in 15-24 year olds, globally ⁴². Suicide ideation and suicidal planning have estimated life course prevalence of approximately 9.1 % and 3.1 %, respectively⁴³. The suicidal process among adolescents has been described as an “*iceberg model*”, encompassing that “fatal self-harm (i.e., suicide), which is an overt but uncommon behavior (the tip of the iceberg); self-harm that results in presentation to clinical services, especially general hospitals, which is also overt, but common; and self-harm that occurs in the community, which is common but largely hidden (the submerged part of the iceberg)”^{44 45}. Although suicide risk is determined by comprehensive models of distal (cultural context and access to lethal means and methods) and proximal factors (genetics, personal traits, and socio-economic, including educational, adversities), psychiatric disorder is a particularly important risk factor that also is potentially amenable. In fact, large number of the psychiatric disorders have been found to be associated with an increased suicide risk, and 90 % of individuals who die of suicide have had a psychiatric disorder⁴⁶. It is also true that only a small minority of individuals with psychiatric disorders will eventually die due to suicide⁴⁷. Surprisingly, autistic condition have not been included in classical studies in suicidology as other psychiatric conditions have, moreover autistic subjects were explicitly excluded in previous such studies⁴⁸.

During the last decade, a shift regarding suicidality research in autism occurred. Raja and colleagues⁴⁹ concluded in 2011 that their study was the first known to investigate suicidality in autistic adults, some ten years later, there is a substantially increased evidence in the field of suicidal process in autistic population⁵⁰⁻⁵⁵. Although alarming reports of all steps of the suicidal process (from suicidal ideation to suicide) autistic health care needs in this respect have not been fully established in the most recent suicide prevention guidelines.

2.2.4 Education and autism

Information on formal educational outcomes in autism is largely missing. This lack mirrors an unfortunate lag in research, and the fact that the earlier cohorts of autistic children never attended mainstream schooling with formal curriculum, when instead institutional care was

common. In fact, according to the systematic review by Levy and Perry, “school attendance and completion was rare” and may have been explained by “philosophy of institutionalization and lack of special education services”²³. The early outcomes studies until the early 2000s reported broad, mostly descriptive constructs of outcome, in terms of *poor*, *very poor*, or *good*. Criteria for educational achievement were vague and potentially unreliable^{56 57}, and school-administrated specific entities such as grades or formal graduation were not reported⁵⁷.

Mainstreamed schooling of autistic children has increased in western countries since the 1980s. Parallel with this change, some studies investigating educational outcomes in autism emerged⁵⁷. However, assessments of performance of autistic students in these studies were conducted by researchers and clinicians and not by objective indicators regularly used in school settings and with teachers` involvement²². According to these studies, autistic students underperform in domains of reading comprehension and problem-solving compared to non-autistic students⁵⁸. Intellectual ability in autistic students was found to often but not always predict these educational outcomes. Genetic research, on the other hand, has indicated that there is an autism-related positive genetic correlation with educational attainment^{59 60}, which yet is to be confirmed in clinical settings.

The research regarding effects of other neurodevelopmental conditions on educational performance is largely missing, although recent smaller studies explored the impact of ADHD indicating worse academic performance in autistic students with co-occurring ADHD as compared to those without ADHD^{61 62}.

Whether educational outcomes differ in autistic females and males is not known. Whether sex has a protective role regarding education in autistic females as reported in general population⁶³ is yet to be fully understood. Recent Danish study on educational attainment upon the final year of compulsory schooling found increased risks in almost all students with mental health conditions (one of which was autism) compared to students in general population⁶⁴. This study noted that proportions of autistic females taking the final examen were higher as 0.43 [95 % CI, 0.41 - 0.44] compared to autistic males 0.39 [0.3-0.40]. This may indicate an advantage in females, contrasting findings on more general lower cognitive abilities observed in autistic females⁶⁵.

2.2.5 Autism and self-harm

Studies on self-harm in autistic people focused under a long time on self-injurious behaviors (e.g., head banging, self-biting, hair-picking), and confirmed that those behaviors are highly prevalent⁶⁶. A systematic review and meta-analysis reported that a staggering 42 % of autistic individuals engaged in self-injurious behaviour⁶⁶. However, these behaviours were not investigated in the context of suicidality but ascribed to core problems of autism⁴⁸. After alarming reports of an increased risk of suicide in autism^{67 68}, particularly in individuals without intellectual disability and females⁶⁸, the investigation of suicidality in autism became urgent. Several recent systematic reviews have shown that self-harm in *all* its non-fatal forms

is prevalent in autism, and results indicate that more than half of autistic individuals have engaged in some form of self-harm^{69 70}. In spite of the emergence of this important body of research during last decade, methodological limitations hamper the generalizability of its results (e.g., small sample sizes, exclusion of individuals with ID, cross-sectional design, and information bias resulting from self-reports).

There are only a few large studies exploring whether psychiatric co-morbidities explain the high prevalence of self-harm in autism. These have generated conflicting results: A recent Finnish study concluded that the increased risk of intentional self-harm in young autistic individuals was explained by co-morbid psychiatric conditions⁷¹. In contrast, a Taiwanese cohort study showed that autism was an independent risk factor for self-harm⁷². Hence, it remains to be determined whether autism increases risk of self-harm independently of co-occurring psychiatric conditions. This knowledge is required to fully disclose the risk of self-harm in autistic populations, and whether it is comparable to the high risks reported in depression, anxiety disorders and other neurodevelopmental conditions such as ADHD. This disclosure is paramount to further develop and potentially include the specific needs of autistic people in clinical and other guidelines for suicide prevention.

Studying the risk of self-harm in full and half siblings of probands with autism may help shed light on gradients in familial risk, and directly comparing probands with autism with their siblings can help account for genetic and environmental factors that siblings share. However, the generalizability of the only study on this topic, while otherwise well conducted, is limited since it included foremost older birth cohorts, and thus perhaps not reflecting associations for autistic populations diagnosed today⁶⁸.

Sex paradox of suicidality has been described (a phenomenon that females are much more likely to have suicidal ideation and engage in self-harm, yet males are at higher risk of dying due to completed suicide). Whether such protective effect of sex is also present in autistic females is debated. A Swedish mortality study found that females were more likely to die due to suicide than males relative to controls of the same sex in general population (OR 13.05 95 % CI [8.73–19.50], 6.28 [4.79–8.23] females and males, respectively)²⁷. In contrast to this, others reported no significant differences between sexes in autistic individuals^{9 28 29}. Whether being a female or a male with autism makes it more perilous to self-harm in respect to the risk of later suicide is yet to be understood. The knowledge on subgroups that may gain most of early interventions is urgently needed to guide public-health efforts particularly important in the population of autistic adolescents and young individuals³⁰.

2.2.6 Knowledge gaps

Firstly, evidence regarding formal educational outcomes among autistic students in mainstream schooling is largely missing. In Sweden, the first step in education is the compulsory school (*grundskola* in Swedish) that is mandatory in Sweden, and almost all autistic children without ID attend mainstream school today. Autistic and non-autistic students along with each other are supposed to perform equally well academically at the same

time and room. However, classroom conditions may pose particular challenge to autistic individuals considering core features of autism e. g. sensory sensitivity, social, and communicative capacity. Data on objective indicators at the end of compulsory education, e.g., binary outcome, either an individual reaches the goal of qualification for upper secondary schooling or not in autistic individuals without ID is missing. Whether there are factors to alleviate or aggravate risk of non-qualification and whether there are, within the autistic group subgroups that perform better, is missing. In particular, the role of ADHD (a common comorbidity in autism and a known predictor of scholastic underperformance in general populations) in educational outcomes in autism, e.g., whether autism could “neutralize” adverse effects of ADHD, is unknown.

Secondly, whether autism regardless of co-existing psychiatric conditions such as depression, anxiety and ADHD are associated with increased risk for self-harm severe enough to require hospitalisation visits is not clear in the light of contradicting results from previous studies. The role of intellectual ability level in autistic individuals that self-harm (both fatal and non-fatal self-harm) is unclear, although some previous research indicate a protective role of sub-normal IQ (Intelligence Quotient)⁴² others found higher IQ to be associated with increased risk of NSSI⁷³. This knowledge may better our awareness of autistic individuals who self-harm, and potentially lead to more informed follow up planning.

The prognostic implications of detailed knowledge on topographies such as methods used, sex differences in autistic self-harm and how it differs from general population would help inform tailored interventions to prevent repetition of self-harm in this populations.

Thirdly, are there differences in educational attainments later on, along the educational pathway, in other words what are the risks for non-completion of upper secondary education in autistic students compared with non-autistic peers? Whether sex or parental factors impact completion of upper secondary school in autistic students is not known. Data on how ADHD, potentially treatable condition, influences school completion in autistic students is largely missing. Better knowledge is needed in order to inform sound decision making and may be an important point of intervention.

Fourthly, how does engagement in severe self-harm in autistic individuals compared to non-autistic peers influences premature death of suicide is not yet known. Self-harm an important outcome in the light of consequences on one’s life and well-being as well as a predictor/prodromal stage and behaviour that may facilitate openness to suicide. Whether the association between self-harm and suicide across the whole autistic spectrum is influenced by co-morbid conditions, factors related to self-harm, individual, familial, and social characteristics is unknown and such data may guide focused interventions in autistic self-harmers. The prognostic implications of detailed knowledge on sex differences in autistic self-harmers and how it differs from general population would help to further knowledge needed to target autism-specific subgroups at particularly high risk of suicide.

2.3 KEY CONCEPTS IN EPIDEMIOLOGY

Epidemiology studies the distribution and determinants of diseases in populations with the overarching aim to inform public health practise⁷⁴. It departs from the notion that the distribution of health-related problems in the population is not random, but that an outcome is caused by one (or more) exposure(s).

Study designs may be categorized as either *experimental* or *observational*. In an experimental study (randomized controlled trial, RCT), investigators *randomly allocate* exposure to subjects which eventually leads to subpopulations (exposed and unexposed) being comparable regarding other factors (unknown and known) that are likely to influence the outcome. Experimental studies are thus considered to be more rigorous and causally informative. Yet, such random allocation is not always possible on a large enough scale, for a long enough time, either for ethical (e.g., study participants cannot be subjected to harmful exposures for research purposes), practical or economic reasons. Experimental studies also suffer from biases, arising, e.g., in relation to non-adherence, low retention or lack of representativeness of the study sample. Observational studies, where the investigator only observes exposures and outcomes, aiming to disclose and understand the basis for any relationship, may hence be the only feasible but indeed also the preferred method of study.

2.3.1 Bias

Bias (imprecision) can be defined as the result of any systematic error in the design, conduct or analysis of a study that flaws estimates of exposure-outcome associations⁷⁵. Information bias may occur if the information related to exposure, outcome, or any covariate, is erroneous, thus leading to misclassification. One example of information bias in a cohort study is medical surveillance (detection) bias that occurs when exposed group due to their medical condition undergo more thorough controls that are more likely to lead to identification of another condition of interest for the study. Selection bias arises when ascertainment of study subjects (exposed or nonexposed) results in distortion of the measure of exposure-outcome association. One important source of selection bias in cohort studies is differential loss to follow-up.

2.3.2 Confounding

Confounding is a particular type of bias, and refers to the influence of factors (confounders, confounding variables) related to both exposure and outcome, and ‘temporally prior’ to both, on the exposure-outcome association. In other words, a confounding variable differs between exposed and nonexposed and is also associated with the outcome. Confounding may lead to overestimation or underestimation of true association between exposure and outcome, i.e., the confounder is “responsible” for at least a part of the association that is being investigated. Direct Acyclic graphs (DAGs) are commonly used to present and reason visually about causal pathways and the ordering and role of different factors⁷⁶, Figure 1.

Figure 1. DAGs illustrating how a confounding factor **C** biases the association between the exposure **E** and outcome **O** (left), and how controlling for **C** removes this bias.



2.3.3 Collider bias

Collider bias (collider - stratification bias) is introduced if investigators condition on or control for a common “effect” of the exposure and outcome. Conditioning (for example by restriction) on or adjusting for a collider variable in the study design or statistical analyses entails that this common “effect” is mirrored as spurious exposure-outcome association⁷⁶. DAGs illustrating collider bias are presented in Figure 2.

Figure 2. DAGs illustrating closed collider path between exposure **E** and outcome **O** via **B** (left), and no association between **E** and **O**. Controlling for **B** opens the collider path linking **E** and **O** via **B** (right) inducing a noncausal association between **E** and **O**.



2.3.4 Interaction

In some situations, two variables modify the effect of each other related to the given outcome. This phenomenon is called interaction (or effect modification) and means that the effect of the exposure on the outcome varies according to presence or absence of the other variable (the effect modifier). In the presence of an effect modifier, the effect of exposure on the given outcome may be magnified (synergistic or positive interaction) or diminished (antagonistic or negative interaction). Observed joint effects of an exposure and an effect modifier may thus exceed the effects of the sum of both effects expected based on their respective independent effects⁷⁴. The magnitude of interaction may be measured by comparing risk differences (additive model) or relative risks (multiplicative model).

2.3.5 Measures of association

Measures of associations are addressed on the absolute or relative scale in epidemiology, and are calculated as⁷⁷:

The *difference* in the risks (or incidence rates):

(outcome risk in exposed) – (outcome risk in non-exposed)

The *ratio* of the risks (or incidence rates):

(outcome risk in exposed) / (outcome risk in non-exposed).

Absolute risk differences are often the more useful presentation of research results for decision making in public health or clinical settings. The relative risk is instead important for understanding mechanisms including in relation to aetiology or prognosis.

2.3.6 Sibling design- informative genetic approach

Potential confounding related to observed and unobserved genetic and environmental factors can be reduced by utilizing sibling design. This study design capitalizes on any discordance in a sibling cluster regarding exposure (or outcome) and enables comparison between groups that are naturally “matched” regarding shared confounding factors such as genes or childhood socio-economic conditions^{75 78}. Comparison of siblings within the cluster that are differentially exposed, e.g., having or not an autism diagnosis, but share other factors, e.g., 50% (in full siblings) or 25 % (in half-siblings) of genes and the aspects of the family environment, such as parenting style or living conditions, can thus meaningfully isolate the independent effect of the exposure. Also, the examination of any gradient in exposure-outcome association related to type of control individuals - that are respectively full or half-siblings, or controls from the general population - helps to elucidate to what degree genetic factors explain the association.

3 RESEARCH AIMS

3.1 OVERARCHING AIM

According to identified knowledge gaps the overarching aim of this thesis was to investigate two critical domains in young adulthood of autistic individuals in most recent birth cohorts, namely educational attainment in regular education and potentially fatal self-harming behaviours.

3.2 SPECIFIC AIMS

3.2.1 Study I

Study I investigated formal educational attainment of autistic students without intellectual disability at the final year of compulsory education, and how students' sex, socioeconomic status of the family and presence of ADHD influenced this outcome. Additionally, we assessed how subject grades differed in autistic compared to non-autistic students and whether a prolonged schooling affected the results.

3.2.2 Study II

Study II aimed to clarify the association between autism and self-harm, and whether autism independently of common psychiatric comorbidity such as depression, anxiety disorders and ADHD increases the risk of self-harm. Furthermore, we investigated the role of sex, and method used to self-harm. Additionally, we assessed family-level confounding.

3.2.3 Study III

Study III aimed to establish the likelihood of completion of upper secondary mainstream education in autistic students without ID compared to their non-autistic peers. Additionally, we elucidated the role of sex and cooccurring ADHD in autistic students' performance.

3.2.4 Study IV

Study IV aimed to scrutinize the association of self-harm presented to health care services to suicide mortality in autistic compared to non-autistic adolescents and younger adults. Additionally, we explored how this associations differ by sex and method of self-harm.

4 MATERIALS AND METHODS

4.1 DATA SOURCES

All four studies constituting this thesis rely on secondary data, and utilize information prospectively collected in administrative and health-care registers in Sweden.

Studies I-III are based on *Stockholm Youth Cohort (SYC)*⁷⁹ with data linkage from national and regional registers as listed here:

The Total Population Register (held by Statistic Sweden since 1968) provides demographic data for each individual alive in Sweden (the name, sex, place of residence, birth date, county of birth, immigrant background, civil status)⁸⁰. This register has been used to provide the background population in the SYC. Since all individuals are assigned unique identity number present also in all other national and regional registers the linkage of registers was possible.

The Multi-Generation Register (held by Statistics Sweden) contains data on each subject's parents and siblings in SYC (coverage about 95-97 percent of the Swedish population born from 1932 onwards). The register allows identification of intergenerational cohorts.

National Population and Housing census held by Statistics Sweden (1960-1990) provides individual and household level information such as employment, income, housing).

The Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) is held by Statistics Sweden, it integrates individual level socio-economic data from various sources covering social insurance, education, labour market, disposable income immigration status (person's and parental country of birth) from 1990 onward.

The National School Register (held by Statistics Sweden since 1973) provides subjects grades, grades in the core subjects (Swedish, English, mathematics) awarded at the final (9th) year of compulsory school (since 1988). Students graduate from compulsory school at age 16 but prolonged time to graduate is allowed by law until age of 20. Results in upper secondary education are recorded since 1973. Data from this register was used in studies I and III.

The National Patient Register (held by National Board of Health and Welfare since 1964) includes all inpatient psychiatric admissions since 1973, and outpatient care since 2001 with coverage of around 80 %⁸¹. Each admission is accompanied with primary and secondary diagnoses using the ICD versions 7-10. The estimate of positive predictive value of in-patient diagnoses is 85 % - 95 %⁸².

The Cause of Death Register provides information on all deaths (the primary and contributory causes registered in the death certificate). This register was utilized in study IV to identify suicide deaths in index persons and their parents.

Stockholm Adult Psychiatry Care Register (held by Stockholm County since 1997) is a regional register that pertains data from adult out- and inpatient psychiatric care inclusive

diagnoses registered upon contact with services. Until 2004 DSM-IV was used, since 2005 diagnoses were set according to ICD-10⁸³.

Clinical database for Child and Adolescent Psychiatry in Stockholm (held by Stockholm County since 2001), is a regional register that provides data from Child and adolescent psychiatry services in in- and outpatient settings. Until 2008 DSM-IV diagnostic classification were used, since 2009 diagnoses were coded according to ICD-10.

Habilitation Register (Stockholm County since 1997) records data on utilization of habilitation services based on disability.

VAL Databases (held by Stockholm County since 1997) is a regional register, collected by care services in Stockholm County.

For the Study IV national registers were utilized (Total Population Register, National Patient Register, The Longitudinal Integration Database for Health Insurance and Labour Market Studies, The Multi-Generation Register and The Death Cause Register).

Table 1. presents short summary of materials and methods used in studies in this thesis.

Table 1. The overview of the materials and methods in the four studies founding this thesis

	Study I	Study II	Study III	Study IV
Overall research focus	Education compulsory school (autism without ID)	Self-harm in autistic individuals	Education upper secondary school (autism without ID)	Suicide after self-harm
Study design	Total-population regional cohort in Stockholm	Total-population regional cohort in Stockholm Sibling analysis	Total-population regional cohort in Stockholm	Total-population national cohort
Study population	SYC (regional cohort)	SYC (regional cohort)	SYC (regional cohort)	National cohort
Data source	National and regional registers	National and regional registers	National and regional registers	National registers
Study population N = total number n = autistic participants	N = 364,957 n = 6,138	N = 410,732 n = 9, 070 2, 317 (+ID)	N = 418,188 n = 3,918	N = 2,822,789 n = 86,427
Follow up Time	2001-2011	2001-2011	2001-2016	1996-2021
Explanatory variable	Record of diagnosis of autism without ID	Record of diagnosis of autism with and without ID	Record of diagnosis of autism without ID	Records of diagnoses of autism with and without ID and self-harm
Main outcome variable	Passing core subjects (Math, English and Swedish)	Record of contact with hospitals for self-harm	Completion of upper secondary education	Suicide death
Measure of risks	Rate Difference (RD)	Relative risk (RR)	Odd Ratios (OR) CI 95 %	Hazard Ratios (HR) CI 95 %
Statistical analyses	Poisson models with identity-link and robust variance estimates	Modified Poisson regression	Logistic regression model	Cox proportional hazard regression model

ID = Intellectual disability; CI = Confidence Intervals

4.2 MEASURES

4.2.1 Exposure

In all four studies of this thesis, the exposure (explanatory or independent variable) was defined as corresponding diagnostic codes in WHO's International Classification of diseases (ICD): ICD-9 (in use in Sweden 1987-1996): 299; ICD-10 (in use in Sweden 1997-2022): F84.0, F84.1, F84.2, F84.5, F84.8, F84.9.

In study IV the exposure was defined as a duality of a diagnosis autism and a record of self-harm captured in National Patient Register by presence of diagnostic codes according to ICD-10: X60-X84, Y10-Y34; ICD-9: E950-E958, E980-E988 and ICD-8 (in use in Sweden 1969-1986): E950-E958, E980-E988.

4.2.2 Outcomes

In Study I, the main outcome was qualification for upper secondary schooling defined as having at least a passing grade in three core subjects (Mathematics, Swedish and English) as recorded in the Register for compulsory school leaving grades. We also examined subject-specific grades in the three core subjects as secondary outcomes.

The outcome in the Study III was defined as binary variable *completion of upper secondary education with qualification*, ascertained by having a final exam grade registered before or during the time student is expected to reach this objective i.e., year the individual turned 20. Information was retrieved by the Swedish Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) and the National School Register (UREG).

In Study II, the outcome variable was registered discharge diagnoses of self-harm, as defined by the, ICD-10 codes X60-X84 (purposely self-inflicted poisoning or injury) and Y10-Y34 (events of undetermined intent), retrieved from National Patient Register.

In Study IV the outcome of interest was death due to suicide defined as deaths due to intended self-inflicted poisoning or injury or ditto events of undetermined intent using the same diagnostic codes as were employed to identify self-harm. The data was retrieved from the Cause of Death Register.

4.2.3 Covariates

Socioeconomic status is a multimodal concept and for the purpose of this work we utilized recorded on following modalities:

- Disposable household income adjusted for year of ascertainment and family size (in quintiles) closest to birth;
- Educational qualification of either parent was studied as a categorical variable (≤ 9 years, 10–12, ≥ 13 years);

- Migration background was identified by country of birth for index persons and their parents.

Familial mental health was studied as a binary variable i.e., having or not any history of a psychiatric disorder in the mother or the father (identified as ICD-9 diagnostic codes 290-319, and records according to ICD-8 290-219)

In study II, the birth order, for the purpose of sibling analysis we assessed the risk of self-harm in full and half siblings of individuals with autism as compared with the general population and adjusted for age and birth order and additionally for maternal and paternal age at birth as these are likely to be non-shared characteristics between sibling pairs.

In study IV, data on suicide mortality from the Cause of Death Register, ICD-10 X60-X84, Y10-Y34, ICD-9 E950-959, and ICD-8 codes (used in Swedish practice between 1969-1986) to identify parental suicide.

4.3 STUDY DESIGN

The main epidemiological study designs are cross-sectional, case-control, and cohort studies. All studies composing this thesis are observational, longitudinal prospective cohort studies. *Cohort study design* is used in analytical epidemiology to ascertain distribution of outcome(s) in exposed and unexposed individuals. Exposure is a factor which may influence the probability of occurrence of a given outcome. Cohort subsets (exposed/unexposed) are selected and then followed for a period of time. The frequency of the outcomes within differentially exposed groups are subsequently measured. This study design allows studying multiple outcomes that may be associated to the single exposure, and investigations of rare events. It allows the calculation of incidence rates, risk ratios, and other outcome measures, such as survival curves and hazard ratios.

4.4 STATISTICAL ANALYSES

To study effects of the exposure (independent variable/s) on the outcome (dependant variable) regression models are commonly used. The models used in the present thesis are described below.

4.4.1 Poisson regression

This model is used to describe the number of certain events occurring in fixed time interval. We assume that the rate at which the event occurs is constant (the probability of event per time unit should be equal per every unit). The Poisson regression takes similar approach as the logistic regression, but the natural logarithm transformation is used (\log_e) for the expected rate. A modified Poisson regression model, i.e., Poisson regression model *with robust standard error (variance)* allows application on binary outcomes. This model uses “robust” (i.e., Huber-White standard errors) instead of estimate of expected standard error. In study I modified Poisson regression with identity link and robust variance⁸⁴ was used to calculate adjusted rate difference with corresponding 95% confidence intervals (CIs) between autistic

(autism without ID overall, and with or without comorbid ADHD) and non-autistic individuals' qualification for upper secondary education.

4.4.2 Logistic regression

Logistic regression models can be applied to estimate relationships between one or more independent variable(s) with an outcome (dependent variable) in situations when the outcome is dichotomous (can take only two values). The other application of the logistic model is for prediction. The measure of the association between exposure and outcome (controlling at the same time for covariates) is calculated by the *odds ratio*. The odds ratio is the ratio of the odds of an outcome given the presence of an exposure and the odds of that outcome in the absence of the exposure. If analyses are performed for rare outcomes, in a cohort study the adjusted odds ratio may be used as a surrogate of the relative risk. This model was performed in study III to generate odds ratios with 95 % confidence intervals of completion of upper secondary education in autistic as compared to non-autistic students. A fixed effects conditional logistic regression analysis was used in study II to compare the risk of self-harm in individuals with autism with that of their non-autistic full siblings.

4.4.3 Cox regression

Survival analysis (time-to event-data) is commonly performed using Cox regression (a.k.a. the Cox proportional hazard model)⁸⁵. It is one of the available mathematical instruments that allows several time-dependent exposures to be considered simultaneously. The measure of outcome frequency is the hazard rate; the ratio between the hazard of an outcome in the two groups of exposure (exposed and unexposed). An assumption of this model is that the hazard ratio is constant over time.

5 RESULTS

5.1 EDUCATIONAL OUTCOMES IN PRIMARY AND SECONDARY EDUCATION

5.1.1 Study I

A total of 364,957 individuals were old enough to graduate compulsory school from 2001 through 2011. These included 6,138 individuals (nearly 2% of the total sample) who were diagnosed with autism without ID. In this group of autistic people, 42% had comorbid ADHD according to the registers. We analysed to what degree students met eligibility criteria at the expected age for graduation (16 years) and age at 20 (allowing for the maximum extended time to graduate).

The main findings were that:

- Compared to non-autistic students, 29 % more autistic students, 95 % CI (28.0–30.0) were not qualified for upper secondary education at age 16. At age 20, the fully adjusted RD decreased to 22 %, 95 % CI (21.1–23.4).
- The RD for failing to meet eligibility criteria for upper secondary education comparing autistic students was higher among females than males, at age 16 as well as at age 20. At age 16, 32 % more autistic than non-autistic students, 95 % CI (29.9–34.3) were not eligible when restricting the sample to females, compared to 27 %, 95 % CI (25.4–28.4) among the males in the fully adjusted model. At age 20, these RDs decreased to 26 %, 95 % (CI 24.3– 28.4) in females, and 20 %, 95 % CI (18.7–21.4), in males.
- Autistic students were more likely to fail to meet qualification criteria for upper secondary education relative to non-autistic individuals at both ages 16 and 20 in the group of individuals with lower familial income than in the group with higher familial income. At age 16, 29 %, 95 % CI (26.3–32.7) more autistic individuals from the lowest familiar income quintiles compared to their non-autistic peers with from the same group failed to meet eligibility criteria, compared to 24 % (21.2–26.7) among individuals with familiar income in the highest quintile. At age 20, the RDs decreased across income quintiles such that 24%, (20.8–27.0), more autistic individuals from the lowest familiar income quintiles failed to meet eligibility criteria, compared to 17% (14.3–19.1) from the highest quintile.
- Comorbid ADHD increased the RDs for not qualifying for upper secondary education among autistic students both at age 16, adding a further 8 %, 95% CI (5.1–10.2), and nearly 6 %, (3.4–8.2) at age 20 non-qualifiers, compared to autistic individuals without comorbid ADHD.
- Similar patterns of non-eligibility were found for all core subjects, and compared to the non-autistic group, a larger proportion of the autistic group had non-passing grades in all core subjects at both ages 16 and 20 (Figure 3).

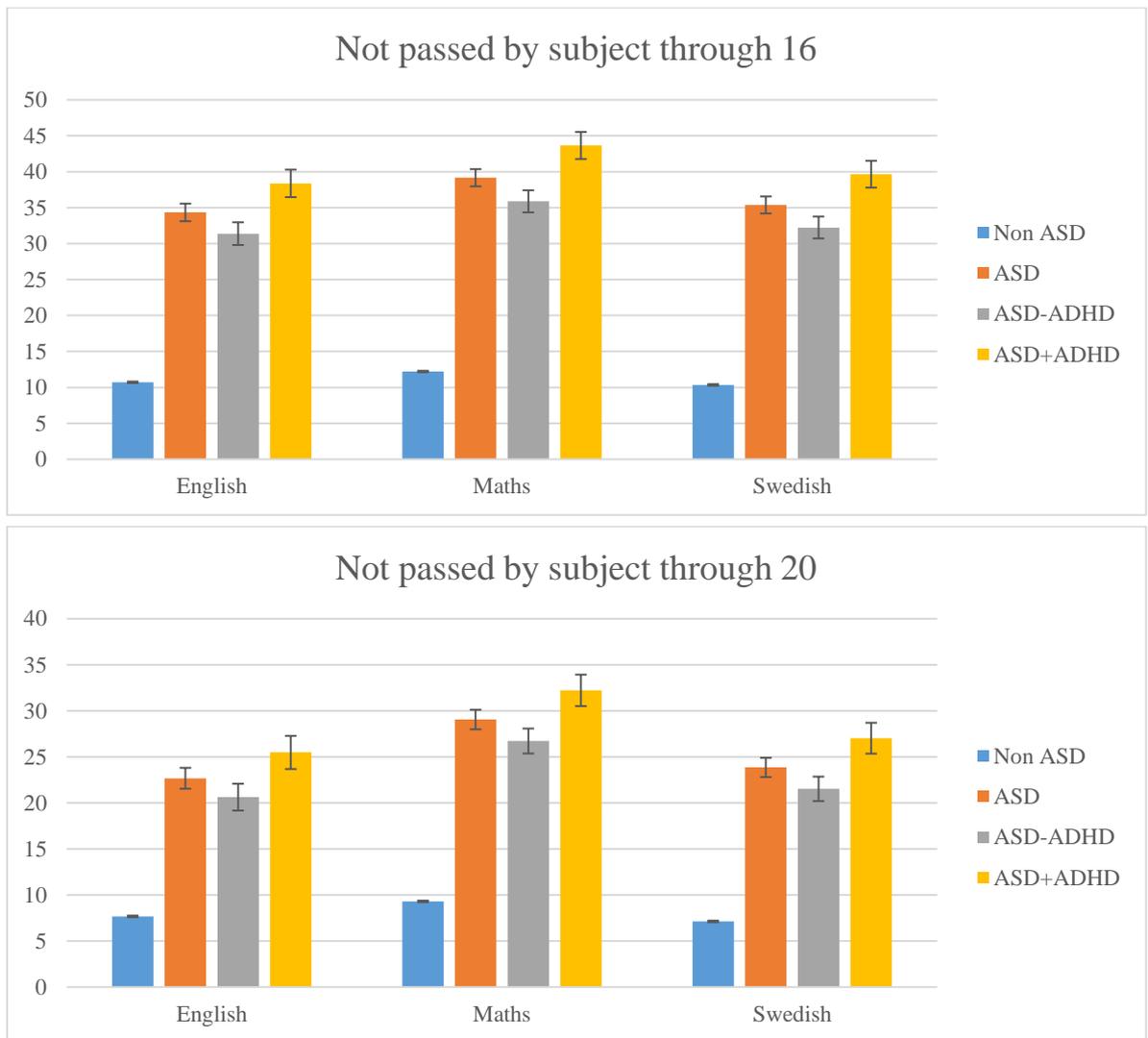


Figure 3. Proportions (with 95 % Confidence Intervals) of individuals not passing core subjects (Mathematics, English and Swedish) at 16 and 20 years in relation to presence of autism without intellectual disability and ADHD

5.1.2 Study III

In the study III final exam grade registered before student turned 20, the (mean) age for completion of upper secondary schooling was investigated. Total of 242,308 individuals were old enough to have completed upper secondary education of whom 3,918 (62 % male) were identified as having an autism diagnosis without ID.

The main findings were that:

- In the autistic group 32.3 % compared to 9.5 % of non-autistic group did not achieve this educational goal.
- Discrepancy between sexes was such that odds of non-completion in autistic females OR = 3.46 [3.06-3.91] was higher than that in autistic males (OR 2.63 [95 % CI 2.39-2.91]). This effect modification by sex was statistically significant (p-value <.0001).

- The presence of ADHD increased the likelihood of non-completion in autistic students, and highest odds were observed in the group with both diagnoses (6.03 [5.44- 6.69]), followed by the subgroup with only autism diagnosis (4.99 [4.53- 5.50]), and the group with diagnosis of ADHD only (3.95 [3.74- 4.15]).

5.2 SELF-HARM AND SUICIDE

5.2.1 Study II

The study population comprised of 410,732 individuals born to 245,117 mothers followed up from at least 10 to a maximum of 27 years of age. Of these, 9,070 had a diagnosis of autism (6,753 of whom had no ID and 2,317 had a recorded diagnosis ID).

The main findings were that:

- Nearly 3 % of autistic individuals had been hospitalized at least once for self-harm between the ages of 10 and 27 years, compared with 0.8 % of their non-autistic peers.
- Hospitalizations for self-harm were more common in autistic individuals without ID (3.6 %), than in those who had both diagnoses (1.3 %).
- Although poisoning was the most common self-harm method among admitted individuals regardless of autism, over 15 % of all admissions in the autistic group were because of self-cutting compared to 8 % in the non-autistic group.
- The risk of self-harm was increased in autism, particularly in the subgroup without ID, also when occurring without other comorbidities. Risks were about fivefold and similar for single diagnoses of either autism without ID (RR 5.9 [95 % CI 4.9–7.0]), ADHD (6.1 [5.6–6.8]), or depression (4.6 [4.2–5.0]), and somewhat lower in anxiety disorders (3.0 [2.8–3.3]). Individuals with autism without ID and either ADHD, depression, or anxiety disorder additionally, had about a tenfold increase in risk for self-harm as compared with those without any diagnoses in the fully adjusted model.
- Non-autistic full (1.6 [1.3–2.0]) and half siblings (1.4 [1.1– 1.9]) of individuals with autism had a higher risk of self-harm as compared with population controls. These associations were more apparent for siblings of children with autism without intellectual disability.

5.2.2 Study IV

For this analysis, 2,822,789 individuals were identified and followed from age 12 up to age 37 years, by December 2021. Of these, 3.1 % (86,427) had a diagnosis of autism (36.7 % of those were females). In the autistic group 6.3 % (5,405) had a record of at least one visit to medical services due to self-harm, compared to 1.4 % (37,994) in the non-autistic population. At the end of follow-up, 3,917 individuals had died due to suicide.

The main findings were that:

- In autistic individuals with a record of self-harm the likelihood of suicide was substantially higher (HR 31.4 95 % CI [21.7-36.4]) than both in non-autistic self-harmers 20.4 [18.9-22.0] and autistic individuals who did not engage in self-harm (2.1 [1.8-2.5]). This gradient and size of risks did not change materially, after adjusting for socioeconomic and parental factors.
- The presence of ADHD and ID did not markedly influence risks of suicide mortality in self-harmers. Adjustment for both neurodevelopmental conditions (ADHD and ID) left more than twenty-fold increased risk of suicide in autistic self-harmers.
- The risk of suicide was higher when autism and self-harm was present together than what should be expected from the risks associated with autism and self-harm per se. Additive interaction between autism and self-harm was indicated by the Relative Excess Risk Due to Interaction, RERI, which was clearly > 0 , and more specifically 6.0 (2.4-9.5).
- Among *females*, the relative risk of suicide in relation to self-harm was almost twice as high in autistic (HR 37.6, 95 % CI [27.5-47.8]), than in non-autistic individuals (21.4 [18.8-24.4]). The relative risk of suicide in relation to self-harm was also higher in the autistic (16.7 [13.5-20.8]) than in the non-autistic (13.8 [12.5-15.3]) *males*. Thus while RERIs were > 0 for both males and females, the additive interaction between autism and self-harm appeared more pronounced in females.
- All methods of self-harm conveyed higher risks of consequent suicide in the autistic self-harmers. The risk conveyed by self-cutting was, however, notably greater in the autistic (34.1 [24.9-46.7]) versus the non-autistic group (23.7 [19.7-28.6]). Within the autistic group of self-harmers, the level of risk corresponding to self-cutting appeared even higher than that observed for violent self-harm (34.1 [24.9-46.7], and 29.9 [21.1-42.4], respectively).

6 DISCUSSION

6.1 SUMMARY OF THE MAIN FINDINGS

This thesis has investigated two domains of outcomes in autistic individuals' including educational attainment, at the end of compulsory (primary and lower secondary) (Study I) and upper secondary (Study III) mainstream schooling, and self-harm, per se (Study II), and in relation to suicide (Study IV) in Sweden.

The results suggest that autistic youth without ID in mainstream settings are at risk of lower formal educational attainment in both primary and secondary schooling compared to their non-autistic peers. The most vulnerable are autistic females and students with co-occurring ADHD. They also confirm a substantial burden of self-harm in autistic individuals, including a discrepantly high risk of fatal outcomes of such harm.

6.2 FINDINGS IN THE CONTEXT OF PREVIOUS RESEARCH

6.2.1 School outcomes

In the two large total-population studies (I and III), we analysed objective indicators, real life measures administered by schools and teachers, of educational attainment. At the end of compulsory education (study I) autistic students were considerably less likely to reach eligibility criteria compared to their non-autistic peers. At age 16, which is the expected age for graduation in Sweden, 29 % fewer autistic students without ID were qualified for upper secondary education than non-autistic peers. This difference decreased somewhat at age 20. Comorbid ADHD, female sex and lower family income further increased the likelihood of autistic students not meeting the qualification criteria for upper secondary education, indicating the moderating role of these covariates. Findings are in line with recent cohort study from Denmark focusing on educational performance in compulsory schooling in adolescents with 29 specific mental disorders (autism spectrum was one of those). Autism as well as all the other conditions were associated with underperformance⁶⁴. However, this study included only Danish-born children with parents born in Denmark. In contrast to our findings, a higher proportion of autistic girls were found to take the final exam at the end of compulsory schooling compared to autistic male students (RR 0.43 [95 % CI, 0.41-0.44] and 0.39 [0.3-0.4] for girls and boys, respectively). Whether diagnostic practices differ between Sweden and Denmark such that autistic females with higher ability are less often diagnosed with autism in Sweden as compared to Denmark, is not known. Yet, such scenario may partly explain the differences in findings. Another recent study that investigated the influence of several mental disorders (autistic students were excluded) on school performance, defined as qualification for upper secondary schooling found that ADHD was the diagnosis most

strongly associated with educational underachievement⁸⁶. This is in line with our findings that ADHD exacerbated the risk of adverse outcomes in autistic students.

Study III demonstrates that autistic students without ID have an almost fivefold higher odds of non-completion of secondary education compared to their non-autistic peers. This strong association between autism and non-completion of upper secondary education was not explained by co-existing ADHD, moreover the risk of non-completion was higher in those identified with only autism than in students with only ADHD. Students with both autism and ADHD did worse than all other groups. This study also found an important sex discrepancy in that the risk of non-completion was particularly high in autistic females. The results of the study III on educational attainment in secondary education, are difficult to directly compare to the other studies (due to the differences in methodology and choice of measures and outcomes). They are, however, in line with previously described general underperformance of the autistic students^{57 23 25}. In the present study, ADHD played a substantial role in the profound underachievement of autistic students without ID which also is in line with previous evidence confirming ADHD as a risk factor of academic underperformance^{61 87}.

As in study I, again, autistic females were particularly vulnerable to adverse outcomes, and we could confirm significant modification of effect by sex on autism regarding completion of secondary education. This contrasts findings in the general population where females show a relative advantage in educational achievements as compared to males⁶³. Autistic females *get their diagnosis later* in ages⁷⁹, and were found to have generally *greater impairment* in social/communication skills, cognitive ability⁶⁵. Whether autistic female phenotype with higher functioning individuals is differentially underdiagnosed might partly explain negative outcomes since timely support is likely to be missed.

6.2.2 Self-harm and suicide

In study II, a clear overrepresentation of hospital admissions for self-harm in adolescents and young adults with autism in comparison to their typically developing peers was found. These results, confirm those of a previous case–control study⁸⁸. Yet, present study used a more detailed case ascertainment, also including data from outpatient health services (comprising child and adolescent as well as adult psychiatric care). Autistic individuals were more likely to be admitted to hospitals for self-harm regardless of common comorbid psychiatric disorders, which is consistent with a large study from Taiwan⁸⁹. However, Jokiranta-Olkonemi and colleagues reported the opposite, after adjusting for a range of comorbid psychiatric conditions, autism was not significantly associated with self/harm⁹⁰. While adjusting for comorbidities that can be regarded as mediators of the relationship between autism and self-harm investigators may have introduced collider bias that explain discrepancies between their and present study.

Sibling-analyses indicated that autism was associated to self-harm independently of shared familial factors (i.e., the 50 % of genes and the aspects of the family environment, such as parenting style or living conditions, that is shared by siblings). These results were in line with

previous research⁸⁸ that found that siblings of autistic individuals were somewhat more likely to have self-harmed than the general population.

Self-poisoning was the most common self-harm method in study II, in line with hospital-based studies on general population^{44,45}. However, autistic individuals had a more notable increased risk for admissions because of self-cutting than poisoning, in the study II.

In the study IV greatly increased risk of suicide in both autistic and non-autistic self-harmers were observed, yet notably higher in the autistic group. This is in line with previous results on association between self-harm and suicide mortality in the general population⁴⁵, and studies indicating high burden of self-harm inclusive suicide in autistic individuals^{88,91}.

Sex differences were observed in present study, *relative* to risks of suicide in individuals of the same sex in general population, autistic females demonstrated higher relative risks than those observed in males. These results are in line with previous studies on autistic patients^{68,91}, in contrast to the findings on influence of sex in general psychiatric population⁹².

Although, self-poisoning was the most common self-harm method in both autistic and non-autistic individuals in the present study, self-cutting was associated with particularly high relative risks of consecutive suicide in both groups, but more so among those with autism. Self-cutting is associated with higher levels of impulsivity and tends to be more repetitive⁹³, and impulsivity and insistent on sameness are traits that are also innate in autism⁹⁴. These features may contribute to perilousness of self-cutting in autism. Some evidence of higher suicidal intent in autistic self-harmers who engage in self-cutting is previously reported⁹⁵, and may be in line with findings in present study. Self-cutting is generally regarded as a behavior with less suicidal intention than self-poisoning, and patients presenting with self-cutting may be less likely to receive psychosocial assessment or to be admitted to in-patient care⁹⁶. Higher risks of suicide mortality consequent to self-cutting among autistic self-harmers observed in present study imply the need of careful reconsideration of the existing attitude in psychiatric praxis.

6.3 METHODOLOGICAL CONSIDERATIONS

6.3.1 Data sources

This thesis is based on the data from Sweden's rich administrative and health data registers. Such research allows the investigation of the entire populations with negligible loss to follow-up. Sample size was, e.g., large enough to study an event as rare, and serious, as suicide with sufficient precision. In studies like studies presented here, that utilize pre-existing, a.k.a., secondary data, collected primarily for administrative purposes and secondarily used for research rely on the quality and completeness of this data. The Swedish civil registration

systems have long tradition and high coverage⁸⁰, and as such it is important for research due to its efficiency and feasibility. The long follow-up and rich data on confounding variables and effect modifiers are other strengths in present studies. The multisource identification of autism allowed to study a complete, and thus more heterogenous, population of the autistic individuals representative of this broad group today. This identification process involved retrieving “cases” also from outpatient clinics. Thus, also individuals with a less severe symptom burden were included on our studies. There are some drawbacks, however, to consider when interpreting results from register-based studies. Foremost, these studies are obviously limited to data that exist in registers. Since this data is collated for administrative and not research purposes, important information on potentially confounding or effect modifying factors are lacking. For example, information on symptom severity in autism, IQ, and “softer aspects” of the school environment such as teachers’ attitude towards and competence to teach autistic students, and/or peer relations was not available to us.

6.3.2 Psychiatric epidemiology – what is a psychiatric disorder?

Defining and measuring psychiatric conditions is one of the major challenges of the psychiatric research and practice and should be considered in the context of this thesis. What is “normal” and what is “pathologic”? What is a diagnosis? This question is particularly important in the psychiatric discipline due to the lack of clinically useful biological indicators, and the fact that all diagnoses are defined as symptom constellations. Furthermore, psychiatry deals with cognition, emotion regulation and behaviours and is thus strongly dependent on the socio-cultural context. The diagnostic process may also be biased in different directions. Negative attitudes and stigma towards psychiatric care and diagnoses may refrain from care-seeking and hinder diagnostic evaluation when called for. Yet, there may also be drivers of care-seeking. For example, individuals facing challenges may request formal diagnoses, since such diagnoses may prompt benefits or other types of societal support. In spite of the evolvement of the diagnostic guidelines (DSM and ICD) over the years, the psychiatric nosology is still being questioned regarding its validity⁹⁷, and the complexity of defining and assessing the clinical boundaries of the psychiatric conditions⁷⁵ persist.

6.3.3 Selection bias

Selection bias is not an important drawback in observational studies based on health care and administrative registers, such as the studies founding this thesis. This is because both non-participation and loss to follow-up are negligible in these data that cover the total population.

6.3.4 Confounding

A range of potential confounders were considered (assessed and controlled for) in the present studies, however possibility of residual confounding may never be ignored. Confounding by indication is important in the studies II and IV, whether individuals who have contacts with health care services for any reason (such is the case of autism), are potentially more likely to be detected and registered when presenting their (less severe) self-harm. If this is differential

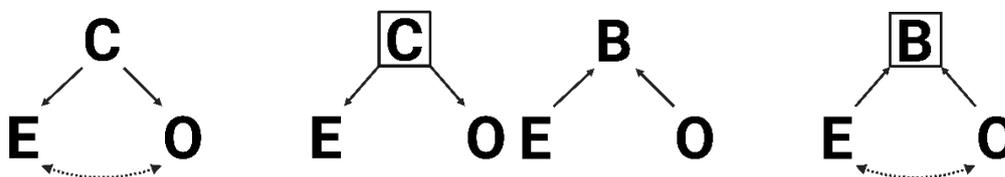
in relation to our exposure (i.e., if autistic people are more likely than the general population to seek help and are more likely than the general population to be diagnosed and registered as having self-harmed), then our results may overestimate the true associations.

6.3.5 Problem of comorbidities in autism and collider bias

Autism has consistently been associated to heightened psychiatric morbidity^{12 14}, and mental health challenges may be nearly universal parts of the lived experience of the autistic people of all ages. However, some indication that more cohesive and precise terminology when referring to conditions that occur along with autism is needed. It may be important to distinguish whether autism and the other condition *share etiologic origin* (and may share defining characteristics i.e., sub phenotype) or are *resulting from autism* related disparities or health influences of behaviours developed to cope with symptoms of autism^{15 98}. In epidemiology this is an issue of major importance, conditions occurring more often in autistic than individuals in general population could confound results and jeopardize the causal inference, and thus need to be controlled or adjusted for. However, overadjustment can as well lead to spurious results. To deal with this issue we have considered ADHD a condition that that is as autism with an early onset and shares genetic and phenotypic characteristics, “truly co-occurring”¹⁵. The issue of depression, condition that may at least partly occur due to problems autistic individuals face, thus, to be resulting from autism, is more difficult to characterize in terms of role on association between autism and given outcome (self-harm in study IV).

We may assume that autism⁹⁹ (exposure) and self-harm⁹² (outcome) independently have a common effect (depression). If this assumption is correct, controlling for depression (“effect” of both exposure and outcome) may distort the association between autism and self-harm (Figure 4).

Figure 4. Illustration of theoretical framework for confounding **C** (left) and collider variable **B** (right)¹⁰⁰.



It is also tempting to address depression or other psychiatric disorders as mediators of associations between autism and adverse outcomes such as school failure or self-harm, i.e., to elucidate any direct versus any indirect effect of autism *per se* by adjustment for such disorders. Such an adjustment, however, rests on important assumptions that there is no confounding, not only of the exposure-outcome association, but also of the exposure-

mediator or mediator-outcome associations. If these assumptions are not met, adjustment for a mediator may introduce strong bias.

In the studies comprising this thesis, that were based on data that lacked granular information on some risk factors, we thus refrained from adjustment for psychiatric co-morbidities that could have resulted from autism to avoid overadjustment and collider bias.

7 ETHICAL CONSIDERATIONS

All studies were approved by Regional Ethical Boards in Sweden, the Ethical Board in Stockholm (Study I-III) and Linköping (Study IV). The studies did not entail any experiments on humans or animals. They instead raise possible ethical issues related to breaches of integrity due to the utilization sensitive data from registers as collated by health and other services. The possible stigmatization of autistic individuals related to disclosure of negative outcomes is another ethical problem. These issues are considered below.

7.1 REGISTER STUDIES

To minimize integrity issues, and protect against inappropriate use or disclosure, all data was managed with uttermost care according to rules and regulations of data security. Confidentiality has been always maintained. All data were pseudo-anonymized before being made available to the research group, and only aggregated results are presented. Keys linking the study subject's identifier to personal identity numbers are held by Statistics Sweden and is not available to our research group or any other partner.

7.2 AUTISM AND ASPECTS OF STIGMA

Autism is in our studies presented in the light of adverse effects of this condition, this may risk labelling of the autistic specific population as particularly prone to poor educational and health outcomes, possibly instigating stigma. Stigmatizing could lead to discrimination of the autistic people in the labour market and elsewhere. However, information on these outcomes, and the underlying within-group-risk-factors, is essential for service planning and interventions to reduce inequalities, increase quality of life in autistic individuals and prevent suicides in these individuals in the long run.

This ethical consideration requires careful consideration of the language use in scientific as well as lay communication of the research. In formulating such communication, it is essential to avoid ableist language (the assumption that disabled people are inferior to nondisabled ones) to avoid marginalization of autistic people. Furthermore, it is important to ensure that the information will be of practical use for services, autistic individuals, and their families and can have a positive impact on the lives of concerned individuals. For example, this could

be done through emphasis of the exploration of any modifying factors and amenable societal interventions and highlighting also beneficial outcomes.

8 CONCLUSIONS

This thesis provides evidence for substantial disparities regarding the two investigated outcome domains, educational performance in mainstream schooling, and self-harming behaviours between autistic and non-autistic individuals.

Autistic individuals without ID attend mainstream education are expected to perform equally and along with their non-autistic peers in pursue of knowledge as well as self-image and self-esteem. These are all foundations of future life prospects. This thesis, however, demonstrates that autistic students are at risk of substantial underperformance during the primary and secondary stages of education. This risk was particularly high among autistic females and autistic students with a diagnosis ADHD. In societies advocating inclusion, these discrepancies may be regarded as unacceptable inequalities rather than problems owned solely by autistic individuals and their families. Findings from this thesis thus emphasize an urgent need of further development of the education system to strengthen the support to autistic students.

This thesis adds evidence of profound burden of self-harming behaviour, including that such behaviour is not only more common, but also more strongly linked to suicide, in autistic individuals from adolescence to the middle age. It has furthermore expanded the knowledge on autism-specific features of self-harm, indicating that self-cutting may play a particularly adverse role in suicidality. Inferring from this evidence, suicidality in autistic individuals who present to medical services with self-harm should be carefully assessed and treated. The results further suggest that the appraisal of psychiatric morbidity and method of self-harm are important aspects of the suicidality assessment of autistic patients.

9 FUTURE PERSPECTIVES

Using large population-based cohorts with prospective data in Sweden, the aim of the present work was to elucidate two critical domains of outcomes. Firstly, the formal educational outcomes in autistic students without ID in mainstream schools, and secondly self-harm behaviours and its relationship to suicide in autistic adolescents and young adults.

The findings highlight several issues and raise new questions for future research. For example, the clear indication that sex modifies the risks of poor outcomes in autism warrants further investigation. Moreover, adequate diagnostic instruments, validated in the autistic population are needed in psychiatry (and fortunately, some efforts in this area are being made)¹⁰¹. Research to develop therapeutic actions that can meet care needs and prevent suicide among autistic self-harmers is also urgently need. Additionally, work should also be

devoted to elucidation of the underlying mechanisms behind self-harm in autism. Specifically, it is important to disentangle how co-morbid psychiatric or somatic conditions, subclinical and clinical features core symptoms in autism, and psychological consequences related to the disability in day-to-day life, respectively, all affect the risk for and consequences of self-harm in autistic people.

The findings of substantial disparities in educational attainment, a formal necessary requirement for higher education and gainful employment, urgently incites new research of how the education system can be developed to mitigate barriers faced by autistic students. Educational outcomes are determined by factors at several levels including at the cultural/societal (e.g., support systems, educational policies, and values), social (e.g., school environment such as the physical environment, attitudes towards inclusion, peer relation, bullying), familial (e.g., genetic factors and parental support, educational capital, and socioeconomic position) and individual (student's characteristics). Further work is needed to identify how interventions in all these levels may contribute to higher educational attainment in autistic students. Such work may include, but indeed not be limited to, epidemiological approaches such as cross-country comparisons and natural experiments utilizing policy changes as instrument variables.

Another perspective for future research includes biases based on contemporary teachers' perceptions regarding teaching and rating of autistic students. Such efforts are ongoing like recent work in Sweden on interventions aimed to increase teachers' understanding of autistic children¹⁰².

Future interventional research work should be planned and executed in co-creation with relevant actors to ensure feasibility, acceptability, and appropriateness. Relevant actors include autistic individuals and their families, education and health service policy makers and commissioners, health care and social service providers as well as school leaders and teachers.

9.1 CLINICAL IMPLICATIONS

On the individual level, close monitoring of suicidality in all autistic individuals seeking care for self-harm is needed. This assessment probably should extend beyond evaluation of psychiatric morbidity and include far more general issues of the living experience of autistic people. Furthermore, there is evidence of a variety of barriers to the provision of evidence-based mental health care for autistic people. These may include limited experience and knowledge of autism among health care practitioners, resulting in lower confidence working with autistic adults¹⁰³. Thus, capacity building, including education about autism, of the medical work force may be an important means of strengthening the health system and care for autistic people.

On the health policy level, a more exhaustive inclusion of health care needs specific to the autistic population, including updated clinical guidelines, is called for.

10 ACKNOWLEDGEMENTS

I feel great honour and immense gratitude for the collaboration with my main supervisor **Cecilia Magnusson**. Thank you for giving me the opportunity to work on this project and for having the courage to let me into the mesmerizing world of epidemiology and public health research while being fully aware of the challenges of supervising a PhD student working as a clinician. Thank you for important philosophical discussions on essence of what we study and how we live. With your impeccable scientific stringency, your exemplary research ethics, you are a never-ending inspiration. You have my profound admiration.

Dheeraj Rai, my co-supervisor, thank you for always finding the way to encourage me, and for sharing your enthusiasm towards research.

Selma Idring Nordström, my co-supervisor, sincere thanks for your knowledge and all the encouragement during my PhD journey, and for sharing the inspiring moments of beauty in art and life. Every conversation with you was energizing and inspiring, you have always made me feel welcome, in research and in your home. Najtoplije hvala!

Michael Lundberg, thank you for helping me find the way in the labyrinth of SAS, for being a co-writer and an impeccable statistic support, I have learned from you, and I have always felt welcome. Thank you for all the conversations from Cox regression models to hiking expeditions to Sarek.

Bo Runeson and **Anna Stenseth**, thank you for giving me the opportunity to attend The Research School for clinicians in psychiatry organized in cooperation between Karolinska Institutet and Stockholm County. This school has been an excellent way to introduce me to research.

Christina Dalman and **Göran Rydén**, thank you for supporting me in the very beginning of my PhD studies, and for your wise attitude to encourage a psychiatrist to do research.

To **Mini Ruiz**, my sister, my friend, my colleague, and my guide in all the questions big and small from the first day I moved to Sweden. Thank you for your pedagogic brilliance and your generous support and never-ending encouragement. Thank you for always being tuned on to where I was for the moment to help me find the solution on how to move forward. And many thanks to the four wise and inspiring young women, **Fransisca**, **Esmeralda**, **Matilde** and **Miranda** all who have a very special place in my life!

Christian Rück, thank you for your wise and always present mentorship, and for sharing with me your insights and passion regarding the intricate interplay of psychiatry and society.

Viktor H. Ahlqvist, my friend and my guide, thank you for all the support, discussions, and ideas on epidemiology, rakija, and life in general, and not less for organizing “anxiety free dinners” along my PhD journey.

Peiwen Liao, Nora Döring, Iryna Culpin, Anna Ohlis, Gergö Hadlaczky, Anton Lager, my teachers, and co-authors, thank you for being patient with me and always sharing your enthusiasm towards research.

Thank you, **Maki, Megan, Melody, Sophie, Sara, Diego, Fanny, Kirsi, Martin,** current and former PhD students, and my brilliant colleagues in GPH, for all the small talk on statistics, epidemiology, PhD journey and life in general.

Maia Alvariza, my dear colleague, and a source of constant support over the years, thank you for your encouragement and your wisdom that never failed to calm me. Without your help this work would never have been done. Thank you for taking such a good care of my patients while I was away and never complaining about that.

I am deeply grateful to **Margot Björklund Kitanović** and all our working colleagues at psychiatric ward 23 at S:t Görans Hospital. You provide rewarding and joyful working environment in spite (or perhaps because!) all the daily difficulties, you inspire me every day of my clinical work!

Ulla-Britt Hjelmblink and **Eva-Lii Mark,** my wise friends, and guardians in issues big and small, thank you both for your ever present and warm friendship and support.

I am grateful to **Vera Stojanović,** my first ever teacher in the elementary school, you made us convinced that school is a safe base and a joyful playground to explore the world. Hvala Vam, draga učiteljice!

Thank you, **Luna Kaić,** for your love and for finding the right words when I did not know how to navigate in my studies, you make me sure that the world of tomorrow is a bright and brilliant place.

I would like to thank **Ivan Mirković** and **Zlatica Mamužić** my dear friends, for all the years of love and understanding. And for all the dances, the wonder, and the curiosity that we share!

My extended families, **Sofia Bubak, Tara Vujić, Gustaf,** and **Oscar Fredell** for inviting me to the worlds of your interests, thoughts, and ideas, and for never failing to make me feel that I am your family.

I am immensely grateful to my parents, **Jela** and **Milan Kostić** for the love, encouragement and for the unshakable belief (from the very beginning of my life) that I literally, can achieve whatever I want.

Thank you, **Peter Fredell** for your love and never-failing support and encouragement through these years, and for reading *The Book of Why*, not once but twice!

11 REFERENCES

1. Zeidan J, Fombonne E, Scora J, et al. Global prevalence of autism: a systematic review update. *Autism Research* 2022;15(5):778-90.
2. Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet (London, England)* 2014;383(9920):896-910. doi: 10.1016/s0140-6736(13)61539-1
3. Manouilenko I, Bejerot S. Sukhareva—prior to Asperger and Kanner. *Nordic journal of psychiatry* 2015;69(6):1761-64.
4. Kanner L. Autistic disturbances of affective contact. *Nervous child* 1943;2(3):217-50.
5. Asperger H, Frith UT. 'Autistic psychopathy' in childhood. 1991
6. Roman-Urrestarazu A, Dumas G, Warrier V. Naming Autism in the Right Context. *JAMA Pediatr* 2022;176(7):633-34. doi: 10.1001/jamapediatrics.2021.6036
7. Sinclair J. Why I dislike “person first” language. *Autonomy, the Critical Journal of Interdisciplinary Autism Studies* 2013;1(2)
8. Bottema-Beutel K, Kapp SK, Lester JN, et al. Avoiding ableist language: Suggestions for autism researchers. *Autism in Adulthood* 2021;3(1):18-29.
9. Buijsman R, Begeer S, Scheeren AM. 'Autistic person' or 'person with autism'? Person-first language preference in Dutch adults with autism and parents. *Autism* 2022;13623613221117914. doi: 10.1177/13623613221117914
10. Association AP. Diagnostic and Statistical Manual of Mental Disorders (DSM-V). Arlington: American Psychiatric Association; 2013.
11. Lai MC, Kasseh C, Besney R, et al. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The lancet Psychiatry* 2019;6(10):819-29. doi: 10.1016/s2215-0366(19)30289-5
12. Lugo-Marin J, Magan-Maganto M, Rivero-Santana A, et al. Prevalence of psychiatric disorders in adults with autism spectrum disorder: A systematic review and meta-analysis. *Research in Autism Spectrum Disorders* 2019;59:22-33.
13. Collaborators. GMD. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* 2022 Feb;9(2):137-150 2022;2022 Feb;9(2):137-150. doi: doi: 10.1016/S2215-0366(21)00395-3. Epub 2022 Jan 10. PMID: 35026139; PMCID: PMC8776563.
14. Hossain MM, Khan N, Sultana A, et al. Prevalence of comorbid psychiatric disorders among people with autism spectrum disorder: An umbrella review of systematic reviews and meta-analyses. *Psychiatry research* 2020;287:112922. doi: 10.1016/j.psychres.2020.112922
15. Rubenstein E, Bishop-Fitzpatrick L. A matter of time: The necessity of temporal language in research on health conditions that present with autism spectrum disorder. *Autism*

16. Milner A, Page A, LaMontagne AD. Long-term unemployment and suicide: a systematic review and meta-analysis. *PloS one* 2013;8(1):e51333. doi: 10.1371/journal.pone.0051333
17. Hahn RA, Truman BI. Education Improves Public Health and Promotes Health Equity. *International journal of health services : planning, administration, evaluation* 2015;45(4):657-78. doi: 10.1177/0020731415585986
18. Rogge N, Janssen J. The Economic Costs of Autism Spectrum Disorder: A Literature Review. *J Autism Dev Disord* 2019;49(7):2873-900. doi: 10.1007/s10803-019-04014
19. Wolff S. The history of autism. *Eur Child Adolesc Psychiatry* 2004;13(4):201-8. doi: 10.1007/s00787-004-0363-5
20. Pellicano E, Dinsmore A, Charman T. What should autism research focus upon? Community views and priorities from the United Kingdom. *Autism* 2014;18(7):756-70. doi: 10.1177/1362361314529627
21. Rutter M, Greenfield D, Lockyer L. A five to fifteen year follow-up study of infantile psychosis. II. Social and behavioural outcome. *The British journal of psychiatry : the journal of mental science* 1967;113(504):1183-99. doi: 10.1192/bjp.113.504.1183
22. Eaves LC, Ho HH. Young adult outcome of autism spectrum disorders. *J Autism Dev Disord* 2008;38(4):739-47. doi: 10.1007/s10803-007-0441
23. Levy A, Perry A. Outcomes in adolescents and adults with autism: A review of the literature. *Research in Autism Spectrum Disorders* 2011;5(4):1271-82.
24. Henninger NA, Taylor JL. Outcomes in adults with autism spectrum disorders: a historical perspective. *Autism* 2013;17(1):103-16. doi: 10.1177/1362361312441266
25. Shattuck PT, Narendorf SC, Cooper B, et al. Postsecondary education and employment among youth with an autism spectrum disorder. *Pediatrics* 2012;129(6):1042-49.
26. Steinhausen HC, Mohr Jensen C, Lauritsen MB. A systematic review and meta-analysis of the long-term overall outcome of autism spectrum disorders in adolescence and adulthood. *Acta psychiatrica Scandinavica* 2016;133(6):445-52. doi: 10.1111/acps.12559
27. Howlin P, Magiati I. Autism spectrum disorder: outcomes in adulthood. *Current opinion in psychiatry* 2017;30(2):69-76. doi: 10.1097/ycp.0000000000000308
28. Enner S, Ahmad S, Morse AM, et al. Autism: considerations for transitions of care into adulthood. *Current opinion in pediatrics* 2020;32(3):446-52. doi: 10.1097/mop.0000000000000882
29. Gustafsson J-E, Allodi Westling M, Alin Åkerman B, et al. School, learning and mental health: A systematic review: Kungl. Vetenskapsakademien 2010.
30. Brännlund A, Nordlander E, Strandh M. Higher education and self-governance: The effects of higher education and field of study on voice and agency in Sweden. *International Journal of Lifelong Education* 2012;31(6):817-34.
31. Eide ER, Showalter MH. Estimating the relation between health and education: What do we know and what do we need to know? *Economics of Education Review* 2011;30(5):778-91.

32. Galobardes B, Shaw M, Lawlor DA, et al. Indicators of socioeconomic position (part 1). *Journal of Epidemiology & Community Health* 2006;60(1):7-12.
33. Sörberg Wallin A, Koupil I, Gustafsson JE, et al. Academic performance, externalizing disorders and depression: 26,000 adolescents followed into adulthood. *Soc Psychiatry Psychiatr Epidemiol* 2019;54(8):977-86. doi: 10.1007/s00127-019-01668-z
34. Kosidou K, Dalman C, Fredlund P, et al. School performance and the risk of suicide attempts in young adults: a longitudinal population-based study. *Psychological medicine* 2014;44(6):1235-43. doi: 10.1017/s0033291713001852
35. Kosidou K, Dalman C, Fredlund P, et al. School performance and the risk of suicidal thoughts in young adults: population-based study. *PloS one* 2014;9(10):e109958. doi: 10.1371/journal.pone.0109958
36. Björkenstam C, Weitoft GR, Hjern A, et al. School grades, parental education and suicide--a national register-based cohort study. *Journal of epidemiology and community health* 2011;65(11):993-8. doi: 10.1136/jech.2010.117226
37. Oquendo MA, Baca-Garcia E. Suicidal behavior disorder as a diagnostic entity in the DSM-5 classification system: advantages outweigh limitations. *World Psychiatry* 2014;13(2):128-30. doi: 10.1002/wps.20116
38. Turecki G, Brent DA, Gunnell D, et al. Suicide and suicide risk. *Nature reviews Disease primers* 2019;5(1):74. doi: 10.1038/s41572-019-0121-0
39. Hawton K, Saunders KE, O'Connor RC. Self-harm and suicide in adolescents. *Lancet (London, England)* 2012;379(9834):2373-82. doi: 10.1016/s0140-6736(12)60322-5
40. Klonsky ED, May AM, Saffer BY. Suicide, Suicide Attempts, and Suicidal Ideation. *Annual review of clinical psychology* 2016;12:307-30. doi: 10.1146/annurev-clinpsy-021815-093204
41. Oumaya M, Friedman S, Pham A, et al. [Borderline personality disorder, self-mutilation and suicide: literature review]. *L'Encephale* 2008;34(5):452-8. doi: 10.1016/j.encep.2007.10.007
42. Organization WH. Suicide worldwide in 2019: global health estimates. 2021
43. Knipe D, Padmanathan P, Newton-Howes G, et al. Suicide and self-harm. *Lancet (London, England)* 2022;399(10338):1903-16. doi: 10.1016/s0140-6736(22)00173-8
44. Hawton K, Saunders KE, O'Connor RC. Self-harm and suicide in adolescents. *The Lancet* 2012;379(9834):2373-82.
45. Geulayov G, Casey D, McDonald KC, et al. Incidence of suicide, hospital-presenting non-fatal self-harm, and community-occurring non-fatal self-harm in adolescents in England (the iceberg model of self-harm): a retrospective study. *The lancet Psychiatry* 2018;5(2):167-74. doi: 10.1016/s2215-0366(17)30478-9
46. Bertolote JM, Fleischmann A. Suicide and psychiatric diagnosis: a worldwide perspective. *World Psychiatry* 2002;1(3):181-5.
47. Nordentoft M, Mortensen PB, Pedersen CB. Absolute risk of suicide after first hospital contact in mental disorder. *Archives of general psychiatry* 2011;68(10):1058-64. doi: 10.1001/archgenpsychiatry.2011.113
48. Moseley R, Gregory N, Smith P, et al. Links between self-injury and suicidality in autism. *Molecular autism* 2020;11(1):1-15.

49. Raja M, Azzoni A, Frustaci A. Autism spectrum disorders and suicidality. *Clinical practice and epidemiology in mental health: CP & EMH* 2011;7:97.
50. Hannon G, Taylor EP. Suicidal behaviour in adolescents and young adults with ASD: Findings from a systematic review. *Clinical Psychology Review* 2013;33(8):1197-204. doi: <https://doi.org/10.1016/j.cpr.2013.10.003>
51. Richa S, Fahed M, Khoury E, et al. Suicide in autism spectrum disorders. *Arch Suicide Res* 2014;18(4):327-39. doi: 10.1080/13811118.2013.824834
52. Zahid S, Upthegrove R. Suicidality in Autistic Spectrum Disorders. *Crisis* 2017;38(4):237-46. doi: 10.1027/0227-5910/a000458
53. Segers M, Rawana J. What do we know about suicidality in autism spectrum disorders? A systematic review. *Autism research : official journal of the International Society for Autism Research* 2014;7(4):507-21. doi: 10.1002/aur.1375
54. Hedley D, Uljarević M. Systematic review of suicide in autism spectrum disorder: current trends and implications. *Current Developmental Disorders Reports* 2018;5(1):65-76.
55. Blanchard A, Chihuri S, DiGuseppi CG, et al. Risk of self-harm in children and adults with autism spectrum disorder: a systematic review and meta-analysis. *JAMA network open* 2021;4(10):e2130272-e72.
56. Howlin P, Moss P, Savage S, et al. Social outcomes in mid- to later adulthood among individuals diagnosed with autism and average nonverbal IQ as children. *J Am Acad Child Adolesc Psychiatry* 2013;52(6):572-81.e1. doi: 10.1016/j.jaac.2013.02.017
57. Keen D, Webster A, Ridley G. How well are children with autism spectrum disorder doing academically at school? An overview of the literature. *Autism* 2016;20(3):276-94. doi: 10.1177/1362361315580962
58. Ashburner J, Ziviani J, Rodger S. Sensory processing and classroom emotional, behavioral, and educational outcomes in children with autism spectrum disorder. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association* 2008;62(5):564-73. doi: 10.5014/ajot.62.5.564
59. Dardani C, Riglin L, Leppert B, et al. Is genetic liability to ADHD and ASD causally linked to educational attainment? *International journal of epidemiology* 2021;50(6):2011-23.
60. Verhoef E, Grove J, Shapland CY, et al. Discordant associations of educational attainment with ASD and ADHD implicate a polygenic form of pleiotropy. *Nature communications* 2021;12(1):1-14.
61. Chiang HL, Kao WC, Chou MC, et al. School dysfunction in youth with autistic spectrum disorder in Taiwan: The effect of subtype and ADHD. *Autism research : official journal of the International Society for Autism Research* 2018;11(6):857-69. doi: 10.1002/aur.1923
62. Mansour R, Ward AR, Lane DM, et al. ADHD severity as a predictor of cognitive task performance in children with Autism Spectrum Disorder (ASD). *Research in developmental disabilities* 2021;111:103882. doi: 10.1016/j.ridd.2021.103882
63. Serbin LA, Zelkowitz P, Doyle A-B, et al. The socialization of sex-differentiated skills and academic performance: A mediational model. *Sex Roles* 1990;23(11-12):613-28.

64. Dalsgaard S, McGrath J, Østergaard SD, et al. Association of mental disorder in childhood and adolescence with subsequent educational achievement. *JAMA psychiatry* 2020;77(8):797-805.
65. Frazier TW, Georgiades S, Bishop SL, et al. Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. *Journal of the American Academy of Child & Adolescent Psychiatry* 2014;53(3):329-40. e3.
66. Steinfeldt-Kristensen C, Jones CA, Richards C. The prevalence of self-injurious behaviour in autism: A meta-analytic study. *Journal of autism and developmental disorders* 2020;50(11):3857-73.
67. Schendel DE, Overgaard M, Christensen J, et al. Association of psychiatric and neurologic comorbidity with mortality among persons with autism spectrum disorder in a Danish population. *JAMA pediatrics* 2016;170(3):243-50.
68. Hirvikoski T, Mittendorfer-Rutz E, Boman M, et al. Premature mortality in autism spectrum disorder. *The British journal of psychiatry : the journal of mental science* 2016;208(3):232-8. doi: 10.1192/bjp.bp.114.160192
69. Cassidy S, Bradley P, Robinson J, et al. Suicidal ideation and suicide plans or attempts in adults with Asperger's syndrome attending a specialist diagnostic clinic: a clinical cohort study. *The lancet Psychiatry* 2014;1(2):142-7. doi: 10.1016/s2215-0366(14)70248-2
70. Cassidy S, Bradley L, Shaw R, et al. Risk markers for suicidality in autistic adults. *Mol Autism* 2018;9:42. doi: 10.1186/s13229-018-0226-4
71. Jokiranta-Olkonemi E, Gyllenberg D, Sucksdorff D, et al. Risk for Premature Mortality and Intentional Self-harm in Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders* 2020 doi: 10.1007/s10803-020-04768-x
72. Chen MH, Pan TL, Lan WH, et al. Risk of Suicide Attempts Among Adolescents and Young Adults With Autism Spectrum Disorder: A Nationwide Longitudinal Follow-Up Study. *J Clin Psychiatry* 2017;78(9):e1174-e79. doi: 10.4088/JCP.16m11100
73. Chang SS, Chen YY, Heron J, et al. IQ and adolescent self-harm behaviours in the ALSPAC birth cohort. *J Affect Disord* 2014;152-154:175-82. doi: 10.1016/j.jad.2013.09.005
74. Szklo M, Nieto FJ. *Epidemiology: beyond the basics*: Jones & Bartlett Publishers 2014.
75. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*: Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia 2008.
76. Nohr EA, Liew Z. How to investigate and adjust for selection bias in cohort studies. *Acta obstetricia et gynecologica Scandinavica* 2018;97(4):407-16. doi: 10.1111/aogs.13319
77. Gordis L. *Epidemiology E-Book*: Elsevier Health Sciences 2013.
78. D'Onofrio BM, Lahey BB, Turkheimer E, et al. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *American journal of public health* 2013;103 Suppl 1(Suppl 1):S46-55. doi: 10.2105/ajph.2013.301252
79. Idring S, Rai D, Dal H, et al. Autism spectrum disorders in the Stockholm Youth Cohort: design, prevalence and validity. *PloS one* 2012;7(7):e41280.

80. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016;31(2):125-36. doi: 10.1007/s10654-016-0117-y
81. Forsberg L, Rydh H, Jacobsson A, et al. Kvalitet och innehåll i patientregistret. Utskrivningar från slutenvården 1964-2007 och besök i specialiserad öppenvård (exklusive primärvårdsbesök) 1997-2007.(Quality and content of the Patient Register)(2009-125-15). *Book Kvalitet och innehåll i patientregistret Utskrivningar från slutenvården 1964-2007 och besök i specialiserad öppenvård (exklusive primärvårdsbesök) 1997-2007(Quality and content of the Patient Register)(2009-125-15)(Editor ed^ eds) City* 2009
82. Ludvigsson JF, Andersson E, Ekblom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450. doi: 10.1186/1471-2458-11-450
83. Jørgensen L, Ahlbom A, Allebeck P, et al. The Stockholm non-affective psychoses study (snaps): the importance of including out-patient data in incidence studies. *Acta psychiatrica Scandinavica* 2010;121(5):389-92. doi: 10.1111/j.1600-0447.2009.01500.x
84. Zou G. A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology* 2004;159(7):702-6. doi: 10.1093/aje/kwh090
85. Bender R. Introduction to the use of regression models in epidemiology. *Methods in molecular biology (Clifton, NJ)* 2009;471:179-95. doi: 10.1007/978-1-59745-416-2_9
86. Bortes C, Nilsson K, Strandh M. Associations between children's diagnosed mental disorders and educational achievements in Sweden. *Scandinavian Journal of Public Health*;0(0):14034948221089056. doi: 10.1177/14034948221089056
87. Loe, I. M., & Feldman, H. M. (2007). Academic and educational outcomes of children with ADHD. *Ambul Pediatr*, 7(1 Suppl), 82-90. doi:10.1016/j.ambp.2006.05.005
88. Hirvikoski T, Boman M, Chen Q, et al. Individual risk and familial liability for suicide attempt and suicide in autism: a population-based study. *Psychological medicine* 2019;1-12. doi: 10.1017/s0033291719001405
89. Chen M-H, Pan T-L, Lan W-H, et al. Risk of Suicide Attempts Among Adolescents and Young Adults With Autism Spectrum Disorder: A Nationwide Longitudinal Follow-Up Study. *The Journal of clinical psychiatry* 2017;78(9):e1174-e79.
90. Jokiranta-Olkonemi E, Gyllenberg D, Sucksdorff D, et al. Risk for Premature Mortality and Intentional Self-harm in Autism Spectrum Disorders. *J Autism Dev Disord* 2021;51(9):3098-108. doi: 10.1007/s10803-020-04768-x
91. Kølves K, Fitzgerald C, Nordentoft M, et al. Assessment of Suicidal Behaviors Among Individuals With Autism Spectrum Disorder in Denmark. *JAMA Network Open* 2021;4(1):e2033565-e65. doi: 10.1001/jamanetworkopen.2020.33565
92. Beckman K, Mittendorfer-Rutz E, Lichtenstein P, et al. Mental illness and suicide after self-harm among young adults: long-term follow-up of self-harm patients, admitted to hospital care, in a national cohort. *Psychological medicine* 2016;46(16):3397-405.
93. Hawton K, Harriss L, Rodham K. How adolescents who cut themselves differ from those who take overdoses. *European child & adolescent psychiatry* 2010;19(6):513-23.

94. Licence L, Oliver C, Moss J, et al. Prevalence and Risk-Markers of Self-Harm in Autistic Children and Adults. *J Autism Dev Disord* 2020;50(10):3561-74. doi: 10.1007/s10803-019-04260-1
95. Moseley RL, Gregory NJ, Smith P, et al. Links between self-injury and suicidality in autism. *Mol Autism* 2020;11(1):14. doi: 10.1186/s13229-020-0319-8
96. Kapur N, Murphy E, Cooper J, et al. Psychosocial assessment following self-harm: results from the multi-centre monitoring of self-harm project. *Journal of affective disorders* 2008;106(3):285-93.
97. Maj M. Why the clinical utility of diagnostic categories in psychiatry is intrinsically limited and how we can use new approaches to complement them. *World Psychiatry* 2018;17(2):121.
98. Caron C, Rutter M. Comorbidity in child psychopathology: concepts, issues and research strategies. *Journal of child psychology and psychiatry, and allied disciplines* 1991;32(7):1063-80. doi: 10.1111/j.1469-7610.1991.tb00350.x
99. DeFilippis M. Depression in Children and Adolescents with Autism Spectrum Disorder. *Children* 2018;5(9):112.
100. Lee H AJ, Nunan D. In Catalogue Of Bias. Collider bias. 2019
101. Cassidy SA, Bradley L, Cogger-Ward H, et al. Measurement Properties of the Suicidal Behaviour Questionnaire-Revised in Autistic Adults. *J Autism Dev Disord* 2020;50(10):3477-88. doi: 10.1007/s10803-020-04431-5
102. Leifler E. Teachers' capacity to create inclusive learning environments. *International Journal for Lesson & Learning Studies* 2020
103. Maddox BB, Crabbe S, Beidas RS, et al. "I wouldn't know where to start": Perspectives from clinicians, agency leaders, and autistic adults on improving community mental health services for autistic adults. *Autism* 2020;24(4):919-30. doi: 10.1177/1362361319882227