Sex differences in the internalising problem trajectories of autistic and non-autistic children across childhood and adolescence

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Name: Elna Suominen

Date: 13/06/2024

Overview

This thesis focused on sex/gender differences in internalising problems of autistic children and young people.

Part 1

The first part of this thesis is a systematic review and meta-analysis looking at whether there is a sex/gender difference in internalising problems of autistic children and young people. This study synthesised cross-sectional effects from forty-eight studies, encompassing a total of 10,045 autistic CYP. No significant sex/gender difference was found in mean internalising problem scores between autistic males and females. For anxiety symptoms, studies with lower risk of bias were more likely to report a smaller sex/gender difference in anxiety. Self-report data, and community sample were associated with a greater sex/gender difference.

Part 2

The second part contains the empirical paper, which investigated trajectories of internalising problems in autistic and non-autistic males and females from a large prospective UK birth cohort study, and whether these trajectories differ based on sex. The study found sex and autism specific trajectories in internalising problems for CYP. This implies the importance of developing of effective and timely interventions, particularly for adolescent autistic females, who appear most at risk.

Part 3

The third part is a critical appraisal of the research. It focuses on three themes: my relationship to autism research as a non-autistic researcher, the challenges of using advanced statistical methods as a trainee clinician, and the benefits and challenges of using secondary data in the context of my research.

Impact statement

This thesis investigated sex/gender differences in internalising problems of autistic and non-autistic children and young people (CYP) across childhood and adolescence.

The presented findings contribute to the field of autism research in two key ways. Firstly, the literature on sex/gender differences in internalising problems has been inconsistent in trying to ascertain whether autistic CYP exhibit the sex differences found in non-autistic CYP. This thesis is the first to provide a comprehensive synthesis of the existing literature, which brings some clarity to the questions asked by other researchers regarding whether factors such as sampling biases or IQ might contribute to the inconsistency of the previous research regarding the presence and direction of a sex difference.

Secondly, the empirical paper illustrates the developmental effects of age on the direction and magnitude of the sex difference in internalising problems of autistic and non-autistic CYP. It is one of the first studies investigating longitudinal effects of sex on internalising problems in a large prospective community-based cohort study. It is also one of the first to directly compare autistic and non-autistic males and females. The research replicated the "double whammy effect" of autistic female adolescents experiencing significantly more internalising problems than autistic male and non-autistic adolescents.

The present findings have important implications for clinical practice. Providing insight into the developmental trajectories of internalising problems helps us understand critical timings for interventions, and whether these differ based on sex and autism. For instance, the present study reveals autistic female adolescents as a possible high need group for psychological intervention. This is important to consider when assessing autistic children and when commissioning services for children and young people.

Currently, psychological interventions appear less effective for autistic CYP. This thesis showed that levels of internalising problems for autistic CYP increase dramatically after age seven, suggesting that early intervention might be crucial.

Moreover, the differing trajectories between autistic and non-autistic males and females suggest that the causal mechanisms for the development of internalising problems are likely influenced by factors related to sex/gender. The present findings are thus key for inspiring further investigation into causal factors that might explain why the trajectories of internalising problems differ based on sex and autism. For example, the high levels of internalising problems found in females in adolescence could relate to pubertal processes or by being more sensitive to the social pressures and transitions occurring adolescence. Understanding such processed will help develop and deliver more effective interventions for autistic and non-autistic CYP.

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PART 1: Literature Review

Systematic Review and Meta-Analysis of Sex/Gender Differences in Internalising Problems of Autistic Children and Young People

Abstract

Background: For autistic CYP, the findings are inconsistent regarding the presence and direction of a sex difference in internalising problems. This systematic-review and meta-analysis investigated whether autistic males and females differ cross-sectionally in internalising problems in childhood and adolescence.

Methods: Studies measuring internalising problems in autistic male and female CYP using validated internalising measures were included. Searches included Medline, Embase, PsycINFO, ASSIA and Web of Science databases. PRISMA guidelines were followed. Random-effects meta-analysis was used calculate hedge's g based on mean difference and standard deviations. Meta-regressions and narrative syntheses were completed to investigate impacts of age, IQ, and study characteristics on the pooled effect size.

Results: Forty-eight studies were included, encompassing a total of 10,045 autistic CYP. No significant sex difference was found in internalising problems (Hedges g=0.08 [-0.08; 0.24], p=0.30), anxiety (Hedges g= 0.08 [-0.02; 0.17], p=0.10) or depression symptoms (Hedges g= 0.05 [-0.16; 0.25], p=0.58). The heterogeneity in the pooled sex difference in internalising problems was high. For anxiety symptoms, studies with lower risk of bias were more likely to report a smaller sex difference in anxiety (β= -0.04, p = 0.02). Self-report data and community sample were associated with a larger sex/gender difference than parent-report (β=0.38, p=0.02), and clinical sample (β=0.21, p=0.02), respectively.

Conclusions: The meta-analyses indicated that autistic males and females do not differ in internalising problems in childhood and adolescence, implying possible aetiological differences to non-autistic children. However, the high heterogeneity cautions against drawing conclusions with certainty. The moderating effects of study characteristics suggest that sampling biases could contribute to inconsistencies found in the literature.

Introduction

Autism Spectrum Disorder (ASD, henceforth 'autism') is a neurodevelopmental condition characterised by differences in social communication and sensory processing, intense or focused interests, and a preference for certainty, routines, and sameness (Autistica, 2024; American Psychiatric Association [APA], 2013). It is a lifelong condition with strong genetic influences (Hodges et al., 2020). It has been estimated that in the UK 1.6 % of the population are autistic (Baron-Cohen et al., 2009). The estimated frequency of autism varies cross-culturally; In Europe it has been estimated as 0.5%, in America as 1%, in Asia 0.4%, in Australia as 1.7% and 1% in Africa (Salari et al., 2022). According to Salari (2022), reasons for such variation may include cross-cultural differences in interpretation of child behaviour, awareness of autism, and methodological differences.

Multiple terms have been used to refer to autism within communities, research literature, and clinical settings including "autistic", "ASD", "people with autism", etc. The guidance the National Autistic Society UK (2024), encourage the use of "identity first" terminology, i.e., "autistic child" as opposed to "person first" terminology, i.e., "child with autism". Additionally, they request people to avoid using the term "disorder", unless specifically referring diagnostic labels and criteria, such as ICD-11 (World Health Organisation [WHO], 2019) or DSM-5 (APA, 2013), to move away from the view of autism as pathological. This is in line with research by Kenny et al (2016), showing that UK autism community members, including autistic people, their parents and broader support network, preferred the terms "autistic", "autism", and "on the autism spectrum". The use of these terms is also supported by research on the views of autistic adults in Australia (Bury et al., 2023), and "English-speaking individuals across the globe" (Keating et al., 2023). Therefore, in this thesis, I will use the terms "autism", and "autistic" to refer to individuals on the autism spectrum, and this

will include those with clinical or research diagnoses of autism, Pervasive Developmental Disorder not otherwise specified (PDD-NOS), and Asperger's.

Traditionally, autism has been found to be more common in males, at a rate of 4:1. However, more recently Loomes et al (2017) found this rate to be 3:1 when accounting for methodological issues. Although, sex dependent heritability is likely to play a role in such sex difference, at least part of it is caused by a male bias in autism phenotype and diagnostic criteria, due to being developed based on largely male samples, as well as flawed epidemiological study recruitment and inclusion procedures (D'Mello et al., 2022; Napolitano et al., 2022).

Several researchers have suggested that in order to better understand autism, it may be important to understand sex and/or gender differences in autistic traits and co-occurring difficulties (Lai et al., 2015; Mandy & Lai, 2017; Strang et al., 2020). Biological sex refers to sex assigned at birth, which is based on physical characteristics, such as reproductive organs, chromosomes, hormones (Short et al., 2013). A person's gender identity, which includes the concepts of masculinity and femininity, is socially constructed, and may not always align with sex assigned at birth or with binary classifications. Most individuals' identities are informed by both sex and gender. However, although distinct, the effect of these can be difficult to separate due to the impact of cultural socialisation that takes place from birth (Lai et al., 2015). Ideally, we could examine the influence of these separately, but most studies discussed in this paper have not defined explicitly whether they are referring to sex or gender. Therefore, unless specified, "sex/gender" will be used to denote this (Lai et al., 2015).

Anxiety and depression have been identified as common co-occurring problems for autistic individuals. Hollocks et al (2019) estimated the rate of anxiety to be 27% and rate of depression to be 23% in autistic adults, which is significantly higher than the 15.7% observed within the general population (McManus et al., 2016). The heightened risk of mental health problems compared to non-autistic individuals has also been found in autistic children and young people (CYP) (Gadow et al., 2004; Gadow et al., 2005). For example, studies have found 34-37% of autistic CYP to experience clinical levels of anxiety and 48-50% to experience clinical levels of depression symptoms (Johnston & Iarocci, 2017; Mylett et al., 2023). In comparison, in non-autistic CYP the rates of anxiety and depression are estimated as 19.1% and 14.9%, respectively (Barker et al., 2019).

In CYP literature, mental health symptoms are often described in terms of "internalising" and "externalising" symptoms. Internalising symptoms refer to more inwardly focused emotional problems, such as symptoms of depression and anxiety, in comparison to more outwards oriented externalising problems, which tend to refer to behavioural problems of the sort seen in oppositional defiant disorder and conduct disorder (Achenbach, 1966; Achenbach & Edelbrock, 1978; Francis et al., 2019;). These groupings were established through factor analyses of issues identified in children and young people referred to therapy clinics (Achenbach et al., 2016).

The internalising and externalising problem categories offer a dimensional perspective on children's emotional and behavioural issues, suggesting that an individual's challenges can be placed on a spectrum between impairment and functionality (Doyle et al., 2016). This approach differs from the categorical conceptualisation of mental health used in DSM-5 (APA, 2013) and other diagnostic models. The dimensional approach can capture

psychosocial problems in both clinical and non-clinical populations. Accordingly, the groupings of internalising and externalising problems have been incorporated into well-established measures of child psychosocial wellbeing, such as the Strengths and Difficulties Questionnaire (Goodman, 2001), and the Child Behaviour Checklist (Achenbach, 1999).

Autistic CYP have been found to experience higher internalising problems that non-autistic CYP, in both clinical and community settings (Li et al., 2020; Skokauskas & Gallagher, 2012; Tseng et al., 2011). Several factors have been proposed to contribute to the higher levels of internalising problems in autistic individuals, such as individual traits associated with autism. These include differences in social communication (Dellapiazza et al., 2021), difficulties in emotion regulation (Conner et al., 2020; Rieffe et al., 2011), and in recognizing and describing emotions, and distinguishing them from bodily sensations, also known as alexithymia (Milosavljevic et al., 2016; Taylor, 2000). Cognitive inflexibility, including difficulty tolerating uncertainty and preference for sameness (Richler et al., 2010), are also linked to higher rates of internalising problems (Jenkinson et al., 2020).

Moreover, non-autistic people can struggle to understand and accommodate autistic individuals, potentially resulting in social marginalisation and isolation (Botha and Frost, 2020; Mitchell et al., 2021; Trundle et al., 2023). Such social issues might increase internalising problems in autistic CYP, as social and environmental factors, such as peer-victimisation (Greenlee et al., 2020; Trundle et al., 2023), parenting style (Dieleman et al., 2017; Maljaars et al., 2014), and negative life events (Fung et al., 2015; Taylor & Gotham, 2016; Weiss et al., 2015) have been linked with internalising problems in autistic CYP. Perhaps due to the unfavourable effects of the environment, many autistic individuals attempt to camouflage their autistic traits. This refers to conscious and unconscious strategies and

behaviours that aim to mask autistic traits in social interactions (Hull et al., 2021). Camouflaging has also been associated with higher levels of internalising problems (Bernardin et al., 2021; Hull et al., 2019; Wood-Downie et al., 2020).

There are a few reasons to hypothesise that there may be a sex/gender difference in internalising problems of autistic children and adolescents. Firstly, robust sex differences have been documented in non-autistic CYP (Martel et al., 2013). It would thus be reasonable to expect that similar patterns are found in autistic CYP. Moreover, some research suggests that female children and adolescents show higher levels of camouflaging than males, and also experience it as more stressful (Bernardin et al., 2021; Hull et al., 2019; Wood-Downie et al., 2020).

Nevertheless, sex/gender differences in internalising problems among the autistic population remains relatively poorly characterised, with existing studies providing conflicting conclusions. A number of studies have reported higher level of internalising problems in females (Mandy et al., 2012), others in males (Prosperi et al., 2021), and some studies report no significant sex differences (Brereton et al., 2006; Gadow et al., 2004; Mayes et al., 2020).

Some researchers have hypothesised that the inconsistent effects of sex/gender found in the literature could be due to moderating effects of the developmental effects of age and IQ (Lai et al., 2019; Mandy et al. 2012). Such developmental effects have been found in non-autistic males and females (Toumbourou et al., 2011; Wesslehoeft et al., 2015). For example, Oswald et al (2016) found a sex/gender difference in early adolescence but not in late adolescence in internalising problems among autistic young people. Gotham et al (2015) found a similar sex/gender difference in trajectories of internalising problems, where adolescent females

displayed more internalising problems. This could also indicate a moderating effect of IQ, as higher IQ has been shown to predict internalising problems in autistic CYP (Fung et al., 2015; Greenlee et al., 2016; Mayes et al., 2011), although some studies show the opposite effect (Amr et al., 2012, Rosa et al., 2016). ADHD traits have also been proposed to moderate the magnitude of the sex difference in internalising problems of autistic CYP, as ADHD traits are more common in males (Rucklidge, 2008) and highly associated with both autism and internalising symptoms (Mayes et al., 2012; Mayes et al., 2020; Reiersen et al., 2007; Steinhausen et al., 2006).

The inconsistencies in the sex/gender differences (or lack of) found in the literature on internalising problems of autistic children could also relate to methodological differences such as type of sample or informant used. For example, Ooi et al (2016) found that parent-child agreement on reporting anxiety symptoms ranged from low-to-moderate, where children rated themselves significantly higher on their anxiety symptoms compared to their parents. Methodological issues, such as sampling from predominantly male clinical populations, have also been suggested to contribute to the inconsistent findings (Oswald et al., 2016; Lai et al., 2015)

While there are previous meta-analyses investigating sex/gender differences in autistic traits (Hull et al., 2017; Saure et al., 2023; Wood-Downie et al., 2021), only a few papers have summarised sex/gender differences in internalising problems of autistic CYP. Hull and colleagues (2017) provided a brief narrative review of studies investigating sex differences in internalising problems in autistic adults and CYP but did not complete a meta-analysis. Natoli et al (2023) pooled the effects from seven studies looking at sex/gender differences in internalising problems in young autistic children, aged 1 to 6, as part of a wider systematic

review on sex/gender differences in autistic traits and co-occurring conditions. They concluded that there were no significant sex/gender differences in internalising problems for young autistic children but noted issues with high heterogeneity.

Despite providing a helpful overview of sex/gender differences in internalising problems found in autistic CYP, the number of studies included in Natoli and colleagues' (2023) study was small and only focused on a narrow age range. Given the inconsistency in findings regarding the sex/gender difference in internalising problems, a more comprehensive systematic review and meta-analysis is needed to synthesise the research on differences in internalising found in autistic males and females. The present study aims to address this gap.

The aim of the present study was to review and synthesise the existing research to elucidate whether there is a sex/gender difference in the internalising problems of autistic children and young people. Given the possible influences of age, IQ and type of informant on the level of internalising problems found in autistic CYP, we wished to ascertain whether sociodemographic factors such as age and IQ, or study characteristics would moderate this effect. Thus, we hoped to answer the following questions:

1. Is there a sex/gender difference in internalising symptoms of autistic males and females?
2. What is the direction of the effect?
3. Is the sex/gender difference in internalising problems moderated by sociodemographic and study-related factors?

Methods

Search strategy

The systematic review was registered on PROSPERO before any searches were completed (PROSPERO 2023 CRD42023466929). There was one deviation made to the published protocol; instead of a second review double extracting all included papers as proposed in the PROSPERO, it was agreed that they would double extract 20%, due to time constraints of the project. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used as guidance for the reporting of this systematic review (Page et al., 2021). See Appendix 1 for the PRISMA checklist.

The searches were completed in the following databases: EMBASE, PsycInfo, Medline, Web of Science and ASSIA. The search terms can be found in Table 1. They focused on the following topics: The condition of interest, which was autism, the exposure which was sex or gender, the outcome which was internalising problems, and the age range which was children and young people.

Table 1.

	Condition	**Exposure**	**Outcome**	**Population**
Search terms	Autism Spectrum Disorder(s) Autism Autistic ASD	Sex Gender	Emotional problem* Internali?ing Psychiatric Comorbidit* Mental health psychopathology anxi*	Child* Childhood adolescen* teen* young adult* youth* young person young people

	Asperger*	Depress*
	Pervasive development*	
	disorder*	
	PDD	

Summary of search terms for the systematic literature review

The search terms within each topic were separated by the "OR" operator, and the search terms between topics were separated by the "AND" operator to ensure that each paper found in the search would contain at least one term within each topic. Each topic apart from sex/gender had to be found within the abstract or title of the paper. The terms of sex and gender were searched within the whole paper due to the sex/gender difference not being the primary analysis in most papers. The only restriction applied on the search was that on the ASSIA database the option for returning only peer reviewed items was ticked. No date restrictions were applied. The search was completed on the 12th of October 2023. The full search strategy can be found in Appendix 2.

Inclusion and Exclusion Criteria

The results of the searches were reviewed against the inclusion and exclusion criteria, described below (Table 2). These criteria were set regarding the characteristics of participants within a sample, the exposure and outcome of interest, and type of study. The included studies were grouped according to the type of outcome reported in the study, e.g., anxiety, depression, or internalising. The population of interest was autistic children and young people. This included individuals with a research or clinical diagnosis of autism, or diagnoses of Asperger's or Pervasive Developmental Disorder Not otherwise specified (PDD-NOS; DSM-IV). This is also referred to as A-typical Autism (ICD-11; World Health Organization, 2019).

Table 2

Participants	Included	- Children and adolescents, with mean sample age below 19 - Diagnosis of Autism, PDD-NOS/A-typical autism or Asperger's, using recognized diagnostic criteria at the time of the publication
	Excluded	- Samples with mean age over 19 - Samples with only males or only females - Samples with participants not meeting the criteria for ASD, PDD or Asperger's
Exposure	Included	- Studies that included sex or gender as a variable - Studies that segregated data based on sex and/or gender
	Excluded	- Studies that did not include a sex or gender variable or provide results separated by sex or gender
Outcome	Included	- Studies using reliable, validated, quantitative and continuous measures of child or adolescent internalising symptoms, anxiety, and/or depression. - Studies reporting continuous scores
	Excluded	- Studies using non-continuous, poorly validated, or qualitative measures - Data not pertaining to scores on internalising measures, such as frequencies - Measures not assessing internalising symptoms, anxiety, or depression
Type of study	Included	- Studies that have been peer-reviewed - Studies written in English or Finnish - Cross-sectional or longitudinal studies - Studies that investigate an intervention and provide baseline data
	Excluded	- Studies only using qualitative data or analyses - Case studies, review articles, book chapters or discussion papers - Grey literature

Summary of the study inclusion and exclusion criteria

Data extraction

The results of each search were uploaded onto EndNote and any duplicates were removed. The primary author screened the titles and abstracts of the study against the exclusion and inclusion criteria. A second reviewer, another trainee clinical psychologist, double coded

10% of the results against the exclusion and inclusion criteria. The manuscripts of the studies that appeared to meet the eligibility criteria or appeared unclear in terms of eligibility were retrieved in full. The rationale for inclusion and exclusion of studies was recorded and illustrated via a PRISMA diagram (see results).

Data were extracted from each study by both the primary and secondary reviewer, and included country, number of males and females, mean age, ethnicity of participants, mean IQ, type of setting, the results of the study including means and standard deviations for internalising measure scores, percent of participants with ADHD diagnosis, and outcome measure used. For longitudinal studies, data from the first time point was used. If the study reported ratings from multiple informants, the parent-report data was chosen over other informant data (i.e., child report) for consistency. If the study did not report the necessary data for inclusion in the meta-analysis, original authors were contacted to request this. Studies that did not present the data required by the present study, or provide it upon request, were synthesised narratively where possible.

Risk of Bias

The JBI appraisal checklist for analytical cross-sectional studies was used to assess risk of bias within studies meeting eligibility criteria (Joanna Briggs Institute, 2016). The JBI appraisal checklist was selected as it is widely used, and it has been deemed suitable for systematic review of studies including an observational exposure (Mamikutty et al., 2021). The cross-sectional tool was chosen as this systematic review concerned cross-sectional rather longitudinal outcomes. In the case of RCTs or intervention studies, only baseline data was used. The JBI appraisal checklist for analytical cross-sectional studies has been found

comparable to other risk of bias tools, such as the ROBINS-I (Glasgow et al., 2020) and AHRQ (Chen et al., 2022).

The selected studies were rated in eight domains: Clarity of inclusion criteria, description of sample and setting, valid and reliable measure of exposure, objective, standard measure of the condition, confounding factors identified, and appropriate strategies to account for them, a reliable and valid measure of outcome, and appropriate statistical analysis. The studies were rated as "no", "unclear", or "yes", according to these domains. The tool full tool can be accessed in Appendix 3. For the purposes of this study, the exposure was sex and/or gender, the condition was autism, and the outcome was internalising symptoms. For the exposure domain, which in this case was sex/gender, studies were rated as "yes", if they specified whether they are investigating sex or gender, and if they defined or provided a rationale for this. The identification and management of confounding variables was evaluated in view of the analysis of the sex/gender difference in outcome, even when this was not the main analysis of the study. The secondary review independently evaluated 20% of the included studies.

Data Synthesis

A descriptive summary was compiled for all studies selected based on the eligibility criteria, including the authors, participant characteristics, type of study, measure(s) used and the results. Studies that provided means and standard deviations for males and females were synthesised using meta-analytic methods.

R and Rstudio software were used to complete the quantitative synthesis, utilising the "metacont" and "metareg" functions within the [meta] package (Balduzzi et al., 2019).

Separate analyses were completed for studies reporting internalising, anxiety, and depression scale scores. Higgins' I^2, Cochran's Q, and Tau^2 statistics were calculated to assess statistical heterogeneity and to determine whether the data gathered was suitable for pooling. An I^2 value of 0% indicates no observed heterogeneity and larger values indicate greater heterogeneity (25%=low, 50%=moderate, 75%=high). A random effects model was conducted to calculate the pooled mean differences utilising the inverse variance method and the Hartung Knapp adjustment for random effects. Pooled effect sizes were calculated using Hedge's g, based on the extracted mean internalising scores, and standard deviations. Forest plots were created in RStudio to display the results.

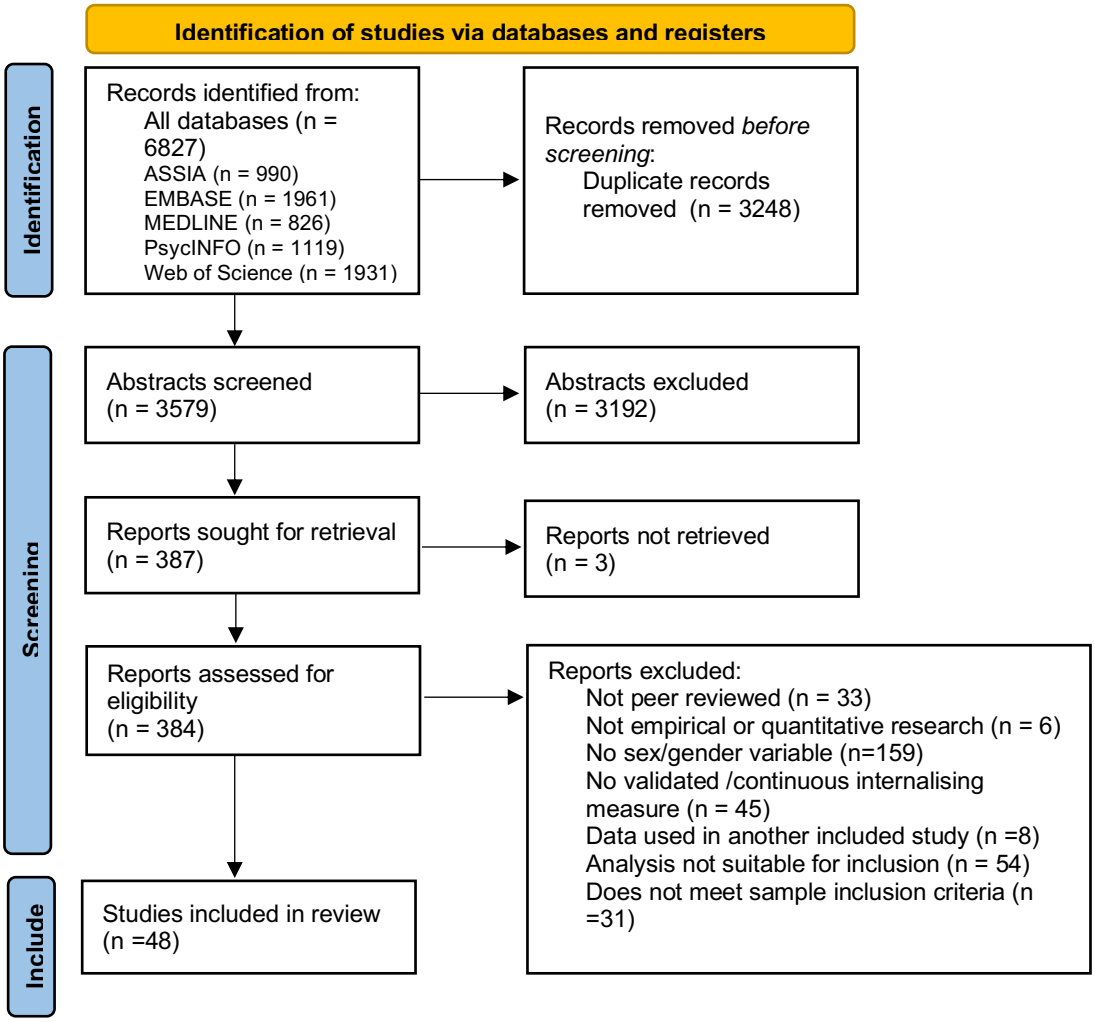
Meta-regression analyses were completed to investigate the impact of possible moderators driving the heterogeneity within effect size. These included the year of publication, mean age of the sample, mean IQ, female to male ratio, type of measure (parent-report, teacher-report, or self-report), type of sample (Community, clinical, or mixed) and risk of bias (the sum of ratings where no was rated as 0, unclear as 1, and yes as 2). Separate analyses were completed for each moderator variable to prevent loss of power due to list wise deletion. Ethnicity and percent of sample with ADHD were not included as moderators due to limited and inconsistent reporting of this within the selected studies.

Results

The search results are summarised in Figure 1. The total number of records identified was 6827 (ASSIA n=990, Embase n=1961, MEDLINE n=826, PsycINFO n=1119, Web of Science n= 1931). After removing the duplicates, the abstracts, and titles of 3579 records were screened against the inclusion and exclusion criteria. As a result, 387 reports were sought for full retrieval, with 3 reports not available for full screening. Out of 3 reports

assessed for eligibility, 48 were selected for inclusion. Exclusion reasons included not being peer-reviewed, not being empirical studies, not having a sex/gender variable for the outcome of interest, not having a validated or continuous measure of internalising, anxiety or depression, the analysis not being suitable for inclusion, the sample not meeting the inclusion criteria and the data already having been used in another included study. The summary of the included studies can be found in Table 3.

Figure 1



PRISMA diagram

Table 3

	Study type	Country	Type of sample	Sample size	Percent females	Mean Age	Outcome	Measure
Amr et al., 2011	Cross-sectional	Egypt, Saudi-Arabia and Jordan	Clinical	60	38.3	8.2	Internalising	Child Behaviour Checklist, parent-report (CBCL-P)
Bernardin et al., 2021	Cross-sectional	USA	Mixed	78	29.5	15.0	Internalising	The Depression, Anxiety and Stress Scale - 21 Items (DASS-21), self-report
Boonen et al., 2014	Cross-sectional	Netherlands	Community	206	15.0	9.9	internalising	Strengths and Difficulties Questionnaire, parent report
De Clercq et al., 2021	Longitudinal	Belgium	Clinical	140	17.0	10.1	internalising	Child Behaviour Checklist, parent-report (CBCL-P)
Fombonne et al., 2022	Cross-sectional	USA	Clinical	472	23.1	9.2	internalising	Strengths and Difficulties Questionnaire, parent report
Guerrera et al., 2019	Cross-sectional	Italy	Clinical	472	18.9	5.5	Internalising	Child Behaviour Checklist, parent-report (CBCL-P)
Hartini et al., 2016	Cross-sectional	Indonesia	Community	54	25.9	10.1	Internalising	Child Behaviour Checklist, parent report
Horiuchi et al., 2014	Cross-sectional	Japan	Clinical	173	25.4	7.9	Internalising	Strengths and Difficulties Questionnaire, parent-report
Horwitz et al 2023	Cohort	Netherlands	Clinical	152	27.0	11.1	internalising	Child Behaviour Checklist, self-report
Hurtig et al., 2009	Cross-sectional	Finland	Community	46	26.1	13.0	Internalising	Child Behaviour Checklist, parent-report (CBCL-P)
Mandy et al., 2012	Cross-sectional	UK	Clinical	325	16.0	9.8	Internalising	Strengths and Difficulties Questionnaire, parent-report
Nasca et al., 2020	Cross-sectional	USA	Community	80	50.0	9.0	Internalising, Anxiety, Depression	Behavior Assessment System for Children- Second edition (BASC-2), parent-report.
Nguyen et al., 2014	Cross-sectional	UK	Community	54	50.0	13.7	Internalising	Strengths and Difficulties Questionnaire, self-report
Nordahl et al., 2020	Cross-sectional	USA	Community	300	30.3	3.0	Internalising, Anxiety, Depression,	Child Behaviour Checklist, parent-report (CBCL-P)
Penner et al., 2022	Cross-sectional	Canada	Clinical	451	22.2	10.0	Internalising	Child Behaviour Checklist, parent-report (CBCL-P)
Pisula et al., 2016	Cross-sectional	Poland	Community	70	50.0	13.8	Internalising	Child Behaviour Checklist, self-report (CBCL-C)
Prosperi et al., 2021	Cross-sectional	Italy	Clinical	214	50.0	3.8	Internalising, Anxiety	Child Behaviour Checklist, parent-report (CBCL-P)
Ross et al., 2022	Cross-sectional	USA	Community	733	49.0	9.0	Internalising	Child Behaviour Checklist, parent-report (CBCL-P)
Sanchez et al., 2022	Cross-sectional	USA	Community	89	19.1	11.3	Internalising	Behavior Assessment System for Children- Second edition (BASC-2), parent-report.
Solomon et al., 2011	Cross-sectional	USA	Community	40	50.0	12.2	Internalising, Anxiety, Depression	Behavior Assessment System for Children- Second edition (BASC-2), parent-report
Worley et al., 2011	Cross-sectional	USA	Community	70	37.1	8.3	Internalising	Autism Spectrum Disorders-Comorbid for Children (ASD-CC), parent-report
Wright et al., 2023	Cohort	Canada	Clinical	365	15.6	3.4	Internalising	Child Behaviour Checklist, parent-report (CBCL-P)

Ambrose et al., 2020	Cross-sectional	Australia	Community	48	50.0	10.1	Anxiety	Anxiety Scale for Children - ASD-parent repot (ASC-ASD-P)
Boulter et al., 2014	Cross-sectional	USA and UK	Mixed	114	12.3	12.7	Anxiety	Spence Children's Anxiety Scale Child Report (SCAS-C)
Cariveau et al., 2021	Cross-sectional	USA	Clinical	682	14.2	7.4	Anxiety	The Early Childhood Inventory-4 (ECI-4), parent-report, or Child and Adolescent Symptom Inventory (CASI)
Chandler et al., 2016	Cross-sectional	UK	Community	277	18.1	6.8	Anxiety, Depression	Developmental Behaviour Checklist (DBC-P), parent report
Chang et al., 2015	Cross-sectional	Taiwan	Community	101	16.9	15.6	Anxiety	Beck Anxiety Inventory (BAI)
Emerson et al., 2023	Cross-sectional	Australia	Community	118	33.9	10.1	Anxiety	Anxiety Scale for Children - ASD-parent repot (ASC-ASD-P)
Factor et al., 2017	cross-sectional	USA	Clinical	57	17.5	7.3	Anxiety	Child Behaviour Checklist, parent report
Harrop et al., 2023	Cross-sectional	USA	Community	146	18.5	9.4	Anxiety	Parent-Rated Anxiety Scale for Autism Spectrum Disorder (PRAS-ASD)
Kaat & Lecavalier 2015	Cross-sectional	USA	Mixed	46	17.4	12.4	Anxiety, Internalising, Depression	Revised Child Anxiety and Depression scale, parent report
Lohr et al 2017	Cross-sectional	USA	Clinical	100	12.0	12.9	Anxiety	The Screen for Child Anxiety-Related Emotional Disorders (SCARED), self-report
Magiati et al., 2016	Cross-sectional	Singapore	Community	241	18.3	10.3	Anxiety	Spence Children's Anxiety Scale Parent Report (SCAS-P)
May et al. 2014	Longitudinal	Australia	Clinical	56	50.0	13.0	Anxiety	Spence Children's Anxiety Scale Parent Report (SCAS-P)
Muratori et al., 2019	Cross-sectional	Italy	Clinical	989	17.1	3.7	Anxiety	Child Behaviour Checklist, parent-report (CBCL-P)
Neil et al., 2016	Cross-sectional	UK	Community	69	14.5	10.4	Anxiety	Spence Children's Anxiety Scale Parent Report (SCAS-P)
Storch et al., 2012	Cross-sectional	USA	Clinical	72	19.4	10.8	Anxiety	Pediatric Anxiety Rating Scale (PARS)
Syriopoulou-Delli et al., 2019	Cross-sectional	Greece	Community	291	26.5	10	Anxiety	School Anxiety Scale-Teacher Report (SAS- TR)
Varela et al., 2020	Cross-sectional	USA	Clinical	349	19.8	8.9	Anxiety	Behavior Assessment System for Children- Second edition (BASC-2), parent-report.
Wijnhoven et al., 2018	cross sectional	Netherlands	Clinical	168	22.6	11.3	Anxiety	Spence Children's Anxiety Scale Parent Report (SCAS-P)
Gadow et al., 2004	Cross-sectional	USA	Clinical	172	20.9	4.2	Anxiety, Depression,	The Early Childhood Inventory-4 (ECI-4), parent-report
Gotham et al., 2015	Longitudinal	USA	Clinical	109	11.9	10.7	Anxiety, Depression	Child Behaviour Checklist, parent-report (CBCL-P)
Johnston & Iarocci 2017	Cross-sectional	Canada	Community	67	15.0	9.8	Anxiety, Depression	Behavior Assessment System for Children- Second edition (BASC-2), parent-report
Mayes et al., 2011	Cross-sectional	USA	Clinical	891	10.1	6.6	Anxiety, Depression	Pediatric Behavior Scale (PBS)
Oswald et al., 2016	Cross-sectional	USA	Community	32	43.8	14.9	Anxiety, Depression	The Revised Child Anxiety and Depression Scale—Parent Version
Brereton et al., 2006	Cross-sectional	Australia	Clinical	367	15.0	7.4	Depression	Developmental Behaviour Checklist parent-report (DBC-P)
Leader et al 2022	Cross-sectional	Ireland	Community	95	20.0	9.5	Depression	Child Behaviour Checklist, parent report

Wijnhoven et al., 2019	Cross-sectional	Netherlands	Clinical	93	23.7	11.2	Depression	Children's Depression Inventory 2 (CDI2), self-report

Summary of included studies

Study characteristics

The 48 included studies were conducted in the following countries: USA (n = 20), UK (n=5), Netherlands (n = 4), Canada (n = 3), Australia (n=4), Italy (n=3), Taiwan, Poland, Greece, Finland, Indonesia, Belgium, Ireland, Singapore, Egypt, Saudi-Arabia, and Jordan (all n = 1). Most of the included studies were cross-sectional (n= 43), but baseline data was also included from five longitudinal (including cohort) studies. Study sample sizes ranged from 32 to 989. A total of 10,045 autistic CYP were included in this review. Twenty-three studies recruited samples from a clinical setting, 22 from a community setting, and 3 included data from community and clinical settings ("mixed").

Participant characteristics

All participants had either a research or clinical confirmation of autism, as per the inclusion criteria. The mean age of participants varied between 3.4 and 16.0 years old, the median being 10.0 (IQR=3.24) years old. The proportion of females in the study populations ranged from 10% to 50%. The mean IQ of the samples ranged from 60.93 to 110.16.

Out of 48 studies, 18 provided information on ethnicity (Cariveau et al., 2021; Chandler et al., 2015; DeClerq et al., 2021; Fombonne et al., 2022; Gadow et al., 2004; Gotham et al., 2015; Harrop et al., 2023; Kaat & Lecavalier, 2015; Lohr et al., 2017; Magiati et al., 2016; Mandy et al., 2012; Nasca et al., 2020; Nordahl et al., 2020; Penner et al., 2022; Storch et al., 2012; Syriopolou-Delli et al., 2019; Varela et al., 2020; Wijnhoven et al., 2018). White ethnicities were reported as the largest group across most studies, ranging from 20% to 91% of the sample. Black ethnicities, including black Caribbean and African ethnicities, were represented in seven studies, with percentages ranging from 3.2% to 23.8%.

“Hispanic”/”Latino” individuals were reported in varying proportions, ranging from 1% to 15.3%. Asian ethnicities, including South Asian, East Asian, Southeast Asian, and West Asian, were represented in several studies, with percentages ranging from 0.8% to 93%. Other ethnic groups, such as Jewish, “Indigenous/Native Hawaiian/Other Pacific Islander”, and Arab, were represented in singular studies, at varying degrees of prevalence (< 1%- 6%). Furthermore, “biracial”/”mixed” individuals were represented in a few studies at 5.1%- 12%. Several studies (n=5) only reported percentage of white people or “non-white”/ ”POC”/”minority” individuals.

Outcome characteristics

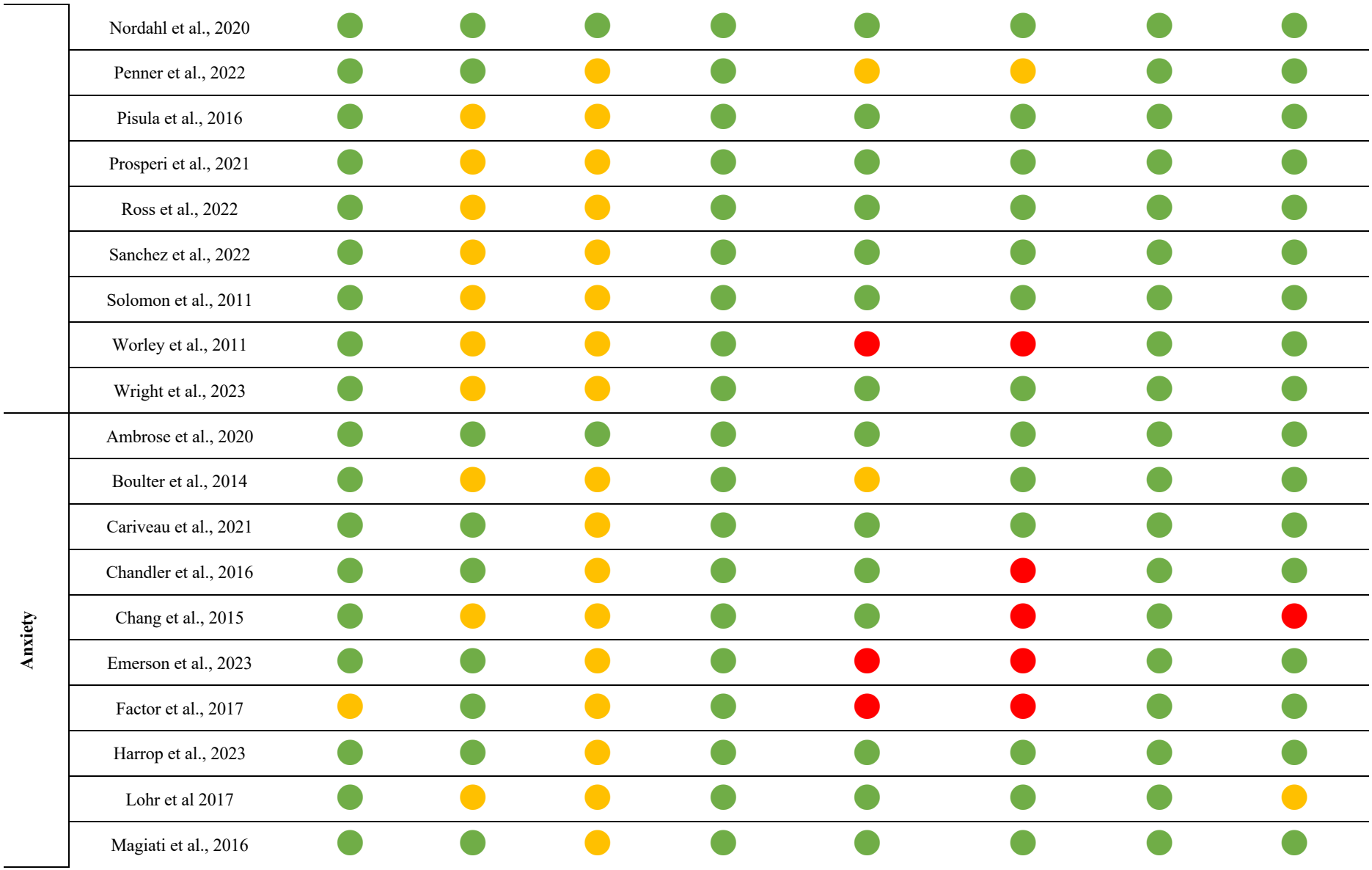
Out of the selected studies, 23 studies included a measure of internalising problems, 28 studies included an anxiety measure, and 14 studies measured depression.

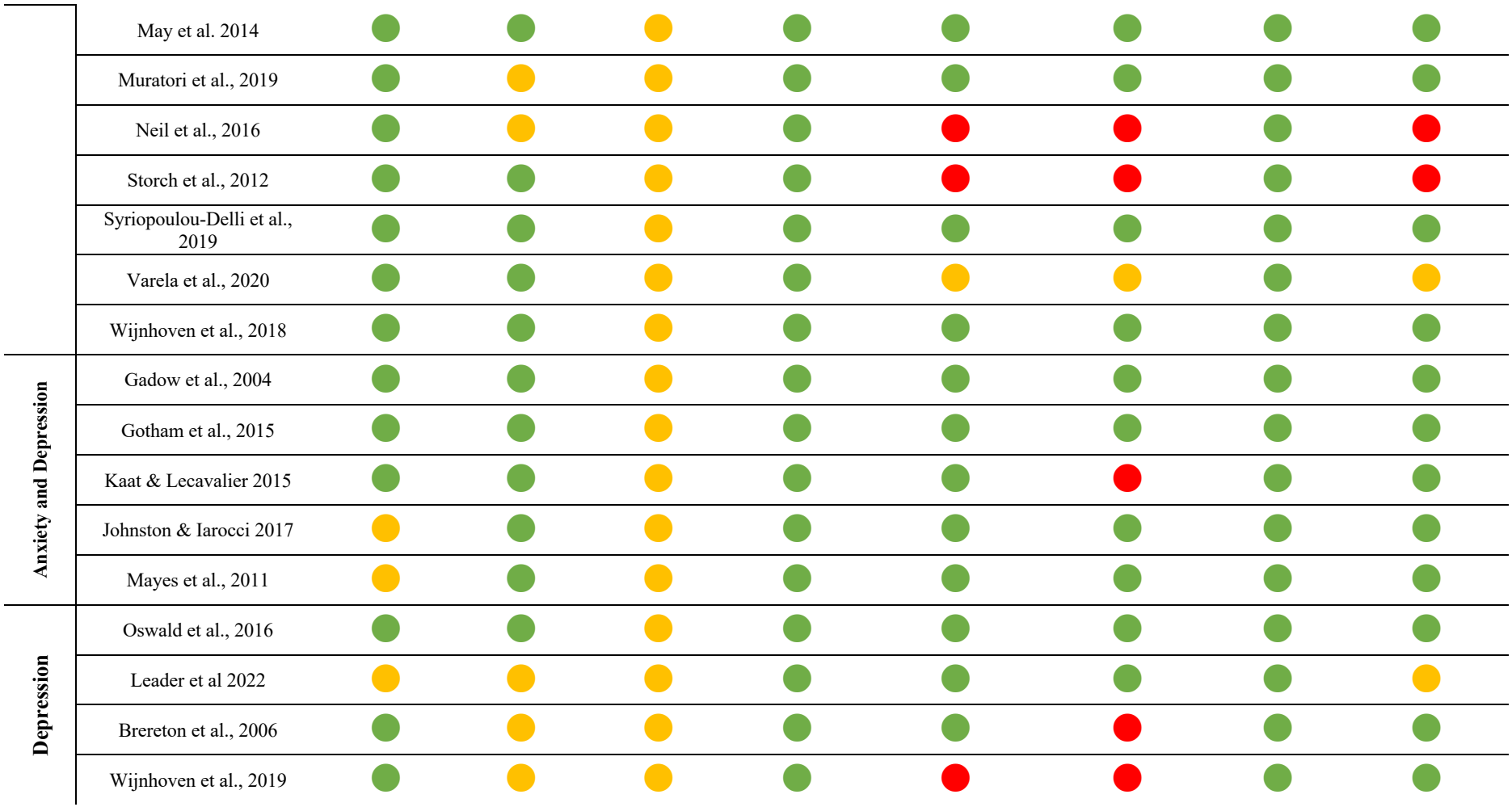
Risk of bias within studies

Joanna Briggs Institute (JBI) Quality Appraisal checklist tool was used to evaluate risk of bias within all the included studies. There was moderate agreement with the second reviewer (Cohen’s Kappa= 0.51 [95% CI=-0.005-1.00]). The results are summarised in Table 4. Only two studies were evaluated as low risk of bias across all eight domains. However, 15 studies had low risk of bias across seven domains, with the only “unclear” domain being the definition or rationale regarding how they operationalised sex and/or gender. The risk of bias evaluation showed that 31 studies included unclear or missing information in two or more domains, with issues relating to the following domains being most commonly observed: 1) including a rationale or definition for the exposure (e.g. sex/gender) (n=46), 2) information on the setting and sample (n=21), 4) identifying (n = 8) or using appropriate strategies to deal with confounding factors (n = 13).

Table 4

	Author	Defined inclusion criteria	Subjects & setting described	Valid & Reliable exposure measure	Objective, standard measure of condition	Confounding factors identified	Strategies to deal with confounding factors	Valid, Reliable outcome measure	Appropriate statistical analysis
Internalising	Amr et al., 2011	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢
	Bernardin et al., 2021	🟢	🟡	🟡	🟢	🟡	🟢	🟢	🔴
	Boonen et al., 2014	🟢	🟡	🟡	🟢	🟢	🟢	🟢	🟢
	De Clercq et al., 2021	🟢	🟢	🟡	🟢	🟢	🔴	🟢	🟢
	Fombonne et al., 2022	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢
	Guerrera et al., 2019	🟡	🟡	🟡	🟢	🟢	🟡	🟢	🟢
	Hartini et al., 2016	🟡	🟡	🟡	🟢	🔴	🔴	🟢	🟢
	Horiuchi et al., 2014	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢
	Horwitz et al 2023	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢
	Hurtig et al., 2009	🟢	🟡	🟡	🟢	🟢	🟢	🟢	🟢
	Mandy et al., 2012	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢
	Nasca et al., 2020	🟢	🟢	🟡	🟢	🟢	🟢	🟢	🟢
	Nguyen et al., 2014	🟢	🟡	🟡	🟢	🟢	🟢	🟢	🟢


Nordahl et al., 2020
Penner et al., 2022
Pisula et al., 2016
Prosperi et al., 2021
Ross et al., 2022
Sanchez et al., 2022
Solomon et al., 2011
Worley et al., 2011
Wright et al., 2023
Anxiety
Ambrose et al., 2020
Boulter et al., 2014
Cariveau et al., 2021
Chandler et al., 2016
Chang et al., 2015
Emerson et al., 2023
Factor et al., 2017
Harrop et al., 2023
Lohr et al 2017
Magiati et al., 2016



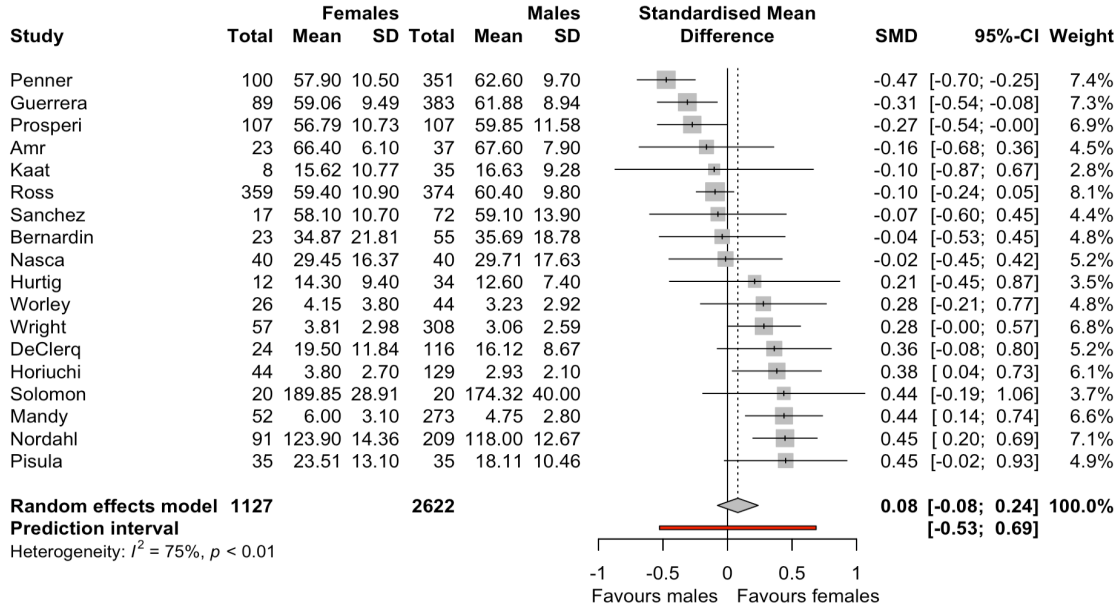
Risk of bias summary by study. Green indicates evaluation as low risk of bias ('Yes'; rated as '2'), red indicates evaluation as high risk of bias ('No'; rated as '0'), and yellow indicates that the appraisal of risk of bias was unclear from the study information available ('Unclear'; rated as '1').

Synthesis

Internalising problems

Mean difference between males and females in internalising symptoms

Figure 2



Meta-analysis of the mean difference in internalising symptoms of male and female autistic children and adolescents.

Out of 23 included studies, 18 were suitable for inclusion in the meta-analysis. The remaining five were ineligible due to not including mean internalising scores for each sex/gender or providing them upon request (Boonen et al., 2014; Fombonne et al., 2022; Hartini et al., 2016; Horwitz et al., 2023; Nguyen et al., 2014). One study presented with low risk of bias ("yes") in all seven domains. Seven studies had missing or unclear information in one domain. The remaining studies had unclear or missing information in two or more domains.

A random effects analysis revealed a non-significant effect, suggesting that there is no sex/gender difference in internalising problems in autistic CYP (Hedges *g*=0.08 [-0.078; 0.238], t(17)= 1.07, p= 0.301). Higgins' I^2, Cochran's Q, and Tau² statistics indicated a high level of heterogeneity (I^2= 75.4% [61.1%; 84.4%], Q(17)= 69.03, p<0.0001, T^2= 0.075 [0.024; 0.171].

As illustrated by Figure 1, the standardised mean differences reported by studies ranged from -0.47 to 0.45, where a positive mean difference indicated females experiencing more internalising problems, and a negative mean difference suggested that males experience more internalising problems. Two of the studies showed males experiencing significantly more internalising problems than females (Guerrera et al., 2019; Penner et al., 2022), three of the studies reported the opposite with females experiencing significantly more internalising problems (Horiuchi et al., 2014; Mandy et al., 2012; Nordahl et al., 2020), and the remaining studies found no significant difference between males and females.

The studies not included in the meta-analysis did not find significant effects of sex/gender in internalising problems (Boonen et al., 2014; Fombonne et al., 2022; Hartini et al., 2016; Nguyen & Ronald, 2014).

Moderators of the sex difference in internalising symptoms

Meta-regression was conducted to analyse the impact of possible moderators on the heterogeneity in the pooled effect sizes of sex/gender difference in internalising problems. Separate analyses were completed for the following variables: age, IQ, type of informant,

type of sample, risk of bias, proportion of females to males within the sample, and publication year. This was done to prevent loss of power due to list wise deletion.

Age

A mixed effect meta-regression was conducted to analyse the proportion of the heterogeneity explained by differences in age. Eighteen studies were included in the regression analysis. Mean age of the sample within these studies varied from 3 to 15 years old. The analysis showed that the mean age of the sample did not explain any of the heterogeneity within the results, implying that age had no impact on the effect size (β=0.0045, r^2=0.0%, F(1, 16) = 0.041, p = 0.843).

A narrative synthesis shows that seven studies investigated age by sex/gender interactions in internalising problems. Three studies found a significant interaction whereby male internalising symptoms decreased or remained the same with age, whereas female internalising symptoms increased over time towards adolescence (Fombonne et al., 2022; Horowitz et al., 2023; Penner et al., 2022). Solomon et al (2011) and De Clerq et al (2021) found a significant sex/gender difference emerge between males and females in adolescence, at mean ages of 14 and 16, respectively, with females exhibiting more internalising symptoms. Mandy et al (2012) did not find a significant relationship between age and sex/gender in their study, although this could be due to low power.

IQ

Twelve studies were included in the meta-regression analysis with IQ as a covariate. The mean IQ within these studies ranged from 60.93 to 103.97. Eight studies included individuals

with intellectual disabilities, the percent of the sample with IQ below 70 ranging from 11.1% to 61.5% (61.5%, Amr et al., 2011; 12.3%, De Clerq et al., 2021; 18.9%, Horiuchi et al., 2014; 33%, Kaat & Lecavalier, 2015; 11.1%, Mandy et al., 2012; Prosperi et al., 2021; Ross et al., 2022; Wright et al., 2023).

Mean IQ was not a significant moderator, as differences in the mean IQ between samples did not explain any heterogeneity in the effect sizes (β=0.008, r^2=0%, F(1, 10) = 0.923, p = 0.359.

Sample characteristics and bias

The proportion of females to males, the type of informant used in the study, year of publication, setting and risk of bias ratings were entered as covariates into separate univariate regression analyses. These were utilised as indicators of potential moderating effects of methodological biases on the size of the sex/gender difference found in studies. The ratio of females to males ranged from 0.19 to 1 between the 18 studies. The female to male ratio was not a significant moderator of the mean difference in internalising problems and did not explain any of the heterogeneity (β= -0.067, r^2=0%, F(1, 16) = 0.079, p = 0.782).

Eight studies contained samples recruited from a community setting, eight from a clinical setting and two had a sample from a mixed setting (See Table 3 for a summary). The analysis revealed that the type of setting that the sample was recruited from did not significantly explain any variation in the magnitude of the sex difference found in the included studies ($\beta_{Community}$=0.176, (β_{Mixed}=-0.078, r^2=0%, F(2, 15) = 0.768, p =0.482). The publication year accounted for 16.83% of the heterogeneity found within the pooled effect sizes but it was not significant (β= -0.029, r^2=16.83%, F(1, 16) = 3.39, p=0.084). The risk of bias ratings

appeared to explain some of the heterogeneity in the pooled effect sizes, but this was also not significant (β=0.072, r^2=12.7%, F(1, 16) = 2.14, p =0.163, N=18).

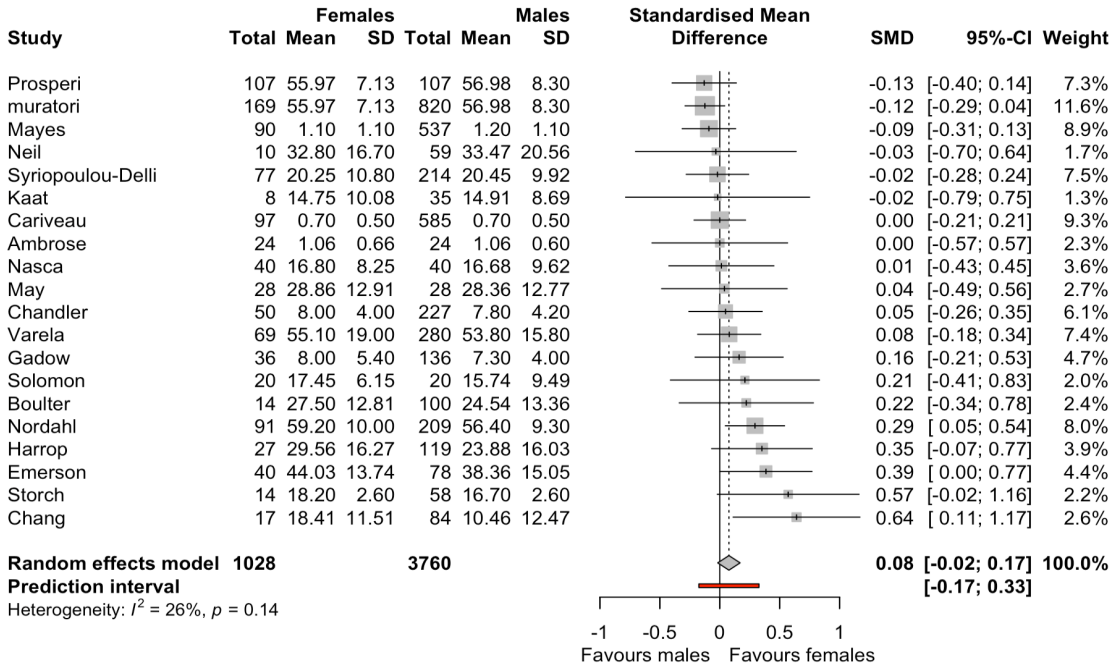
Out of the eligible studies, three used self-report measures (Bernardin et al., 2021; Pisula et al., 2016; Solomon et al., 2012), whereas the rest used parents as informants. The type of informant did not account for heterogeneity, and was not a significant moderator of the mean difference in internalising problems between males and females (β=0.220, r^2=0.0, F(1,16) = 0.996, p = 0.333).

A narrative synthesis of informant type found that three studies contained multiple informant sources. Mandy et al (2012) discovered that parents reported higher levels of internalising symptoms for girls than for boys, but this difference did not emerge in comparison to teacher-report. Hurtig et al (2009) reported that both female and male adolescents tended to disclose more internalising problems than their parents, and Pisula et al (2016) found that adolescents reports were not significantly different from those of their parents.

Anxiety

Mean difference between males and females in anxiety symptoms

Figure 3



Meta-analysis of the mean difference in anxiety symptoms of male and female autistic children and adolescents

Out of the 28 studies that investigated sex/gender differences in anxiety, 20 studies were eligible for inclusion in the meta-analysis. Eight studies were ineligible for the meta-analysis due not including mean anxiety scores for each sex/gender or providing them upon request (Factor et al., 2017; Gotham et al., 2015; Johnston & Iarocci, 2017; Lohr et al., 2017; Magiati et al., 2016; Oswald et al., 2016; Wijnhoven et al., 2018).

In terms of risk of bias, two of the studies were rated with low risk of bias across all seven domains, eight studies had low risk of bias across six domains with unclear rating in one of the domains, and the rest of the studies had an unclear or a high risk of bias rating in two or more of the seven domains.

The meta-analysis revealed a non-significant effect of sex/gender on anxiety symptoms (Hedges *g*= 0.076 [-0.017; 0.170], t=1.71, p=0. 104). There was low heterogeneity within the pooled studies, as indicated by the Higgins' I^2, Cochran's Q, and Tau² statistics (I^2=25.6% [0.0%; 56.8%], Q(19)= 25.53, p=0.144, T^2= 0.012 [0; 0.054]). Eighteen of the pooled studies showed statistically insignificant effects, ranging from -0.13 to 0.57. Only two studies found a significant mean difference implying that girls experienced more anxiety than boys, with effect sizes of 0.29 (Boulter et al., 2014) and 0.64 (Chang et al., 2015).

A narrative synthesis of the studies not included in the meta-analysis showed that three studies found girls to experience significantly more anxiety symptoms than boys (Lohr et al., 2017; Oswald et al., 2016; Wijnhoven et al., 2018), one study found the opposite (Gotham et al., 2015), and three studies found that there was no significant effect of sex/gender (Factor et al., 2017; Johnston & Iarocci, 2017; Magiati et al., 2016)

Moderators of the mean difference in anxiety symptoms

Mixed effect meta-regression analyses were conducted to analyse the impact of possible moderators on the heterogeneity in the pooled effect sizes of sex/gender difference in anxiety. Separate analyses were completed for the following variables: age, IQ, type of informant, risk

of bias, proportion of females to males within the sample, type of sample and publication year.

Age

Twenty studies were included in the meta-regression. The mean age in the included studies ranged from 3 to 15 years of age. The analysis revealed that the mean age explained 24.43% of the heterogeneity within the pooled mean difference, although this was not significant (β= 0.025, r^2=24.43%, F(1, 18) = 3.92, p=0.063. The effect indicated a slight increase in the sex/gender difference with age, with girls experiencing more anxiety.

A narrative synthesis was completed on the studies including age as a covariate. Six studies investigated the effect of age on the sex/gender difference in anxiety. Gotham et al (2015) found that in late school age, males had higher levels of anxiety than females but over time females showed greater increases in anxiety symptoms throughout adolescence, causing this difference to disappear by the age of 21. Horwitz and colleagues (2023) found a similar pattern in 11 to 21-year-olds, where there was a decrease in male anxiety symptoms with age, whereas for females, these symptoms increased over time. Oswald et al (2016) found that in early adolescence females were reporting higher levels of separation anxiety and panic than males, but by late adolescence this difference diminished. The rest of the studies found no significant interaction effects between age and sex/gender for anxiety symptoms (May et al., 2014; Solomon et al., 2011; Varela et al., 2020).

IQ

The regression analysis of the effects of IQ included 13 studies. The mean IQ in these studies ranged from 72.7 to 108.5. Nine studies reported samples including participants with intellectual disabilities, the proportion varying from 11% to 44% of the sample (43.1%

Cariveau et al., 2021; 35% Chandler et al., 2016; 37.3% Gadow et al., 2004; 33% Kaat & Lecavalier, 2015; 35.6% Mayes et al., 2011; Muratori et al., 2019; Prosperi et al., 2021; 33.9% Varela et al., 2020). The meta-regression did not find IQ to account for any heterogeneity within the effect sizes and it was not a significant moderator (β=0, r^2= 0, F(1,11) = 0.00, p = 0.998).

Sample characteristics and bias

The proportion of females to males, the type of informant used in the study, year of publication, study setting, and risk of bias ratings were entered as covariates into separate univariate regression analyses to check for the moderating or confounding effects of study characteristics on the sex/gender difference between autistic males and females.

The proportion of females to males in study samples, which ranged from 1 to 0.14, did not significantly account for any of the heterogeneity within the pooled sex/gender difference in anxiety (β=-0.064, r^2= 0%, F(1, 18) = 0.176, p= 0.680). Out of the 20 studies looking at sex/gender differences in anxiety, 10 of the studies had a community sample, 2 mixed, and the rest of the samples were clinical (see Table 3 for a summary). The type of setting that the sample was recruited from explained 94.9% of the heterogeneity between studies, where a community sample significantly predicted a greater sex/gender difference in the anxiety symptoms, compared to a clinical sample ($\beta_{Community}$=0.2077, p=0.017, β_{Mixed}=0.170, p=0.489, r^2=94.9%, F(2, 17) = 0.355, p =0.052).

The publication year varied from 2009 to 2023. It did not significantly account for heterogeneity in the pooled mean difference in anxiety between males and females (r^2=0, β= -0.001, F(1,18) = 0.018, p= 0.894). On the other hand, the risk of bias ratings explained 76.5%

of the heterogeneity between studies, where studies with higher ratings (lower risk of bias) were more likely to report a smaller sex/gender difference in anxiety (β= -0.0438, R^2=76.5%, F(1, 18) = 6.95, p = 0.017).

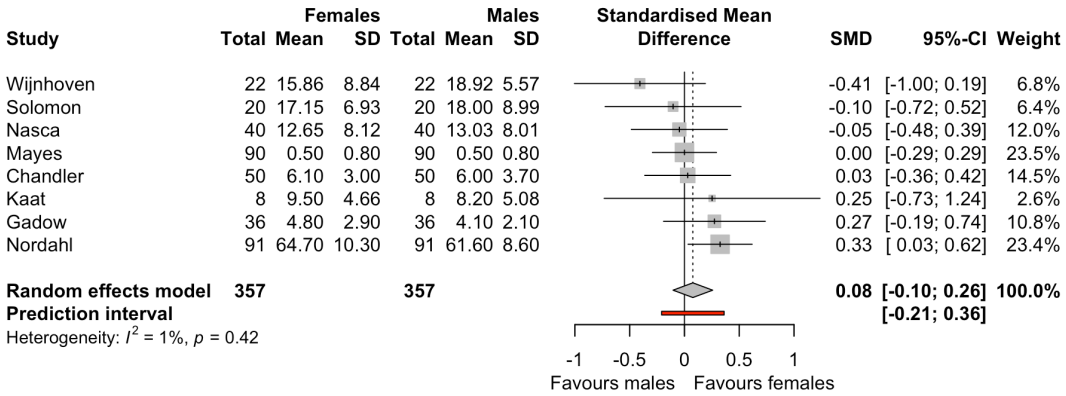
Regarding the type of informant, 15 studies included parent-report data, four studies included child-report anxiety ratings (Boulter et al., 2014; Chang et al., 2015; Emerson & Adams, 2023; Solomon et al., 2012), and one included teacher-report (Syriopolou-Delli et al., 2019). The type of informant explained 28.99% of the heterogeneity in the effect sizes (r^2=28.95%, F(2, 17) = 3.93, p = 0.040), where the self-report data was associated with a larger sex/gender difference than parent-report (β=0.379, p=0.015).

A narrative synthesis found that five studies provided data from different types of informants. Gadow et al (2004) found higher anxiety ratings from teachers than parents for both males and females. Boulter et al (2014) found that in both child- and parent report measures girls reported more anxiety than boys, but the sex/gender difference in anxiety was only significant in parent report. Kaat and Lecavalier (2015) found parent-report and child-report to correlate highly for anxiety in general, but parents reported more symptoms of social anxiety than their children. Horwitz et al (2023) and Oswald et al (2015) both discovered similar patterns of sex/gender and age interaction in parent- and adolescent-report of anxiety symptoms, suggesting agreement in report of anxiety symptoms between parents and their children.

Depression

Mean difference between males and females in depression symptoms

Figure 4



Meta-analysis of the mean difference in depression symptoms of male and female autistic children and adolescents.

In 14 studies investigating depression symptoms, eight studies were eligible for being synthesised by meta-analysis (See Figure 4). Six studies were ineligible due to not providing means or mean differences in their papers, or upon request (Brereton et al., 2006; Gotham et al., 2015; Horwitz et al., 2023; Johnston & Iarocci, 2017; Leader et al., 2022; Oswald et al., 2016). One study had low risk of bias across all seven domains, four studies received low risk of bias ratings in all but the exposure domain, and the rest of the studies had lacking or unclear information in two or more domains.

The analysis revealed that there was no significant difference in depression symptoms between autistic males and females once the effects were pooled (Hedges *g*= 0.076 [-0.104; 0.258], t=1.0, p=0.350. The Higgins' I^2, Cochran's Q, and Tau^2 statistics revealed low

heterogeneity (I^2= 0.6% [0.0%; 67.8%], Q(7)=7.04, p=0.424, T^2= 0.007 [0; 0.164]). The standardised mean difference ranged from -0.41 to 0.33 between studies but only one study (Nordahl et al., 2018) showed a significant mean difference, with females experiencing more depression symptoms than males.

A narrative synthesis of the studies not included in the meta-analysis indicated that two studies found males to experience significantly more symptoms of depression than females (Gotham et al., 2015; Leader et al., 2022), one found the opposite (Oswald et al., 2016), two found no significant relationship between sex/gender and depression symptoms (Brereton et al., 2006; Johnston & Iarocci 2017).

Moderators of the mean difference in depression symptoms

Meta-regression analyses were not completed for depression due to the low number of studies eligible for inclusion (Deeks et al., 2023). Narrative synthesis was completed for age, IQ, and type of informant as moderators of the sex/gender difference in depression symptoms.

Age

The mean age in the included studies ranged from 3 to 15 years of age. The studies that found males to experience more depression symptoms described mean ages of 9.5 and 11, respectively (Gotham et al., 2015; Leader et al., 2022). Nordahl et al (2020) and Oswald et al (2016) found females to experience more depression symptoms and represented the opposite ends of the age range in mean ages found in studies: 3 and 15, respectively.

Oswald and colleagues (2016) found age to interact with the sex/gender difference in depression symptoms. They found that that females tended to show more depressive

symptoms than the males during early adolescence, whereas by late adolescence males' symptoms increased, closing the difference. However, Gotham et al (2015) found the opposite pattern, where males tended to have higher levels of depression symptoms than females at age 13 but females showed greater symptom increases throughout adolescence, resulting in no gender difference by the age of 21. Horwitz et al (2023) also found depressive symptoms to increase in females in adolescence, whereas in males they found a decrease.

IQ

Ten studies out of 13 reported mean IQ for their sample. These ranged between 72.7 (Chandler et al., 2016) and 110.2 (Oswald et al., 2016). Six studies included children with intellectual disabilities, the percent of the sample with an intellectual disability varying between 35.6% and 69.8% (69.8% Brereton et al., 2006; 35% Chandler et al., 2016; 37.3% Gadow et al., 2004; 44% Gotham et al., 2015; 33% Kaat & Lecavalier, 2015; 35.6% Mayes et al., 2011; 40% Leader et al., 2022). Leader and colleagues' (2022) regression analysis within their study revealed that male sex/gender and presence of intellectual disability significantly predicted depression symptoms in pre-school children, but gender/sex was no longer a significant predictor after adding sleep problems into the model, suggesting this could be mediating the effect.

Type of informant

Two studies (Solomon et al., 2012; Wijnhoven et al., 2019) that used child self-report data found small non-significant effects of males experiencing more internalising problems. Seven studies included parents as informants (Brereton et al., 2006; Chandler et al., 2016; Gadow et al., 2004; Johnston & Iarocci, 2017; Mayes et al., 2011; Nasca et al., 2020; Nordahl et al.,

2020). These tended to find no significant difference or females to experience more depressive symptoms, suggesting that parents may be more likely to rate depression symptoms slightly higher in females.

Six studies used multiple informants (Gotham et al., 2015; Horwitz et al., 2023; Kaat & Lecavalier, 2015; Leader et al., 2022; Oswald et al., 2016; Wijnhoven et al., 2019). Wijnhoven et al (2019) included child and parent-informant data in their study, which revealed that the sex/gender effects were opposite depending on the type of informant, where parents reported significantly more depression symptoms in females than males, whereas CYP self-report indicated the opposite. A similar pattern was found by Horwitz et al (2023) in 11-year-olds. In 16-year-olds, they found that parents and adolescents both reported females to experience more symptoms of depression than males, suggesting stronger parent-child agreement in adolescence. This is supported by Oswald et al (2016) who found similar patterns of sex/gender and age interaction in parent- and adolescent-report of depressive symptoms.

Discussion

This systematic review and meta-analysis investigated whether autistic children and adolescents show a significant sex/gender difference in internalising symptoms, the direction of this effect, and whether variables such as mean age or IQ of the sample, or characteristics of the study account for heterogeneity in effect sizes between studies. This synthesis encompassed 48 studies and 10,045 autistic children and young people.

The meta-analyses revealed that there were no significant sex/gender-differences in internalising problems, including anxiety and depression symptoms, in autistic children and

young people. However, the high heterogeneity in the pooled effect for internalising symptoms indicated that the results must be interpreted with caution. Similar findings were made by Natoli and colleagues (2023) who's meta-analysis found no significant sex/gender difference in internalising problems of young autistic children. They also concluded that there were high levels of heterogeneity in the literature. Such high heterogeneity also corresponds with research on the mental health of autistic adults (Hollocks et al., 2019; Lai et al., 2019), suggesting that this may be a wider issue in autism research.

The present finding of mean age of the sample not moderating sex/gender difference in internalising problems was surprising, given that multiple studies reported sex/gender and age interaction, with females experiencing increased or higher levels of internalising problems at adolescence (Gotham et al., 2015; Oswald et al., 2016; Wright et al., 2021). There was a small effect of the sex/gender difference being more pronounced in older samples for anxiety, but this was not statistically significant. The lack of moderation effect for age in internalising symptoms could relate to most of the samples included in this study having a mean age between 8 and 12 years old, with only two studies reporting a mean age in the adolescent range, as the narrative synthesis pointed towards a larger difference in adolescence (De Clerq et al., 2021; Oswald et al., 2016; Salomon et al., 2011). Additionally, within individual studies, most of the samples had a large age range, meaning that opposing effects across the developmental trajectory could obscure one another (Mandy et al., 2012; Nasca et al., 2020; Worley & Matson, 2011).

The mean IQ of the sample did not account for any heterogeneity in the sex/gender difference in internalising symptoms or anxiety, which contradicts the hypothesis that sex/gender differences found in autistic samples could relate to the heterogeneity in cognitive abilities of

the samples in different studies (Mandy et al., 2012; Mayes et al., 2020; Natoli et al., 2023). These findings are in line with research by Lai et al (2019), who found that IQ did not account for any heterogeneity in the effect sizes of anxiety and depression disorder prevalence in autistic adults. This implies that the absence of a sex difference may be applicable to autistic children and young people who have a co-occurring learning disability, as well as those with normal range IQ.

Moreover, some authors have suggested that methodological issues and biases such as samples predominantly consisting of males, and over-reliance on samples from clinical settings have contributed to the lack of sex/gender difference found in some of the studies (Lai et al., 2015; Oswald et al., 2016). This is supported by the present findings showing that the type of informant, study quality and type of sample accounted for heterogeneity in the sex/gender difference in anxiety symptoms. More specifically, the sex/gender difference in anxiety was larger in community than clinical samples. This could be due to a ceiling effect whereby most children referred to clinics already display a relatively high level of anxiety. Females recruited from clinics might also have more pronounced social difficulties or sensory sensitivities, leading to more internalising symptoms, than those recruited from the community or cohort studies, due the underdiagnosis of autistic females (D'Mello et al., 2022; Happé & Frith, 2020).

Furthermore, autistic young people reported a larger sex/gender difference in anxiety than parents, but this effect was small. Similar effects have been found in non-autistic CYP where girls report more internalising problems than boys (Sourander et al., 1999). Jamison and Schuttler (2015) found in their research that autistic females had more negative self-ratings

than their parents across internalising and externalising problems, and social challenges, possibly indicating a more negative self-concept.

Clinical implications

This meta-analysis has a few implications regarding clinical practice. Firstly, the lack of sex difference in internalising problems of autistic CYP indicates that the aetiology and causal mechanisms driving the higher rates of internalising problems in autistic individuals may not be influenced by sex/gender. Given the sex/gender difference found in non-autistic CYP, this could evidence different underlying developmental processes in the incidence of internalising problems between autistic and non-autistic CYP. Understanding the reasons driving the higher levels of internalising problems in autistic CYP is crucial for developing more effective psychological interventions for autistic individuals, particularly, as current psychological interventions may be experienced as less effective by autistic than non-autistic CYP (Kreslins et al., 2015; Weston et al., 2016). Thus, understanding the lack of sex differences in internalising problems among autistic CYP is essential for developing interventions that are informed by the distinct developmental processes at play.

Secondly, the present finding regarding the informant effect on anxiety symptoms indicates that when assessing internalising problems in autistic CYP, using both self- and parent-report measures, and interviews might be important. The absence of a sex/gender difference in internalising problems also suggests that autistic males and females can be compared against the same norms when assessing internalising problems using standardised measures (Mayes et al., 2020).

Limitations

A substantial amount of the heterogeneity in the meta-analyses remained unaccounted for, particularly for internalising problems, after accounting for a priori-defined moderators. This suggests that there could be other contributors to the sex/gender differences in co-occurring internalising problems in autistic children and young people. For example, variables such as the ethnic composition of the sample, or co-occurring ADHD symptoms were not included as co-variates in the meta-analyses, due to variability in how these were reported within studies. Moreover, meta-regression analyses were completed list-wise instead of conducting multiple meta-regression, to preserve power. However, this meant that it was not possible to examine potential interaction effects between covariates, or to see if an effect remains meaningful once controlling for other possible moderators.

The present study did not examine gender and sex as separate constructs due to inconsistency in defining this within the studies included. Differences in how gender and sex were operationalised in each study could contribute to the heterogeneity in sex/gender differences in internalising problems. This could be an issue particularly in autistic children as the rates of gender diversity are higher in this population (Kallitsounaki et al., 2023). Furthermore, this paper focused on cross-sectional effects of sex/gender on internalising symptoms, rather than focusing on developmental and sub-class trajectories of internalising problems in autistic males and females from childhood to adolescence. However, there is a limited number of studies investigating such trajectories (Gotham et al., 2016; Horwitz et al., 2023; Wright et al., 2023).

Future research

Examining sex and the non-binary gender expressions in relation to internalising problems in autistic children and young people might help researchers distinguish the impact of biological mechanisms that could account for sex/gender differences, such as puberty and pubertal timing, and environmental factors, such as sexism, gendered social expectations, and stigma (Turnock et al., 2022). For example, in non-autistic CYP, early maturation and interpersonal stress have been shown to increase internalising problems, particularly in girls (Rudolph & Flynn, 2007; Winer et al., 2016). In autistic CYP, there is some evidence of sex differences in pubertal timing and tempo, and puberty mediating the rise in depressive symptoms in autistic youth (Corbett et al., 2022; Corbett et al., 2024). Such differences in pubertal trajectories could thus explain some of the heterogeneity not accounted for by the moderators in the present study. Furthermore, research directly comparing autistic and non-autistic males and females regarding the developmental effects of sex/gender on trajectories of internalising would help confirm the finding that autistic and non-autistic differ in the developmental impact of sex on internalising problems. This might further elucidate possible underlying processes.

Finally, majority of the included studies used samples with most participants belonging to white western populations. More research completed in ethnically and culturally diverse samples would clarify how sex/gender differences in internalising symptoms might interact with cultural considerations, such as societal acceptability of autism diagnosis, cultural differences in camouflaging, and other risk factors such as minority stress (Keating et al., 2021). Additionally, more diverse samples would help with generalising these findings and contributing to cultural differences in how autism and co-occurring difficulties manifest.

Conclusion

There was no evidence for a consistent sex difference in internalising problems in autistic children and young people. However, some potential moderators in effect size included age, publication year of the study and the type of informant. A considerable part of heterogeneity was likely to be driven by methodological issues. Future research should examine developmental trajectories of internalising problems in autistic males and females over time, consider sex and gender separately, and investigate sex/gender differences in co-occurring internalising problems in culturally and ethnically diverse populations.

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PART 2: Empirical paper

Sex differences in the internalising problem trajectories of autistic and non-autistic children across childhood and adolescence

Abstract

Background: In non-autistic children and young people (CYP), sex differences in trajectories of internalising problems are well documented. For autistic children, the developmental effects of sex on internalising are less understood. The present study investigated whether autistic and non-autistic children differ in their trajectories of internalising problems, and whether these trajectories differ based on sex.

Methods: Participants included autistic and non-autistic CYP from a large population-based UK birth cohort (The Millennium Cohort Study). Internalising symptoms were measured by parent-report Strengths and Difficulties Questionnaire at six timepoints across the ages of three to seventeen. Latent Growth Curve models were used to model the trajectories of internalising problems, in four groups: autistic males, autistic females and non-autistic males and non-autistic females, while controlling for SES, ethnicity, ADHD diagnosis, IQ and perinatal risk factors.

Results: Autistic males (N=433) displayed higher internalizing levels at age five (model estimated mean difference = 0.53, 95% CI [.14, .91]), but autistic females (N=132) surpassed them by age nine (model estimated mean difference = -0.69, 95% CI [-1.20, -.18]. After controlling for SES, ethnicity, ADHD diagnosis, IQ and perinatal risk factors, the mean differences between autistic males and females remained but became non-significant. possibly reflecting issues with power. Main effects of autism ($ß_{intercept}$=0.81, p<0.001; $ß_{linear}$= 0.45, p<0.001) and sex (($ß_{intercept}$=- 0.06, p=0.007; $ß_{linear}$= 0.16, p<0.001) were found on the starting level and growth in internalising problems.

Conclusions: There are sex and autism specific trajectories in internalising problems for CYP. This implies the importance of developing of effective and timely interventions, particularly for adolescent autistic females, who appear most at risk.

Introduction

The relationship between autism spectrum condition ('henceforth autism') and mental health problems is firmly established, with a high proportion of autistic children, young people and adults reporting mental health problems. For example, 20-40% of autistic people report experiencing depression or anxiety (Hollocks et al., 2019; Lai et al., 2019; Simonoff et al., 2008). This is much higher than the 3-16% found in the general population (McManus et al., Baxter et al., 2014). In the general population, mental health problems typically start in childhood (Kessler et al., 2007). In line with this, the pattern of increased emotional and mental health problems in autistic people is already found at a young age (Mylett et al., 2023; Skokauskas & Gallagher, 2011).

In children and young people (CYP), mental health problems are often divided into internalising (i.e., symptoms of anxiety, depression, somatic problems) and externalising problems (i.e., behavioural and conduct problems) (Achenbach et al., 2016). This was borne out of research using factor analysis to analyse the types of problems experienced by CYP seen in clinics for mental health problems (Achenbach, 1966). Since then, internalising and externalising problems have become widely known and adopted in clinical practice and research (Achenbach et al., 2016). They have been incorporated into popular measures of children's social, behavioural, and psychological problems, such as the Strengths and Difficulties Questionnaire (Goodman, 2001), and the Child Behaviour Checklist (Achenbach, 1999). These allow internalising problems to examined in a dimensional way, applicable to both clinical and community settings.

Some causal explanations for the disparity in the higher levels of internalising problems experienced by autistic people involve individual characteristics such as emotion regulation

difficulties (Conner et al., 2020; Rieffe et al., 2011), referring to ones' ability to manage and cope with the intensity and duration of their emotions (Cai et al., 2018a), and alexithymia, which refers to limited ability to recognise and describe one's emotions, and to distinguish them from bodily sensations (Taylor, 2000). Aspects of cognitive inflexibility, such as difficulty tolerating uncertainty and preference for sameness (aversion with changes to routines, environments, and rituals; Richler et al., 2010), have been also proposed to underlie the higher rates of internalising problems found in autistic individuals (Jenkinson et al., 2020). Ozsivadjian et al (2020) suggest that cognitive inflexibility could exacerbate social difficulties due to difficulty predicting how others might behave, which would lead to more uncertainty in the social domain and thus anxiety. It can also influence emotional coping behaviours such as excessive rumination, which has also been associated with internalising problems (Bos et al., 2018).

Other explanations for the high level of internalising problems in autistic individuals are based in the social and environmental difficulties faced by autistic people. For example, Mitchell et al (2021) have described "the double empathy problem" (Mitchell et al., 2021), which highlights that both autistic and non-autistic individuals struggle to understand each other, and that as a result autistic individuals face social issues such as marginalisation and isolation (Mitchell et al., 2021; Trundle et al., 2023). Social issues and peer problems have also been shown to increase internalising problems (Dovgan & Mazurek, 2019). Autistic people, particularly females, have also been shown to try to camouflage their social communication difficulties, which has been associated with more anxiety and depression (Hull et al., 2019; Hull et al., 2021).

In children and young people, accounts of the causal and maintaining factors underlying internalising problems have received less attention, even though it is during this life stage that mental health problems commonly first emerge. The investigation of factors influencing co-occurring internalising problems in autistic CYP is important in improving our understanding of their aetiology, and for identifying those most at risk before problems become entrenched (Colizzi et al., 2020). This is particularly important as internalising problems have been associated with poorer quality of life in both autistic adults and CYP (Oakley et al., 2021).

Sex is one such characteristic suggested to influence internalising problems in autistic CYP. In this chapter, I will mainly refer to biological sex due to this being the variable of interest in the present study. However, in discussing this, I will also refer to the social aspects of gender, as due to the strong societal influences of how each sex is socialised, for many individuals the effects sex and gender are highly interlinked and can be difficult to distinguish (Lai et al., 2015).

Currently, sex differences in autistic CYP's internalising difficulties are poorly understood. Some cross-sectional studies have found a sex difference in autistic CYP, reporting males to experience more internalising problems (Guerrera et al., 2019; Penner et al., 2022), whereas others report females to present with higher levels of internalising (Lohr et al., 2017; Oswald et al., 2016; Wijnhoven et al., 2018). Many studies have not found any significant differences (Boonen et al., 2014; Fombonne et al., 2022; Hartini et al., 2016). The meta-analysis completed in the previous chapter on cross-sectional sex differences in autistic CYP, found no significant sex differences in internalising, although there was a high amount of heterogeneity.

The investigation of sex differences in internalising problems of autistic individuals is made more difficult by the rate of diagnosis in autism being lower in females than males (Loomes et al., 2017), often resulting in research samples with an underrepresentation of females (D'Mello et al., 2022). Some have suggested that this is partially due to autism manifesting differently in females than males, arguing for the existence of a "female autism phenotype", i.e., a female-typical presentation of autism that does not fit current conceptualisations of the condition, which are based on male-majority samples (Mandy et al., 2012). The potential bias in diagnosis could mean that autistic females are less represented in studies examining sex differences in internalising problems (Loomes et al., 2017)

The inconsistencies in the sex differences found within autistic CYP could be explained by the relatively small number of studies adopting prospective longitudinal designs to investigate the developmental differences in internalising based on sex. Such developmental effects are well documented in the general population, where females tend to experience more growth in internalising towards adolescence than males (Papachristou et al., 2020; Sterba et al., 2007; Toumborou et al., 2011).

One potential explanation for this relates to differences in pubertal timing and its effects on internalising (Graber, 2013; Hayward & Sanborn, 2002). Pubertal changes, and particularly earlier maturation in girls, have been associated with sex differences in internalising problems found in general population (Graber, 2013; Hayward & Sanborn, 2002). This has been suggested to result from girls being more sensitive to interpersonal stress following puberty, and increased vulnerability to sexual abuse and harassment due to early maturation (Angold et al., 1998; Rudolph & Flynn, 2007; Skoog & Özdemir, 2016). Pubertal changes could also be distressing for autistic CYP due to preference for sameness and higher levels of

gender dysphoria experienced by autistic CYP (Corbett et al., 2020). Other explanations for the developmental changes in internalising problems include increases in interpersonal stress in relation to parent-child and peer relationships, and poorer emotion regulation (Cyranowski et al., 2000; Patton et al., 2008; Toumborou et al., 2011).

Accordingly, Georgiades and colleagues (2017) have argued that autism research needs a new focus on "chronogeneity", the study of the heterogeneity of autism across time, including variance across time on both group and individual level. Duncan and Duncan (2009) posit that appropriate developmental models must consider individual differences in developmental trajectories over time. Thus, studying autism and its co-occurring conditions over time might help form a "more precise and dynamic picture of autism" (Georgiades et al., 2017) and contribute to the developmental model of co-occurring internalising problems in autism.

Longitudinal methodologies, such as latent growth curve modelling (LGCM), lend themselves to examining development over time (Curran et al., 2010). LGCM is a form of structural equation modelling that lends itself to examining growth over time (Burant, 2016). There are numerous advantages to LGCM, including being able to examine growth on average as well as on an individual level, being able to assess the fit of the model to the data, being robust to the effects of missing data, and ability to model more complex non-linear trajectories (Preacher, 2018). Curran and Willoughby (2003) also highlight that LGCM allows us to investigate "unobservable" phenomena such as developmental trajectories and are thus crucial for furthering our understanding in developmental psychopathology. The ability to add covariates into the models allows one to ask more theoretically broad questions

such as what impacts the starting point, direction, and steepness of the developmental trajectories (Curran and Willoughby, 2003).

There is a growing literature in modelling the developmental trajectories of autistic traits and co-occurring conditions. Cronshaw and Midouhas (2023) used mixed-effect (non-latent) growth curve models to analyse trajectories of internalising and externalising problems in autistic CYP using data from the millennium cohort study. The autistic CYP showed increases in internalising problems over time, whereas the non-autistic CYP showed the opposite pattern. Mandy et al (2022) used latent growth curve models to analyse trajectories of social, internalising, and externalising problems in autistic CYP using data from the Millennium Cohort Study. They found that internalising problems tended to increase over time, and that the timing of autism diagnosis impacted the trajectories of internalising. Autistic CYP diagnosed in early childhood had higher levels of internalising problems but CYP with later diagnosis showed steeper growth in internalising problems.

Neither Cronshaw and Midouhas (2023) or Mandy et al (2023) examined sex or gender differences in the trajectories of internalising problems. Hollingdale et al (2023) utilised non-latent growth curve modelling to examine sex differences in a large cohort of CYP to discover that autistic traits moderated the impact of ADHD traits on the trajectories of internalising in males but not females, where autistic traits increased the levels of internalising experienced from ages 9 to 17. However, although providing some evidence for the interaction of autism and sex on trajectories of internalising problems, the participants included in this sample did not have an autism diagnosis.

A few studies have investigated sex differences in trajectories of internalising in autistic CYP (Corbett et al., 2024; Gotham et al., 2015; Wright et al., 2023). Wright et al (2023) used percentile plots and latent growth curve analyses in 397 two- to ten-year-old autistic CYP, of which 84% were male. They discovered that autistic CYP showed more internalising problems across time than non-autistic CYP, and that in autistic CYP, female sex was associated with a higher starting level in internalising symptoms. However, this difference was found in a clinical sample with a relatively small proportion of females which may result in recruitment bias of girls with higher levels of internalising problems. Moreover, this study did not capture the time windows of puberty and adolescence.

Gotham and colleagues (2015) used generalized mixed-effects models to examine developmental trajectories of anxiety and depression in 109 autistic and non-autistic CYP with a developmental delay. Their sample spanned the ages of 6 to 24 years old. Similar to Wright et al (2021), they found steeper growth over time in anxiety and depression symptoms for autistic females than males. The sample for this study, like Wright et al (2021), was recruited from specialist clinics and had a relatively small sample size, with only 12% (N=13) females.

Corbett et al (2024) used linear mixed models to investigate the impact of autism diagnosis and puberty on longitudinal depression symptoms in a community sample of 244 autistic and non-autistic CYP, across ages 10-to-13. They found that depressive scores were elevated in autistic CYP in early puberty and decreased with advancing pubertal stage, and that females had higher depressive scores than males. This study suggests that the findings of higher levels of internalising problems in autistic females in older childhood might be generalizable to the wider population beyond clinic samples. However, Corbett et al (2024) did not directly

investigate the impact of autism and sex on trajectories of depression and looked at a relatively narrow age range. Therefore, there are no studies to my knowledge, that specifically focus on the sex difference in trajectories of internalising problems over the whole childhood, including adolescence, using large naturally occurring samples from cohort studies, with enough autistic females to reach adequate power for comparisons. The present study aims to address this gap.

The aim of this paper was to use latent growth curve modelling to describe and compare trajectories of change in internalising problems in autistic and non-autistic males and females, recruited from a large cohort of UK children and young people. This study aimed to answer the following research questions:

1. To describe trajectories of internalising problems during childhood and adolescence for autistic and non-autistic males and females.
2. To investigate whether initial levels and trajectories of internalising problems are different for autistic versus non-autistic CYP (i.e., main effect of autism)
3. To investigate whether initial levels and trajectories of internalising problems are different for males versus female CYP (i.e., main effect of sex)
4. To investigate whether any sex differences in initial levels and trajectories of internalising problems are different for autistic versus non-autistic CYP (i.e., interaction between autism and sex)
5. To investigate the sex difference between autistic male and female CYP across trajectories of internalising

Methods

Participants and recruitment

The data used in this study were sourced from the Millennium Cohort Study (MCS), a prospective research project tracking the health and progress of children and young people born in the UK between September 2000 and January 2002 on numerous physiological, social, and psychological outcomes. The study so far comprises of seven sweeps (points of data collection) completed between the ages of 9 months and 17-years-old (Table 5). The data accessed for this study encompassed all available sweeps (1 – 7) and were obtained from the UK Data Service.

Table 5

Sweep	1	2	3	4	5	6	7
Age of child	9 months	3 years	5 years	7 years	11 years	14 years	17 years

A summary of the MCS data collection time points

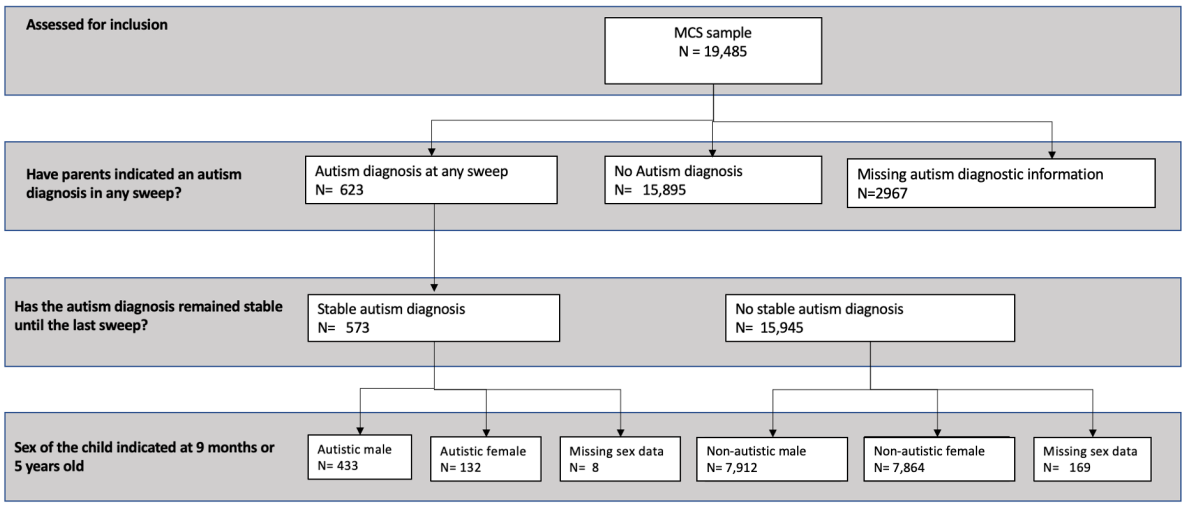
The first sweep included 19,231 cohort members and their families. To be included in the MCS, children had to meet three specific criteria: being born within specified dates, residing in the UK at nine months of age, and being eligible for Child Benefit at the same age.

For the present study, the sample was then divided into groups based on whether the child had received an autism diagnosis (See Figure 5 for participant flow chart). To be included in the autism diagnosis group, parents were required to have reported that their child has received a diagnosis of autism spectrum disorder. Parents were asked in four of the seven sweeps (aged 5, 7, 11 and 14) 'Has a doctor or other health professional ever told you that your child had Autism, Asperger's Syndrome or other autistic spectrum disorder?'. The child was included in the autism group, if their parent had answered 'Yes' at the last sweep that

they partook in. This was to ensure that CYP who may have been misdiagnosed and later had their diagnosis changed were not included in the autistic group. In other words, cohort members were excluded from the autism group if their diagnosis was not 'stable' across time. Out of 623 participants, 50 participants did not present with a stable diagnosis, and were thus excluded from the autistic group. This yielded 573 autistic and 15,945 non-autistic participants. Of the total sample, 2,967 of the participants did not provide autism diagnostic information and were thus excluded.

The participants were subsequently further stratified by sex at birth, as indicated by parents at 9 months, or 5 years old for those not included in the first sweep, resulting in four participant groups: autistic males, autistic females, non-autistic males, and non-autistic females. Sensitivity analyses were conducted between samples including a stable and non-stable autism diagnosis (see Appendices 6-9).

Figure 5



Participant flow chart

Variables and Measures

Internalising

The MCS measured child internalising problems using the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001). The SDQ is a brief screening tool for emotional and behavioural difficulties in children and young people. It consists of five subscales: emotional problems, peer problems, behavioural problems, inattention and hyperactivity, and prosocial subscale. The measure can be completed as a self-report, parent-report, or a teacher-report measure. In the MCS, the SDQ was administered by parent-report at ages 3, 5, 7, 11, 14 and 17 years old. Completing the SDQ involves rating difficulties on a 3-point scale: "Not true" (0), "Somewhat true" (1) and "Certainly true" (2).

SDQ has good validity and reliability in populations of children and young people (Goodman, 2001; Kersten et al 2016; Stone et al., 2010). It has also been found valid and reliable in autistic populations (Findon et al., 2016). SDQ is highly correlated with other well-established measures of internalising problems such as the Child Behaviour Checklist (Stone et al., 2010). SDQ has also been used in previous research on internalising problems in autistic children and adolescents and shown to detect internalising disorders in autistic young people (Colvert et al., 2021; Simonoff et al., 2013).

In the present study, the parent-report emotional problems subscale of the SDQ was used to measure internalising problems. The individual items are listed below in Table 6. The SDQ has an internalising subscale which consists of the emotional and peer problem subscales. However, given that differences in social communication is one of the core traits of autism and autistic CYP have been shown to consistently experience more peer problems than non-autistic CYP (Petrina et al., 2014), it is likely that including the peer problems subscale in the

measure of internalising would inflate the levels of internalising problems found in autistic males and females. Thus, the emotional problems subscale was adopted as a measure of internalising problems rather than the full internalising scale with peer problems.

Table 6

Item
3. Often complains of headaches, stomach-aches, or sickness
8. Many worries, often seems worried
13. Often unhappy, downhearted, or tearful
16. Nervous or clingy in new situations, easily loses confidence
24. Many fears, easily scared

Strengths & Difficulties Questionnaire, Emotional Problems sub-scale. Items are rated as 0 – "Not true"; 1 – "Somewhat true"; 2 – "Certainly true".

Covariates

A number of covariates were included to investigate and control for confounding effects on the differences between groups on the trajectories of internalising problems. These included factors that have been shown to covary with sex, autistic traits, and internalising symptoms, such as family socio-economic status, ethnicity, and perinatal risk factors (Bourne et al., 2023; Getahun et al., 2017; Lund et al., 2012). Variables were also included to investigate possible mediating effects of traits related to autism, such as IQ and ADHD diagnosis, as IQ (Edirisooriya et al., 2021) and ADHD traits (Mayes et al., 2012; Reiersen et al., 2007; Steinhausen et al., 2006) are highly associated with both autism and internalising symptoms.

The complete list of covariates can be found in Table 7. All variables apart from IQ were assessed at 9 months old, with a small proportion of observations recorded at 3 years old for families joining the study at sweep 2. IQ was assessed at 7 years old. Please see Appendix 4 for more detail on how each covariate was measured.

Table 7

Confounder	**Variable**
Sociodemographic characteristics	Ethnicity (White or minoritized ethnicity) Parent SES (total banded income; recorded at 9 months or 3 years) Parent education (highest NVQ level or equivalent)
Peri-natal risk factors	Birth weight (KG) Admitted to Special Baby Unit (yes or no) Gestational age (days) Alcohol use during pregnancy (yes or no) Smoking during pregnancy (yes or no)
Variables related to neurodiversity	ADHD diagnosis IQ (computed factor score)

A Summary of the covariates included in the study.

Ethics

Ethical approval for the MCS was obtained from the UK National Health Service Research Ethics Committee prior to each sweep of the MCS. Informed written consent was provided by the parents of cohort members at each sweep.

Consent for the present study was granted under application 19439/001 by the UCL Research Ethics Committee.

For the purposes of the present study, the MCS data were accessed from the UK Data Service under an End User License (EUL), and in line with their data access policy.

Data analytic plan

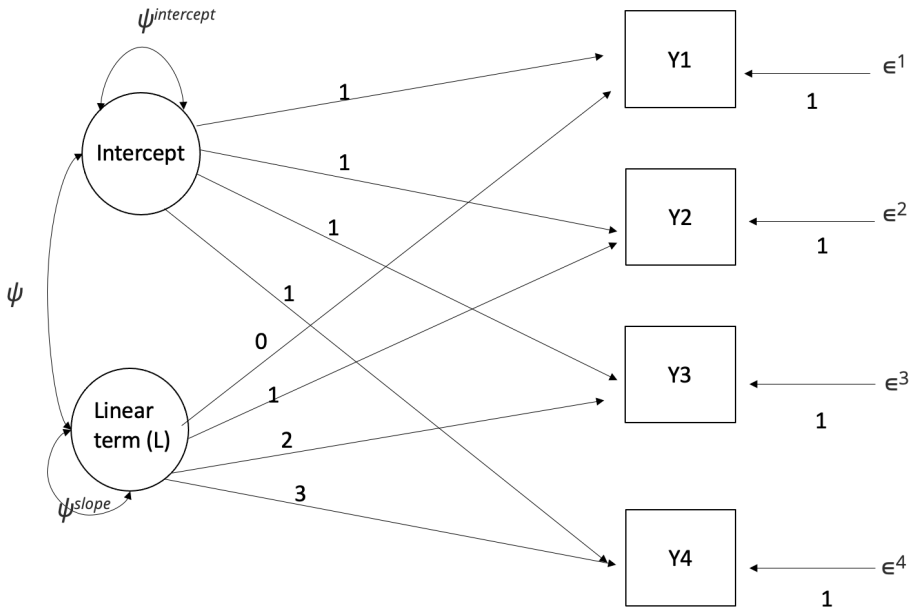
Stata (StataCorp, 2023) was used to process the data and to complete descriptive analyses. MPlus (Muthen & Muthen, 1998-2017) software was subsequently used to impute missing data on the covariates and to conduct the LGCM analyses.

Latent growth curve modelling (LGCM) is a multivariate structural equation modelling technique which involves estimating individuals' change across time on one or more outcome variables (Berlin et al., 2014). LGCM is increasingly used as longitudinal methodology as it adopts the observed repeated measures as indicators of one or more latent factors to estimate the unobserved growth trajectories and is robust to the effects of measurement error that might exist in the predictor or outcome variables (Curran et al., 2010).

LGCM involves estimating fixed effects, such as the mean intercept and slope on both individual and group level, as well as random effects, consisting of the between-person

variability in slopes and intercepts, at each time point (Curran et al., 2010). As illustrated in Figure 6, the loadings for the intercept are fixed to 1 as the intercept stays constant for individuals across time, whereas the slope loadings increase by 1 for each time point to imply that the measured variables are equally spaced in time (Duncan & Duncan, 2009). The loadings can also be fixed to uneven intervals to reflect unequally spaced time-points. However, the approximation of equally spaced time points is relatively robust to slight variation in the spacing of observations, as is the case in the present study (Bollen & Curran, 2006). The intercept and slope are allowed to covary, and this reflects the relationship between intercept and slope; that is, how the rate of change is impacted by the starting point. LGCM allows for both time dependant and time fixed covariates to be added into the model.

Figure 6



Adapted from Preacher et al (2008). A linear growth curve model, where the circles represent latent variables, such as mean intercept and slope indicated by the linear term (L), the squares (Y1-Y4) represent the measured variables (i.e., measurements at different time-

points), the numbers represent fixed loadings, ψ denotes the variances and covariances for each element of change, and the ∈ symbols describe the measurement errors.

Latent growth curve models are usually fitted for linear, quadratic, or cubic forms of change (Preacher, 2018). A linear trajectory implies a constant rate of increase or decrease across the time, where the steepness and direction of the trajectory depend on the sign and magnitude of the linear term (L) (Nini et al., 2017). In a quadratic model, the trajectory has a variable rate of change across time, showing two distinct phases of acceleration and deceleration. The quadratic term (Q^2) indicates both the direction and steepness of the curvature of the trajectory. A cubic function implies that the trajectory can have more than two distinct phases of acceleration and deceleration. It typically follows a curvature, similar to the quadratic function, until an inflection point, at which the curvature changes again (Nini et al., 2017). The sign of the cubic term (C^3) implies the direction, and steepness of change. In quadratic and cubic LCGMs the slope loadings for the quadratic and cubic terms are squared and cubed, respectively.

In the present study, LGCM was utilised to describe the trajectories of internalising problems across six timepoints; three, five, seven, eleven, fourteen, and seventeen years of age. This is often referenced as an acceptable number of time points for LGCM, although the number of time points one should have also depends on sample size and the complexity of the model (Bollen & Curran, 2006; Duncan et al., 2006). Separate models were fitted for four different groups: Autistic males, autistic females, non-autistic males, and non-autistic females. Linear, quadratic, and cubic forms of change were explored and assessed for best fit using the standardized root mean square residual (SRMR), the root mean square error of approximation (RMSEA), the comparative fit index (CFI). These are commonly used fit indices in structural

equation modelling (Kline, 2023). The model with the best fit was adopted and models falling below the following cut offs were rejected: RMSEA<0.06 (Kline, 2023), CFI >0.90, and SRMR<0.06 (Hu & Bentler, 1999).

Table 8

	Covariates
Step1 models	No covariates added
Step 2 models	Ethnicity, income, parental education level, gestational age, birthweight, alcohol use while pregnant, smoking while pregnant, baby spending time in special baby unit after birth, type of delivery
Step 3 models	Ethnicity, income, parental education level, gestational age, birthweight, alcohol use while pregnant, smoking while pregnant, baby spending time in special baby unit after birth, type of delivery, ADHD diagnosis, IQ

A summary of the steps in which covariates were added to the models to adjust for potential confounding effects.

The process for adding covariates is summarised in Table 8. The models for each group were initially run without accounting for covariates (Step 1 models). Subsequently, time-fixed covariates were added to the model as covariates to account for potential confounding effects (Step 2 models). In the next step (Step 3 models), ADHD status and IQ were added as covariates in addition to the covariates included in the Step 2 models, to investigate potential mediating effects. At each step, model estimated means and standard errors were obtained from the model output and used to calculate t-tests for mean difference between groups at each time point.

Finally, I examined the whole sample to further examine whether the trajectories significantly differ based on the autism diagnosis and sex. To accomplish this, I regressed the intercept and slope factors for each trajectory on sex, the autism status variable, and the interaction of the two, whilst controlling for potential confounders. This was conducted to allow the examination of how sex and autism diagnosis affect the starting points and rates of change in internalising problems.

Results

Descriptive analyses

The sample consisted of 433 (2.7% of whole sample) autistic males, 132 (0.8%) autistic females, 7,912 (48.4%) non-autistic males, and 7,864 (48.1%) non-autistic females. Most of the sample were white (81.5%). The next largest groups were Pakistani and Bangladeshi (6.9%), black (3.8%) and mixed ethnicity (3.1%) groups (see Table 8 for a more detailed breakdown of all the descriptive statistics). The distribution of ethnicities within the sample corresponds with the UK 2011 and 2021 census data (Office for National Statistics [ONS], 2015; ONS, 2022). The family income and parent education levels were also representative of the UK population (ONS, 2020; ONS, 2023).

The rates of co-occurring ADHD diagnoses within the autistic group, presented in Table 9, corresponded with the rates found in other studies (Bougeard et al., 2021). The prevalence of ADHD diagnoses in the non-autistic group, were representative of the UK prevalence estimates (Hire et al., 2018).

Pearson's Chi square analyses were used to compare group characteristics (See Appendix 5 for full comparisons). The analyses indicated that the autistic group had a significantly lower representation of ethnically minoritized individuals ($X^2(1) = 17.97$, $p < 0.001$). Parents of autistic CYP had a significantly higher proportion of parents in the lower income brackets compared to parents of non-autistic children ($X^2(2) = 11.706$, $p = 0.003$). More males ($X^2(1) = 169.99$, $p < 0.001$), and more autistic CYP presented with ADHD ($X^2(1) = 1.8e+03$, $p < 0.001$).

The groups significantly differed in IQ, $F(3, 13390) = 23.96$, $p < .001$, where females had higher IQ ($M = 100.8$, $SD = 14.4$) than males ($M = 99.2$, $SD = 15.5$), $t(13402) = -6.4$, $p < 0.001$, and autistic CYP ($M = 95.5$, $SD = 17.4$) had a significantly lower IQ than non-autistic CYP ($M = 100.1$, $SD = 14.9$), $t(13405) = 6.11$, $p < 0.001$. Within both non-autistic and autistic groups females had higher IQ than males, but this difference was only significant in the non-autistic group ($t(12994) = -5.9$, $p < 0.001$). The mean internalising scores per group over time are presented in Table 10.

Table 9

		Autistic		Non-autistic	
		Males (N=433) *Frequency (%)*	Females (N=132) *Frequency (%)*	Males (N= 7,912) *Frequency (%)*	Females (N= 7,864) *Frequency (%)*
ADHD	No ADHD diagnosis	284 (65.6%)	109 (82.6%)	7,715 (97.5%)	7,813 (99.4%)
	ADHD diagnosis	149 (34.4%)	23 (17.4%)	196 (2.3%)	50 (0.6%)
Ethnicity	White	384 (88.7%)	117 (88.6%)	6,487 (82%)	6,452 (82.0%)
	Mixed	15 (3.5%)	3 (2.3%)	224 (2.2%)	244 (3.1%)
	Indian	2 (0.5%)	1 (0.8%)	212 (2.7%)	196 (2.5%)
	Pakistani and Bangladeshi	10 (2.3%)	3 (2.3%)	531 (6.7%)	549 (7.0%)
	Black	13 (3.0%)	4 (3.0%)	295 (3.7%)	272 (3.5%)
	Other	6 (1.4%)	2 (1.5%)	114 (1.4%)	106 (1.4%)
	Missing	3 (0.7%)	2 (1.5%)	49 (0.6%)	45 (0.6%)
SES (Family income)	£ 0 - £16,500	163 (37.6%)	44 (33.3%)	2,386 (35.8%)	2,447 (31.1%)
	£16,500.01 - £28,000	119 (27.5%)	39 (29.5%)	2,049 (25.9%)	2,011 (25.6%)
	> £28,000	105 (24.2%)	31 (23.5%)	2,335 (29.5%)	2,284 (29.0%)
	Missing income information	46 (10.6%)	18 (13.6%)	1,142 (14.4%)	1,122 (14.3%)
Parental Education	NVQ levels 1-2 (GCSE level)	184 (42.5%)	49 (37.1%)	2,947 (37.3%)	2,962 (37.7%)
	NVQ levels 3, 4, 5 (A-level - higher education)	187 (43.2 %)	59 (44.7%)	3,567 (45.1%)	3,482 (44.3%)

	Missing education information	62 (14.3%)	24 (18.2%)	1,398 (17.7%)	1,420 (18.1%)
Delivery type	Vaginal	288 (66.5%)	86 (65.2%)	5,262 (66.5%)	5,450 (69.3%)
	Assisted or surgical (forceps, caesarean, etc)	139 (32.1%)	44 (33%)	2,588 (32.7%)	2,369 (30.1%)
	Missing information	6 (1.4%)	2 (1.5%)	62 (0.8%)	45 (0.6%)
Baby in Special Baby Unit or NICU	Yes	55 (12.7%)	21 (15.9%)	821 (10.4%)	632 (0.8%)
	No	191 (44.1)	46 (34.8%)	3,115 (39.4%)	2,881 (36.6%)
	Missing information	187 (43.2%)	65 (49.2%)	3,976 (50.3%)	4,351 (55.3%)
Alcohol use while pregnant	Yes	153 (35.3%)	38 (28.8%)	2,587 (32.7%)	2,493 (31.7%)
	No	280 (64.7%)	94 (71.2%)	5,325 (67.3%)	5,371 (68.3%)
Smoking while pregnant	Yes	172 (39.7%)	36 (27.2%)	2,218 (28.0%)	2,071 (26.3%)
	No	261 (60.3%)	96 (72.7%)	5,694 (71.9%)	5,793 (73.7%)
Demographic variable			N	Mean (SD), range	
IQ (age 7)	Autistic	Male	306	95.35 (15.6), 50.1- 140.1	
		Female	92	96.0 (16.5), 53.4- 135.6	
	Non-autistic	Male	6,421	99.4 (15.4), 49.5- 141.9	
		Female	6,575	100.9 (14.4) 49.6- 140.0	
Gestational age (days)	Autistic	Male	411	253.2 (17.1), 179-300	
		Female	122	272.9 (18.1), 175-298	
	Non-autistic	Male	7,494	275.4 (14.3), 170-301	
		Female	7,501	275.8 (13.8), 168-301	
Birthweight (KG)	Autistic	Male	413	3.36 (0.66), 0.91-5.73	
		Female	123	3.22 (0.71), 0.62-4.76	
	Non-autistic	Male	7,573	3.40 (0.60), 0.68-6.55	
		Female	7,572	3.28 (0.58), 0.39-7.23	

Descriptive statistics of the sample.

Table 10

	T1 (3 years)	*T2 (5 years)*	*T3 (9 years)*	*T4 (11 years)*	*T5 (14 years)*	*T6 (17 years)*
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
Autistic males	1.66 (1.75)	2.37 (2.10)	3.13 (2.42)	4.32 (2.58)	4.06 (2.56)	3.88 (2.68)
Autistic females	1.68 (1.64)	1.86 (1.95)	2.72 (2.42)	4.35 (3.03)	5.10 (2.65)	5.11 (2.90)
Non-autistic males	1.35 (1.49)	1.31 (1.56)	1.42 (1.72)	1.61 (1.81)	1.61 (1.89)	1.48 (1.88)
Non-autistic females	1.38 (1.51)	1.42 (1.59)	1.54 (1.72)	1.88 (1.94)	2.29 (2.18)	2.40 (2.34)

Observed mean internalising scores per group at each time point.

Data distribution

The outcome data consisting of the SDQ scores showed positive skew at each time point, ranging between 1.2 and 1.5, whereas kurtosis ranged between 1.0 and 3.0. However, the levels of skewedness and kurtosis were within the bounds of acceptable levels for structural equation modelling (skewness: 2, kurtosis: 7; Curran et al., 1996). The rate of missingness was 23.4 - 35.2% for the first three time points and 41.4-51.9% for the subsequent time points.

Latent growth curve models

Model fit

The model fit indices for all models are presented in Table 11. For autistic males and females, the cubic models had the best fit across unadjusted and adjusted models, and these were also within the bounds of acceptable fit. In the non-autistic male and female groups, for both unadjusted and adjusted models, the fit indices also indicated the best fit for the cubic models. However, the models had issues with non-convergence and thus the quadratic models of change were adopted for non-autistic groups to avoid over fitting.

Table 11

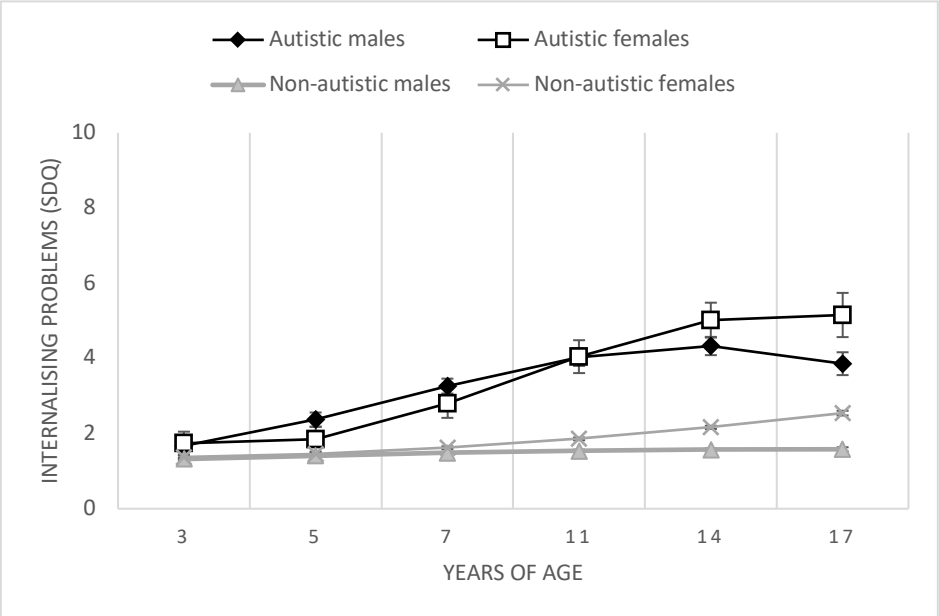
			linear	**quadratic**	**cubic**
Unadjusted Models	Autistic males	RMSEA	0.138	0.083	0.059
		CFI	0.720	0.925	0.977
		SMSR	0.108	0.052	0.031
	Autistic females	RMSEA	0.166	0.149	0.082
		CFI	0.784	0.869	0.977
		SMSR	0.121	0.073	0.037
	Non-autistic males	RMSEA	0.058	0.039	0.018
		CFI	0.917	0.976	0.996
		SMSR	0.059	0.024	0.011
	Non-autistic females	RMSEA	0.061	0.039	0.026
		CFI	0.923	0.976	0.994
		SMSR	0.050	0.024	0.013
Step 1 adjusted models	Autistic males	RMSEA	0.076	0.052	0.045
		CFI	0.752	0.913	0.959
		SMSR	0.067	0.846	0.026
	Autistic females	RMSEA	0.089	0.075	0.031
		CFI	0.810	0.899	0.988
		SMSR	0.086	0.053	0.036
	Non-autistic males	RMSEA	0.038	0.028	0.017
		CFI	0.921	0.967	0.993
		SMSR	0.036	0.018	0.010
	Non-autistic females	RMSEA	0.038	0.024	0.015
		CFI	0.927	0.979	0.995
		SMSR	0.031	0.016	0.009
Step 2 adjusted models	Autistic males	RMSEA	0.073	0.054	0.041
		CFI	0.740	0.895	0.960
		SMSR	0.064	0.040	0.025
	Autistic females	RMSEA	0.085	0.076	0.050
		CFI	0.802	0.881	0.966
		SMSR	0.084	0.053	0.038

Non-autistic males	RMSEA	0.035	0.026	0.015
	CFI	0.923	0.967	0.993
	SMSR	0.034	0.017	0.010
Non-autistic females	RMSEA	0.036	0.022	0.014
	CFI	0.926	0.978	0.994
	SMSR	0.029	0.015	0.009

Model fit for change in internalising problems over time.

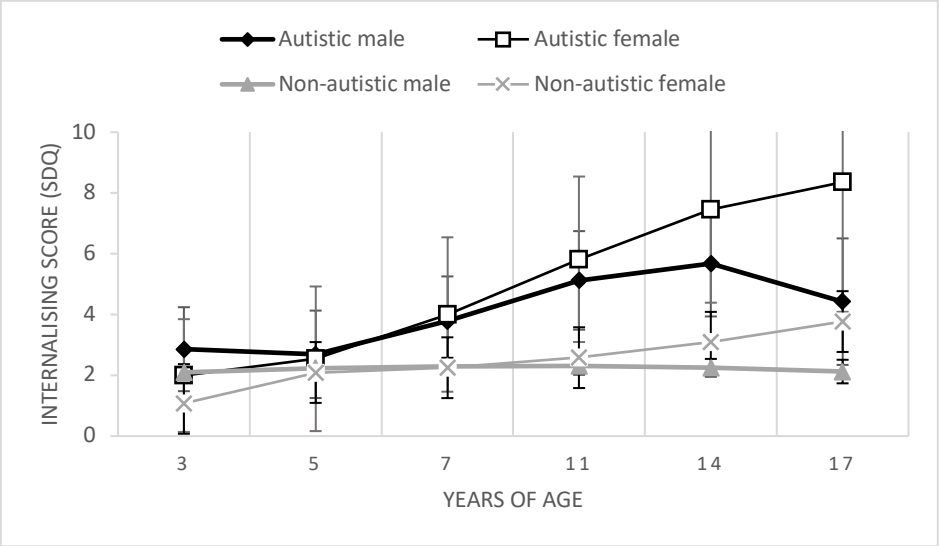
Trajectories of internalising problems over time

Figure 7



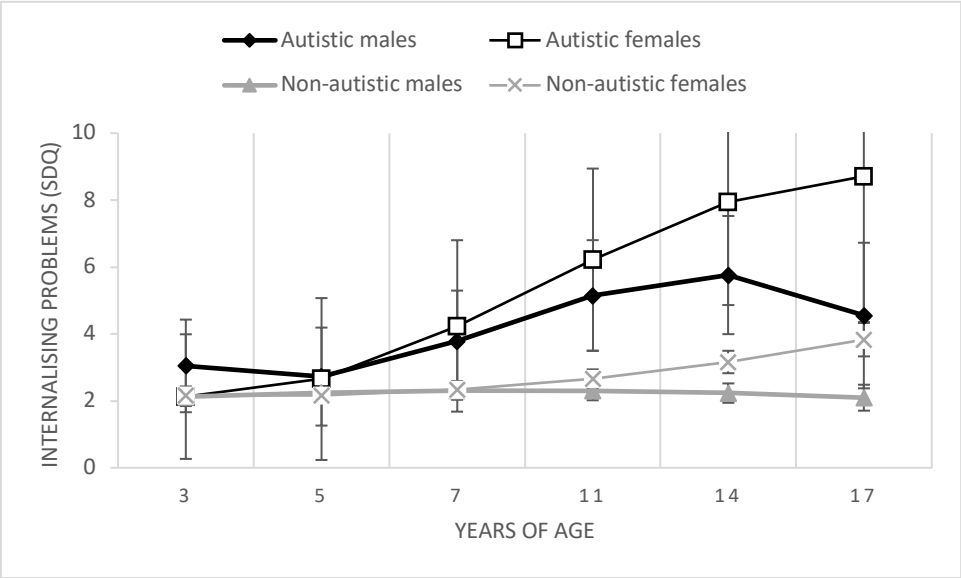
Model 1 mean trajectories of internalising symptoms across six time points. The error bars represent 95% Confidence Intervals. Model parameters can be found in Tables 12 and 13.

Figure 8



Model 2 mean trajectories of internalising symptoms across six time points, after controlling for ethnicity, SES variables, and perinatal risk factors. The error bars represent 95% Confidence Intervals. Model parameters can be found in Tables 12 and 13.

Figure 9



Model 3 mean trajectories of internalising symptoms across six time points, after controlling for ethnicity, SES variables, and perinatal risk factors, IQ and ADHD. The error bars represent 95% Confidence Intervals. Model parameters can be found in Tables 12 and 13.

Step 1 models

As illustrated by Figure 7, autistic males showed a positive acceleration in growth as indicated by the positive linear and quadratic terms (M_L=.49, SE=.15, p=.001; M_{Q2}=.26, SE=0.08, p=.001; see Table 12 for all growth parameters), followed by slight deceleration in adolescence as the growth in internalising problems appeared to plateau and decrease. Autistic females started at a similar level to autistic males but demonstrated slower growth until the age of 5, followed by a steeper acceleration from age 5 until 14, and slightly slower growth from 14 to 17. For non-autistic females, the increase in internalising problems appeared relatively consistent across time with acceleration towards adolescence, as indicated the positive quadratic term (M_{Q2}=.04, SE=.003, p<.001). Non-autistic males exhibited a relatively flat trajectory, but this was characterised by faster growth in early- to mid-childhood followed by a slight tapering off in adolescence, as suggested by the small but negative quadratic coefficient (M_L=.100, SE=.015, p<.001; M_{Q2}=-.02 SE=.002, p<.001). For more information on the covariances and individual trajectories for all models, please see Appendix 10.

Statistical analysis of the mean difference in model estimated means using t-tests confirmed that autistic males and females did not significantly differ in their starting levels of internalising problems at three years old (M_{diff}=-.07, 95% CI [-.43, .29]; See Table 13 for all model estimated means and mean differences). The analyses showed that autistic males showed significantly higher levels of internalising problems than autistic females at age five M_{diff}=.53, 95% CI [.14, .91], but autistic females surpassed them at age 14 (M_{diff}=-.60, 95% CI [-.65, -.54])

Examining the starting levels of internalising problems for the non-autistic males and females suggested that non-autistic females started at a significantly higher level than non-autistic males (M_{diff}=-.53, 95% CI [-.86, -.19]), and that non-autistic females consistently experienced significantly more internalising problems than non-autistic males. Moreover, comparing the model estimated means between autistic and non-autistic females and autistic and non-autistic males suggested that the autistic children experienced higher internalising problems than non-autistic children at all time points (see Table 13).

Step 2 models

As illustrated by Figure 8, and the model parameters in Table 12, the trajectories of internalising problems for each group generally maintained similar shapes to Step 1 models after adding the step 2 covariates. However, there were slight changes to the autistic groups, such as autistic males appearing to present with slight deceleration between the ages of 3 and 5 compared to the acceleration found in the previous model (M_L=-0.41, SE=1.72, p>0.05). The autistic females exhibited steeper acceleration (M_Q=.73, SE=.91, p>.05), as implied by the larger positive quadratic term. Moreover, the autistic males presented with a steeper decrease in internalising problems at adolescence (M_L=-1.14, SE=.64, p>.05; M_Q= 1.14, SE=.64, p>.05; M_C=-0.17, SE=.09, p>.05). However, these slope terms were not statistically significant, possibly reflecting issues with power after adding in the covariates.

As shown in Table 13, after accounting for the impact of the Step 2 covariates on the internalising problem trajectories, the differences between the model estimated means at each time point were no longer significantly different between autistic males and females. However, this could be due to reductions in power (and thus higher standard errors) due to a more complex model, as the mean differences were larger in magnitude (i.e., Step 1 at 17

years old: $M_{diff=}$ -.97, CI 95% [-1.04, -.88] vs. Step 2 17 years old: M_{diff}=-3.93, CI 95% [-8.39, .53]). This is also supported by the smaller confidence intervals in the non-autistic groups, which had much larger sample sizes and less complex model.

Non-autistic males and females significantly differed in starting and end points, where males now experienced more internalising problems in early childhood (M_{diff}=1.02, 95% CI [.72, 1.32], they had equal levels of internalising problems from age seven ($M_{diff=}$.14, 95% CI [-.19, .47]) and females surpassed them at age 14 (M_{diff} =-.84, 95% CI [-1.28, -.39], mimicking the trend found in autistic males and females. Autistic males and females showed significantly higher internalising problems than non-autistic males and females from age seven for males (M_{diff} =1.48 CI 95% [.27, 2.70] and age 11 for females (M_{diff} =3.24, CI 95% [1.02, 5.45]).

Step 3 models

Adding ADHD diagnosis and IQ into the model did not appear to change the shape of the trajectories much, as illustrated by Figure 9. The growth parameters (Table 12) were comparable to those of the Step 2 latent growth curve models.

In the step 3 models, the sex difference in starting levels of internalising problems in non-autistic CYP reduced and became insignificant (M_{diff}=-0.04, CI 95% [-.42, .34], suggesting this difference to have been possibly driven by differences in ADHD diagnosis or IQ, such as males having more ADHD diagnoses and lower IQ. The only group differences that remained significant in Step 3 models, were the differences in adolescence between non-autistic males and females, and between autistic and non-autistic groups (see Table 13).

Table 12

	Growth parameter	Autistic males		Autistic females		Non-autistic males		Non-autistic females	
		Mean (SE)	**Variance (SE)**	**Mean (SE)**	**Variance (SE)**	**Mean (SE)**	**Variance (SE)**	**Mean (SE)**	**Variance (SE)**
Step 1 Models	Intercept	1.674 (.086) ***	1.972 (.716) *	1.740 (.158) ***	2.236 (.940) *	1.321 (.017) ***	1.127 (.073) ***	1.376 (.018) ***	1.172 (.072) ***
	Linear term	.493 (.152) **	1.880 (1.361)	-.505 (.217) **	1.937 (1.576)	.100 (.015) ***	0.456 (.05) ***	0.052 (.016) **	0.456 (.05) ***
	Quadratic term	.258 (.080) **	.501 (.277)	.705 (.118) ***	.257 (.278)	-.010 (.003) **	.016 (.002) ***	.036 (.003) ***	.021 (.002) ***
	Cubic term	-.054 (.011) ***	.011 (.005) *	-.093 (.017) ***	.004 (.005)	NA	NA	N/A	NA
Step 2 Models	Intercept	2.859 (0.705) ***	2.145 (0.750) **	1.993 (0.946) *	1.878 (0.953) *	2.097 (0.138) ***	1.014 (0.070) ***	2.110 (0.136) ***	1.078 (0.069) ***
	Linear term	-1.142 (1.222)	2.171 (1.317)	-0.083 (1.723)	1.878 (1.597)	0.169 (.124)	0.437 (0.049) ***	-0.105 (0.121)	0.457 (0.05) ***
	Quadratic term	1.144 (0.642)	0.471 (0.249)	0.725 (0.905)	0.154 (0.274)	-0.033 (0.025)	0.015 (0.002) ***	0.087 (0.026) **	0.021 (0.002) ***
	Cubic term	-0.171 (0.088)	0.009 (0.005) *	-0.091 (0.124)	-0.003 (0.005)	NA	NA	NA	NA
Step 3 Models	Intercept	3.038 (.690) ***	2.043 (.754) **	2.023 (.920) *	2.121 (1.002) *	2.118 (.139) ***	1.012 (.070) ***	2.158 (.136) ***	1.079 (.068) ***
	Linear term	-1.245 (1.244)	2.006 (1.316)	-.114 (1.723)	1.811 (1.688)	.160 (.125)	.433 (.049) ***	-.086 (.123)	.454 (.050) ***

Quadratic term	1.118 (.651)	.424 (.246)	.753 (.897)	.177 (.275)	-.033 (.025)	.015 (.002) ***	.084(.026) **	.021 (.002) ***
Cubic term	-.162 (.089)	.008 (.005)	-.094 (.122)	.003 (.005)	NA	NA	NA	NA

*Mean growth parameter estimates for the unadjusted growth curve models. * p < 0.05. ** p <0.01. *** p <0.001.*

Table 13

			3 years old	5 years old	7 years old	11 years old	14 years old	17 years old
Step1 models	Autistic males	Mean estimate	1.67	2.37	3.26	4.02	4.33	3.86
	Autistic females	Mean estimate	1.74	1.85	2.80	4.05	5.02	5.15
	Non-autistic males	Mean estimate	1.32	1.41	1.48	1.54	1.57	1.58
	Non-autistic females	Mean estimate	1.38	1.46	1.62	1.86	2.16	2.54
	Autistic males vs females	Mean difference [95% CI]	-.07 [-.43, .29]	.53 [.14, .91]	.46 [.043, .88]	-.02 [-.50, -.45]	-.69 [-1.20, -.18]	-1.30 [-1.94, -.66]
	df=563		p=.719	p=.008	p= .0305	p= .923	p=. 008	p< .001
			M=F	M>F	M>F	M=F	M<F	M<F
	Non-autistic males vs females	Mean difference [95% CI]	-.53 [-.86, -.19]	-.05 [-.09, -.01]	-.14 [-.19, -.09]	-.32 [-.37, -.27]	-.60 [-.65, -.54]	-.96 [-1.04, -.88]
	df= 15774		p= .002	p=0.014	< .001	< .001	< .001	< .001
			F>M	F>M	F>M	F>M	F>M	F>M
	Autistic vs non-autistic females	Mean difference [95% CI]	.36 [.09, .64]	.38 [.15, .61]	1.17 [0.90, 1.45]	2.19 [1.89, 2.48]	2.85 [2.51, 3.19]	2.61 [2.12, 3.10]
	df= 7994		p=.010	p=.001	p<.001	p<.001	p<.001	p<.001
			A>N	A>N	A>N	A>N	A>N	A>N
	Autistic vs non-autistic males	Mean difference [95% CI]	.35 [0.23, .48]	.96 [.826, 1.09]	1.78 [1.63, 1.93]	2.49 [2.33, 2.65]	2.76 [2.60, 2.93]	2.28 [2.04, 2.51]
	df = 8343		p<.001	p<.001	p<.001	p<.001	p<.001	p<.001
			A>N	A>N	A>N	A>N	A>N	A>N

Step 2 Models	Autistic males	Mean	2.86	2.69	3.79	5.12	5.68	4.42
	Autistic females	Mean estimate	1.99	2.54	4.00	5.82	7.45	8.35
	Non-autistic males	Mean estimate	2.10	2.23	2.30	2.31	2.25	2.12
	Non-autistic females	Mean estimate	1.08	2.09	2.25	2.58	3.09	3.77
	Autistic males vs females	Mean difference [95% CI]	.87 [-1.85, 3.58]	.15 [-2.78, 3.07]	-.22 [-3.23, 2.80]	-.70 [-4.00, 2.61]	-1.77 [-5.36, 1.81]	-3.93 [-8.39, .53]
	df=563		p=.531	p=.921	p= .888	p= .680	p=.331	p=.083
			M=F	M=F	M=F	M=F	M=F	M=F
	Non-autistic males vs females	Mean difference [95% CI]	1.02 [.72, 1.32]	.14 [-.19, .47]	.05 [-0.32, .43]	-.27 [-.67, .13]	-.84 [-1.28, -.39]	-1.65 [-2.28, -1.01]
	df= 15774		p<.001	p=.400	p=.777	p=.183	< .001	< .001
			M>F	M=F	M=F	M=F	M<F	M<F
	Autistic vs non-autistic females	Mean difference [95% CI]	.92 [-.159, 1.99]	.45 [-1.31, 2.21]	1.70 [-0.43, 3.83]	3.24 [1.02, 5.45]	4.36 [1.74, 6.99]	4.59 [.69, 8.48]
	df= 7994		p=.094	p=.613	p=.118	p=0.004	p=.001	p=0.021
			A=N	A=N	A=N	A>N	A>N	A>N
	Autistic vs non-autistic males	Mean difference [95% CI]	.76 [-0.44, 1.97]	.46 [-.61, 1.53]	1.48 [.265, 2.70]	2.81 [.54, 4.09]	3.43 [2.12, 4.74]	2.17 [.25, 4.10]
	df = 8343		p=.214	p=.401	p=.017	p<.001	p<.001	p=.027
			A=N	A=N	A>N	A>N	A>N	A>N
Step 3 Models	Autistic males	Mean estimate	3.04	2.75	3.72	4.99	5.57	4.50
	Autistic females	Mean estimate	2.02	2.57	4.05	5.91	7.57	8.47
	Non-autistic males	Mean estimate	2.12	2.25	2.31	2.30	2.23	2.10
	Non-autistic females	Mean estimate	2.16	2.16	2.32	2.66	3.17	3.84

Autistic males vs females	Mean difference [95% CI]	1.02 [-1.64, 3.66]	.18 [-2.83, 3.19]	-.33 [-3.40, 2.74]	-.92 [-4.23, 2.39]	-2.00 [-5.55, 1.55]	-3.97 [-8.47, .53]
df=563		p=.452	p=.905	p= .835	p= .586	p=.270	p=.083
		M=F	M=F	M=F	M=F	M=F	M=F
Non-autistic males vs females	Mean difference [95% CI]	-0.04 [-.42, .34]	-.09 [-.24, .41]	-0.02 [-0.39, .36]	-.36 [-.76, .04]	-.93 [-1.38, -.49]	-1.75 [-2.37, -1.12]
df= 15774		p=.838	p=.591	p=.929	p=.078	p<.001	< .001
		M=F	M=F	M=F	M=F	M<F	M<F
Autistic vs non-autistic females	Mean difference [95% CI]	-.14 [-2.23, 1.96]	.41 [-1.33, 2.16]	1.73 [-.29, 3.73]	3.25 [1.05, 5.44]	4.40 [1.81, 6.99]	4.63[.77, 8.49]
df= 7994		p=.899	p=.644	p=0.092	p=0.004	p<.001	p= .018
		A=N	A=N	A=N	A>N	A>N	A>N
Autistic vs non-autistic males	Mean difference [95% CI]	.92 [-.29, 2.13]	.50 [-.57, 1.58]	1.14 [.19, 2.64]	2.69 [1.41, 3.96]	3.34 [2.03, 4.65]	2.40 [.67, 4.14]
df = 8343		p=.135	p=.356	p=.023	p<.001	p<.001	p=.007
		A=N	A=N	A>N	A>N	A>N	A>N

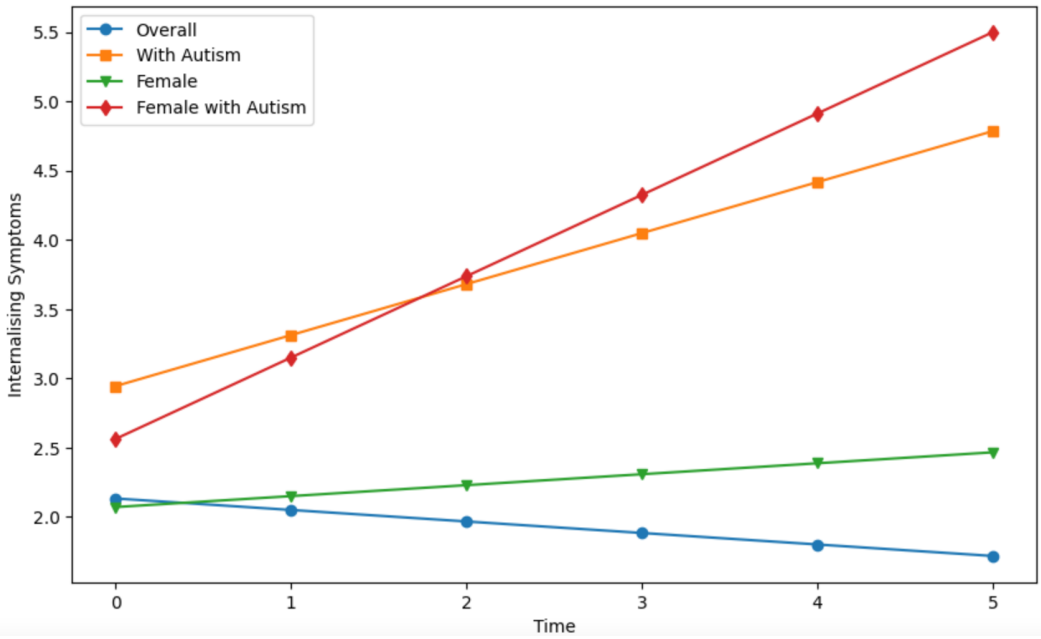
Statistical comparison of model estimated means between autistic and non-autistic males and females at each time-point using t-tests. M=male, F=female, A=autistic, N=non-autistic.

Regression of sex and autism status onto internalising problem trajectories

The final step was to investigate whether autism diagnosis and sex, and the interaction between the two significantly influence the starting points and growth in internalising problems. Thus, autism status, the sex of the child, and the interaction between the two were regressed onto the internalising problems across the six time points for all groups combined, to assess this. The step 2 covariates were included as controls. ADHD diagnosis and IQ were excluded to avoid overly controlling for variables closely related with autism.

The regression model showed an acceptable fit for the linear form of change on the three model fit indices (RMSEA=0.036, CFI=0.931, SMSR=0.031). Given that the linear form showed good fit, it was chosen for ease of interpretation and parsimony in the regression analyses. (See Appendix 11 for the fit statistics for models fitted to the other forms of change).

Figure 10



Adjusted means for the intercept and slope regressed onto autism diagnosis and sex with control variables held constant.

The overall trajectory of internalising problems in the whole cohort followed a slight negative trajectory of decreasing internalising problems across time ($M_{intercept}$=2.133, SE= 0.10, p<0.001; M_{linear}=-0.084, SE=0.04, p=0.023) (Figure 10). Regressing the autism diagnosis status onto the slope revealed autism diagnosis to be significantly positively associated with the intercept and slope, whereby individuals with autism started 0.81 points higher on internalising symptoms compared to individuals without autism, and their internalising problems increased by 0.45 points more than non-autistic children, holding all other variables constant ($ß_{intercept}$=0.811, SE=0.23, p<0.001; $ß_{linear}$= 0.451, SE=0.09, p<0.001). Sex was significantly negatively associated with the intercept, and positively associated with the slope, where females started 0.06 points lower than males, and their internalising problems increased 0.16 points more than males at each time point ($ß_{intercept}$=- 0.062, SE=0.023, p=0.007; $ß_{linear}$= 0.162, SE=0.01, p<0.001). The interaction between sex and autism diagnosis was not significant, although this could be a power issue due to the unequal group sizes.

Adding IQ and ADHD as covariates into the regression model produced comparable results, where autism ($ß_{intercept}$=0.75, SE=0.24, p<.001; $ß_{Slope}$=0.37, SE=.09, p<.001**)** predicted larger increases on both the intercept and slope, compared to ADHD ($ß_{intercept}$=0.13, SE=0.10, p=.160; $ß_{Slope}$=0.20, SE=0.04 p<.001**),** and IQ ($ß_{intercept}$=-.11, SE=0.03, p<0.001; $ß_{Slope}$=-0.03 SE= .009, p<0.001). Sex also continued to significantly explain variation in the starting points and trajectories of internalising problems ($ß_{intercept}$= - .056 SE=0.024, p=.015; $ß_{slope}$=0.17, SE=0.01, p<0.001) (see Appendix 12 for full model parameters).

Table 14

Growth parameter	Mean (SE)	Residual variance (SE)
Intercept	2.133 (0.104) ***	1.135 (0.032) ***
Linear term	-0.084 (0.037) *	0.110 (0.004) ***
	Covariance (SE)	
Intercept-Linear	-0.110 (.009) ***	

Growth parameter estimates for the regression model. N=16,304.

Table 15

	Covariate	ß (SE)
Intercept on	Autism	0.811 (0.232) ***
	Sex	- 0.062 (0.023) **
	Autism*Sex	-0.319 (0.174)
	Ethnicity	0.462 (0.038) ***
	Income	-0.301 (0.028) ***
	Parental education	-0.224 (0.027) ***
	Baby in special baby unit	0.146 (0.045) **
	Gestational age	0.031 (0.025)
	Birthweight	-0.084 (0.023) ***
	Alcohol during pregnancy	0.010 (0.024)
	Smoking during pregnancy	0.086 (0.029) **
	Delivery type	-0.031 (0.025)
Slope (L) on	Autism	0.451 (0.085) ***
	Sex	0.162 (0.008) ***
	Autism*Sex	0.057 (0.064)
	Ethnicity	-0.112 (0.012) ***
	Income	-0.023 (0.010) *
	Parental education	-0.003 (0.010)
	Baby in special baby unit	-0.005 (0.018)
	Gestational age	-0.021 (0.009) *
	Birthweight	0.014 (0.009)
	Alcohol during pregnancy	-0.020 (0.009) *
	Smoking during pregnancy	0.037 (0.011) **
	Delivery type	-0.004 (0.009)

*Intercept and slope regressed onto the autism, sex, and the controlling variables.1=autism diagnosis, 0=no autism diagnosis, 1=female, 0=male. * p < 0.05. ** p <0.01. *** p <0.001.*

Sensitivity Analyses

Sensitivity analyses were completed for all the above models using the non-stable autism diagnosis which resulted in larger size groups for autistic males and females (Autistic males: N= 472; autistic females: N=143; non-autistic males: N=7873; non-autistic females: N=7853). The results from these analyses were comparable to those completed with the stable autism diagnosis (see appendices 5-9). However, with the increased sample size for the autistic male group, the step 2 model cubic slope and quadratic variance became significant, suggesting that the non-significant slope factors and variance are likely to reflect issues with power.

Discussion

The present study described trajectories of internalising problems in autistic and non-autistic males and females and examined whether these differ between autistic and non-autistic CYP, and between males and females. The study investigated whether the sex difference in trajectories differed as a function of autism diagnosis.

The present findings indicated that autistic CYP presented with higher starting points and steeper trajectories of internalising problems compared to non-autistic CYP. Across both autistic and non-autistic groups, female sex was associated with a lower starting point in internalising problems and a steeper trajectory. There was some evidence for a cross-over effect in both autistic and non-autistic males and females, whereby males showed higher levels of internalising problems in early childhood, and this reversed in adolescence with females experiencing more internalising problems, as the internalising problems in males started to decrease. The lack of significant interaction between sex and autism suggests that

the sex differences in autism might follow similar pattern to those in non-autistic CYP, although this could also reflect issues with power. Nevertheless, the present findings provide some evidence that the developmental sex differences in internalising problems, found in general population (Sterba et al., 2007; Toumborou et al., 2011), are also present in autistic CYP.

The present findings correspond with the existing literature, showing autistic females to display steeper trajectories of internalising problems (Corbett et al., 2024; Gotham et al., 2015), and more internalising problems than males in adolescence (Fombonne et al., 2022; Horowitz et al., 2023; Penner et al., 2022; Solomon et al., 2012). Although, in the study by Gotham et al (2015), the cross over between males and females happened at a much later age- between the age of 17 and 18, compared to the findings of the present study. Such cross over effect between autistic males and females might explain why previous studies have found inconsistent or no significant sex differences in internalising problems between autistic males and females. It suggests that the opposite effects on each end of the age range might cancel each other out, particularly in samples with a wide age range (Nasca et al., 2020).

Moreover, some have suggested that the higher levels of internalising problems in autistic individuals, and the sex differences could be driven by aspects of neurodiversity, such as differences in IQ (Blanken et al., 2017; Mayes et al., 2022) and ADHD traits (Hargitai et al., 2023). The present findings demonstrated that the internalising problem trajectories of autistic individuals maintained their shapes after ADHD and IQ were added as covariates. Additionally, the effects of autism and sex on trajectories of internalising problems persisted after adding ADHD and IQ into the model. This suggests that differences in ADHD traits and IQ do not mediate the differences in internalising problems found in autistic CYP.

Furthermore, this study replicated the well-documented finding that autistic CYP experience more internalising problems than non-autistic CYP (Lai et al., 2019; van Steensel, 2013; Wright et al., 2023), although this difference did not emerge until seven years old, after adjusting for sociodemographic and perinatal risk factors. This could be due to some of the autistic traits associated with internalising problems, such as difficulties with emotion regulation- and awareness, and cognitive inflexibility being relatively common in all children between the ages of 3 and 5 years old, leading to less pronounced differences between autistic and non-autistic individuals (Buttelmann & Karbach, 2017; Denham et al., 2009; Evans et al., 1997; Pons et al., 2004).

The present finding that both autism and female sex increase the steepness of the internalising problem trajectory suggests that autistic females are likely to face a much higher risk of internalising problems as they enter adolescence. Although the present study does not speak to the underlying causal processes, one can hypothesise that the sex difference found in autistic CYP is likely to reflect an interplay between individual autistic characteristics and social pressures experienced in adolescence by most CYP.

Adolescence is typically a time of changes such as a heightened sensitivity to peer influence and rejection, as well as transitions to more demanding environments such as secondary school (Andrews et al., 2021). Mandy et al (2018) found that autistic females were more likely to experience increases in social impairment in adolescence than autistic males, which could make adjusting to the social changes more difficult or lead to painful social rejections. Aspects of cognitive inflexibility, such as insistence of sameness, has also been shown to increase with age, and to associate with internalising problems (Richler et al., 2010). For instance, Baribeau et al (2021) showed that 90% of 3 to 9-year-old children with trajectories

characterised by high insistence of sameness behaviours also showed high levels of anxiety over time. Ozsivadjian et al (2020) have hypothesised that such aspects of cognitive inflexibility, could further exacerbate social difficulties.

Although both autistic males and females are likely to come up against transitions and social changes in adolescence, research shows that autistic females could be more motivated to engage socially than autistic males (Sedgewick et al., 2016), and more susceptible to interpersonal stress (Nenniger et al., 2021). Thus, compared to autistic males, autistic females could experience a "double whammy" of interpersonal stress in adolescence, compounded by social communication difficulties, emotion dysregulation and social stigma (Cai et al., 2018b; Jones et al., 2105; Perry et al., 2022). This could also lead to increased pressures to camouflage, or "use strategies to minimise autism in social situations" (Hull et al., 2021, p.2). Camouflaging has been associated with internalising problems in autistic CYP and adults. (Hull et al., 2021; Ross et al., 2023; Bernardin et al., 2021). Late identification of autism in females (Gould & Ashton-Smith, 2011; Zener, 2019) could also mean that by adolescence autistic females have had less support or received less school-based adjustments (May et al., 2014) than male autistic children, which could also negatively impact on their self-esteem (Stagg and Belcher, 2019; Deniz & Toseeb, 2023; Seers & Hogg, 2021).

The increases in internalising problems found from older childhood to adolescence across the groups could also correspond with pubertal changes. Research in non-autistic CYP has shown that girls experience more internalising symptoms than boys after puberty commences, and that this could be mediated with higher sensitivity to interpersonal stress in girls during and after puberty (Angold et al., 1998; Rudolph & Flynn, 2007). Earlier pubertal maturation and more peer problems have been in associated with more internalising problems in both boys

and girls (Winer et al., 2016). Earlier maturation might particularly increase internalising problems in girls due to higher risk of sexual abuse and harassment (Skoog & Özdemir, 2016). Given the higher levels of peer problems experienced by autistic CYP (Petrina et al., 2014), and higher vulnerability to victimisation (Douglas & Sedgewick, 2024), the effects of puberty could be more pronounced in autistic CYP. Corbett et al (2024) found that the effects of age and autism on increasing internalising problems in adolescents was at least partially mediated by the interaction between autism and puberty, whereby depressive scores were elevated in autistic youth in early puberty and decreased with advancing pubertal stage. Given that Corbett et al (2022) also found that autistic females to start puberty earlier but males to have a faster pubertal tempo, this could explain why females experience higher internalising problems in adolescence, and why males' internalising problems decrease sooner than females' across both autistic and non-autistic groups.

Nevertheless, increased social stress or puberty may not explain why autistic males, on average, appear to start with higher levels of internalising problems compared to autistic females. Several studies suggest that gender stereotypes may significantly influence how parents respond to their children's negative emotions, such as sadness or anxiety (Cassano & Zeman, 2010; Chaplin et al., 2005). For instance, Cassano et al (2007) found that parents of children aged 6 to 10 were more likely to encourage their daughters to express sadness and offer problem-solving advice compared to their sons. Therefore, it could be that male children are socialised to be less expressive of anxiety and sadness as they become older, leading parents to rate them lower for internalising problems. Although, less research has been conducted on emotion socialisation in autistic CYP, research by Jordan et al (2021) suggests that parents of autistic CYP generally engage in similar emotion socialisation behaviours than those of non-autistic CYP. This suggests that a similar socialisation effect to

that seen in non-autistic CYP could be influencing parents' ratings of internalising problems in autistic boys.

Clinical implications

The findings of this study illustrate high-risk groups and critical timings for intervention. The escalation of internalising problems for autistic CYP, particularly females, in adolescence identify them as a high need group for support. The present findings also imply that autistic males may benefit from psychological support sooner than autistic females due to reaching peak internalising problems earlier than autistic females. This indicates that child and adolescent mental health services (CAMHS) should consider prioritising these groups for intervention.

Commissioners of mental health services should also consider allocating funding to more specialised interventions for autistic CYP. For example, some adapted cognitive behavioural therapy (CBT) programmes have been found effective in in treating internalising disorders in autistic CYP, such as an adapted CBT group programme for anxiety by Chalfant et al (2007). Schwartzman et al (2024) have provided some preliminary evidence for the effectiveness of a CBT programme for depression called CBT-DAY, which combines neurodiversity-affirming approach with CBT to target emotional reactivity and self-esteem in autistic CYP. Nevertheless, Linden et al (2023) concluded in their systematic review of randomised clinical trials investigating psychological interventions for internalising disorders in autistic CYP, that the current evidence base shows limited efficacy in treating anxiety and depression in autistic CYP and adults, and that interventions targeting core traits of autism, such as those focusing on social skills training, are not recommended.

Moreover, this study contributes to the understanding of co-occurring conditions in autism. The sex difference in trajectories of internalising problems points to potential hypotheses for future research in what might drive these differences, such as interpersonal stress, camouflaging, and thus help increase our understanding of the aetiology of anxiety and depression in autistic individuals. This is important for developing more effective psychological interventions for autistic individuals.

Finally, the trajectories of internalising symptoms in autistic children show that the internalising problems start to increase beyond the levels experienced by non-autistic children after seven years of age, suggesting that this might be a crucial time for early psychosocial interventions targeting internalising problems. This could look like making parenting programmes, such as the EarlyBird, more readily available to parents (Dawson-Squibb et al., 2019), or adopting universal approaches focusing on more accessible adjustments for individuals with suspected or diagnosed neurodiversity and reducing social stigma through educational campaigns and peer support spaces (Crompton et al., 2023).

Strengths, limitations, and future avenues for research

The present study is among the first to use advanced longitudinal methodologies such as LGCM to investigate and describe differences between autistic and non-autistic males and females in trajectories of internalising problems in a large community sample. This paper addressed a gap in the literature by investigating sex differences in internalising problems of autistic children and adolescents in a cohort sample with a relatively high number of females, with a non-autistic comparison group.

Nevertheless, the study had some limitations. Firstly, the relatively smaller proportion of autistic females compared to autistic males, and non-autistic CYP meant that the more complex models using cubic form of change and covariates may have been under powered to detect a significant effect of the interaction between sex and autism diagnosis on the intercepts and slopes of internalising problem trajectories. Diallo et al (2014) recommend at least 100 but ideally 150 participants for non-linear LGCMs across 6 time points, which was barely satisfied by the autistic female group, at N=132, suggesting that issues with power were likely. This was also indicated by the non-significant model parameters in the autistic groups. Moreover, the skew in data could have rendered the use of maximum likelihood estimation less effective, as according to Yuan et al (2005), violations to the assumption of normality can influence standard errors, which could lead to model parameters and standard errors to be over or underestimated.

Furthermore, we were unable to investigate the differential effects of sex and (non-binary) gender. This would be an important consideration for future research, particularly given the high rates of gender diversity among autistic individuals (Corbett et al., 2023; Warrier et al., 2020). Trying to unpick the effects of sex and gender might help disentangle the social and biological effects of sex/gender on internalising problems.

Additionally, this study only included participants whose parents reported a clinical diagnosis of autism. This meant that CYP from groups that are underdiagnosed, such as females or ethnically minoritized CYP may have been underrepresented in this study. This is supported by the fact that the descriptive analyses showed the autistic group to include less ethnically minoritized CYP than the non-autistic group. In future research, using research diagnosis of

autism in community cohort studies might help increase the number of autistic CYP from underrepresented backgrounds.

The present study also used passive case ascertainment methods. Case ascertainment refers to how cases are identified in studies. This can involve active methods, such as screening the sample and actively assessing participants for the investigated condition, such as autism, regardless of whether they have been seen clinically, and passive methods such as reviewing existing databases and clinical records or asking parents for existing diagnostic information (Loomes et al., 2017). Employing active case-ascertainment methods, such as using autism screening questionnaires to identify cases, could help achieve more balanced samples in terms of underdiagnosed groups (Loomes et al., 2017). Moreover, the present study relied on parent report of autism diagnosis which meant that the diagnosis status of the cohort member could not be confirmed, leading to potential risk of overlap between autistic and non-autistic groups.

Importantly, the present paper was not co-produced with autistic individuals and thus may not reflect a topic of interest to the target population, and/or could lack important perspectives in explaining the findings. This is a major limitation and should be rectified with future research being co-produced to ensure the research on autism serves the population in question. In addition, future research building upon the current findings could incorporate time dependent covariates such as peer victimisation, cognitive inflexibility, language development, or coping skills to investigate the processes and factors driving the sex differences in the trajectories of autistic individuals.

Conclusion

The present paper illustrates that autistic males and females show different developmental trajectories of internalising problems, and that these are also distinct from those of non-autistic males and females. This reveals autistic female adolescents as a high-risk group in need for timely and targeted psychosocial interventions. The steep increase in internalising problems of autistic individuals in general after early childhood, suggest that intervening early with more universal psychosocial interventions, perhaps focusing on reducing social stigma and environmental adjustments, might be needed. Future research on distinguishing the effects of gender and sex is imperative to further understand the causal processes underlying the sex differences found in this study.

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PART 3: Critical Appraisal

Critical Appraisal

Reflexivity refers to an "ability to locate yourself in the picture, to understand, and factor in, how what you see is influenced by your own way of seeing, and how your very presence and act of research influences the situation in which you are researching" (Fook, 1999, p.11). In the final part of my thesis, I will reflect on how my own position, or "way of seeing", has influenced my research, and what I have learned from it. I will further reflect on some of the limitations of my research. I will start by discussing my relationship to autism research as a non-autistic researcher. Subsequently, I will reflect on the challenges of using advanced statistical methods as a trainee clinician. Finally, I will evaluate the benefits and challenges of using secondary data in the context of my research.

Investigating autism "from the outside in"

When commencing on my thesis project, investigating internalising problems in autistic children and young people, I was relatively naïve to the field of autism research. Importantly, I am a non-autistic researcher with no family members or close friends that are autistic. Therefore, I do not have experience of what it is like to be autistic or live in our society as an autistic individual. It is important for researchers to reflect on the beliefs and values that they bring to their research (Stark et al., 2021). The values that were important to me when starting this project were: a) viewing autism as a difference or a neurodivergence rather than a disorder, b) recognising that autistic individuals are valued members of the society that can thrive with sufficient adaptations made to do so, and c) considering autistic individuals as the experts of their experiences whose voices should be centred in research.

One of the ways in which I tried to embody such values in my research was the intentional and thoughtful use of language. The National Autistic Society UK (2024) advocates for the use of "identity first" language, such as "autistic child," rather than "person first" language, like "child with autism." They also recommend avoiding the term "disorder" except when referencing diagnostic criteria like ICD-10 or DSM-5, to reduce the perception of autism as a pathology. This preference is reinforced by research from Kenny et al (2015), which found that members of the UK autism community, including autistic individuals, parents, and their support networks, favour the terms "autistic," "autism," and "on the autism spectrum." Dwyer et al (2022) have also cautioned research from using other terms and language that positions autistic traits and characteristics as pathological or maladaptive, such as talking about “risk factors” or using negative terms such as “rigid”, “deficits”, and “comorbidities”.

Therefore, in my research I endeavoured to use identity first language. I used the term “co-occurring” to convey my position of internalising problems in autism being associated but difficulties, rather than signs of pathology inherently linked to autism. Similarly, I tried to avoid pathologizing language such as the examples described above.

Conversely, using strengths-based on non-pathological language can be more difficult when referring to traits and concepts that are widely used and characterised in psychological literature, such as “cognitive inflexibility” (Morris & Mansell, 2018) and “intolerance of uncertainty” (Rosser, 2019). These are traits that are not exclusive to autism but are often considered as highly associated traits in autism literature (Lage et al., 2023). These could be framed in a more strengths-based way, for example referring to “adherence to routines. However, not using terms that are well characterised in the literature could cause the piece of research to be more disjointed from the rest of the body of research. Additionally, if concepts

are not well defined or characterised uniformly across literature, this can make synthesising literature more difficult. I tried to approach this issue by discussing these traits as dimensional characteristics associated with autism rather than global characteristics representing all autistic CYP. However, future research should consider more strength-based or neutral framing of autistic traits and other psychological concepts.

Furthermore, as a non-autistic researcher it is important to centre autistic individuals as experts. Thus, one of the limitations of my project was the lack of community participation. Participatory research is a broad term encompassing various research methods and approaches that utilise inclusive and community-engaged practices (Cargo & Mercer, 2008). It involves working together with members of a community, such as autistic individuals, with them ideally contributing to each stage of the project (Den Houting, 2021). There is a hierarchy in participation research. Lower levels of participation research might involve autistic individuals consulting on aspects of the project ("doing for"), whereas higher levels would involve true co-production, working as equal partners jointly deciding and collaborating on all parts of the project ("doing with") (Arnstein, 1969; Den Houting, 2021).

Ideally, this would mean that the research aims, and questions are decided together. Co-producing from the start ensures that the research topic is of importance to the lives of the group it represents and allows the coproduces to frame the question and aims in a way that addresses their knowledge and lived experience (Bell & Pahl, 2018).

Despite my intentions to consult members of the autistic community regarding the interpretation of my results, I was unable to accomplish this due to time constraints and competing demands. Not inviting consultation or co-producing my research with autistic

individuals could mean that my research question regarding the impact of sex on internalising problems is not of interest or experienced as relevant by autistic individuals. It could also mean that my interpretation of my findings could be incongruent with the experiences of autistic CYP. For example, autistic individuals might not resonate with my interpretation of the sex difference found in adolescence resulting partially from autistic girls being more sensitive to social pressures. Accordingly, Strang et al (2020) have queried whether the concepts of sex and gender are experienced or understood differently by autistic CYP, compared to non-autistic CYP. For example, autistic CYP might experience less pressure to conform to gendered roles and expectations (Strang et al., 2020). Therefore, consulting autistic individuals in the interpretation of research findings is important going forward.

On the contrary, doctoral research might provide a challenging setting for co-production. A doctoral thesis is intended to be an assessment of an individual's skills in research. However, true co-production is intended to foster an equal working relationship with community partners, which involves having equal say in decisions (Oliver et al., 2019). This would make assessing an individual's work more difficult. Moreover, co-production and participation work can be costly and time-consuming (Oliver et al., 2019). On professional doctorate courses, time for research and financial resources are often limited. This could make fair compensation of community partners more difficult. Additionally, doctoral researchers might be more constrained in being able to enact the suggestions made by experts of experience. Thus, there could be a higher risk of engaging with participatory research in a tokenistic manner. In line with this, Oliver and colleagues (2019) argue that participation and co-production, if not done properly, can be harmful to the community partners, and foster distrust in academia.

In conclusion, engaging in research as a non-autistic researcher meant that careful consideration was needed about not being complicit in societal narratives pathologizing autism. I tried to do this via intentional use of strength-based and neutral language, where possible. As a non-autistic researcher, one of the limitations of my thesis was lack of participation by autistic individuals. Participatory research is key in further understanding the experiences of autistic CYP and the effects of sex on internalising problems. However, the constraints of doctoral research mean that careful consideration should be taken when engaging in participatory research as part of a thesis, to avoid tokenistic and potentially harmful practices.

Engaging with complex statistical methods as a trainee clinician

Completing my research project on the developmental trajectories of internalising problems in autistic CYP involved the use Latent Growth Curve Modelling (LGCM). LGCM is a type of structural equation modelling (SEM) well suited to modelling longitudinal trajectories in latent variables. LGCM is used to estimate changes in individuals over time on one or more outcome variables (Berlin et al., 2014). It involves fixing the loadings for intercept and slope to specific values, allowing the intercept and slope to be calculated for each individual and on group basis (Curran et al., 2010). These are referred to as fixed effects. LGCM also estimates random effects, which represent the variability in slopes and intercepts between individuals, at each time point (Curran et al., 2010).

More complex longitudinal modelling methods, such as LGCM, are becoming more widely used in clinical research, requiring clinicians to upskill themselves in such methods. Curran and Willoughby (2003) argue that to meet the complexity of human behaviour, equally complex theories and thus statistical models are required. However, such methodologies and

their theoretical underpinnings and assumptions are rarely taught in depth on graduate programmes and papers on methods such as LGCM often assume prior knowledge in more complex statistics (Yuan et al., 2005).

Prior to commencing on this project, I had no experience in structural equation modelling or LGCM. The most complex statistical methods I had used were multiple regressions in SPSS. Thus, the learning curve in developing my skills in LGCM was steep. Using LGCM as a clinical doctorate trainee rather than a statistician, new to the field of SEM, presented with challenges in choosing the correct methodology, and in interpretation of results. I will next consider each challenge in turn.

Choosing the correct methodology

When I chose the LGCM methodology for my project, this was done based on a relatively basic understanding of LGCM, supported by the guidance of my research supervisors. Although, I researched and learned about LGCM, my understanding regarding the underpinning theory and traditions of SEM were weak. However, I learned more throughout completing the analyses and having to problem-solve issues. This left me with a few considerations regarding the choice of model and methodology.

When choosing my model, the primary aim of the research was to describe the trajectories of internalising problems in autistic males and females, and non-autistic males and females across six time points. LGCM is particularly well suited to modelling change over time as it incorporates time into the model by fixing factor loadings for the slope into constrained values and for the intercept the loadings to 1s (Hox & Stoel, 2005). LGCM uses latent variables which refer to variables that are not directly measurable, or that we cannot infer

from data with full certainty (Borsboom, 2008). Given that internalising problems, unlike someone's height, is not something that can be directly measured or inferred from data, LGCM was a good fit epistemically for modelling this variable. LGCM also allows non-linear patterns of growth, which was important, as developmental processes can be complex and may not follow linear form of change (Grimm et al., 2011). Finally, LGCM is robust to missing data (Curran et al., 2010), which was essential to avoid losing power, particularly in the autistic female group due to small group size.

The secondary aim was to compare the trajectories between the groups. This was done via a combination of regressing the intercept and slope onto the sex and autism variables, as well as the interaction between the two. The regression approach which uses a single conditional model with groups included as covariates, also referred to as the dummy approach, assumes that all other model parameters remain the same between groups, including variances, covariances, time-specific error variances, and the functional form of the growth model (Bollen & Curran, 2006). However, this may not be the case, as suggested by the different forms of change fitting the non-autistic and autistic groups, and the results from the individually fitted models. Therefore, it may have been more effective to compare the models directly via using multi-group LGCM. It involves constraining the mean parameter estimates such as slopes and intercepts to be equal across groups to see if the trajectories differ between groups using chi-square. This approach is limited in not allowing different forms of change between groups. Moreover, neither of these approaches allow one to examine at which ages or points the groups differ.

Therefore, I compared the model estimated means for each time point by using a t-test which gave me a crude measure of differences between the groups at each time point. The limitation

of this approach was that it was very sensitive to the larger standard errors in the conditional step 2 and 3 models, possibly resulting from the more complex models in relation to small sample size.

Another point of consideration involves the assumptions underlying the models. I used the maximum likelihood estimator as this is robust to missing data. However, due to my lack of deep understanding of SEM and LGCM, which a statistician would have, I may have run into issues with underlying assumptions such as normality. According to Yuan (2005), maximum likelihood estimation is based in normal theory. Violations to this can lead to standard errors being over- or underestimated, which could then lead to issues in over- or under-detecting significant model parameters, and this in turn could also influence the inferential comparisons made between the model estimated means for each time point. Additionally, non-normality could lead to incorrect model rejection (Curran et al., 1996). Although my data appeared to be within acceptable bounds of skewedness and kurtosis, it did not fully follow normal distribution. However, I used multiple indices of model fit which should safeguard for incorrect model rejection (Maydeu-Olivares, 2017). Nevertheless, if I were to complete these analyses again, I would consider the underlying assumptions in more detail, and apply appropriate corrections or changes to the models.

These issues speak to the challenges of clinicians increasingly using complex models for testing theories around development, without adequate training around SEM and related methods such as LGCM (Yuan, 2005). In line with this, Breckler (1990) found that only 19% of the psychological and social research articles he reviewed, acknowledged the assumption of multivariate normality and end even fewer made compensations for probable violations. As more complex longitudinal methods are becoming more widely used in developmental

and clinical psychology, doctoral courses might benefit from adding some teaching around this to their curriculum.

Interpretation of results

Curran and Willoughby state that "we must be absolutely certain that the way in which we think we are empirically evaluating our research question is the way in which we actually are evaluating the question." (Curran & Willoughby, 2003, p. 581). Although, in this statement they are referring to using appropriate models to evaluate a theory, this statement also speaks to the issues that clinicians less experienced in statistics face when trying to interpret their results. In line with the section above, issues in understanding the underlying theory, and incorrect model specifications can lead to incorrect interpretation of parameter estimates, statistical significance, effect sizes, and model fit indices. This in turn can lead to inaccurate theoretical inferences. One of the challenges I experienced was understanding the remit of the inferences available to me from the model results. For example, I initially tried to draw inferences regarding group differences by merely comparing the descriptive shapes of the models in relation to each other. However, with the support of an experienced statistician I was able to understand that I needed to complete further testing to make those inferences.

Additionally, interpreting the changes to the non-linear model coefficients in line with changes to the trajectories of internalising problems, and mapping this onto theoretical hypotheses around the development of internalising problems was challenging. However, using visual representations of the trajectories was helpful in making the results clearer and more accessible.

In summary, the more complex theories of development necessitate clinical scientist practitioners to become better equipped at using complex modelling techniques, such as

LGCM. Due to the less rigorous statistical training received by clinical doctorate trainees, and other clinical professionals, this can create issues with the correct model choice, specification, and interpretation. Therefore, seeking mentorship from statisticians can be important.

Using Secondary Data

My research project involved the use of secondary data from the Millennium Cohort Study (MCS), which is a prospective longitudinal study following a large cohort of children born in the UK from 9 months till the age of 17. The MCS entailed a multi-disciplinary approach, measuring a large number of variables pertaining to social, psychological and physiological outcomes. The data can be accessed for free by registering at UK Data Service.

Secondary data analysis refers to "any further analysis of an existing dataset which presents interpretations, conclusions or knowledge additional to, or different from, those produced in the first report on the inquiry as a whole and its main results" (Hakim, 1982, p. 1). This presents with both benefits and challenges.

Benefits of secondary data analyses

Using secondary data in this project was beneficial in having access to a large prospective dataset of CYP situated in the community. As discussed above, the investigation of developmental trajectories using advanced longitudinal statistical methods requires large datasets to draw reliable inferences. Recruiting a large cohort and following them prospectively for a sufficiently long period of time requires a substantial amount of financial resource, time, and professionals to carry out the work. Therefore, without access to

secondary data this thesis project, involving significant time- and financial constraints, would not have been feasible.

In addition, using a naturalistic cohort sample might ward against selection or recruitment bias. The underdiagnosis of females could mean that those with more problems are more likely to come into contact with clinics, possibly making samples from such settings less representative (D'Mello et al., 2022). Using a prospective community sample meant that the researchers actively approached families in the community, which may have resulted in a more representative sample.

Challenges

The main limitation from using secondary data in the context of investigating sex differences in internalising problem trajectories of autistic CYP, was the lack of control over variables included in the study. For example, the study only looked at sex at birth rather than also including a question about gender.

Biological sex, determined at birth based on physical traits like reproductive organs, chromosomes, and hormones (Short et al., 2013), differs from gender identity. Gender identity, which encompasses concepts of masculinity and femininity, is socially constructed and may not align with the sex assigned at birth or fit within binary classifications. While most people's identities are shaped by both sex and gender, distinguishing between the two can be challenging due to the pervasive influence of cultural socialisation from birth (Lai et al., 2015).

Several researchers have argued the importance of distinguishing between sex and gender in autism research (Lai et al., 2015; Mandy & Lai, 2017; Strang et al., 2020). Lai et al (2015)

posits that culture-based gender roles might lead to autistic females to adopt masking strategies to emulate social behaviour and scripts copied from peers or media, whereas sex-related biological mechanisms are also likely to exert developmental effects. Strang et al (2020) suggest, that distinguishing the effects of sex and gender might be particularly important due to the high levels of gender diversity in autistic individuals. Therefore, including both sex and gender as variables is key for starting to elucidate the influence of sex and gender on internalising symptom trajectories in autistic individuals.

Furthermore, the MCS was not specifically designed to investigate autism, and thus the assessment of autism was not robust. In the study parents were asked from age five onwards whether "a doctor or other health professional ever told you that your child had Autism, Asperger's Syndrome or other autistic spectrum disorder?". Thus, the diagnostic information relied upon parent disclosure of autism, and was not confirmed using standardised assessment procedures. This may have introduced error or bias into the autism diagnosis variable.

Requiring a clinical autism diagnosis may have excluded individuals from underdiagnosed population groups (D'Mello et al., 2022). A better way to assess autism in a cohort study may be to introduce a brief screening measure, such as the Social Communication Questionnaire (SCQ; Eaves et al., 2006), and to invite those who exceed the clinical threshold for further testing or confirm existing diagnosis with their healthcare provider. Conversely, this could introduce additional ethical consideration as parents would need to consent to neurodevelopmental screening, and researchers would need to form a protocol of how individuals with further support or assessment needs are connected with local services.

To conclude, using secondary data provides an opportunity for researchers to test longitudinal hypothesis without requiring extensive resources. It allows the use of large and representative samples. However, the researcher is left with less control over how variables of interest are operationalised and measured, and what kind of research questions the data can answer.

Conclusion

Critical appraisal of one's research is an important tool for learning and improving as a researcher. There are some key conclusions that I draw from my experience of completing this project. Firstly, reflexivity is particularly important as a non-autistic researcher to avoid perpetuating unhelpful narratives about autism. Whilst participatory research is important, its place in doctoral research should be carefully considered to avoid tokenistic or harmful engagement with autistic communities. Secondly, as a non-statistician clinical researcher, it may be important to learn about the theoretical and technical underpinnings of more advanced statistical methods, or to recruit help from statisticians in choice of models and interpretation. This ensures that our empirical methods are fit for the complexity of our theoretical questions and hypotheses. Finally, prospective cohort studies allow researchers to access large datasets in a cost-effective way but can provide constraints in how groups and variables are operationalised or measured. I hope these reflections, along with my research, will not only provide answers but also inspire further questions and reflections in my fellow researchers.

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The Appendices

Appendix 1: PRISMA Checklist

PRISMA Checklist

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Appendix 2: Search Strategy

Systematic Review Search Strategy

PsycInfo

1. Exp Autism Spectrum Disorders/
2. (Autism OR Autistic OR ASD OR Asperger* OR Pervasive development* disorder* OR PDD).tw.
3. (Emotional problem* OR Internali?ing OR Psychiatric OR Comorbidit* OR Mental health OR psychopathology OR anx* OR depress*).tw.
4. (Sex OR Gender).mp.
5. (Child* OR Childhood OR adolescen* OR teen* OR young adult* OR youth* OR young person OR young people).tw.
6. 1OR2
7. 3AND4AND5AND6

Medline

1. Exp Autism Spectrum Disorder/
2. (Autism OR Autistic OR ASD OR Asperger* OR Pervasive development* disorder* OR PDD).tw.
3. (Emotional problem* OR Internali?ing OR Psychiatric OR Comorbidit* OR Mental health OR psychopathology OR anx* OR depress*).tw.
4. (Sex OR Gender).mp.
5. (Child* OR Childhood OR adolescen* OR teen* OR young adult* OR youth* OR young person OR young people).tw.
6. 1OR2
7. 3AND4AND5AND6

EMBASE

1. Exp Autism/
2. (Autism OR Autistic OR ASD OR Asperger* OR Pervasive development* disorder* OR PDD).tw.
3. (Emotional problem* OR Internali?ing OR Psychiatric OR Comorbidit* OR Mental

health OR psychopathology OR anx* OR depress*).tw.
4. (Sex OR Gender).mp.
5. (Child* OR Childhood OR adolescen* OR teen* OR young adult* OR youth* OR young

person OR young people).tw. 6. 1OR2

7. 3AND4AND5AND6

ASSIA

1. MAINSUBJECT.EXACT.EXPLODE("Autism") OR ABSTRACT,TITLE(Autism OR Autistic OR ASD OR Asperger* OR Pervasive development* disorder* OR PDD)
2. ABSTRACT,TITLE(Emotional problem* OR Internali?ing* OR Psychiatric OR Comorbidit* OR Mental health OR psychopathology OR anxi* OR depress*)
3. FULLTEXT(Sex OR Gender)
4. ABSTRACT,TITLE(Child* OR Childhood OR adolescen* OR teen* OR young

   adult* OR youth* OR young person OR young people)

5. 1AND2AND3AND4

WEB of Science

1. TS=(Autism OR Autistic OR ASD OR Asperger* OR "Pervasive development* disorder*" OR PDD)
2. TS=("Emotional problem*" OR Internali?ing OR Psychiatric OR Comorbidit* OR "Mental health" OR psychopathology OR anx* OR depress*)
3. TS=(Sex OR Gender)
4. TS=(Child* OR Childhood OR adolescen* OR teen* OR "young adult*" OR youth* OR

   "young person" OR "young people")

5. 1AND2AND3AND4

TS= topic search including title, abstract, author Keywords, Keywords Plus®

Appendix 3: Risk of Bias Tool

Joanna Briggs Institute Risk of Bias Tool

Copy of Joanna Briggs Institute Risk of Bias Tool removed for copyright purposes.

Appendix 4: Measurement of covariates

Covariates

This section provides information on how each covariate was measured.

Ethnicity:

Ethnicity was assessed in the MCS at 9 months by parent-report, using the following categories derived from the 2001 UK Census: White, Indian, Pakistani, Bangladeshi, Black Caribbean and Black African.

Family socioeconomic status (SES):

Family SES was measured using banded family income (single parent income or combined if there are two resident parents). This was measured at the first MCS sweep (9-months-old), with the exception of 27 families whose SES was measured at the second sweep due to joining late.

Parent education level

Parent education level was measured by asking parents their NVQ- or NVQ-equivalent level of education at the first MCS sweep (9-months-old), except for 27 families whose SES was measured at the second sweep due to joining late.

Child IQ:

IQ was assessed in the MCS at 7 years old using three intellectual ability assessment tests: BAS Pattern Construction, BAS Word Reading and the National Foundation for Educational Research Progress in Maths. General intellectual ability will be indexed with age-adjusted factor scored from the above tests, in line with previous research using the MCS data (Flouri et al., 2019; Hanscombe et al., 2012).

ADHD diagnosis:

Parents were asked at sweeps from ages 3 till 14 whether the participating child has been diagnosed with ADHD by a doctor or another health professional. This variable was marked as yes if the child had been given an ADHD diagnosis and this had not changed in a subsequent sweep.

Child birthweight:

The main respondent was asked to report the child's birth weight in kilograms during the first MCS sweep at the age of 9 months.

Child gestational age

Child gestational age was measured in days during the first MCS sweep at the age of 9 months.

Alcohol use while pregnant

Mothers were asked at 9 months (3 years of age for families joining at the second sweep): "Thinking back to when you were pregnant with (child's name), which of these best describes how often you usually drank then? 1) Every day 2) 5-6 times per week 3) 3-4 times per week 4) 1-2 times per week 5) 1-2 times per month 6) Less than once a month 7) Never. For the purposes of the present study this was re-coded into a binary variable based on whether the mother drank while pregnant.

Smoking while pregnant

Mothers were asked at 9 months (3 years of age for families joining at the second sweep):

- Have you smoked at all in the past two years?
- And did you change the amount you smoked during your pregnancy?

These were used to create a binary variable of whether the mother had smoked during pregnancy.

Type of delivery

Parents were asked at 9 months (3 years of age for families joining at the second sweep) what type of labour they had: a) vaginal birth, b) assisted or forceps, c) planned caesarean, d) emergency caesarean or e) other. Due to power issues this was re-coded into a binary variable with categories “vaginal birth” or “surgical/assisted birth”.

Baby in special baby unit

Parents were asked at 9 months (3 years of age for families joining at the second sweep) if their baby had been admitted to the special baby unit following birth.

Appendix 5: Statistical comparisons of group characteristics and correlation matrix

Statistical comparisons of group characteristics

Variable	Group comparisons	Statistic
Ethnicity	AM vs AF vs NM vs NF	$X^2(3) = 18.36$, $p<0.001$
	Autistic vs non-autistic	AC ≠ NC, $X^2(1) = 17.97$, $p< 0.001$
	Males vs females	F=M, $X^2(1) =0.138$ p= 0.710
	Autistic males vs Autistic females	F=M, $X^2(1) =0.0515$ p= 0.820
	Non-autistic males vs Non-autistic females	F=M, $X^2(1) = 0.0008$, p= 0.978
Income	AM vs AF vs NM vs NF	$X^2(6) = 13.8271$ p= 0.032
	Autistic vs non-autistic	AC ≠ NC, $X^2(2) =11.706$, p=0.003
	Males vs females	F=M, $X^2(2) = 0.858$, p = 0.651
	Autistic males vs Autistic females	F=M, $X^2(2) =0.5991$, p= 0.741
	Non-autistic males vs Non-autistic females	F=M, $X^2(2) = 1.6307$, p= 0.442
Parental education	AM vs AF vs NM vs NF	AM =AF =NM =NF, $X^2(3)$ =3.0088, p= 0.390
ADHD	AM vs AF vs NM vs NF	X^2 (3) = 2.0e+03, $p<0.001$
	Autistic vs non autistic	AC ≠ NC, $X^2(1) =1.8e+03$, $p<0.001$
	Males vs females	F≠M, $X^2(1) = 169.99$, $p<0.001$
	Autistic males vs Autistic females	F≠ M, $X^2(1) =13.7852$ $p<0.001$
	Non-autistic males vs Non-autistic females	F≠ M, $X^2(1) = 87.1236$, $p<0.001$

Chi square analyses for group differences. AM= Autistic male, AF= Autistic female, NM= Non-autistic male, NF= non-autistic female, F= female, M= male.

Correlation matrix

	1.	*2.*	*3.*	*4.*	*5.*	*6.*	*7.*	*8.*	*9.*	*10.*	*11.*	*12.*	*13.*	*14.*	*15.*	*16.*	*17.*	*18.*	*19.*
1. Intern. T1	1																		
2. Intern. T2	.421***	1																	
3. Intern. T3	.350***	.514***	1																
4. Intern. T4	.272***	.393***	.500***	1															

5. Intern .T5	.234***	.333***	.408***	.552***	1													
6. Intern. T6	.189***	.268***	.323***	.460***	.569***	1												
7. Autism	.036***	.101***	.164***	.248***	.210***	.188***	1											
8. Sex	.005	.020*	.013	.041***	.136***	.187***	-.097***	1										
9. ADHD	.028**	.070***	.112***	.153***	.120***	.110***	.332***	-.102***	1									
10. IQ	-.123***	-.136***	-.142***	-.154***	-.146***	-.123***	.056***	0.065***	-.092***	1								
11. Ethnicity	.111***	.090***	.058***	.001	.032***	.003	-.033***	.003	-.032***	-.116***	1							
12. Income	-.161***	-.128***	-.137***	-.126***	-.148***	-.133***	-.029***	.000	-.050***	.232***	-.158	1						
13. Parental educ.	-.113***	-.078***	-.086***	-.097***	-.113***	-.112***	-.101***	-.010	-.004	0.174***	.078***	.037***	1					
14. Birthweight	-.076***	-.067***	-.055***	-.049***	-.063***	-.071***	-.002	-.100***	-.006	.123***	-.140***	.091***	.058***	1				
15. Gestational age	-.016	-.020*	-.018*	-.030***	-.024*	-.026*	-.025**	0.015	-.013	.050**	-.009	-.011	.014	.386***	1			
16. Special baby unit	.045***	.042***	.038***	.029*	.034*	.030**	0.024*	-.035**	.010	-.061	.011	-.011	.011	-.366***	-.271***	1		
17. Delivery type	.016	-.005	-.001	-.013	-.0016	0.022*	-.004	.028***	-.004	-.025**	.037***	-.096***	-.062***	.058***	.123***	-.091***	1	
18. Smoking preg.	.082***	.064***	.068***	.078***	.089***	.101***	.038***	-.026**	-.065***	-.127***	-.120***	-.238***	-.203***	-.130***	.022**	-.-24*	.056***	1
19. Alcohol preg.	-.033***	-.019*	-.029***	-.018**	-.033***	-.036***	.006	-.012	-.002	.080***	-.152***	.113***	.068***	.052***	.069***	-.051***	.006	.137***	1

*Correlation matrix including all the study variables. * p < 0.05. ** p <0.01. *** p <0.001.*

Appendix 6: Sensitivity analyses for descriptive statistics using non-stable autism diagnosis

Sensitivity analyses for descriptive statistics using non-stable autism diagnosis

		Autistic		Non-autistic	
		Males (N=472) *Frequency (%)*	Females (N=143) *Frequency (%)*	Males (N= 7,873) *Frequency (%)*	Females (N= 7,853) *Frequency (%)*
ADHD	No ADHD diagnosis	318 (67.37%)	120 (83.9%)	7,681 (97.6%)	7,802 (99.4%)
	ADHD diagnosis	154 (32.6%)	23 (16.1%)	191 (2.4%)	50 (0.6%)
	Missing	-	-	1 (0.01%)	1 (0.01%)
Ethnicity	White	417 (88.4%)	127 (88.8%)	6,454 (82.0%)	6,442 (82.0%)
	Mixed	15 (3.2%)	3 (2.1%)	224 (2.9%)	244 (3.1%)
	Indian	2 (0.5%)	1 (0.7%)	212 (2.7%)	196 (2.5%)
	Pakistani and Bangladeshi	13 (2.8%)	4 (2.8%)	528 (6.7%)	548 (7.0%)
	Black	16 (3.4%)	4 (2.8%)	292 (3.7%)	272 (3.5%)
	Other	6 (1.3%)	2 (1.4%)	114 (1.5%)	106 (1.4%)
	Missing	3 (0.6%)	2 (1.4%)	49 (0.6%)	45 (0.6%)
SES (Family income)	£ 0 - £16,500	179 (37.9%)	48 (33.6%)	2,370 (30.1%)	2,443 (31.1%)
	£16,500.01 - £28,000	127 (26.9%)	41 (28.7%)	2,041(25.9%)	2,009 (25.6%)
	> £28,000	117 (24.8%)	35 (24.5%)	2,335 (29.5%)	2,280 (29.0%)
	Missing income information	49 (10.4%)	19 (13.3%)	1,142 (14.4%)	1,121 (14.3%)
Parental Education	NVQ levels 1-2 (GCSE level)	199 (42.2%)	52 (36.4%)	2,932 (37.2%)	2,959 (37.7%)
	NVQ levels 3, 4, 5 (A-level - higher education)	203 (43.0 %)	65 (45.5%)	3,551 (45.1%)	3,476 (44.3%)
	Missing education information	70 (14.8%)	26 (18.2%)	1,390 (17.7%)	1,418 (18.1%)
Delivery type	Vaginal	288 (66.5%)	86 (65.2%)	5,262 (66.5%)	5,450 (69.3%)
	Assisted or surgical (forceps, caesarean, etc)	139 (32.1%)	44 (33%)	2,588 (32.7%)	2,369 (30.1%)
	Missing information	6 (1.4%)	2 (1.5%)	62 (0.8%)	45 (0.6%)
Baby in Special Baby Unit or NICU	Yes	62 (13.1%)	21 (14.7%)	814 (10.3%)	632 (8.0%)
	No	207 (43.8%)	51 (35.7%)	3,099 (39.4%)	2,881 (36.6%)
	Missing information	203 (43.0%)	71 (49.7%)	3,960 (50.3%)	4,351 (55.3%)
Alcohol use while pregnant	Yes	163 (34.5%)	42 (29.4%)	2,577 (32.7%)	2,489 (31.7%)
	No	309 (65.5%)	101 (70.6%)	5,296 (67.3%)	5,364 (68.3%)

Smoking while pregnant	Yes	178 (37.7%)	38 (26.6%)	2,212 (28.0%)	2,069 (26.4%)
	No	294 (62.3%)	105 (73.4%)	5,661 (71.9%)	5,784 (73.7%)
Demographic variable			N	Mean (SD), range	
IQ (age 7)	Autistic	Male	341	95.26 (17.5), 50.1- 140.1	
		Female	101	96.0 (16.0), 54.4- 135.6	
	Non-autistic	Male	6,386	99.4 (15.4), 49.5- 141.9	
		Female	6,566	100.9 (14.4) 49.6- 140.0	
Gestational age (days)	Autistic	Male	450	272.9 (16.8), 179-300	
		Female	133	273.4 (17.7), 175-298	
	Non-autistic	Male	7,455	275.4 (14.3), 170-301	
		Female	7,490	275.8 (13.8), 168-301	
Birthweight (KG)	Autistic	Male	452	3.35 (0.65), 0.91-5.73	
		Female	134	3.23 (0.69), 0.62-4.76	
	Non-autistic	Male	7,534	3.40 (0.60), 0.68-6.55	
		Female	7,561	3.28 (0.58), 0.39-7.23	

Descriptive statistics of sample

Appendix 7: Sensitivity Analyses for Step 1 Models using non-stable autism diagnosis

Sensitivity Analyses for Step 1 Models using non-stable autism diagnosis

		linear	quadratic	cubic
Autistic males	RMSEA	0.138	0.083	0.058
	CFI	0.720	0.925	0.978
	SMSR	0.108	0.052	0.028
Autistic females	RMSEA	0.156	0.137	0.067
	CFI	0.812	0.891	0.985
	SMSR	0.112	0.067	0.034
Non-autistic males	RMSEA	0.057	0.043	0.019
	CFI	0.920	0.965	0.996
	SMSR	0.058	0.027	0.011
Non-autistic females	RMSEA	0.036	0.022	0.026
	CFI	0.926	0.978	0.994
	SMSR	0.029	0.015	0.013

Model fit for change in internalising problems over time, using non-stable autism diagnosis

Growth parameter	**Autistic males**		**Autistic females**		**Non-autistic males**		**Non-autistic females**	
	Mean (SE)	**Variance (SE)**	**Mean (SE)**	**Variance (SE)**	**Mean (SE)**	**Variance (SE)**	**Mean (SE)**	**Variance (SE)**
Intercept	1.683 (.086) ***	1.715 (.716) **	1.718 (.149) ***	2.422 (.979) *	1.319 (.017) ***	1.125 (0.74) ***	1.376 (0.018) ***	1.174 (0.072) ***
Linear term (L)	.534 (.152)***	2.253 (1.361)	-.488 (.217) *	2.308 (1.634)	0.097 (.015) ***	-0.441 (0.050)	0.052 (0.016) **	0.457 (0.051) ***
Quadratic term (Q^2)	.211 (.080)**	.620 (.277) *	.657 (.112) ***	.317 (.284)	-0.009 (0.003) ***	0.015 (0.002)	0.036 (0.003) ***	0.021 (0.002) ***
Cubic term (C^3)	-.047 (.011) ***	.012 (.005) *	-.087 (.016) ***	.005 (.005)	NA	NA	NA	NA

Appendix 8: Sensitivity Analyses for Step 2 Models using non-stable autism diagnosis

Sensitivity Analyses for Step 2 Models using non-stable autism diagnosis

		linear	quadratic	cubic
Autistic males	RMSEA	0.074	0.050	0.039
	CFI	0.747	0.911	0.965
	SMSR	0.063	0.036	0.023
Autistic females	RMSEA	0.082	0.072	0.048
	CFI	0.819	0.895	0.969
	SMSR	0.079	0.050	0.036
Non-autistic males	RMSEA	0.057	0.026	0.015
	CFI	0.920	0.967	0.993
	SMSR	0.058	0.017	0.010
Non-autistic females	RMSEA	0.036	0.022	0.014
	CFI	0.926	0.978	0.994
	SMSR	0.029	0.015	0.009

Model fit for change in internalising problems over time, using non-stable autism diagnosis

	Autistic males		**Autistic females**		**Non-autistic males**		**Non-autistic females**	
Growth parameter	**Mean (SE)**	**Residual variance (SE)**	**Mean (SE)**	**Residual variance (SE)**	**Mean (SE)**	**Residual variance (SE)**	**Mean (SE)**	**Residual variance (SE)**
Intercept	3.038 (0.670) ***	1.735 (0.701) *	2.195 (0.949) *	1.884 (0.953) *	2.084 (0.138) ***	1.012 (0.070) ***	2.163 (0.137) ***	0.905 (0.143) ***
Linear term	-0.512 (1.238)	2.447 (1.312)	-0.524 (1.709)	1.563 (1.609)	-0.147 (0.124)	0.422 (0.049) ***	-0.079 (0.122)	0.949 (0.276) **
Quadratic term	0.740 (0.644)	0.582 (0.263) *	0.823 (0.886)	0.146 (0.271)	-0.028 (0.025)	0.015 (0.002) ***	0.083 (0.026) **	0.280 (0.054) ***
Cubic term	-0.118 (0.087) *	0.011 (0.005)	-0.097 (0.122)	0.002 (0.005)	NA	NA	NA	NA

*Mean growth parameter estimates for the multivariate growth curve models including step 2 covariates. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.*

Appendix 9: Sensitivity Analyses for regression model using non-stable autism diagnosis

Sensitivity Analyses for regression model using non-stable autism diagnosis

Table 23

	linear	**quadratic**	**cubic**
RMSEA	0.035	0.026	0.015
CFI	0.929	0.974	0.994
SMSR	0.031	0.015	0.008

Model fit for the regression model using non-stable autism diagnosis

Growth parameter	**Mean (SE)**	**Residual variance (SE)**
Intercept	2.067 (0.093) ***	1.130 (0.032) **
Linear term	-0.074 (0.034) *	0.109 (0.004) ***
	Covariance (SE)	
Intercept-Linear	-0.111 (.009) ***	

Growth parameter estimates for the regression model, including non-stable autism diagnosis.

	Covariate	**ß (SE)**
Intercept on	Autism	0.864 (0.178) **
	Sex	-0.059 (0.023) **
	Sex*Autism	-0.346 (0.165)
	Ethnicity	0.462 (0.037) ***
	Income	-0.302 (0.026) ***
	Parental education	-0.224 (0.027) ***
	Baby in special baby unit	0.152 (0.046) **
	Gestational age	0.033 (0.026)
	Birthweight	-0.082 (0.023) ***
	Alcohol during pregnancy	0.010 (0.024)
	Smoking during pregnancy	0.089 (0.029) **
	Delivery type	-0.032 (0.025)
Slope (L) on	Autism	0.437 (0.083) ***
	Sex	0.163 (0.008) ***
	Sex*Autism	.033 (0.063)
	Ethnicity	-0.112 (0.012) ***
	Income	-0.022 (0.010) *
	Parental education	-0.004 (0.010)

	Baby in special baby unit	-0.005 (0.018)
	Gestational age	-0.021 (0.009) *
	Birthweight	0.014 (0.009)
	Alcohol during pregnancy	-0.020 (0.009) *
	Smoking during pregnancy	0.039 (0.011) ***
	Delivery type	-0.004 (0.009)

Regression of the intercept and slope onto each covariate within the model, using non-stable autism diagnosis

Appendix 10: Individual trajectories

Individual trajectories

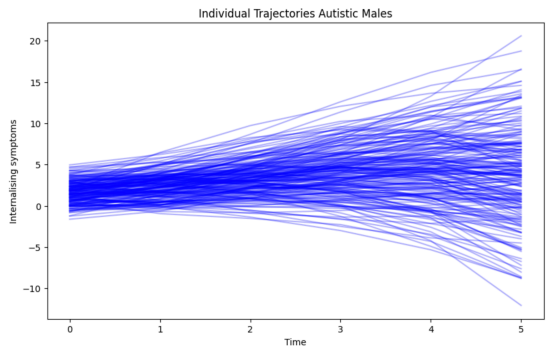
Individual differences in trajectories of internalising problems

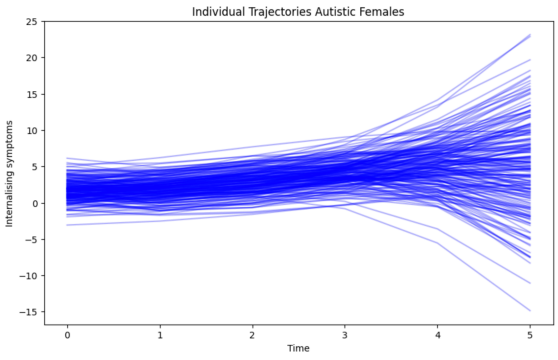
Step 1 models

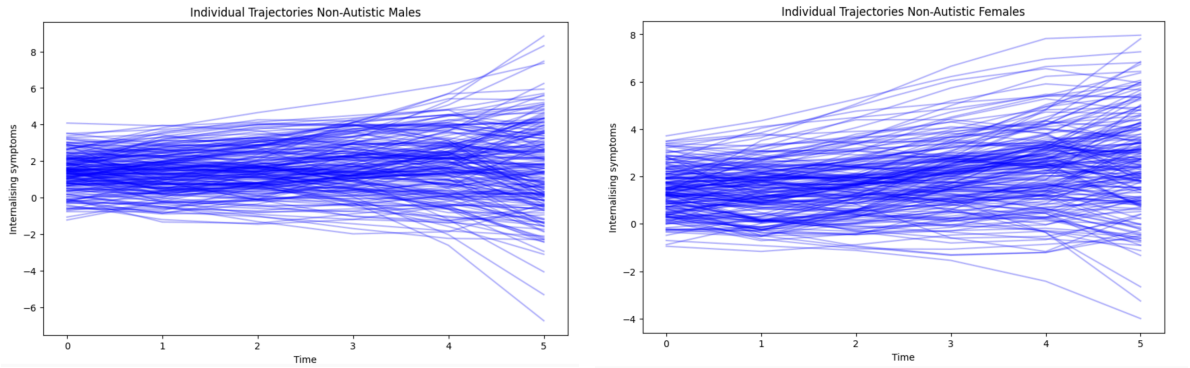
Within each group there was significant variance in intercepts (see Table 13 for variances per each group). However, for the autistic males and females, the variance in slopes was not significant, likely due to power. This is reflected in Figure 9, in which the model estimated individual trajectories show autistic males and females having much more homogenous trajectories until adolescence. For the non-autistic groups, the variances for the different slope terms were significant, reflecting considerable variability between individual trajectories.

	Autistic male				**Autistic females**				**Non-autistic males**				**Non-autistic females**			
	I	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**
I	1	.	.	.	1	.	.	.	1	.	.	.	1		.	.
L	.009	1	.	.	-.670	1	.	.	-.108*	1	.	.	-.138**	1	.	.
Q	-.223	-.796***	1	.	.218	-.702	1	.	-.007	-.076***	1	.	.009	-.082***	1	.
C	.236	.610***	-.953***	1	-.026	.057	-.037	1	NA	NA	NA	NA	NA	NA	NA	NA

*The covariances between the latent variables for the univariate models. * p < 0.05. ** p <0.01. *** p <0.001. I=intercept, L= linear, Q=quadratic, C= cubic.*







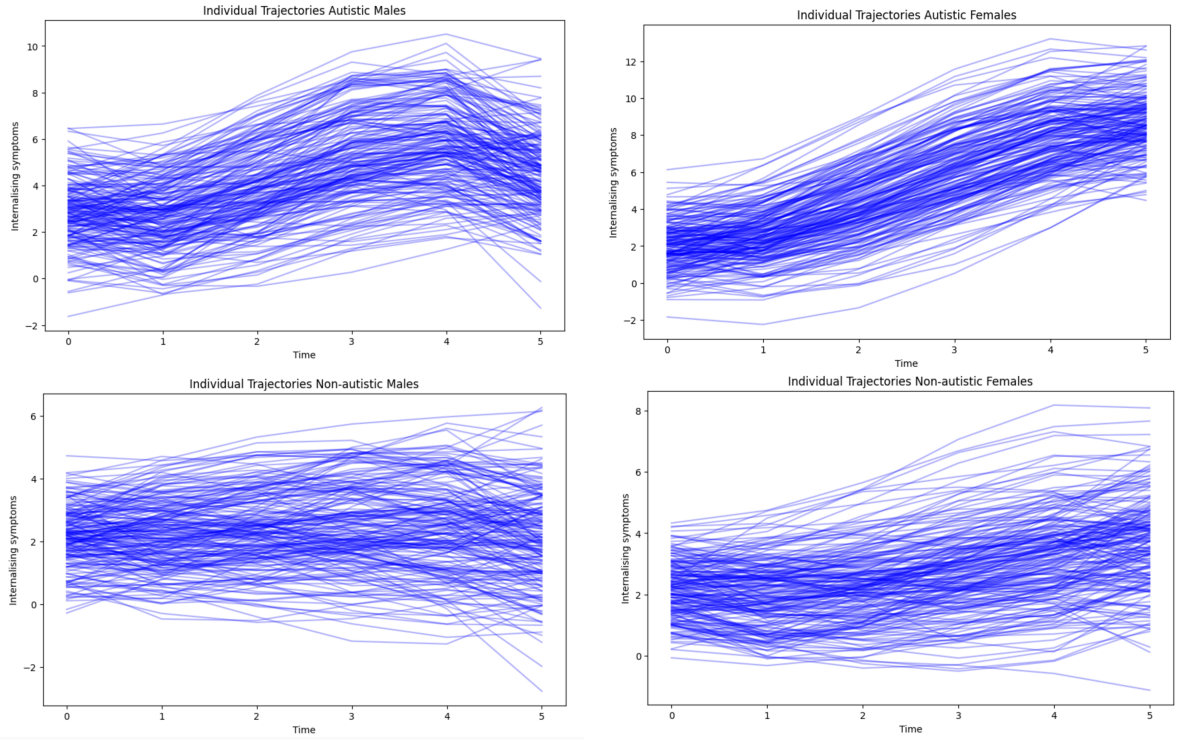
Model estimated individual trajectories per each group for the univariate models. For all groups, the trajectories were simulated for N=200.

Step 2 models

Like in the univariate models, there were significant interpersonal differences in the starting points for all groups, and in the slopes for non-autistic people (see Table 15 for variances per each group). For non-autistic people the variance between people regarding slopes of trajectories was not significant. The individual trajectories became more homogenous for the autistic groups after controlling for the step 1 potential confounders, as illustrated by the autistic male and female trajectories more closely following the shape of the mean trajectory in the figure below. See the table below for the covariances per each group following the addition of the covariates.

	Autistic males				**Autistic females**				**Non-autistic males**				**Non-autistic females**			
	I	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**
I	1	.	.	.	1	.	.	.	1	.	.	.	1	.	.	.
L	-.346	1	.	.	-.272	1	.	.	-.084	1	.	.	-.129*	1	.	.
Q	-.096	-.815	1	.	.085	-.347	1	.	-.011	-.072***	1	.	.008	-.083***	1	.
C	.021	.086	-.063	1	-.011	.017	-.016	1	NA	NA	NA	NA	NA	NA	NA	NA

*The covariances between the latent variables for the univariate models. * p < 0.05. ** p <0.01. *** p <0.001. I=intercept, L= linear, Q=quadratic, C= cubic.*



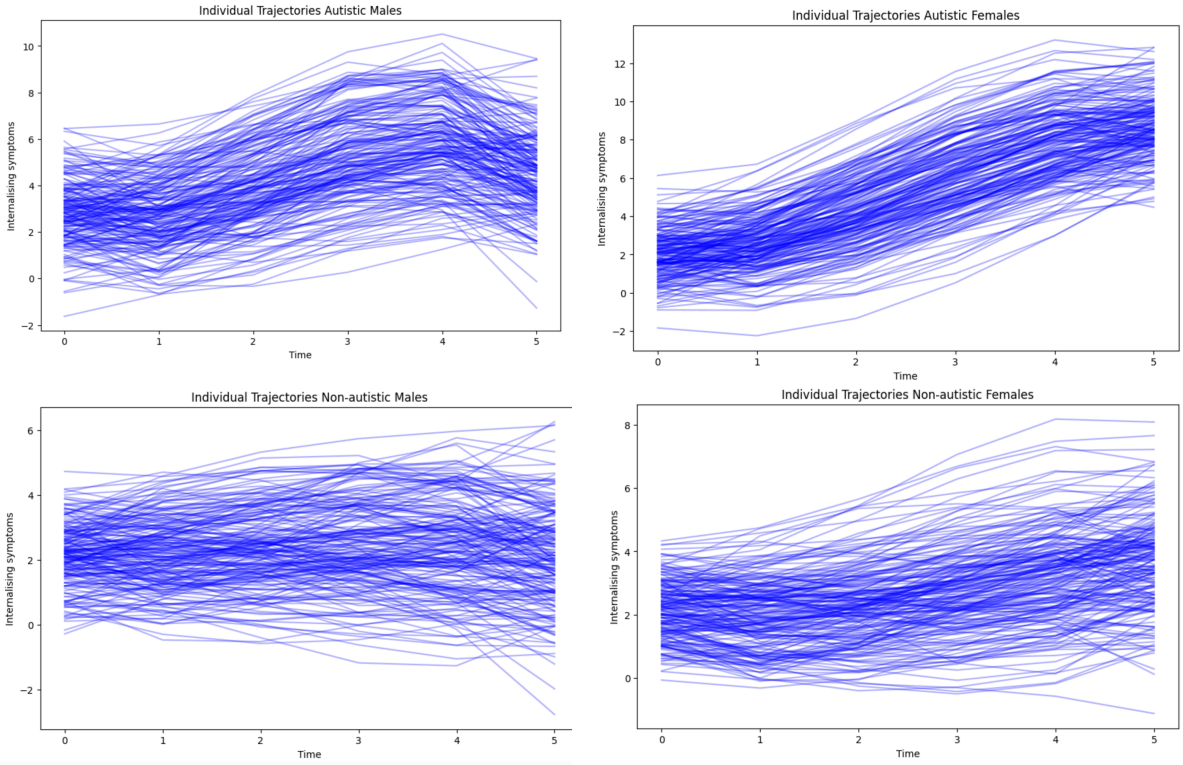
Model estimated individual trajectories per each group for each step 2 model. For all groups, the trajectories were simulated for N=200.

Step 3 Models

These were comparable to the step 2 models.

	Autistic males				Autistic females				Non-autistic males				Non-autistic females			
	I	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**	**I**	**L**	**Q**	**C**
I	1	.	.	.	1	.	.	.	1	.	.	.	1	.	.	.
L	-.233	1	.	.	-.576	1	.	.	-.090	1	.	.	-.194**	1	.	.
Q	-.130	-.736	1	.	.185	-.442	1	.	-.010	-0.072***	1	.	.059	-.852***	1	.
C	.024	.076	-.056	1	-.022	.026	-.018	1	NA	NA	NA	NA	NA	NA	NA	NA

*The covariances between the latent variables for the multivariate models controlling for ADHD and IQ. * p < 0.05. ** p <0.01. *** p <0.001. I=intercept, L= linear term, Q=quadratic term, C= cubic term.*



Model estimated individual trajectories per each group for each step 3 model. For all groups, the trajectories were simulated for N=200.

Appendix 11: Model fit statistics for the regression model

Model fit statistics for the regression model

	linear	quadratic	cubic
RMSEA	0.036	0.026	0.015
CFI	0.931	0.974	0.994
SMSR	0.031	0.015	0.008

Model fit for sex, autism diagnosis and confounding variables regressed onto internalising problems over time, assessed for linear, quadratic, and cubic forms of change.

Appendix 12: Regression model including ADHD and IQ as covariates

Regression model including ADHD and IQ as covariates

	linear	quadratic	cubic
RMSEA	0.034	0.026	0.015
CFI	0.931	0.974	0.994
SMSR	0.03	0.015	0.008

Model fit for the regression model including ADHD and IQ as covariates.

Growth parameter	Mean (SE)	Residual variance (SE)
Intercept	2.104 (0.093) ***	1.131 (0.032) ***
Linear term	-0.076 (0.034) *	0.109 (0.032) ***
	Covariance (SE)	
Intercept-Linear	-0.111 (.009) ***	

Growth parameter estimates for the regression model, including ADHD and IQ as covariates.

	Covariate	ß (SE)
Intercept on	Autism	0.750 (0.080) ***
	Sex	- 0.056 (0.235) **
	Sex*Autism	-.300 (.174)
	ADHD	0.143 (0.095)
	IQ	-0.135 (0.024) ***
	Ethnicity	0.454 (0.037) ***
	Income	-0.292 (0.026) ***
	Parental education	-0.212 (0.027) ***
	Baby in special baby unit	0.153 (0.046) **
	Gestational age	0.034 (0.025)
	Birthweight	-0.078 (0.023) ***
	Alcohol during pregnancy	0.013 (0.024)
	Smoking during pregnancy	0.081 (0.029) **
	Delivery type	-0.032 (0.025)
Slope (L) on	Autism	0.368 (0.086) ***
	Sex	0.167 (0.009) ***
	Sex*Autism	0.079 (0.064)
	ADHD	0.203 (0.036) ***
	IQ	-0.032 (0.009)**
	Ethnicity	-0.113 (0.012) ***

	Income	-0.018 (0.010)
	Parental education	-0.001 (0.010)
	Baby in special baby unit	-0.006 (0.018)
	Gestational age	-0.021 (0.009) *
	Birthweight	0.014 (0.008)
	Alcohol during pregnancy	-0.018 (0.009) *
	Smoking during pregnancy	0.033 (0.011) **
	Delivery type	-0.004 (0.009)

Regression of the intercept and slope onto each covariate within the model, including ADHD and IQ as covariates.