Variable emergence of Autism Spectrum Disorder symptoms from childhood to early adulthood

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Abstract

Objective. Autism spectrum disorder (ASD) is currently considered an early-onset, neurodevelopmental condition. Follow-up studies of clinic-ascertained autism suggest that autistic symptoms typically decline with age, although symptom improvement is limited for some. To date there have been no population-based prospective studies investigating the natural history of autistic symptoms from childhood to adulthood. This study aimed to characterize the development and heterogeneity of autistic symptoms in a UK population-based cohort from childhood to age 25 years. ***Method.*** Data were analyzed in a prospective UK population-based cohort (ALSPAC). Trajectories were derived using five-assessments of parent-rated Social Communication Disorders Checklist (SCDC) spanning ages 7-25 years. Additional measures were used to validate symptom trajectories. ***Results***. We identified three distinct SCDC trajectory classes: low (88.5%), declining (5.0%) and late-emerging (6.5%). Both the declining and late-emerging classes were associated with child and adult ASD measures, low IQ, communication problems, peer problems and worse adult functioning, compared to the low class. Male sex was associated with an increased likelihood of being in the declining trajectory class (OR=2.84, 95% CI=2.19-3.69). This sex difference was not observed in the late-emerging group (OR=1.00, 95% CI=0.80-1.24) compared to the low class. ***Conclusions***. ASD symptom levels emerged early and tended to decline across development although impairment was still present in adulthood for some. For others, autistic symptoms emerged across adolescence and adulthood. This challenges our current understanding that ASD symptoms inevitably first manifest early in development.

Keywords: autism, ASD, longitudinal, trajectories, adult, late-onset, ALSPAC

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Autism spectrum disorder (ASD) is currently considered an early-onset, neurodevelopmental condition characterized by social communication impairments and repetitive, restrictive behaviors (1). Although defined categorically for clinical purposes, its genetic architecture and epidemiological profile suggest ASD lies at the end of a continuously distributed continuum (2-4). It is well established that childhood ASD shows a very high degree of phenotypic and etiological heterogeneity (5), which includes marked variation in both its short-term developmental trajectories (6, 7) and later clinical course (8).

Follow-up studies of clinic-ascertained autism into adulthood suggest that autistic symptoms typically decline with age (9), although one school-ascertained study observed little symptom improvement (10), and broader, global outcomes for ASD are very variable (11, 12). To date, virtually all follow-up studies into adulthood have been conducted on patients referred to clinic during childhood which precludes the study of individuals who may not present with high symptom levels until adolescence or adulthood. Adolescence and early adulthood represent a time of heightened social challenges that include establishing romantic partnerships, transitioning to employment and managing independent living. One population-based study that followed individuals to age 17 years (13) observed an increase in social communication symptoms among females in adolescence, a finding that appears at odds with much of the clinical literature. However, there is growing appreciation that some affected individuals, especially females, may present in clinic with autistic symptoms in adolescence, later, or not at all by "camouflaging" or compensating for their difficulties (14).

Thus, findings on the natural history of autistic symptoms are mixed, and not examined in non-clinical cohorts followed to adulthood. The aim of this study was to characterize the

development and heterogeneity of autistic symptoms in a UK population-based cohort from childhood to age 25 years using the same measure and rater across time. Typically, measures and raters change from adolescence to adult life, precluding the opportunity to reliably examine developmental trajectories. Specifically, we used a latent variable approach to investigate autistic symptom developmental trajectories. We tested the validity of these trajectories by examining associations with established measures of child and adult ASD, child IQ, communication problems, peer problems and adult functioning.

Methods

Sample

We analyzed data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a well-established prospective, longitudinal birth cohort study (15-17). Total possible sample size is N=14,901 children alive at 1 year of age. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Full details are provided in the Supplementary Material.

As a demographic measure, parental income was assessed on a ten-point scale using parent-reported average weekly household income, including social benefits, when the child was approximately 11 years old.

Primary measure of ASD symptoms

Symptoms were primarily assessed using the parent-rated 12-item Social Communication Disorders Checklist (SCDC, range 0-24) (18) at approximately ages 7, 10, 13, 17 and 25 years. This screening questionnaire for autistic symptoms has been shown to have good discriminant validity in childhood/adolescence between pervasive developmental disorder and controls (18,

19) using a cut-point of ≥9. Previous work in ALSPAC found the SCDC at age 7 years to have excellent discriminant validity in identifying cases of ASD (area under the receiver operating characteristic curve = 0.93) (20). The SCDC is yet to be validated in adulthood, although we have found at age 25 years it shows similar neurodevelopmental and genetic correlates as observed in childhood (21). The SCDC also shows acceptable measurement invariance across age and sex in this sample (see Supplementary Material).

Additional measures of ASD

ASD diagnosis in childhood was defined in-line with previous work (22) that reviewed clinical records of children with a suspected developmental disorder and the Pupil Level Annual Schools Census for England (2003) at child age 11.

High-risk for childhood ASD diagnosis was measured by the mean of seven latent factors (23) derived from 93 measures of social, communication and repetitive behaviors characterizing ASD from ages 6 months to 9 years: verbal ability, language acquisition, social understanding, semantic-pragmatic skills, repetitive-stereotyped behavior, articulation and social inhibition: in-line with previous literature (24) we defined the high-risk group as the top 10% of scores.

High-risk for adult ASD diagnosis was assessed using the 28-item version of the Autism-Spectrum Quotient (AQ-28) (25, 26) (range 28-112) that was completed by the young person (self) and parent at age 25 years. The self-rated AQ-28 has been validated as a measure of clinical autism in adults with a 'stringent' cut-point of ≥70 (26); the same cut-off was used for the parent-rated AQ-28 for which there is currently no research to guide appropriate cut-points. Individuals who met this cut-point were categorized as high-risk for adult ASD diagnosis for self- and parent-rated scores separately. The AQ-28 consists of two factors (26), "social behavior" (e.g. social skills, routine, switching and imagination) and "attention to detail" (fascination with numbers/patterns) which were examined separately in sensitivity analyses.

Task-based indicator of ASD. Sensitivity analyses were conducted using age 13 Emotional Triangles Task data indexing theory of mind (27), one of the most widely reported cognitive deficits in ASD (28). Scores are based on participant ratings of the mental state of 16 animated triangles (possible range 0-80: higher scores reflecting better theory of mind); participant scores were excluded where there was evidence that they were not attending to the task in-line with previous work (29).

IQ and childhood and adult communication problems

Low IQ was defined as a score <80 on the Wechsler Intelligence Scale for Children (30) at age 8 years.

Child pragmatic language problems were measured using the parent-reported Children's Communication Checklist (CCC) pragmatic language subscale (31) at age 9 years (derived from five subscales: inappropriate initiation, coherence, stereotyped conversation, use of conversational context and conversational rapport: range 86-162), with a recommended cut-point of ≤132 (31).

Adult communication problems were assessed using the parent-rated Communication Checklist-Adult (CC-A) (32) at age 25 years (derived from three subscales: language structure, pragmatic skills and social engagement: range 0-210). Based on previous work, communication problems were defined as scoring ≤2SD of the mean on any subscale (32).

Peer problems in childhood, adolescence and adulthood

Peer problems were assessed using the parent-rated Strengths and Difficulties Questionnaire (SDQ) subscale (range 0-10) (33) at approximately ages 7, 17 and 25 years; self-reports were also used at age 25 years and defined using the recommended cut-point of ≥4 (33).

Adult functioning

Not in Education, Employment or Training (NEET) status was derived based on self-reports at age 25 years, in-line with the UK Office for National Statistics definition (detailed in the Supplementary Material) (34).

Distress and impairment were measured by parent- and self-rated adult SDQ impact scores which assess distress and impairment associated with mental health problems (e.g. emotional, concentration, behavior problems) (range 0-10), using the recommended cut-points of ≥2 (33). There is currently no research to suggest alternative cut-points in adulthood.

Analyses

Developmental trajectories of social communication problems were derived using growth mixture modelling (GMM) to identify developmental trajectories of ASD symptoms from ages 7 to 25 years in Mplus (35). GMM aims to group individuals into categories (trajectories) based on patterns of change across multiple time-points, with individuals within each category assumed to have the same growth curve (36). Variation in ASD symptom levels is therefore captured using a data-driven approach (i.e. based on observed differences rather than a specified cut-point). Starting with a single k-class solution, k+1 solutions were fitted until the optimum solution was reached. Given the large gap between the last two time-points, models were fit for a piecewise growth model with a single intercept and two linear slope factors, one for ages 7-17 years and one for ages 17 and 25 years: the second slope variance was fixed to zero to avoid nonidentification as only two time-points were included in this growth factor. The GMM therefore included an intercept, one slope for ages 7-17 years and a second slope for ages 17-25 years. Models were run using a robust maximum likelihood parameter estimator (35). Class sizes are reported based on the estimated model with Ns rounded to the nearest integer. As our GMM was run on parent-rated data, sensitivity analyses were conducted limitting the sample to

those with regular parent-offspring contact at age 25 years. *Sex-specific developmental trajectories* were then derived by running GMM for males and females separately. *ASD trajectory associations with other measures* were investigated in Mplus using a bias-free three step approach which accounts for measurement error in class assignment (R3STEP for multinomial regression, DU3STEP for prevalence rates and BCH for sensitivity analyses with continuous measures) (37). Additional sensitivity checks were undertaken on the age 13 task data and age 25 AQ-28 subscales.

Missing data

The primary sample included individuals with at least two time-points of SCDC data (N=8094). GMM was conducted using full information maximum likelihood estimation (35) and associations with other measures ('covariates') conducted where data were available. Analyses examining potential bias arising from missing data were conducted using a range of approaches including complete case analyses, inverse probability weighting and multiple imputation (38-40): more information is provided in the Supplementary Material.

Results

Descriptives

Mean SCDC scores by age and sex, sample size and prevalence of those scoring above the cut-point are shown in Figure 1. Correlations between SCDC scores at each age and individual item frequencies are shown in Supplementary Tables 1 and 2 respectively. Mean SCDC scores for the whole cohort decreased across childhood, increased into late adolescence (13) and using new adult data, scores then declined by age 25 years (Figure 1).

Developmental course of social communication problems

We identified three distinct trajectory classes (see Supplementary Material for details of deriving the best fitting model): low (88.5%, N=7165), declining (5.0%, N=403) and late-

emerging (6.5%, N=526) shown in Figure 2. Male sex was associated with an increased likelihood of being in the declining class (72.7% male: OR=2.84, 95% CI=2.19-3.69, p<0.001). Sex differences were not observed for the late-emerging class (51.5% male: OR=1.00, 95% CI=0.80-1.24, p=0.96) compared to the low class (48.9% male). Higher parental income was associated with a reduced likelihood of being in both the late-emerging (OR=0.91, 95% CI=0.87-0.96, p<0.001) and declining (OR=0.88, 95% CI=0.84-0.92, p<0.001) classes compared to the low class, with similar levels of association between the two (declining vs late-emerging OR=0.96, 95% CI=0.90-1.03, p=0.31). Sensitivity analyses limiting the sample to those with regular parent-offspring contact at age 25 years showed a similar pattern of results (see Supplementary Material).

Social communication trajectory: associations with established measures of ASD, neurodevelopmental problems and functioning

The rates of child and adult ASD/high-risk for ASD diagnosis, low IQ, communication problems, peer problems and adult functioning difficulties, by trajectory class, are shown in Figure 3. As shown in Table 1, both the late-emerging and declining ASD trajectory groups showed higher rates in both childhood and adulthood compared to the low trajectory class.

Comparisons between the late-emerging and declining ASD classes are also shown in Table 1 and Figure 3. The declining class showed higher levels of childhood difficulties than the late-emerging class (childhood ASD diagnosis, high-risk for ASD diagnosis, pragmatic language problems, peer problems) while the late-emerging class showed higher levels of adult difficulties than the declining trajectory group when reported by parents (high-risk for adult ASD diagnosis, adult communication problems, peer problems, distress and impairment). However, for self-reported measures at age 25 years, high-risk for ASD diagnosis and peer problems were similar in the late-emerging and declining classes, although self-rated distress

and impairment were higher in the late-emerging class. Both trajectory classes had similar levels of low IQ in childhood and NEET status in adulthood relative to the low class.

Sensitivity analyses: task-based indicator of ASD in early adolescence and ASD/communication subscales in adulthood

Sensitivity analyses examining emotional triangles test scores at age 13 years and the AQ-28 factors and CC-A subscales at age 25 years are shown in Supplementary Table 3. Theory of mind as indexed by the emotional triangles test at age 13 showed lowest levels in the declining class, with intermediate levels for the late-emerging class. Age 25 associations were consistent across AQ-28 subscales with the exception that while parent-rated scores related to social behavior/interaction were higher in the late-emerging compared to declining class, those relating to attention to detail were equally elevated in both classes relative to the low trajectory class.

Sex specific developmental trajectories

Male-specific analyses identified a similar three-class model: low (88.2%, N=3585), declining (5.7%, N=233) and late-emerging (6.1%, N=249). Female-specific analyses identified a two-class model that did not include a declining class: low (91.9%, N=3702) and late-emerging (8.1%, N=325). Full details of the sex-specific models are given in the Supplementary Material.

Missing data

Additional analyses found a similar pattern of results for both (i) deriving trajectories based on varying levels of missingness, and (ii) examining associations between social communication trajectories and other measures of ASD, IQ and communication problems, peer problems and adult functioning using different approaches to handle missing data (see Supplementary Material).

Discussion

This study aimed to characterize the natural history and heterogeneity of autistic symptoms in a UK population-based cohort from childhood to age 25 years. Using repeated measures of parent-rated social communication problems, we identified three distinct trajectories spanning childhood, adolescence and young adulthood. Most of the sample belonged to a persistently low symptom trajectory group as would be expected in a population-based cohort. In-line with much of the clinical literature, another group showed high autistic symptoms in childhood that declined over time. However, we also detected a third "late-emerging" group who showed initially low ASD symptom levels in childhood that increased across adolescence and into young adulthood. Previous work in ALSPAC has reported an increase in ASD symptoms across adolescence, particularly for females (13); our work differs in that we investigated distinct developmental trajectories of ASD symptoms into young adulthood – identifying both declining and late-emerging groups. Furthermore, we investigated associations with other measures in childhood and adulthood to investigate these different developmental patterns.

The declining symptom trajectory class showed associations with various features that typify ASD diagnosis, including male sex, low IQ, and communication and peer problems. Sensitivity analyses using a more detailed autism measure at age 25, suggested that while social interaction/behaviors somewhat improved into adulthood for this group, attention to detail remained. Also, despite the attenuation of social communication problems in this group from childhood to adulthood, this group still showed elevated levels of distress and impairment in adulthood and were more likely to not be in education, employment or training (NEET) at age 25 years compared to the low symptoms group. This is consistent with previous longitudinal research on clinical cohorts which has shown that ASD symptoms tend to decline with age, but that outcomes vary, and impairment often persists (9-11).

The late-emerging ASD symptom trajectory class is unexpected given that ASD is defined as a childhood-onset neurodevelopmental disorder. This late-emerging group showed similar (elevated) levels of adult impairment as the declining ASD class in terms of not being in education, employment or training (NEET), reported distress and impairment, as rated by both parents and the individuals themselves. However, they did not show the male preponderance typical of ASD. Interestingly, late-onset symptoms have been a growing controversy in relation to another childhood neurodevelopmental disorder, ADHD (41). However, unlike ADHD, where later-onset has not been found to be associated with childhood neurodevelopmental problems, the late-emerging ASD group, at least in this cohort, do not appear to have entirely newly emerging neurodevelopmental difficulties. In childhood the late-emerging ASD group displayed some neurodevelopmental impairment including an elevated level of a broader range of ASD traits, pragmatic language problems and peer problems compared to the low symptom group. It is also noteworthy that while ASD symptoms were relatively low in childhood, they were somewhat elevated compared to the low trajectory class (see Figure 2). Thus, it may be that ASD symptoms were "camouflaged" in childhood for this group, perhaps due to accommodating environments, scaffolding by families or individual characteristics that enabled compensation during this developmental period, but that with increasing demands on social skills with age, social difficulties became more apparent (14). Interestingly, while some previous work has suggested that compensation/camouflaging may be particularly apparent in females (14), we did not observe a female preponderance for this group (although we also did not observed the 'typical' ASD male preponderance).

The timing of the emergence of ASD symptoms in adolescence is also supported by sensitivity analyses using a task-based index of ASD measuring theory of mind at age 13 years, which suggested the late-emerging group had intermediate scores between the low and declining groups at this age. Previous explanations as to why ASD is detected later (in childhood), despite earlier assessments include early symptoms being missed or overshadowed by other

difficulties, 'over-diagnosis' of later symptoms or that symptoms genuinely onset later (42). Our use of a population-based cohort makes misdiagnosis and overdiagnosis unlikely. However, we cannot rule out the possibility of previously overshadowed ASD symptoms or that late reported symptoms actually index another form of psychopathology. For example, post-hoc analyses found the late-emerging group to have elevated emotional problems in young adulthood (results available on request), suggesting that the emerging symptoms identified in this group might reflect internalizing problems. Alternative study designs are needed to infer whether these adult emotional problems are a secondary consequence of the late ASD symptoms or whether some of the late reported ASD symptoms are indexing emotional problems. We also cannot rule out the contribution of measurement error. Alternatively, it is possible that ASD symptoms genuinely show a much more variable age at first manifestation, at least in the general population, than previously realized.

While many of our measures were parent-rated, enabling consistency of rater and measures across development, the inclusion of adult self-reports provided additional insights. By age 25 years, although parents reported that ASD-related difficulties and peer problems were higher in the late-emerging than declining class (defined using parent reports), self-rated ASD-related problems and impairments were similar for each of these groups; thus the observed symptom decline for those with high childhood symptoms could be influenced by rater effects. One explanation is that by adulthood, individuals have better insight into some their own social behavior/interaction related ASD symptoms than parents do. Another possibility is that parents endorse autistic symptoms in their adult offspring more readily when impairment is present: we observed that although the rate of self-rated high-risk ASD was similar in the late-emerging and declining trajectory groups, self-reported distress and impairment was higher in the late-emerging class. Regardless, it seems that later-emerging ASD is problematic in adulthood across a variety of measures and raters.

An important consideration in interpreting the results is whether the meaning of autistic items captured by the same measure (in this study, the SCDC) changes with age. There are many challenges to adopting a developmental perspective in research, one of which is that measures and informants typically change from childhood to adulthood (43). However identical questions (e.g. "does not appear to understand how to behave when out") may capture different impairments at different ages. The SCDC is also yet to be validated in adulthood, although our analyses suggested acceptable measurement invariance across the ages we assessed and we previously have reported that the adult and child SCDC show similar patterns of association with genetic risk scores (21). Further investigation, including qualitative research are beyond the scope of this paper.

Our study should be considered in light of limitations. Like many longitudinal samples, ALSPAC suffers from non-random attrition, whereby individuals at elevated risk of psychopathology are more likely to drop-out of the study (44) - approximately 54% of the original ALSPAC birth cohort were included in our age 25 analyses – which may have led to an underestimation of the number of individuals in high symptom trajectories. However we used a range of statistical methods to assess the effect of missingness and found a similar pattern of results. Our trajectories were also based on a measure of social communication and did not include the repetitive behaviors and restricted interests domains of autism; although this measure has previously been validated against childhood ASD diagnosis in ALSPAC (20), these domains may show a different natural history (45). Also, we could not examine trajectories of self-rated symptoms as these were only available in adult life. The use of a population sample (and size of the sample) is also likely to have affected the trajectory classes that we detected. In particular our model did not include a class with high childhood symptoms that persisted into adulthood, which would be expected in clinical-based samples(9). In model fitting a four-class solution did include a high-persistent trajectory, but this was a small class (1.8%), the inclusion of which did not improve model fit. Post-hoc analyses comparing this model to our three-class solution found

that the majority of those who would have been included in this high-persistent class were included in our declining class (approximately 72%, with the remainder in the late-emerging class): thus, our declining class likely includes a small proportion of individuals for whom symptoms persist into adulthood (reflected in the large confidence intervals for this group). This small 'fourth' class shows a similar prevalence rate to the reported population prevalence of 1% for adult ASD (46, 47). Future work using high-risk, clinical, or larger general population samples would be better placed to characterize differences between ASD symptoms that persist compared to desist or increase across development in those with a diagnosis. However, such samples may not be the ideal ones in which to detect later-emerging problems.

In conclusion, we observed heterogeneity in the natural history of autistic symptoms in the general population. We found that for those with elevated symptoms in childhood, symptom levels tended to decline into young adulthood. Intriguingly, we also identified a group for whom autistic symptoms emerged later – across adolescence and adulthood, but who showed evidence of earlier neurodevelopmental impairment including low IQ and language problems in childhood. Both groups showed elevated levels of distress and impairment in young adulthood. These findings support the continued monitoring of ASD symptoms and associated impairment across development. They also challenge our current understanding that ASD symptoms inevitably manifest early in development. This requires further investigation as the age of ASD symptom manifestation may be much more variable than previously realized.

Disclosures and acknowledgments.

All authors report no competing interests.

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and Lucy Riglin and Anita Thapar will serve as guarantors for the contents of this paper. A comprehensive list of grants funding is available on the ALSPAC website (www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf). The primary outcome measures used in the paper were specifically funded by the Wellcome Trust (204895/Z/16/Z). RW, GDS, ES and KT work in a unit that receives funding from the University of Bristol and the UK Medical Research Council (MC_UU_00011/1 and MC_UU_00011/3). This study was supported by the Wellcome Trust (204895/Z/16/Z).

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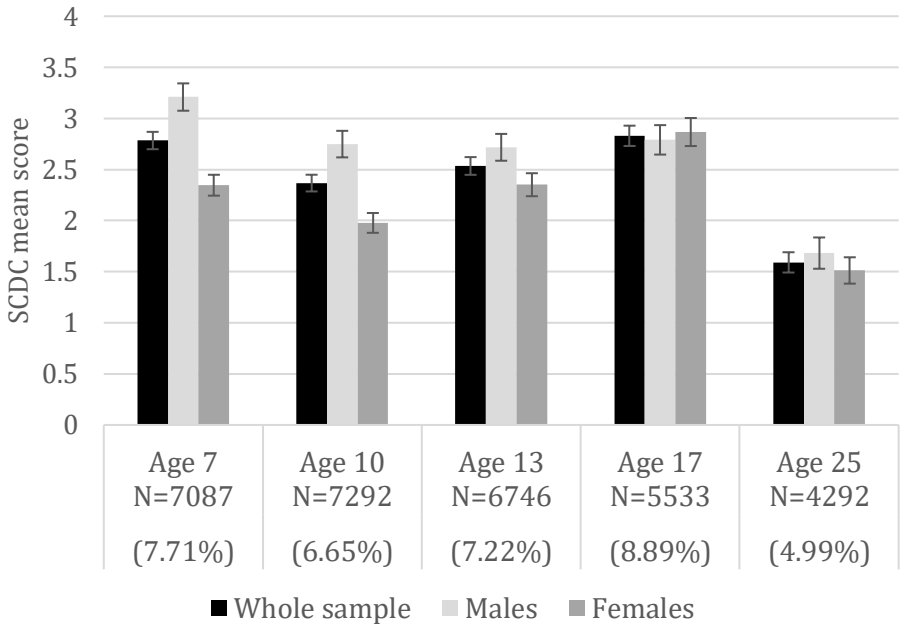
Table 1. Comparison of associated features including other measures of ASD, low IQ, communication problems, peer problem and adult functioning, by trajectory class (see Figure 3 for rates)

	Overall test		Late-emerging vs low class		Declining vs low class		Declining vs late-emerging class	
	$\chi^2_{(df=3)}$	p	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Measures of ASD								
Childhood ASD diagnosis	35.41	<0.001	24.39	(6.45-92.28)	136.45	(46.05-404.32	5.59	(2.24-13.96)
High-risk for childhood ASD	233.06	<0.001	6.01	(4.52-7.98)	15.55	(11.74-20.59)	2.59	(1.77-3.78)
High-risk for adult ASD: parent-rated	188.25	<0.001	32.15	(22.66-45.61)	6.71	(4.02-11.22)	0.21	(0.12-0.37)
High-risk for adult ASD: self-rated	43.25	<0.001	3.33	(2.27-4.89)	2.63	(1.71-4.04)	0.79	(0.43-1.44)
IQ and Communication problems								
Low childhood IQ	56.33	<0.001	4.09	(2.88-5.81)	3.60	(2.54-5.12)	0.88	(0.55, 1.41)
Child pragmatic language problems	106.38	<0.001	11.42	(6.21-21.08)	44.55	(29.47-67.33)	3.89	(2.02-7.50)
Adult communication problems	181.24	<0.001	31.86	(21.95-46.23)	5.91	(3.69-9.49)	0.19	(0.11-0.32)
Peer problems								
Childhood peer problems	107.32	<0.001	5.21	(3.71-7.31)	10.10	(7.25-14.08)	1.94	(1.26-3.00)
Adolescent peer problems	90.21	<0.001	6.29	(4.46-8.88)	6.65	(3.40-13.02)	1.06	(0.49-2.27)
Adult peer problems: parent-rated	202.92	<0.001	23.41	(17.02-32.18)	3.61	(2.28-5.71)	0.15	(0.09-0.26)
Adult peer problems: self-rated	63.11	<0.001	4.22	(2.98-5.99)	2.54	(1.72-3.75)	0.60	(0.35-1.03)
Adult functioning								
NEET	29.26	<0.001	5.81	(3.27-10.29)	3.81	(2.14-6.78)	0.66	(0.29-1.49)
Distress and impairment: parent-rated	183.61	<0.001	56.61	(39.13-81.91)	3.34	(1.73-6.45)	0.06	(0.03-0.11)
Distress and impairment: self-rated	65.76	<0.001	7.41	(4.99-11.01)	2.67	(1.68-4.23)	0.36	(0.19-0.67)

NEET = Not in Education, Employment or Training. Odds ratios based on class as the exposure regardless of temporal precedence, for comparability.

Figure 1. Mean Social Communication Disorders Checklist (SCDC) score by age



Sample including those with at least 2 time-points of SCDC data: maximum N=8094. 95% CI error bars. Prevalence meeting the cut-point (whole sample) in parentheses.

Figure 2. Social Communication Disorders Checklist (SCDC) by class: mean trajectory with 95% confidence intervals

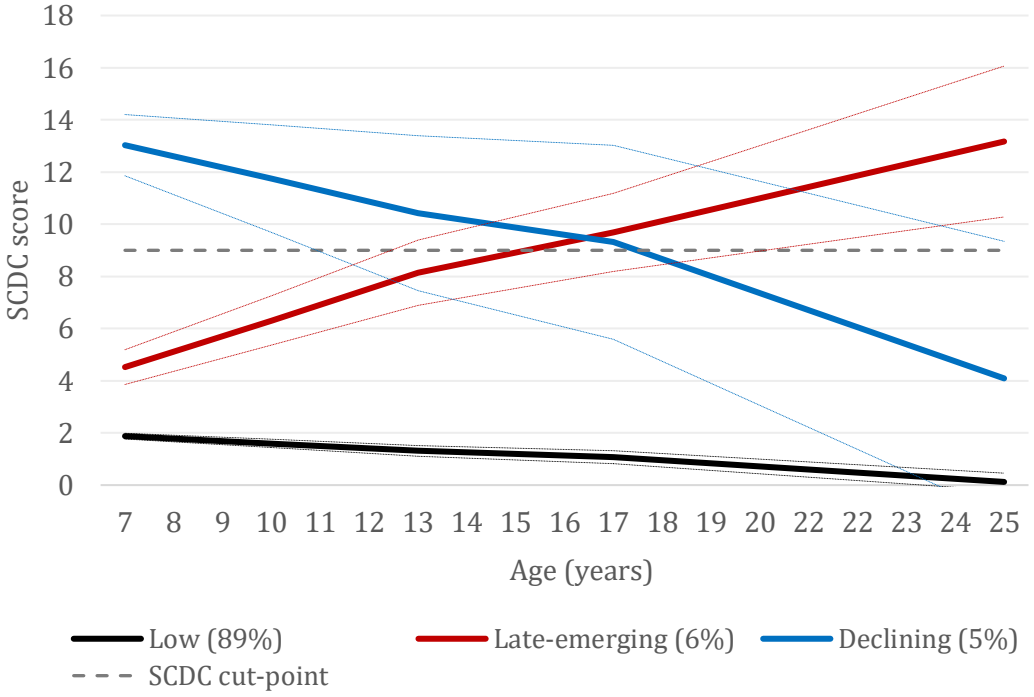
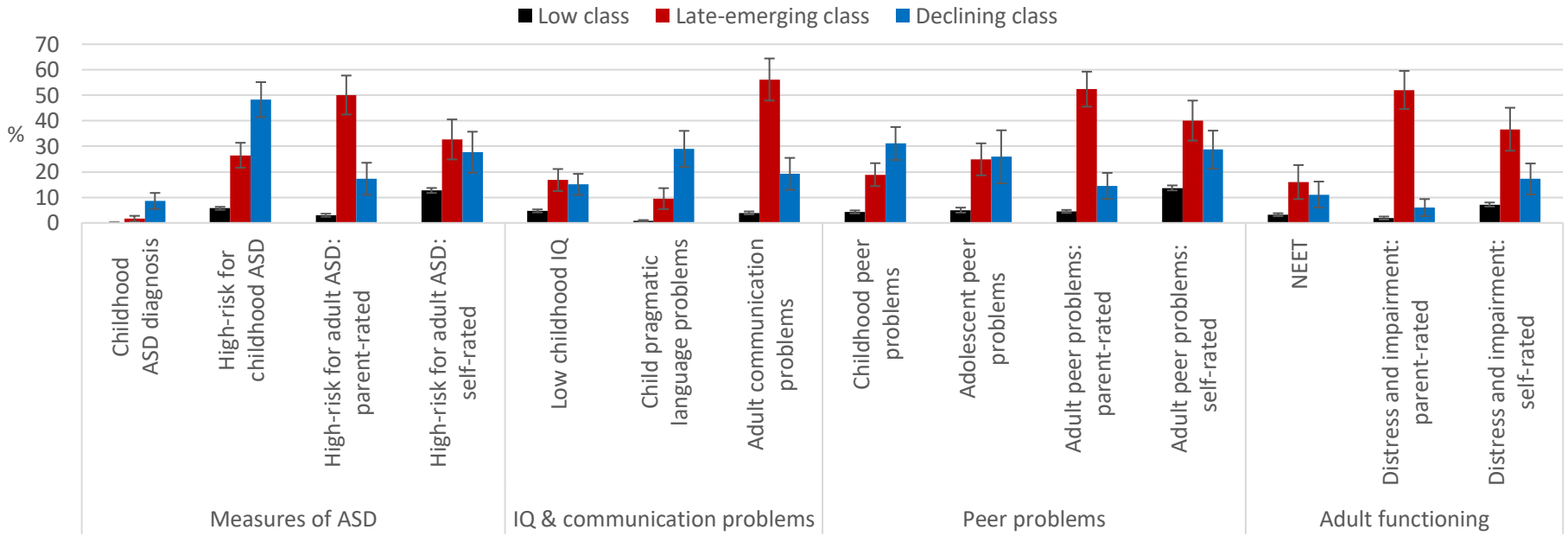


Figure 3. Prevalence of associated features including other measures of ASD, low IQ, communication problems, peer problem and adult functioning, by trajectory class



Error bars depict 95% confidence intervals. NEET = Not in Education, Employment or Training.