Clinical correlates of diagnostic certainty in children with autism

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Abstract

Background

Clinicians diagnosing autism rely on diagnostic instruments and criteria in combination with an implicit knowledge of the specific signs and presentations associated with the condition, based on clinical expertise. This implicit knowledge influences how diagnostic criteria are interpreted but cannot be directly observed. Instead, insight into clinicians’ understanding of autism can be gained by investigating their diagnostic certainty. Modest correlations between the certainty of an autism diagnosis and symptom load have been previously reported. Here, we investigated the associations of diagnostic certainty with specific items of the ADOS as well as other clinical features including head circumference.

Methods

Phenotypic data from the Simons Simplex Collection was used to investigate clinical correlates of diagnostic certainty in individuals with autism. Participants were stratified by the ADOS module used to evaluate them. We investigated how diagnostic certainty was associated with total ADOS scores, age, and ADOS module. We calculated the odds-ratios of being diagnosed with the highest possible certainty given the presence or absence of different signs during the ADOS evaluation. Associations between diagnostic certainty and other cognitive and clinical variables were also assessed.

Results

Some ADOS items showed a larger association with diagnostic certainty than others. Head circumference was significantly higher for individuals with the highest certainty rating across all three ADOS modules. In turn, head circumference was positively correlated with some of those ADOS items that were associated with diagnostic certainty, particularly in ADOS module 2.

Limitations:

The investigated cohort was heterogeneous, possibly impeding the identification of associations that only exist in a subgroup of the population. The scoring of diagnostic certainty may vary between clinicians.

Conclusion

Some ADOS items may better capture the signs that are most associated with clinicians’ implicit knowledge of autism. If replicated in future studies, new diagnostic instruments with differentiated
weighting of signs may be needed to better reflect this, possibly resulting in better specificity in standardized assessments.

**Background**

There are currently no known biomarkers for autism, and no firm biological or neurological definition of the underlying nature of the condition. Autism was initially formulated as a distinct condition based on clinical observations that certain children exhibited differences in social and communicative functions as well as repetitive behaviours and interests (1). Since then, attempts to codify the definition of autism have resulted in several iterations of diagnostic criteria (2). However, the diagnostic criteria do not provide a complete definition of autism, since the codified criteria leave room for interpretation. To apply the criteria for diagnosing autism, a clinician must have additional knowledge of the qualitative expression of different autism signs (3) as well as clinical thresholds for distinguishing autism signs from what is considered to be unusual but normal variations in behaviour (4). This additional knowledge comes from experience and exposure i.e., from encountering autism in a clinical setting or from otherwise observing and interacting with individuals with autism as well as individuals with other distinct conditions. This knowledge gained from experience cannot be easily written down or directly transferred to another person and is thus a form of implicit (or tacit) knowledge (5). The diagnostic practice of a clinician, i.e., who is and is not diagnosed with autism, depends on the codified criteria but also heavily on the clinician's implicit knowledge of and expertise in the condition.

Because clinicians’ implicit knowledge about autism cannot be fully captured in a formal definition, but rather is gained from interacting with autistic individuals, a circularity in the definition of autism arises. Clinicians’ implicit knowledge influence their collective diagnostic practices and thus have a direct impact on the composition of the autism population. The diagnosed population forms the basis of who are included in scientific studies about autism and who otherwise share their experiences of being autistic, which in turn shapes our understanding of the condition and contributes to clinicians’ implicit knowledge. Due to this circularity, clinicians’ implicit knowledge is central to shaping the concept of autism and to our understanding of the condition. Whereas the explicit diagnostic criteria are codified in diagnostic manuals, the implicit knowledge cannot be observed directly. One way to gain insight into this is to ask clinicians about their certainty of a given diagnosis and correlate the certainty to observable characteristics, since the certainty of an autism diagnosis can be a measure of how closely an individual matches the clinician’s understanding of autism.

Clinical assessment is often guided by the results of systematic diagnostic instruments, e.g., the Autism Diagnostic Observation Schedule (ADOS). However, a recent study suggests that use of the ADOS for the evaluation of small children in most cases has very little impact on the final diagnosis, particularly in cases where the clinician is confident of the diagnosis prior to the administration of the ADOS (6). This suggests that diagnostic certainty might be determined predominantly by implicit recognition rather than explicit comparisons to the codified criteria. Previous studies (7–9) found that the certainty of an autism diagnosis correlated with the total symptom load, although the correlation was modest. This means that
a substantial number of individuals with a relatively high ADOS score may not necessarily be diagnosed with the highest certainty and conversely that some might be rated with the highest certainty despite having a relatively low ADOS score. An explanation for this could be that some ADOS items are more indicative of autism than others and may therefore be more strongly associated with diagnostic certainty. The presence of a few highly specific signs could thus result in high certainty despite a low total number of symptoms. We therefore wanted to investigate how individual items in the ADOS are associated with clinicians’ certainty rating. The ADOS was chosen since it is based on clinicians’ direct observations, and thus expected to correspond more closely to factors that determine certainty than, for example, the Autism Diagnostic Interview (ADI).

Another possible explanation for a modest association between certainty and symptom severity is that other factors not directly represented in the ADOS may also contribute to the clinician’s certainty. However, previous studies do not show consistent patterns of association between certainty ratings and factors such as the level of intellectual developmental, age, or sex (7–9). We wanted to further explore the association of such factors as well as some additional phenotypes such as language level and head circumference (HC). HC has been frequently associated with autism (10). A meta-analysis (11) investigated the percentage of autistic individuals with macrocephaly, which is defined as having a HC greater than the 97th percentile and found that 15.7% of individuals with autism met this criterion, compared to around the 3% expected in controls. Since several studies have previously suggested that macrocephaly is associated with at least a subset of autistic individuals, this physical trait may directly or indirectly (by being related to other factors e.g. specific signs) impact the certainty of the clinicians performing autism assessments. We therefore wanted to further explore whether HC is associated with diagnostic certainty.

**Aim/Objective**

In the present study, we aimed to identify the specific clinical correlates of high diagnostic certainty in autism. We investigated the following research questions: Does certainty correlate with total symptom load? Are there specific ADOS items that are more highly associated with certainty than others? Are other variables, such as proband demographics, HC, IQ and language level associated with certainty?

**Methods**

**Participants**

The participants of this study are part of the Simons Simplex Collection (SSC) (12). The SSC is a database that contains behavioural, cognitive, and genetic data from approximately 2,800 individuals meeting the criteria for an autism diagnosis. Probands’ phenotypes were evaluated with a battery of instruments for which descriptions are available on the Simons Foundation Autism Research Initiative website (https://sfari.org). The SSC includes simplex cases only and enrolment to the database is based on referrals from clinical genetic centres, testing laboratories, web-based networks or active online
registration. The inclusion criteria for entry into the SSC database required probands to: 1) be between 4 and 18 years of age; 2) meet the criteria for a diagnosis of autism, Asperger syndrome, or autism spectrum; and 3) have a nonverbal mental age of at least 18 months. For the analyses of diagnostic certainty, only individuals who received a diagnosis of autism according to DSM-IV (autistic disorder) criteria were included. For the analyses of correlations between HC and other variables, all individuals with any autism spectrum diagnosis were included. All analyses were conducted separately for those assessed with each ADOS module. Only a relatively small number of individuals were assessed with module 4 (74 in total, of whom 33 were diagnosed with autistic disorder) and this module was therefore not included. The demographics of the participants separated based on language level (ADOS module) are presented in Table 1.

Table 1: Summary statistics of the included participants, separated by the ADOS module used for assessment. The rows “Verbal IQ” and “Nonverbal IQ” show the mean IQ values including ratio as well as deviation scores. The rows “Verbal IQ, deviation only” and “Nonverbal IQ, deviation only” show mean IQ values based only on deviation scores, since ratio scores were not included in the analyses.
<table>
<thead>
<tr>
<th>Measures</th>
<th>ASD</th>
<th>Autistic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADOS module 1</td>
<td>ADOS module 2</td>
</tr>
<tr>
<td>N</td>
<td>429</td>
<td>514</td>
</tr>
<tr>
<td>Females (%)</td>
<td>66 (15.4)</td>
<td>84 (16.3)</td>
</tr>
<tr>
<td>Mean age (std)</td>
<td>8.0 (3.5)</td>
<td>7.2 (3.2)</td>
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<tr>
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<td>15% hispanic</td>
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<tr>
<td>Verbal IQ (std)</td>
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<tr>
<td>Nonverbal IQ, deviation only (std)</td>
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<td>85.3 (16.8)</td>
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<td>Father bachelor degree (%)</td>
<td>239 (55.7)</td>
<td>316 (61.5)</td>
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<tr>
<td>Father some college (%)</td>
<td>350 (81.6)</td>
<td>442 (86.0)</td>
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<tr>
<td>Mother bachelor degree (%)</td>
<td>237 (55.2)</td>
<td>312 (60.7)</td>
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<tr>
<td>Mother some college (%)</td>
<td>372 (86.7)</td>
<td>466 (90.7)</td>
</tr>
</tbody>
</table>

**Measures**

**Verbal and non-verbal IQ**

The SSC database contains IQ data based on several different instruments, including...
the Differential Ability Scales 2nd edition (DAS-II), Wechsler Intelligence Scale for Children 4th edition (WISC-IV) and the Mullen Scales of Early Learning (MSEL). Most of the IQ scores were calculated as deviation IQ, i.e. using an age-adjusted norm data set with a mean of 100 and a standard deviation of 15. A smaller set of the scores were calculated as ratio IQ, i.e. using norm data to estimate an age equivalent and dividing by the chronological age. Since these two methods produce scores that may not be fully comparable (13), we only included scores calculated with the deviation method in our analysis.

**Normalized head circumference**

HC was measured by using a non-stretchable tape measure, measuring the widest part of the head. Head circumference is strongly associated with factors such as sex, age, height and ancestry. Therefore, a normalized head circumference variable was calculated to have a measure of head size that is not affected by these. This was done as described by Chaste et al. (14) by using the data of all autistic individuals in the SSC to fit a linear model with HC as the dependent variable and height, weight, age, sex and genetic ancestry factors as independent variables. The normalized HC variable was defined as the residuals from the linear model, i.e. the difference between each individual’s measured HC and the expected HC based on the predictor variables.

**Certainty variable**

The SSC contains a variable describing the certainty of the diagnosing clinician that the child has autism. If the child is deemed to lie somewhere on the autism spectrum, a base level of 5 points is given on the certainty variable. The clinician is then asked to rate how certain he/she is that the child meets the criteria for an autism spectrum diagnosis on a scale from 1 to 5 and this is added to the certainty score. In addition, if the child is also deemed to meet the strict DSM-IV-TR criteria for autism, the clinician must again rate how certain they are of this on a scale from 1 to 5, and this is also added to the certainty score which thus has a maximum value of 15. For children who receive an autism spectrum diagnosis but do not meet the criteria for a DSM-IV-TR autism diagnosis, the certainty variable has a maximum value of 10. The certainty variable is thus not directly comparable between these two groups. In this study, all analyses of diagnostic certainty were limited to those who met the strict DSM-IV-TR autism criteria. Among them, the certainty score was highly skewed, with a large proportion having a maximal certainty score of 15, and a decreasing number of individuals with progressively lower scores. For most of the statistical analyses (see below), the certainty scores were thus converted into a binary categorical variable: a certainty rating was coded as 1 if the score was 15, whereas certainty scores lower than 15 were coded as 0. This resulted in a less skewed variable in which the numbers of individuals with and without the highest possible certainty score were closer to each other.

**Autism symptomatology**

Total scores and individual item scores from the ADOS were used as measures of symptom severity as well as symptom presentation. The ADOS module used to assess a participant was used as a proxy of
language level: module 1 indicates no phrase speech, module 2 indicates phrase but not fluent speech, while module 3 indicates fluent speech.

**Vineland and CBCL measures**

The Vineland Adaptive Behaviour Scale was used as a measure of adaptive abilities. Externalizing and internalizing composite scales from the Child Behavior Checklist (CBCL) were also included in our analysis.

**Statistical analyses**

**Association between certainty and total autism symptom score**

Spearman correlation coefficients were calculated between the total ADOS score and the raw certainty score (from 1 to 15). The correlations were calculated separately for each ADOS module.

**Association between certainty and individual ADOS items**

Each ADOS item was converted to a binary variable representing the presence/absence of a clear presentation of a given sign. Thus, ADOS item scores of 0 and 1 were coded as 0 (absence), whereas item scores of 2 and 3 were coded as 1 (presence). For each ADOS item, the association between the binary coding and the binary certainty variable was investigated by calculating odds-ratios. Odds-ratios greater than 1 indicate that the presence of a given sign is associated with a higher likelihood of being diagnosed with the highest certainty, whereas odds-ratios less than 1 indicate a negative association where the presence of a sign is associated with a lower likelihood of being diagnosed with the highest certainty. The *scipy* Python package was used to calculate p-values and 95% confidence intervals for the odds-ratios. The analyses were performed separately for each ADOS module. Within each ADOS module, p-values for each ADOS item were corrected for multiple testing using the Benjamini-Hochberg method (15). For some items, no individuals in one of the two certainty groups had a score of 2 or 3, leading to division by 0 when calculating the odds-ratios. In these cases, the odds ratio was instead estimated using the Haldane-Anscombe correction (16), by adding 0.5 to each of the counts used to calculate the odds-ratio.

**Association between certainty and language level**

The ADOS module with which an individual was evaluated was used as a proxy for the individual’s language level at the time of assessment. Binomial regression was used to investigate the association between language level and certainty, with the binary certainty variable as the dependent variable and the ADOS module as the independent variable. Since the degree to which a given language level is normal/abnormal depends on age, age was also included as an independent variable, as well as an interaction term between age and the ADOS module. Binomial regression was performed using the ‘*glm*’ function in R and the statistical significance of the effects was evaluated using the ‘*Anova*’ function from the *car* package.
Association between diagnostic certainty and IQ, head circumference, and internalizing, externalizing, and adaptive behaviours

The association between certainty and each of the following variables: verbal IQ, nonverbal IQ, the verbal/nonverbal IQ ratio, internalizing behaviour, externalizing behaviour, adaptive behaviour, and normalized HC, was assessed by investigating the group-level difference for each variable between those who were diagnosed with the highest certainty compared to those who were not. This was performed separately for each ADOS module as language level was expected to influence certainty. Statistical significance of the group differences was evaluated using t-tests.

Association between normalized HC and other variables

Pearson correlation coefficients were calculated between normalized HC and ADOS items as well as the binary diagnostic certainty, verbal IQ, nonverbal IQ and verbal/nonverbal IQ ratio. This was performed separately for each ADOS module. Correlations with certainty included only individuals with a DSM-IV diagnosis of autistic disorder, whereas correlations with the remaining variables included all individuals in the SSC who received any autism spectrum diagnosis.

Results

Association between certainty and total autism symptom score

We first investigated how well the certainty rating correlated with the ADOS total scores. For ADOS modules 1, 2, and 3 the correlations were 0.26 (p = 2e-7), 0.26 (p = 9e-8), and 0.23 (p = 1e-9), respectively (Figure 1). Although this shows that certainty significantly correlated with total symptom load, the correlation was modest. There was thus a substantial proportion of the participants with relatively low ADOS scores who were diagnosed with the highest certainty and, conversely, participants who did not receive the highest certainty rating despite having a relatively high ADOS score.

Association between certainty and individual ADOS items

To identify whether some ADOS items were more associated with diagnostic certainty, odds ratios for certainty were calculated for each item. These are shown for ADOS modules 1, 2, and 3 in Figure 2. We found certain items to be associated with a prominent increase in the odds of having the highest certainty, whereas other signs showed no association or even have a small negative association. In both modules 1 and 3, the top five significant items most highly associated with an increased risk of having the highest certainty were characterized by a mix of items covering different symptom domains. However, for module 2, the top five items were within the social interaction domain.

Figure 2 Odds-ratios of ADOS items and certainty: Forest plots showing the odds-ratios of the categorical certainty variable for each ADOS item in each of the modules. An odds-ratio of 1 corresponds to no association, whereas an odds-ratio greater than 1 indicates that an individual with a given ADOS sign has a higher chance of being diagnosed with the highest certainty than an individual without the sign. The
error bars indicate the 95% confidence intervals. Error bars in red indicate that the odds-ratio is statistically significantly different from 1 after correcting for multiple testing using the Benjamini-Hochberg method.

Association of language level and certainty

In addition to the association between certainty and individual ADOS items, we also assessed how certainty was associated with language level. A child’s language level is used to determine which ADOS module to use for diagnostic assessment. Thus, the influence of language level was investigated by examining differences in diagnostic certainty between the ADOS modules. In addition, age was included, as the association of language level and certainty was expected to vary between age groups. Using binomial regression, a significant interaction effect of ADOS module and age was found (p = 3e-9). Figure 3 shows the percentage of the individuals diagnosed with the highest certainty score across ages separately for ADOS modules 1 to 3. Among those evaluated with module 1, a large proportion (around 80%) were diagnosed with the highest certainty for all ages. In contrast, the proportion of those diagnosed with the highest certainty was significantly lower for those assessed with modules 2 and 3 at younger ages, but gradually increased at higher ages. We further investigated whether diagnostic certainty differed according to sex or reported race and ethnicity. These three factors were tested individually while controlling for the effects of the ADOS module and age. No significant effects of sex, race, or ethnicity were found.

Associations between certainty and IQ and internalizing, externalizing, and adaptive behaviours

Associations between diagnostic certainty and other cognitive and behavioral variables were also investigated. Specifically, verbal IQ, nonverbal IQ, verbal/nonverbal IQ ratio, and internalizing and externalizing behaviour as measured by the CBCL, as well as adaptive behaviours, as measured by the Vineland scale were investigated. As diagnostic certainty was strongly associated with language level, the analyses were conducted separately for those who were assessed with different ADOS modules. The distributions of the aforementioned variables for those who were diagnosed with the highest certainty and those who were not are presented in Figure 4. We found a significant difference in verbal IQ between these groups among those assessed with ADOS modules 2 (t = -4.21, p = 3e-5) and 3 (t = -3.26, p = 0.001). Nonverbal IQ was significantly different in ADOS module 2 (t = -3.81, p = 2e-4). The verbal/nonverbal IQ ratio was significantly different in ADOS module 3 (t = -2.78, p = 0.006. There were no differences in internalizing behaviours in any of the ADOS modules. Among those assessed with module 3, those diagnosed with the highest certainty had significantly lower externalizing behaviours (t = -3.15, p = 0.001), Vineland total scores (t = -2.58, p = 0.01), Vineland communication (t = -3.29, p = 0.001), Vineland socialization (t = -2.37, p = 0.02) and Vineland daily living skills (t = -2.32, p = 0.02). Among those assessed with module 2, individuals diagnosed with the highest certainty had significantly lower Vineland communication scores (t = -2.85, p = 0.005) and Vineland socialization scores (t = -2.22, p = 0.03).

Association between certainty and head circumference
Across all ADOS modules, normalized HC was significantly larger in those who were diagnosed with the highest certainty compared to those who were not (t = 2.17, p = 0.03; t = 3.17, p = 0.002; t = 2.03, p = 0.04) (Figure 5). Among those with a normalized HC in the highest 2.5th percentile, 85% were diagnosed with the highest certainty, whereas this was true for only 64% of the participants not meeting this criterion.

Correlation between normalized head circumference and other variables

As normalized HC was associated with diagnostic certainty for all ADOS modules, we further investigated other correlates of HC. The correlation between normalized HC and ADOS items, certainty, verbal IQ, nonverbal IQ and verbal/nonverbal IQ ratio was assessed. The Pearson correlation coefficients that were statistically significant are shown in Figure 6. The ADOS item shared enjoyment was significantly associated with HC for all three modules. No other items, except for shared enjoyment and certainty, were significantly correlated with normalized HC in module 1. Other items that significantly correlated with HC in module 2 and 3 covered signs associated with the social interaction, verbal communication as well as play behavioural domains. The strongest effect was a negative correlation between normalized HC and the verbal/nonverbal IQ ratio among those assessed with ADOS module 2 (r = -0.19, p = 3e-4, Figure 7). The IQ ratio did not correlate significantly with normalized HC in the two other modules.

Discussion

The objective of this study was to explore factors associated with certainty of an autism diagnosis, in order to gain insight into the implicit knowledge that influences the interpretation of diagnostic criteria and clinical decision making in general.

Certainty and ADOS items

As expected from previous research (7, 8), we found a modest correlation between diagnostic certainty and autism symptomatology, confirming that a substantial fraction of participants with a relatively low ADOS score were diagnosed with the highest certainty, whereas conversely, some participants did not receive the highest certainty rating despite having relatively high ADOS scores. By investigating the associations between individual ADOS items and certainty, we found that certain autism signs markedly increased the odds of being diagnosed with the highest certainty, whereas other signs showed only minor associations with certainty, and others even showed a trend towards a negative association. This could suggest that certain signs have a stronger impact on how certain clinicians are in their diagnostic decision, likely reflecting that these characteristics are consistent with how the clinicians expect autism to appear.

This observation may suggest that new ways of constructing assessment instruments could be investigated in the future. Scores on instruments such as the ADOS are traditionally based on an equal weighting of items (17), meaning that each item equally contributes to the severity score. Alternative scoring algorithms (e.g., the calibrated severity score) that only include a select subset of all items have
been developed and found to identify autism with higher specificity (18). However, given that different items may have different associations with recognizable manifestations of autism, it could also be worth considering alternative algorithms with differential weighting of items. Furthermore, it is still an open question as to whether “interactions” between different signs could improve discrimination, e.g., that the presence of two items together may have a higher weight than the sum of each item present separately.

Such considerations may be particularly relevant in relation to the specificity of an instrument, as individuals with other conditions may display a substantial number of signs that may individually also be associated with autism. For example, Havdahl and colleagues (19) found that the presence of behavioural or emotional problems, as well as low IQ, had a marked influence on the discriminatory threshold of many commonly used diagnostic tools such as the ADOS, suggesting issues with specificity in a complex clinical setting. It would be informative to further explore which items (individual or combined) may be solely associated with autism and which items are also commonly observed in individuals with other conditions such as ADHD or intellectual disability.

Another possible explanation for the modest correlation between the ADOS total score and diagnostic certainty is that each ADOS item may cover a range of qualitative expressions of a given sign, whereas only some of these expressions are recognized as autistic with high certainty. The distinction between different qualitative presentations is likely learned with experience, and future research might investigate the association between qualitative variations in signs and diagnostic certainty.

**Correlations between certainty, head circumference, and the IQ ratio**

We found that individuals diagnosed with the highest certainty had a significantly larger normalized HC than those in the group with lower certainty ratings for all three ADOS modules. Furthermore, 85% of individuals with the largest normalized HC, i.e., individuals within the top 2.5th percentile were rated with the highest certainty versus 64% of individuals not meeting this criterion. This could indicate that either merely presenting with a larger head than commonly expected or having characteristics that are associated with having a larger HC in the autism population may influence the certainty of the clinician. Exploring associations between the normalized HC and other variables revealed small but significant positive correlations with several items in the ADOS. Interestingly, certain items overlapped between modules, e.g., shared enjoyment across all three modules, as well as imagination, reciprocal social, and conversation in modules 2 and 3. Most of the significant correlations between HC and ADOS items were within the social interaction, play behavior and verbal communication domains. In addition, many of the ADOS items in modules 2 and 3 that correlated with HC were also associated with an increased likelihood of having the highest diagnostic certainty. For example, the items shared enjoyment, reciprocal social, social overture, quality rapport, and showing, which are all from the social interaction domain, were among the highest OR in module 2 and were also found to be associated with HC. Although previous results on an association between autism symptom presentation and HC have been inconsistent, some
studies indicate that particularly social symptoms may be associated with macrocephaly in autistic individuals (20, 21).

The largest correlation of HC was with the verbal to non-verbal ratio \( (r = -0.19) \), but only in module 2. Deutch and Joseph (22) found a similar association between macrocephaly and verbal to nonverbal discrepancy in 2003 although with a larger correlation coefficient \( (r = -0.35) \). Interestingly Joseph and colleagues (23) found that school age children with an IQ profile of higher non-verbal than verbal IQ had significantly higher autism symptomatology scores within the social interaction domain. Given the associations between diagnostic certainty, macrocephaly, social symptoms, and a low verbal/nonverbal IQ ratio, it would therefore be interesting to further explore whether these characteristics are part of a specific autism presentation that is recognized by clinicians with high certainty.

**Associations between certainty, language level and age**

Diagnostic certainty was associated with the age at assessment, as well as language level (ADOS module), with a significant interaction. A higher percentage of autistic children received the highest certainty rating when assessed with ADOS module 1 than those evaluated with modules 2 and 3, but the difference decreased with age. For those assessed with module 1 (no phrase speech), the percentage of high certainty was high, regardless of age. For those assessed with module 2 (phrase but not fluent speech), diagnostic certainty was lower for children evaluated between 3 and 6 years of age than for children in age equivalent groups who were assessed with module 1. Interestingly the percentage appeared to gradually reach the same high level as for module 1 for the children that are assessed at older ages. This likely reflects the fact that the absence of fluent speech becomes increasingly abnormal with age and, thus, those who are assessed with module 2 at older ages will likely be highly atypical compared to their age equivalent peers. A similar pattern was observed for those assessed with module 3 (although the level of certainty was consistently slightly lower than for module 2), reflecting that a young child with highly developed language may be considered less likely to have autism.

**Association between certainty and other variables**

We found a number of significant associations between certainty and IQ, as well as adaptive and externalizing behaviours, although not consistently across ADOS modules. Associations between diagnostic certainty and other variables have been explored in previous studies (7–9) but these are difficult to compare to our results, as they operationalized certainty differently. They considered the certainty of the clinician’s decision, regardless of whether the decision was autism or no autism. Thus, those who clearly did not meet the criteria would have had a high certainty along with those who clearly did meet the criteria. Furthermore, they investigated all children meeting the criteria for an autism spectrum diagnosis, whereas we limited our focus to individuals meeting the criteria for autistic disorder only. Certainty for a spectrum diagnosis may cover a broader range of signs, corresponding to the broad range of presentations that can fall within the autism spectrum, whereas certainty for an autistic disorder diagnosis may reflect recognition of a less variable presentation.

**Limitations**
The heterogeneity of the sample and large variability observed between variables are relevant for the interpretation of our results and may affect the magnitude of the identified effects. For example, an observed effect could be driven primarily by a smaller part of the population but be diluted by other parts of the population that may have different mechanistic underpinnings. The result might thus be relevant for a small and potentially unknown subgroup, but not for most of the cohort represented in the SSC. Our finding that the correlation between HC and the verbal/nonverbal IQ ratio was only present in ADOS module 2, highlights that when investigating a very heterogeneous autism population, it might be relevant to consider whether the individuals can be stratified based on common features, such as language level or age at autism diagnosis, which may make it more likely that the individuals have something in common. Analysing the whole population may result in the identification of a very small effect that is difficult to interpret. Stratifying may decrease noise and make it more likely to identify larger effects that are relevant to the given subpopulation.

The demographic composition of the SSC may indicate a problem with representativeness, which may also be relevant for the interpretation of our findings. There was a high percentage of probands from families with a college degree and only approximately 10% without at least some college. This points to a higher level of education than that generally found in the adult US population (24). The percentage of non-white groups was also low, particularly in the part of the sample assessed with module 3, which included only 2% African Americans. Predisposing factors of autism associated with, for example, race or the level of education may explain some of these discrepancies. However, it could also reflect a selection bias, with certain demographic groups having better access to assessment facilities, thus impacting the generalizability of the findings from the SSC.

Clinicians’ diagnostic certainty is a subjective rating, which must be expected to be associated with some degree of variability. For example, some clinicians may be certain more often than others, and different clinicians may not have exactly the same understanding of what autism looks like, depending on their clinical expertise and exposure to autism. Two clinicians might thus not have reported the same certainty rating if they were both to assess a given individual. Such differences in how certainty is rated introduce noise and would tend to decrease the size of the observable correlations between the certainty variable and the characteristics of the autistic individuals. Thus, our results likely do not show a universal pattern of how certainty correlates with clinical factors for every clinician, but rather represent an averaged picture across the participating clinicians and indicate those factors that are most commonly associated with certainty.

Conclusions

In this study we investigated clinical correlates of diagnostic certainty and found that certain ADOS items were more strongly associated with certainty than others, suggesting a difference in how much each item corresponds to what clinicians recognize as autistic. We also observed an association between certainty and normalized HC. Furthermore, we found normalized HC to correlate with some of the same ADOS items that were most highly associated with certainty. These items may be associated with a particular
presentation of autism that also includes increased HC and which is recognized as autistic with high certainty by expert clinicians.

**Abbreviations**

ADI: Autism Diagnostic Interview  
ADOS: Autism Diagnostic Observation Schedule  
CBCL: Child Behaviour Checklist  
HC: head circumference  
SSC: Simons Simplex Collection

**Declarations**

**Ethics approval and consent to participate**

The study is based on analysis of data that has previously been collected. The study was approved by the Institutional Review Board of UHC Sainte-Justine Research Center.

**Consent for publication**

Not applicable

**Availability of data and materials**

The data used in this study is from the Simons Simplex Collection and can be accessed by application through the Simons Foundation Autism Research Initiative (SFARI).

**Competing interests**

All authors declare no competing interests.

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**Authors’ contributions**

EMR contributed to the design of the study, performed the correlation analyses of diagnostic certainty, clinical signs, and head circumference, and was the main contributor to writing the manuscript.
BRH contributed to the design of the study, performed the normalization of head circumference, and contributed to revising the manuscript.

AZ contributed to the design of the study and performed the normalization of head circumference and contributed to revising the manuscript.

KJ contributed to the analyses of diagnostic certainty, clinical signs and head circumference and to writing and revising the manuscript.

VC contributed to the design of the study and revision of the manuscript.

ED contributed to the design of the study and revision of the manuscript.

DG contributed to the design of the study and revision of the manuscript.

GH contributed to the design of the study and revision of the manuscript.

SJ contributed to the design of the study and revision of the manuscript.

LM conceptualized the study and contributed to the design of the study and revised the manuscript.

All authors read and approved the nal manuscript.

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References


**Figures**

![Figure 1](image_url)

**Figure 1**

**Correlations between the total ADOS score and clinicians’ certainty rating.** Each blue point represents an individual diagnosed with autism and deemed by the clinician to meet the strict DSM-IV-TR criteria. The black lines indicate the best linear fit. As both the total ADOS score and certainty rating can only take integer values, the points were shifted by small random values (jitter) to ease visual inspection of the correlation.
Figure 2

Odds-ratios of ADOS items and certainty: Forest plots showing the odds-ratios of the categorical certainty variable for each ADOS item in each of the modules. An odds-ratio of 1 corresponds to no association, whereas an odds-ratio greater than 1 indicates that an individual with a given ADOS sign has a higher chance of being diagnosed with the highest certainty than an individual without the sign. The error bars indicate the 95% confidence intervals. Error bars in red indicate that the odds-ratio is statistically significantly different from 1 after correcting for multiple testing using the Benjamini-Hochberg method.
Figure 3

Diagnostic certainty by age and language level. Percentage of individuals being diagnosed with the highest certainty at different ages, among those assessed with each of the ADOS modules. For visual simplicity, participants were grouped into age brackets of 3 years, centered at 3, 6, 9, 12, 15, and 18 years.
Figure 4

**Associations between certainty and IQ and internalizing, externalizing, and adaptive behaviours.** Boxplots showing the distributions of verbal IQ, nonverbal IQ, verbal/nonverbal IQ ratio, internalizing behaviour, externalizing behaviour, Vineland total score, and the scores for the three Vineland subscales communication, socialization and daily living skills. The orange boxes indicate those diagnosed with the highest certainty (15) whereas the blue boxes indicate those diagnosed with a lower certainty (< 15). Asterisks indicate statistically significant differences between those who were diagnosed with the highest certainty and those who were not.
Figure 5

Association between certainty and head circumference. Boxplot showing the distribution of normalized head circumference for each of the ADOS modules. The orange boxes indicate those diagnosed with the highest certainty (15) whereas the blue boxes indicate those diagnosed with a lower certainty (<15). Normalized head circumference was significantly different between the groups for all three ADOS modules.
Figure 6

**Correlation between normalized head circumference and other variables.** Pearson correlation coefficients of different items and variables with normalized HC among those assessed with each of the three ADOS modules. Only variables and items with statistically significant correlations with normalized HC are shown in the figures.
Figure 7

Correlation between normalized head circumference and verbal/nonverbal IQ ratio. Scatter plots showing the correlations between normalized head circumference and verbal/nonverbal IQ ratio among those assessed with ADOS modules 1, 2, and 3.