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The Autism Spectrum Screening Questionnaire (ASSQ)-Revised Extended Version (ASSQ-REV): An instrument for better capturing the autism phenotype in girls? A preliminary study involving 191 clinical cases and community controls

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ABSTRACT

We wanted to develop and validate an extension of the Autism Spectrum Screening Questionnaire (ASSQ)-the ASSQ Revised Extended Version (ASSQ-REV) – for better capturing the female phenotype of autism spectrum disorders (ASD). Clinic girls and Clinic boys, most of whom with ASD and/or attention-deficit/hyperactivity disorder (ADHD), and Community girls without a clinical diagnosis of any kind of neuropsychiatric disorder were compared on the results of the parent-rated ASSQ and on a new set of items (ASSQ-GIRL). The ASSQ-REV discriminated well between cases and non-cases. Certain single ASSQ-GIRL items were much more typical of girls than of boys with ASD. The most striking of these were "avoids demands", "very determined", "careless with physical appearance and dress" and "interacts mostly with younger children". The issue of whether or not there is a gender-specific ASD for phenotype is discussed.

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1. Introduction

Autism spectrum disorders (ASD) – also referred to as pervasive developmental disorders (PDD) – constitute a group of severe developmental/psychiatric disorders with early childhood symptomatic onset (Gillberg, 2010). It is a heterogeneous condition with a strong genetic component. Our current understanding of clinical presentation and pathogenesis is derived primarily from research on males.

ASD is characterized by severe social communication deficits, and stereotyped repetitive behaviours according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text revision *DSM-IV-TR*TM); American Psychiatric Association (APA, 2000). ASD affect at least 1% of the general population of school age children with male:female ratios of about 3–4:1 in population cohorts, and about 5–14:1 in clinical settings, with, in general, the highest sex-ratios reported for cognitively relatively high-functioning children with ASD (Baron-Cohen et al., 2009; Gillberg, Cederlund, Lamberg, & Zeijlon, 2006; Wing & Potter, 2002). However two population surveys (Lesinskiené & Puras, 2001; Mattila et al., 2007) have recently found boy: girl ratios for Aspergers disorder/High Functioning Autism (HFA) of 1.6–2:1. Baker (2002) and Sturm, Fernell and Gillberg (2004) have also recently reported higher rates of clinically referred and assessed girls with ASD without learning disorder (LD).

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There have been very few in-depth descriptions of non-mentally retarded females diagnosed with ASD (Holtmann, Bölte, & Poustka, 2007; Kopp & Gillberg, 1992; Kopp, Berg-Kelly, & Gillberg, 2010; McLennan, Lord, & Schopler, 1993) and even fewer that have attempted to address the issue of whether or not the reason for the much higher male:female ratio in clinical cohorts might be a different phenotype in girls (Kopp & Gillberg, 1992). The results from a clinic study of 100 girls identified as having social and/or attention deficits indicated that ASD in girls with IQ in the low normal to above normal range may remain unidentified and undertreated and therefore would constitute and important target group for more research (Kopp et al., 2010).

There are a number of screening instruments for ASD available for research and clinical practice (Campbell, 2005). Most of these appear to have been modelled around the phenotypes first delineated by Kanner (1943) and Asperger (1944).

In the few existing comparative clinical studies on females and males with clinical symptoms of ASD, some show no statistically significant gender differences after controlling for IQ (Holtmann, Bölte, & Poustka, 2007; Volkmar, Szatmari, & Sparrow, 1993), not even in younger children (Pilowsky, Yirmiya, Schulman, & Dover, 1998; Tsai & Beisler, 1983). However McLennan, Lord, and Schopler (1993) reported that boys with ASD were more impaired than girls with ASD in terms of early social development (in a group of high-functioning clinic attenders). In contrast, females were described as having more severe social deficits during adolescence, particularly as regards peer relationships. Higher rates of restricted repetitive behaviours have been reported by Hartley and Sikora (2009) and Lord, Schopler, and Revicki (1982) in younger boys compared to girls with ASD.

The existence of sex-differences in social relationships as well as in attentional focus – including restricted behaviour – has recently sparked research interest (Baron-Cohen, 1997; Baron-Cohen, Knickmeyer, & Belmonte, 2005; Knickmeyer, Baron-Cohen, Raggatt, & Taylor, 2005; Skuse, 2000, 2005, 2006). Population surveys on autistic traits at all ages (Allison et al., 2008; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Constantino & Todd, 2003; Posserud, Lundervold, & Gillberg, 2006; Skuse et al., 2009; Williams et al., 2008) have all confirmed that males have more autistic traits than females. Other studies have confirmed females' greater empathizing ability, documented from the first few years up to adulthood and boys more of systemizing capacity (Auyeung et al., 2009; Baron-Cohen & Wheelwright, 2004; Connellan, Baron-Cohen, Wheelwright, Batki, & Ahluwalia, 2000). These gender differences would reasonably lead to males being more prone to present with the phenotype we associate with ASD, the symptoms of which are captured in existing autism questionnaires, such as for example the Autism Spectrum Screening Questionnaire (ASSQ) (Ehlers & Gillberg, 1993).

The ASSQ was originally developed to screen for Asperger syndrome in the general population of school age children. It has since been widely used in clinical practice and well validated in research, both in the general population and in clinical samples (Ehlers & Gillberg, 1993; Ehlers, Gillberg, & Wing, 1999; Lesinskiené & Puras, 2001; Mattila et al., 2009; Posserud, Lundervold, & Gillberg, 2009; Posserud, Lundervold, Lie, & Gillberg, 2009). It has been shown to be reliable and valid for ASD across the range of clinical presentations, including in cases with autistic disorder and low IQ. Even though there have been no clear indication that it is sensitive only to the male presentation of ASD, no study has specifically tried to address the issue of a possibly different phenotype in girls. However, some researchers have proposed a need for more "genderspecific" items or different norms for girls and boys with ASD for better capturing more subtle social-communicative difficulties in girls (Baron-Cohen et al., 2009; Posserud, Lundervold, Steijnen, Verhoeven, Stormark, & Gillberg, 2008; Williams et al., 2008).

The aims of the current study were to (1) present the extended revised version of the ASSQ (the ASSQ-REV) which includes items that we posited would be more sensitive to the female presentation of ASD than those included in the original ASSQ, (2) test the validity of the ASSQ-REV, (3) examine its ability to discriminate between ASD and non-ASD cases (4) analyze whether single items of the ASSQ-REV are more often endorsed in girls than in boys (5) find the best predictors of ASD (vs non-ASD) in girls and in boys.

2. Methods

2.1. Subjects

One hundred and ninety one individuals, aged 6–16 years, were included in the study (Table 1). This larger group consisted of three subgroups: (1) Clinic girls (n = 71), (2) Clinic boys (n = 62), and (3) Community girls (n = 58). The two clinic groups comprised of cases with ASD, attention-deficit/hyperactivity disorder (ADHD), and clinically referred cases with other neuropsychiatric diagnoses (Other).

2.1.1. Clinic girls

One hundred girls, 3–18 years of age, with no prior suspicion of LD, were recruited for an in-depth diagnostic study (described in detail in Kopp et al., 2010). They had all been referred to a specialised neuropsychiatric clinic for assessment of social and/or attention deficits.

Girls with previously diagnosed LD (Full Scale Intellligence Quotient (FSIQ) \leq 70) were excluded. However, after full assessment, 12/100 Clinic girls were found to have IQ < 70 (nine of whom were under age 7 years at referral). They were retained in the study because they had not been diagnosed or suspected of LD before entering the study. Other exclusion criteria were inadequate parental command of the Swedish language, and serious physical disorders (e.g. cerebral palsy and severe epilepsy).

Table 1 Distributions (mean (SD)/range) and comparisons of age, FSIQ and questionnaires in different study groups.

	Clin girls ASD n = 27	Clin girls ADHD n = 37	Clin girls Other n = 7	Over-all p-value Clin girls	Clin girls ASD vs ADHD p-value	Clin boys ASD n = 20	Clin boys ADHD n = 35	Clin boys Other n = 7	Over-all p-value Clin boys	Com girls n = 58	Clin boysASD vs ADHD p-value	Clin girls ASD vs boys ASD <i>p</i> -value	Clin girls ADHD vs boys ADHD p-value	Clin girls ASD vs Com girls p-value	Clin girls ADHD vs Com girls p-value
Age years	11 (3.3) 6.3–16.7	13 (2.6) 7.7–16.8	10 (2.9) 6.8–15.2	.008	.017	12 (2.9) 7.4–16.4	11 (2.9) 6.9–16.2	11 (2.5) 6.7–13.9	.60	12 (2.8) 7.1–16.9	.51	.168	.039	.066	.29
FSIQ	95 (17) 54–120	94 (12) 71–121	96 (16) 65–113	.80	.64	90 (14) 75–133	92 (13) 73–126	99 (15) 78–121	.25	108 (12) 74–130	.46	.195	.48	<.001	<.001
ASSQ	24 (9.1) 8-43	13 (6.0) 0–26	10 (5.5) 3–18	<.001	<.001	25 (8.7) 9-41	14 (9.7) 0-41	8 (6.0) 3-20	<.001	3 (3.0) 0–17	<.001	.88	.63	<.001	<.001
ASSQ- GIRL	14 (5.3) 6–26	9 (4.7) 1–20	5 (3.8) 2–10	<.001	<.001	14 (6.7) 1–27	9 (6.4) 0-21	6 (5.1) 0–13	.007	2 (1.9) 0–9	.010	.74	.66	<.001	<.001
ASSQ- REV	39 (13) 14–62	22 (8.9) 1-44	16 (7.6) 6–25	<.001	<.001	38 (14) 10–61	23 (15) 0–57	14 (9.9) 4–31	<.001	4 (4.6) 0–26	.001	.79	.97	<.001	<.001
Conners-10	15 (6.8) 5–29	17 (6.6) 2–27	9 (5.7) 1–19	.021	.21	13 (9.0) ^a 0-28	15 (8.7) ^b 1–30	10 (7.9) 2–24	.35	2 (2.0) ^b 0-8	.43	.40	.40	<.001	<.001

Note: Clin, Clinic; Com, Community. ^a Five missing, ^b One missing.

The Clinic girls were given extremely detailed evaluations including the parent ASSQ. The ASSQ has been psychometrically tested in 7–16-year-old children (Ehlers & Gillberg, 1993; Ehlers et al., 1999; Posserud et al., 2006) but it has been used in slightly younger children in clinical practice. We therefore decided to use it in all children aged 6–16 years in the present study (excluding those in the original cohort who were 3–5 years and those who were 17–18 years). Two girls with missing data from the ASSQ-GIRL were also excluded. This led to a reduction of cases in the original Clinic girls' cohort, so that, in the present context, the Clinic girls comprised 71 cases (27 ASD, 37 ADHD, 7 Other, including 1 Mild LD, 1 LD NOS, 1 ADHD NOS, 3 Tic Disorder and 1 Intermittent Explosive Disorder).

Of the 100 girls originally selected, 60 were 7–16 years of age and had an IQ level \geq 80 at the time of the study. These 60 girls were matched for IQ and age with a group of 60 Community girls (see below).

2.1.2. Clinic boys

Sixty-two boys, 6–16 years of age, referred and evaluated during the same time period and at the same clinic as the Clinic girls. The Clinic boys were all diagnosed and evaluated by one of four experienced neuropsychiatrists/neuropediatricians and selected retrospectively from the medical records. We tried to match them for age (± 6 months), intellectual level (FSIQ \pm 10 IQ points) and main diagnosis with the 6–16-year olds included in the Clinic girls group of the present study. Inclusion criteria included having a fully completed ASSQ-REV and a full IQ assessment. Exclusion criteria were similar as for the Clinic girls and defined as no LD (FSIQ < 70), inadequate parental command of the Swedish language and serious physical disorders. In the event, we ended up with a Clinic boys group of 62 cases of whom 20 had ASD, 35 ADHD and 7 Other, including 2 LD NOS, 4 ADHD NOS and 1 Tic Disorder. In other words, from the diagnostic point of view, this group was very similar to the Clinic girl group.

2.1.3. Community girls

All 60 Clinic girls, aged 7–16 years with a tested $FSIQ \ge 80$ were selected and matched for age (±2 months) with 60 consecutively selected school-girls from the local paediatric outpatient register in Mölnlycke, a community in the Gothenburg region. Girls with a known serious medical illness, neuropsychiatric disorder, major academic problems or LD, girls with sibling/s assessed for suspicion of neuropsychiatric disorder, and girls who had parents without adequate Swedish language skills were excluded. In this respect, the girls selected from the paediatric outpatient register, were "mainstream community girls" who had consulted their paediatrician for common paediatric disorders (such as otitis media and allergies). We therefore use the term Community girls for this group. The further in-depth assessment (see below) revealed that two Community girls met full symptom criteria for ADHD, but this had not been established at the time of the initial recruitment. Thus there were 58 girls in the Community girls group.

The collapsed study group of Clinic girls, Clinic boys and Community girls consisted of 191 children (total group).

2.1.4. Characteristics of the study groups

Mean age was similar across groups. However Clinic girls with ASD were slightly younger than Clinic girls with ADHD and Community girls. Clinic girls with ADHD were slightly older than Clinic boys with ADHD (Table 1). Mean IQ was similar across Clinic groups. However four Clinic girls (3 ASD and 1 Other) and no Clinic boy had LD, documented at neuropsychological testing performed in the context of the present study. Twenty-five of 27 Clinic girls and 10 of 20 Clinic boys with ASD also had diagnosed comorbid ADHD. The ASD subcategories in the girl and boy groups comprised Autistic Disorder (13, 4), Asperger's Disorder (6, 13) and PDD NOS (8, 3). The ADHD subtypes were similar in the girl and boy ADHD groups (combined 21, 21, inattentive 13, 13, hyperactive-impulsive 3, 1). Autistic traits were present (2–3 DSM-IV-TR autistic disorder criteria met) in 10 of 37 girls with ADHD and 10 of 35 boys with ADHD.

2.1.5. Informed consent and ethics

The mothers of all girls provided informed consent to participate. All girls \geq 16 years also provided informed consent personally. The Ethics Committee of the University of Gothenburg approved the study of the Community girls. The Clinic girls and boys were regular clinical patients undergoing in depth clinical investigations. All interviews, questionnaires and other assessment tools were used as part of routine assessment of all patients attending the clinic 1999–2002 (when the clinical cohorts were established).

2.2. Measures

2.2.1. Clinical neuropsychiatric examination

All 129 girls (Clinic and Community) in the study received "identical" full neuropsychiatric examinations, including assessment of each girl by interview and examination and interview with the parent(s) regarding the child's early development and behavioural problems. The examinations extended over several days and lasted on average 20 h for Clinic girls and 10 h for Community girls (difference accounted for by the many more problems present in the Clinic girl group).

All 62 boys in the study received in-depth neuropsychiatric assessment, in accordance with the standard routine of the clinic. The average time for each boy examination was approximately 8 h.

All Clinic girls, Clinic boys and Community girls were screened using a parent interview schedule covering all child psychiatric and developmental diagnoses of the DSM-IV (APA, 1994).

2.2.2. Measures of intellectual functioning

We used the Full Scale Wechsler IQ scales (FSIQ) as a measure of overall intellectual functioning; the *WPSI-R* (Wechsler, 1989) for those 6.0–6.5 years, the *WISC-III* (Wechsler, 1992a) for 6.5- to 16.5-year-olds (n = 185), and the *WAIS-R* (Wechsler, 1992b) for those 16.5–16.9 years of age.

2.2.3. Questionnaires

The following questionnaires were used in the present study; all (except the ASSQ-GIRL instrument, see below) have been shown to have good reliability and validity.

The ASSQ, which was developed to screen for symptoms related to "normal-IQ-autism"/Asperger's Disorder, was completed by parents in girls \geq 6 years (Ehlers et al., 1999). The ASSQ comprises 27 items and is rated on a 3-point scale (0–2, maximum possible 54). For the purpose of the present study, 18 items, clinically believed to tap into the autism phenotype in females, were added to the ASSQ. The 18 items (ASSQ-GIRL) were chosen after focus group discussions with experienced colleagues in the field who had raised one or more of the items/symptoms as being often present in girls and adolescents with ASD. The items cover both behaviourial symptoms belonging to the autistic "triad" and adaptive functions in daily living skills. The 45-item new combined questionnaire (combining the ASSQ with the ASSQ-GIRL) will be referred to as the ASSQ-Revised Extended Version (ASSQ-REV).

The 10-item Conners' scale (Goyette, Conners, & Ulrich, 1978) was completed by all parents of Clinic girls and 57/58 Community girls in the study, and by 56/62 parents of the boys. The Conners' scale comprises 10 items pertaining to attention functions and activity level and is scored on a four-point scale (0–3, maximum possible 30).

2.2.4. Diagnostic process

The *DSM-IV* diagnostic criteria were used throughout, and its exclusion criteria regarding other coexisting diagnoses were disregarded. Diagnoses according to *DSM-IV* were assigned when both symptoms and impairment criteria for a disorder were met. The main diagnosis was used to define the problems considered most handicapping at time of assessment.

On the basis of all available information in the girl group, the first author assigned diagnoses after a thorough discussion with the professionals who had performed the individual assessments (see Kopp et al., 2010). Four different physicians working in the same clinic followed a similar diagnostic procedure for the Clinic boys.

2.2.5. Statistical methods

The SPSS 14.0 and SAS 9.2 were used for the analyses. We used non-parametric tests throughout, since the results for ASSO total scores and individual items were not normally distributed. All significance tests were two-tailed. Due to the many statistical tests carried out, a significance level of alpha = 0.01 was chosen. For continuous variables, the Kruskal–Wallis test was used to analyze differences across ASD, ADHD and Other (both for girls and boys) for the three-group comparison, which, if significant, was followed up with the Mann-Whitney U-tests for pairwise comparisons. For comparisons between two groups Mann–Whitney U-test was used for continuous variables and Mantel Haenszel χ^2 test for ordered categorical variables. Correlations between the ASSQ-results from the different ASSQ versions, age, and FSIQ were analysed with Spearman's correlation coefficient. Convergent validity was measured between the total scores of the ASSQ versions with Pearson's correlations. The internal consistency of the ASSQ-GIRL and ASSQ-REV was measured using Cronbach's alpha for prediction of ASD diagnosis for each item in the different study groups (total group, all girl group, Clinic girls group, Clinic boys group and Community group). The internal consistency of the ASSQ-GIRL was analysed by Pearson correlations across every item with the total sum score corrected for overlap. Univariate logistic regression analysis was used to predict ASD- vs non-ASD-diagnosis, for each study group (total group, all girls group, Clinic girls group, Clinic boys group and the collapsed ASD girls and Community group) and to calculate odds ratio with 95% CI and ROC area under curve (AUC). The five most predictive items for each study group were selected. In order to further examine the prediction of ASD-diagnosis we compared the total scores of the ASSQ, ASSQ-GIRL and ASSQ-REV using logistic regression analyses in different study groups. We also calculated and selected the best items for prediction of ASD- vs non-ASD-diagnosis by using multiple stepwise logistic regression analyses in the different study groups. ROC-curves were used to assess and visualize the discriminating power between ASD and non-ASD cases of the three ASSQ-versions and the selected independent items of the ASSQ-REV for different study groups (calculations described above). Multivariate regression analysis was calculated to further select the combination of ASSQ-REV items that showed the highest predictive ability for ASD (AUC > 0.90).

3. Results

3.1. Mean scores

The girls with ASD did not differ significantly from boys with ASD on the mean scores of the ASSQ, ASSQ-GIRL, and ASSQ-REV (Table 1). In the girl and boy ASD groups, 74% and 70% scored 19 or above, scores shown to be strongly associated with ASD according to Ehlers et al. (1999). The ASD groups of girls and boys had significantly higher means on the three ASSQ-versions compared to girls and boys with ADHD. No mean score differences were found between girls and boys with ADHD. The Community girls differed significantly (p < .001) from the ASD girl group as well as from the ADHD girl group on all ASSQ-versions.

Table 2

Measures	ASSQ	ASSQ-GIRL	ASSQ-REV
	r _s	r _s	r _s
ASSQ ASSQ-GIRL ASSQ-REV Age years FSIQ	1.0 .87*** .98*** 075 35***	1.0 .95*** 084 36***	1.0 078 36***

Note: Spearman's correlation coefficient (r_s) is reported and tested two-tailed.

^{***} *p* < .001.

3.2. Correlations

Significant correlations were found between total scores of the ASSQ and the ASSQ-GIRL in the total group without any significant effect for age (Table 2). However FSIQ was significantly negatively correlated with higher mean scores on the ASSQ-versions in the total group (Clinic and Community groups).

3.3. Response analyses

3.3.1. ASD

The distributions of the response categories no (0), somewhat (1) and definitive (2) of the ASSQ-REV items in the different study groups are listed in Table 3. The distribution of individual ASSQ-REV items across girls and boys with ASD showed non-significant differences on a majority of the items. Only the item 17 "lacks best friend" was significant (p < .005) with higher scores in the ASD boy group. Four further items showed statistical trends (p < .05) with more rated symptoms among girls than boys, item 8 "has a different voice/speech", item 22 "difficulties in completing daily activities because of compulsory repetitions", item 33 "avoids demands" and item 40 "interacts mostly with younger children".

When only taking the response category "definitive" into account, only one item – "avoids demands" – significantly differentiated girls (item much more often endorsed) from boys in the study (p = .008).

3.3.2. ASD and ADHD

Girls and boys with ASD scored higher than girls and boys with ADHD on the majority of ASSQ-REV items (Table 3). Girls with ASD and girls with ADHD differed more often than boys with ASD and ADHD on the ASSQ-REV items (significant differences on 13 and 7 items respectively). Boys with ADHD scored higher than boys with ASD on item 41 "engages in dangerous activities", while girls with ASD were more prone to dangerous activities compared to girls with ADHD.

3.3.3. ADHD

Boys with ADHD were twice as likely than girls to be high scorers (ASSQ \geq 19). However only three individual items significantly differentiated boys from girls ("accumulates facts on certain subjects", "literal understanding") and girls with ADHD more often than the boys with the same diagnosis had the item "avoids demands" endorsed (Table 3).

3.3.4. Community girls

Community girls and girls with ASD differed significantly on all except two items ("old-fashioned" and "eccentric professor"). Girls with ADHD and the Community girls also differed significantly on the majority of items (Table 3).

3.4. Convergent validity of the ASSQ-GIRL

Convergent validity (Pearson) between parent ASSQ-GIRL and the full ASSQ scale was good (r = 0.85 n = 191; p < .001).

3.5. Known-groups validity of the ASSQ-GIRL

The mean total scores of the ASSQ-GIRL differentiated between the ASD and ADHD groups of both girls and boys, but this was not the case with the Conners-10 (Table 1).

3.6. Internal consistency/content validity of the ASSQ-GIRL

The internal consistency of the ASSQ-GIRL (and the ASSQ-REV) items in all study groups was calculated, and Cronbach's α were all high in the "all girls" group, Clinic girls group, Clinic boys group (0.85, 0.85, 0.73, 0.81 and 0.94, 0.94, 0.88, 0.93), and somewhat lower in Community group (0.48) in the ASSQ-GIRL – although higher (0.77) in the ASSQ-REV – showing that the contents of the instruments had a high internal consistency.

Table 3

Distributions of individual items presented in percent of the collapsed response categories somewhat (1) and definitive (2), (figures in brackets represent percentage "definitive" category) in the ASSQ and ASSQ-GIRL for different study groups.

Items	Clinic girls ASD n = 27	Clinic boys ASD n = 20	p-Value	Clinic girls ADHD n = 37	Clinic boys ADHD n = 35	p-Value	Community girls n = 58	Clinic girls ASD vs ADHD p-Value	Clinic boys ASD vs ADHD p-Value	Clinic girls ASD vs Com girls <i>p</i> -Value	Clinic girls ADHD vs Community girls p-Value
ASSO											
1. Is old-fashioned or precocious ^a	52 (18)	75 (25)	.24	27 (3)	29 (6)	.83	29 (3)	.021	.001	.017	.85
2. Is regarded as an "eccentric professor"	33 (15)	50 (25)	.27	3 (0)	23 (0)	.012	12 (2)	<.001	.005	.010	.125
by the other children ^a											
3. Lives somewhat in a world of his/her own with	85 (26)	90 (45)	.26	30 (3)	43 (14)	.144	5(2)	<.001	<.001	<.001	.005
restricted idiosyncratic intellectual interests ^a											
4. Accumulates facts on certain subjects ^a	56 (18)	65 (35)	.36	8 (3)	44 (23)	<.001	0(0)	<.001	.189	<.001	.056
5. Has a literal understanding of ambiguous and	44 (33)	55 (20)	1.0	14 (3)	43 (17)	.006	0 (0)	.001	.59	<.001	.007
metaphorical language ^a											
6. Has a deviant style of communication with an	56 (41)	65 (35)	1.0	13 (5)	15 (6)	1.0	3 (2)	<.001	<.001	<.001	.117
old-fashioned or "robotlike" language ^a											
7. Invents idiosyncratic words and expressions	37 (15)	20 (15)	.56	8 (0)	32 (3)	.014	9 (2)	.002	1.0	.002	.77
8. Has a different voice or speech ^a	78 (48)	50 (20)	.035	27 (16)	34 (3)	.73	7 (0)	<.001	.09	<.001	.001
9. Expresses sounds involuntarily; clear throats,	41 (37)	50 (25)	1.0	32 (22)	46 (20)	.57	3 (3)	.32	.73	<.001	<.001
smacks or screams											
10. Is surprisingly good at some things and	78 (52)	85 (65)	.46	59 (22)	70 (26)	.44	7 (0)	.021	.020	<.001	<.001
surprisingly poor at others ^a											
11. Uses language freely but fails to make	70 (56)	90 (45)	.72	73 (46)	63 (29)	.205	17 (2)	.77	.052	<.001	<.001
adjustments to fit social contexts or the needs of different listeners ^a											
12. Lacks empathy ^a	78 (33)	70 (20)	.42	49 (16)	40 (20)	.88	9(0)	.023	.21	<.001	<.001
13. Makes naïve and embarrassing remarks ^a	48 (33)	60 (25)	1.0	51 (30)	51 (31)	1.0	10(2)	1.0	1.0	<.001	<.001
14. Has a deviant style of gaze	74 (48)	60 (30)	.23	30 (8)	31 (6)	1.0	3 (2)	<.001	.013	<.001	.001
15. Wishes to be sociable but fails to make	81 (48)	70 (50)	.72	57 (13)	54 (20)	.87	9 (3)	.003	.067	<.001	<.001
relationships with peers ^a				. ,	. ,						
16. Can be with other children but only on	70 (37)	85 (35)	.70	73 (19)	51 (11)	.090	15 (0)	.50	.007	<.001	<.001
his/her terms											
17. Lacks best friends	48 (30)	85 (70)	.005	62 (32)	66 (26)	.88	28 (5)	.47	.006	.009	.001
18. Lacks common sense ^a	41 (11)	65 (10)	.28	40 (5)	51 (9)	.35	0(0)	.84	.51	<.001	<.001
19. Is poor at games; no idea of cooperating	89 (63)	95 (80)	.26	51 (19)	51 (20)	1.0	7 (5)	<.001	<.001	<.001	<.001
in a team, scores "own goals" ^a											
20. Has clumsy, ill coordinated, ungainly,	55 (33)	60 (20)	.73	54 (30)	34 (9)	.036	21 (5)	.88	.077	<.001	<.001
awkward movements or gestures ^a											
21. Has involuntary face or body movements	48 (41)	40 (15)	.25	30 (27)	26 (17)	.58	3 (3)	.180	.59	<.001	<.001
22. Has difficulties in completing simple daily	45 (30)	20 (5)	.043	16 (5)	26 (11)	.34	2 (0)	.006	.53	<.001	.010
activities because of compulsory repetition											
of certain actions or thoughts											
23. Has special routines; insists on no change ^a	71 (41)	75 (40)	1.0	27 (8)	48 (17)	.096	3 (2)	<.001	.037	<.001	.003
24. Shows idiosyncratic attachment to objects	63 (30)	50 (40)	1.0	24 (5)	23 (3)	.83	10 (2)	.001	.003	<.001	.113
25. Is bullied by other children	45 (15)	45 (10)	1.0	51 (24)	43 (17)	.46	3 (2)	.43	.85	<.001	<.001
26. Has markedly unusual facial expression	30 (7)	30 (5)	1.0	11 (0)	14 (3)	.56	0(0)	.038	.27	<.001	.021
27. Has markedly unusual posture	41 (11)	30 (15)	.84	13 (5)	17 (3)	1.0	0(0)	.040	.163	<.001	.007
ASSQ-GIRL											
28. Copies you (can be in a very discrete way)	37 (26)	40 (15)	.86	11 (5)	20 (9)	.41	9 (2)	.012	.22	<.001	.62
29. Episodes of eating problems	70 (48)	75 (35)	.86	49 (27)	31 (6)	.044	22 (3)	.064	<.001	<.001	<.001

Table 3	(Continued)
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Items	Clinic girls ASD n = 27	Clinic boys ASD n = 20	p-Value	Clinic girls ADHD n = 37	Clinic boys ADHD n = 35	<i>p</i> -Value	Community girls n = 58	Clinic girls ASD vs ADHD p-Value	Clinic boys ASD vs ADHD p-Value	Clinic girls ASD vs Com girls <i>p</i> -Value	Clinic girls ADHD vs Community girls p-Value
30. No time perception	78 (56)	60 (45)	.32	70 (38)	60 (20)	.145	14 (3)	.29	.31	<.001	<.001
31. Too much of sympathy	41 (5)	55 (20)	.44	30 (8)	34 (14)	.61	9 (0)	.36	.27	<.001	.004
 Extremely interested in pop/rock bands, soap operas or catastrophes involving large numbers of people 	22 (15)	45 (20)	.26	16 (5)	37 (9)	.119	2 (0)	.43	.43	.002	.010
33. Avoids demands	85 (63)	75 (20)	.020	78 (51)	48 (11)	<.001	7 (3)	.42	.110	<.001	<.001
34. Very determined	89 (48)	85 (60)	.84	43 (13)	57 (31)	.109	21 (5)	<.001	.023	<.001	.030
35. Difficulties with choosing; always avoids choosing	59 (52)	85 (45)	.50	54 (24)	48 (17)	.55	14 (3)	.160	.005	<.001	<.001
36. Difficulties with self-care	78 (33)	45 (25)	.105	46 (19)	46 (14)	.88	9 (2)	.034	.72	<.001	<.001
37. Carefree or over meticulous with regard to physical appearance and dress	63 (33)	60 (35)	1.0	32 (5)	51 (14)	.082	9 (2)	.003	.22	<.001	.008
38. Naïve	30 (7)	30 (25)	.44	35 (8)	34 (11)	1.0	7 (0)	.84	.72	.004	<.001
39. Comes too close to other people	33 (26)	35 (15)	.73	27 (13)	34 (6)	1.0	7 (2)	.43	.67	.001	.006
40. Interact mostly with younger children	59 (41)	35 (10)	.039	54 (19)	37 (11)	.204	5(0)	.23	1.0	<.001	<.001
41. Engages in dangerous activities	22 (18)	5 (5)	.151	24 (11)	51 (17)	.054	5(0)	.86	.005	.004	.003
42. Exaggeratedly fanciful	26 (15)	50 (15)	.33	32 (13)	34 (9)	.87	0(0)	.86	.31	<.001	<.001
43. Talks without content	30 (18)	50 (20)	.36	22 (8)	26 (11)	.72	0(0)	.37	.132	<.001	<.001
44. Writes long stories (which can be in stark contrast to level of talk)	18 (11)	35 (10)	.52	11 (0)	9 (6)	.78	2 (0)	.21	.090	.006	.073
45. Acts or lives different parts (TV stars, videos, animals)	41 (33)	40 (25)	.75	13 (3)	26 (11)	.158	2 (0)	.002	.20	<.001	.027

Note: Mantel Haenszel-chi-squares tests were used in calculations of the ordered categorical variables on the original responses no (0), somewhat (1) and definitive (2). ^a ASSQ-items most specific for Asperger's syndrome according to Ehlers and Gillberg (1993).

Table 4

Logistic regression analyses distinguishing ASD from non-ASD diagnosis on the five most important ASSQ-REV items in different study groups.

ASSQ-REV items ^a	Total group n = 191 Odds-ratio (95% Cl)	AUC ^b	All girls n = 129 Odds-ratio (95% Cl)	AUC	Clinic girls n = 71 Odds-ratio (95% Cl)	AUC	Clinic boys n = 62 Odds-ratio (95% Cl)	AUC	ASD girls and Community girls n = 85 Odds-ratio (95% CI)	AUC
3. Lives in own world 6. Has a "robotlike" Janguage	7.9 (4.3–14.4)	0.85	14.6 (5.5–38.5)	0.87	10.1 (3.4–29.4)	0.82	4.6 (2.0–10.7) 4.8 (2.0–11.6)	0.80 0.76	39.6 (9.8–160)	0.90
8. Different voice/speach			5.8 (3.1-11.0)	0.83	3.5 (1.8-6.7)	0.77			22.6 (6.2-81.8)	0.87
10. Uneven abilities 14. Deviant style of gaze	3.8 (2.4–6.0) 4.9 (3.0–8.2)	0.77 0.77	6.8 (3.4–13.4)	0.82	4.5 (2.2-9.2)	0.78			21.1 (6.0–74.8)	0.87
16. Other children on	,						3.1 (1.4–7.0)	0.71		
own terms 19. Poor at games 23. Insists on no change	6.0 (3.5–10.1)	0.84	5.5 (2.9–10.3)	0.84	35(18-70)	0.75	6.9 (2.6–18.5)	0.84	11.9 (4.8–29.9)	0.91
29. Eating problems					515 (116 716)	0170	4.6 (1.9–11.0)	0.76	120(40 244)	0.00
33. Avoius demands 34. Very determined	4.0 (2.5-6.4)	0.79	5.5 (2.8–10.5)	0.83	4.1 (2.0-8.6)	0.77			13.0 (4.9–34.4)	0.90

Note: All *p*-values not given in table p = <.001.

^a Somewhat shortened sentences.

^b AUC = area under the curve.

To further examine the internal consistency of the ASSQ-GIRL we performed correlation analyses across every item with the total sum score minus that item. All ASSQ-GIRL items correlated significantly and with medium to large effects (r = 0.32 to r = 0.62) demonstrating good internal consistency for all items especially when the total group was studied.

3.7. ASD vs non-ASD

Discriminant validity was demonstrated by determining the ability to distinguish ASD from non-ASD participants of all ASSQ-REV items by logistic regression and ROC analyses. The five most important items (p < .01) for each study group are presented in Table 4. Different items showed acceptable to excellent discriminating ability (area under curve AUC > 0.70). Only one item ("lives in own world") distinguished well (AUC ≥ 0.80) across all five groups. The item "different voice/or speech" distinguished in all three girl groups and "robotlike language", "eating problems" and "be with other children on own terms" only in the boy group. The items "avoids demands", "poor at games" and "lives in own world" were found to best distinguish ASD from non-ASD in the collapsed group of ASD girls and Community girls.

3.8. Prediction of ASD

When using univariate logistic regression analyses of the sum scores of ASSQ, ASSQ-GIRL and ASSQ-REV to predict ASDdiagnosis vs non-ASD, differences were found across the five study groups (Fig. 1a–e). All three ASSQ-versions revealed significant effects (p < .001) in all study groups with AUC ≥ 0.79 , except in the Clinic boy group (ASSQ-GIRL AUC = 0.73). The ASSQ captured more ASD-diagnoses than the ASSQ-GIRL or ASSQ-REV in the two groups including boys (Clinic boy group and the total group). In the two groups including Clinic girls the ASSQ and ASSQ-REV showed similar high predictive capacity, while in the collapsed group of ASD girls and Community girls the ASSQ-GIRL and ASSQ-REV were found to have the highest predictive validity for an ASD diagnosis. With further calculations using multiple stepwise regression analyses, three items ("lives in own world", "deviant gaze", and "poor at games") in the total group, and one single item ("poor at games") in the Clinic boy group showed higher predictive ability than the sum score of ASSQ. In the three different girl study groups four items (lives in own world, very determined, avoids demands and poor at games) showed the highest predictive ability; however, they did not surpass the AUC-levels of the ASSQ-versions (Fig. 1a–e).

Other important ASSQ-GIRL items in combination with one or two ASSQ-items calculated with multivariate selection (AUC > 90) showing high predictive ability were: "interacts mostly with younger children", "carefree or overmeticulous with regard to physical appearance or dress" and "acts or lives different parts".

4. Discussion

This study reports on the development of the ASSQ-GIRL, a new set of screening questionnaire items for parents selected after focus-group discussions with very experienced clinicians with a view to better capturing the female phenotype of ASD in school age girls.

The results of present study support the use of at least some of the new ASSQ-GIRL items for screening and clinical purposes in addition to other measurements in the diagnostic process of ASD, especially in girls. Further studies are needed



Fig. 1. ROC curves for the prediction of Autism Spectrum Disorders from parent ASSQ, ASSQ-GIRL, ASSQ-REV and stepwise selected items of the ASSQ-REV. ASSQ-score 19 is marked and indicates most specific for Asperger's syndrome according to Ehlers and Gillberg (1993). (a) AUC 0.99 (ASSQ, 1.00 (ASSQ-GIRL), 1.00 (ASSQ-REV), 1.00 (item 3, 19, 33). (b) AUC 0.94 (ASSQ), 0.91 (ASSQ-GIRL), 0.94 (ASSQ-REV), 0.92 (item 3, 34). (c) AUC 0.86 (ASSQ), 0.79 (ASSQ-GIRL), 0.79 (ASSQ-REV), 0.84 (item 19). (e) AUC 0.99 (ASSQ), 1.00 (ASSQ-GIRL), 1.00 (ASSQ-REV), 1.00 (item 3, 19, 33).

for understanding the clinical presentation of gender differences in ASD. As part of the process the development of gender based specific assessment tools would appear to be an important goal for future research.

4.1. General findings in relation to study aims

The new items in the ASSQ-GIRL (intended to better capture girls with ASD) and the ASSQ discriminated well between ASD and non-ASD cases and between ASD and ADHD cases. However, no overall gender differences were found across 6–16 years old girls and boys with ASD and/or ADHD as regards mean scores of the ASSQ, ASSQ-GIRL or the ASSQ-REV. We could not confirm that the ASSQ-GIRL sum score better captured clinically diagnosed girls with ASD than the sum score of ASSQ

(except in the collapsed group of girls with ASD and Community girls). However some of the ASSQ-GIRL items were more often endorsed in girls with ASD than in boys, and the ASSQ-REV response profiles differed markedly between the two sexes. Some ASSQ-GIRL items together with one or two of the original ASSQ-items showed excellent predictive power in distinguishing ASD from non-ASD especially in the girl groups. At individual item levels, girls with ASD differed more markedly from girls with ADHD compared to boys with these diagnoses. The differences between girls with ASD, girls with ADHD and Community girls were considerable across the majority of ASSQ-REV items. Thus some of the ASSQ-GIRL items and the ASSQ-REV response profile appeared to add important information about the autistic phenotype in girls with ASD.

The finding of similar sum scores from the parent-rated questionnaires ASSQ, ASSQ-GIRL, and ASSQ-REV, in clinic referred girls and boys with ASD is consistent with previous studies on the ASSQ (Ehlers et al., 1999; Mattila et al., 2009) and the Autism Spectrum Quotient in children and adolescents (Auyeung, Baron-Cohen, Wheelwright, & Allison, 2008; Baron-Cohen, Hoekstra, Knickmeyer, & Wheelwright, 2006). However, reliable conclusions about gender differences from these studies have to be treated with prudence, given that, in general, very few girls were included, or the male to female ratio was extremely high limiting the generalisability of the findings.

Majority of ASSQ-REV items (28/45) was scored higher for boys than for girls with ASD, but girls were more often rated to have a "definitely" response than did boys. Various explanations could account for these findings. Firstly, milder cases of boys with ASD might be referred to clinics, in contrast to girls with ASD referred only when more severe obvious/crystallized problems are present (even if the sum score are similar). This has been shown to be the case for girls with ADHD (James & Taylor, 1990; Gaub & Carlson, 1997). Secondly, the overall higher rates of autistic traits found in "normal" boys compared to girls might mask discrepancies between more and less symptomatic boys with ASD (Baron-Cohen et al., 2001, 2006; Constantino & Todd, 2003; Posserud et al., 2006; Skuse et al., 2009; Williams et al., 2008) in contrast to girls whose severe autistic symptoms might set them more clearly apart from "normal" girls. This would be in line with the "male brain theory" advocated by Baron-Cohen (2002).

Turning to look at the ASSQ-REV individual items, interesting gender differences were found. However very few showed statistically significant differences. The most striking differences were in terms of "lacks best friends" (more boys with ASD), and "interacts mostly with younger children", "avoids demands", "has a different voice/speech" plus "difficulties completing simple daily activities" (more girls with ASD).

The items "lack best friends" and "interacts mostly with younger children" were differentially endorsed for boys and girls. Both items are covered by the *DSM-IV* criterion "lacks friends appropriate for developmental age" and mirror underlying dysfunction in social reciprocity. "Lacks best friends" at a glance, would appear to be a more severe qualitative impairment of social-interaction than would "interacts mostly with younger children". However we need to consider that social interactions play an important role in the development of gender-typical play and choice of playmates (Maccoby, 1998). "Normal" boys' preference to play in same-age male groups may unconditionally prevent a boy with ASD from joining in. In contrast, "normal" girls usually play with one or two other girls, and this could provide a girl with ASD scope to choose younger or older girls (Maccoby, 1998). In such constellation, girls with ASD might even be capable "running the show". In contrast to boys, "normal" girls, who are suggested to be more sensitive and caring towards others, might possibly more frequently invite girls with atypical developmental into their play (Gilligan, 1982; Hoffman, 1977).

Another possible interpretation may be that the reported sex differences regarding relationships are related to a greater social drive seen early on in girls development, which eventually, even in girls with ASD, would be stronger than in boys with ASD (Connellan et al., 2000; Knickmeyer et al., 2005). Further studies are needed to better understand the longitudinal development of social interaction in girls and boys with ASD. Williams et al. (2008) argued that additional questions more sensitive to *subtle* social-communicative difficulties in girls may be needed to better capture social deficits in girls.

There might be a risk for parents and professionals to overlook the lack of social reciprocity in girls and see them as more social (and not autistic) than they actually are, already suggested by Wing as early as 1981, and by the present authors in the early 1990s. The studies by Holtmann et al. (2007) and McLennan et al. (1993) have also confirmed that high-functioning adolescent girls with ASD actually show *more* difficulty in establishing peer relationships than boys.

The ASSQ-GIRL item "avoids demands" was scored significantly higher in girls than boys with ASD (and ADHD). This item relates to the concept of "pathological demand avoidance (PDA)" developed in the 1980s by Elisabeth Newson, now often considered a subgroup of ASD (Newson, Le Maréchal, & David, 2003). The avoidance in PDA is connected with social anxiety and obsessive demand resistance, and, in contrast to classic ASD-cases, to better pretend play. On the ASSQ-GIRL, girls and boys with ADHD showed similar high discrepancy rates on "demand avoidance" as in the ASD groups. Some different interpretations are plausible of the reported gender difference regarding "demand avoidance" (i) It could be that parents may have a less demanding attitude towards boys than girls leading girls to "forced" avoidance (ii) Girls with diagnosed ASD and/or ADHD might also meet criteria for a diagnosis of PDA (iii) There could be higher "comorbid" rates of social anxiety in the girl groups than boy groups. High rates of anxiety disorders have previously been reported in this study group of girls with ASD and/or ADHD (Kopp et al., 2010). However no in-depth examination of anxiety disorders was made in Clinic boys, meaning that no head-to-head comparison between anxiety rates in girls and boys cold be achieved. (iiii) Girls might be more likely to avoid demands passively (ignoring, or aching as an excuse to do what has been asked) in contrast to boys who may be more likely to refuse or defy actively (by arguing vociferously or throwing violent tantrums) (Björkqvist, 1994). Similar gender differences have been discussed in relation to defiance and oppositional defiant disorder (ODD) (Ohan & Johnston, 2005). Irrespectively, the cause of this gender-difference in resisting demands seems to be a distinct signal in girls with an underlying disability.

In the original ASSQ-study, 16 of the 27 items were considered most specific for Asperger syndrome (Ehlers & Gillberg, 1993), 6 of these 16 in the present study were endorsed only in boys ("is old-fashioned", "is regarded as an eccentric professor", "lives in own world with restricted idiosyncratic intellectual interests", "accumulates facts on certain subjects", "lacks common sense" and "is poor at games"), and one item was endorsed only in girls ("different voice or speech"). The endorsed "male" symptoms, typical of the generally conceptualised gestalt of Asperger's disorder, highlight the issue of whether or not the current delineation of Asperger syndrome is, in fact, only the male presentation of the disorder. Also, when girls with ASD do not talk in the "robotlike" manner, but "only with a different voice" they may very well remain unidentified.

4.2. ASD vs non-ASD cases

In using logistic regression analyses for examination of every ASSQ-REV item and its ability to distinguish between ASD and non-ASD cases a set of items were identified, showing a striking gender-difference in the Clinic groups. Only one single item, "lives in own world", distinguished well between ASD and non-ASD in all study groups (including Clinic girl group and Clinic boy group). This item mirrors a core deficit in ASD and might be one of the most important ASSQ-items for both genders, covering both "aloofness" and intense preoccupation with "special interests" (see below). Five important items differentiated Clinic girls from Clinic boys ("robotlike language", "other children only on own terms" and "eating problems" in boys and "different voice", and "insists on no change "in girls). The "robotlike language" often considered typical "signs" of verbal autism/Asperger syndrome, according to these results, could be taken to reflect a more "male phenotype". This also accords with our clinical experience of girls with ASD speaking in an unusual way (childish, high pitch or hoarse), however not robotlike. This "gender difference" might be one reason (of several) why boys with ASD are more easily recognised.

"Avoids demands" separated the collapsed group of girls with ASD and Community girls from boys and "very determined" differentiated Clinic boys from the total group, all girls and Clinic girls. All these findings indicate that different ASSQ-REV items are differently loaded depending on gender, clinic and population status.

4.3. Prediction

The logistic regression analyses demonstrated that of the three ASSQ-versions, the original ASSQ was the best predictor for an ASD diagnosis especially among boys with ASD. ASSQ-GIRL and/or ASSQ-REV were as predictive as ASSQ among girls with ASD or even more predictive in the collapsed ASD girl and Community group. Thus, the ASSQ-GIRL distinguished between ASD and non-ASD better in female groups than in the male group.

Rather surprisingly, in the total group, the ASSQ-items "deviant gaze", "poor at games" and "lives in own world", and in the Clinic boy group the item "poor at games", showed better predictive capacities than the total score of ASSQ in the stepwise calculations. The item "poor at games", a typical gender biased item, "games" being a very common leisure activity among normally developing boys, would be more likely to be predictive of atypical development in boys.

Other highly predictive "girl" ASSQ-GIRL items found with multivariate regression analyses were "avoids demands", "very determined", "carefree with regard to physical appearance and dress" and "interacts mostly with younger children". The clinical phenotype of a girl with ASD seems to be a girl very determined, avoiding demands, careless about dress (or over meticulous) and sometimes playing with younger children preferring "acting animals". This possible female ASD phenotype appears different from a typically developing girl with a high sensitivity for social demands and other people's opinions (about dress and physical appearance).

4.4. Conclusions

Studying separate ASSQ-REV items might lead to a better understanding of gender differences among girls and boys with ASD and/or ADHD. Our findings illustrate the importance of studying symptom gender differences at the individual item level (rather than in terms of total scores) in research on screening methods and diagnostic work-up of girls and boys with ASD. Further studies on larger samples are needed and planned to confirm ASD gender differences.

4.5. Limitations

Our study has several limitations. First, the sample of girls and boys with ASD was relatively small. Second, the cases were recruited from a sample of girls and boys referred to a specialist clinic. They were not necessarily representative of all girls and boys with ASD and/or ADHD in the general population, but we believe they were fairly typical of girls and boys referred to clinics for symptoms consistent with these diagnoses. Third, the information regarding autistic symptoms consisted of parent ratings rather than direct observations. The potential effects of parental biases must therefore be considered, especially since girls and boys are differently socialized and parents have different expectations depending on child/parent gender. Fourth, the Clinic boys were included retrospectively and examined by four different professionals, while the Clinic girls were recruited prospectively and examined by the same physician. Girls were assessed during a longer time (10–20 h) compared to boys (8 h). This may have biased the results to some extent, even though the instrument scrutinized here was one and the same parent-rated questionnaire. Fifth, systematic standardised assessment of global impairments was

routinely done in the boy group, meaning that, in spite of the girls and boys being matched for age and IQ, we had no undisputable comparator for overall level of adaptive functioning. Finally, it is possible that a pilot study – performed prior to the definitive project – might have been useful in selecting only the more appropriate ASSQ-GIRL-items, even though it is likely that such a study would have had to be relatively large scale in format, leading to a final much more expensive project than the present one.

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