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Validation of a German version of the dementia screening questionnaire for individuals with intellectual disabilities (DSQIID-G) in Down's syndrome

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Abstract

Background People with Down's syndrome (DS) are at high risk of developing Alzheimer dementia (DS-AD) due to a triplication of the *amyloid precursor protein* gene. While several tools to diagnose and screen for DS-AD, such as the dementia screening questionnaire for individuals with intellectual disabilities (DSQIID), are available in English, validated German versions of such instruments are scarce.
Methods A German version of the DSQIID questionnaire (DSQIID-G) was completed by caregivers before attending our specialist outpatient department for DS-AD. All participants were assessed blind to DSQIID-G scoring using clinical and neuropsychological examinations, including the *Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities* (CAMDEX-DS). ICD-10 and amyloid/tau/neurodegeneration (A/T/N) criteria were applied to detect and categorise cognitive decline.

Results Of 86 participants, 43 (50%) showed evidence of cognitive decline. A definite diagnosis of DS-AD was reached in 17 (19.8%) and mild cognitive impairment in seven (8.3%) participants. Secondary causes of cognitive decline were determined among 13 (15.1%) participants, and in six (7%) cases, the diagnosis remained unclassifiable due to co-morbidities. Compared with cognitively stable individuals, participants with cognitive decline (n = 43) displayed higher DSQIID-G total scores [median (range): 3 (0–21) vs. 19 (0–48), $P < 0.001$]. A total score of >7 provided a sensitivity of 0.94 against a specificity of 0.76, to discriminate DS-AD and participants without cognitive decline according to ROC analysis. The convergent validity against the CAMDEX-DS interview score was good (r = 0.74), and split-half reliability (r = 0.96), internal consistency (Cronbach's α r = 0.96), test–retest reliability (r = 0.88) (n = 25) and interrater reliability (r = 0.81) (n = 31) were excellent.
Conclusions The DSQIID-G showed excellent psychometric properties, including concurrent and internal validity and reliability. The cut-off value for screening was lower than in the original English validation study. For a screening instrument like DSQIID-G, a lower cut-off is preferable to increase case detection.

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Keywords Alzheimer disease, diagnosis, Down's syndrome, DSQIID, screening

Introduction

In most cases, trisomy 21 comprises a triplication of the *amyloid precursor protein* (APP) gene, leading to an increase in APP synthesis and an early cerebral accumulation of its cleavage product $A\beta_{1-42}$. As a result, people with Down's syndrome (DS) display cerebral amyloid deposits as early as in their twenties, and most reach an amyloid load corresponding to Thal phase 5 by age 50 (Davidson *et al.* 2018). People with DS are thus at very high risk of developing Alzheimer dementia (DS-AD), making them the largest at-risk group for genetically determined dementia. Furthermore, this unique genetic predetermination marks DS-AD as a distinct entity within the complex field of dementia in people with intellectual disabilities.

Despite its high prevalence, arriving at a diagnosis of DS-AD still proves difficult, primarily due to the heterogeneous clinical presentations and variable level of intellectual disability in this population (Aylward *et al.* 1997; Deb & Braganza 1999). As in sporadic AD, memory deficits are often present early in the disease course, but they are usually not the main complaint (Fonseca *et al.* 2020). Mostly, caregivers describe alterations in everyday behaviour such as reduced participation in activities, aggression, or a decline of abilities in activities of daily living. In addition, a wide range of differential diagnoses has to be considered. These range from visual or hearing impairments to medical conditions such as obstructive sleep apnoea or endocrinologic disorders, as well as depression, regression and other psychiatric disorders (Nubling *et al.* 2022). Taken together with the lack of normative data for almost all diagnostic neuropsychological instruments, these circumstances make it challenging to diagnose DS-AD using ICD-10/11 or DSM-V criteria (Sheehan *et al.* 2015; Nubling *et al.* 2022).

Both performance-based neuropsychological tests and observer-rated scales are used to diagnose and screen DS-AD (Deb *et al.* 2022; Zeilinger *et al.* 2022). One observer rated screening instrument, dementia screening questionnaire for individuals with intellectual disabilities (DSQIID), was developed by Deb and colleagues in the United Kingdom (Deb *et al.* 2007b). The items were created through interviews of caregivers of adults with DS, particularly taking into account early symptoms of dementia (Deb *et al.* 2007a). DSQIID is easy to use and showed excellent psychometric properties, leading to its translation into several languages and validation in intellectual disabilities other than Down's syndrome (Li *et al.* 2015; Gomiero *et al.* 2017; Kuske *et al.* 2017; Takenoshita *et al.* 2020; Rebillat *et al.* 2021). Furthermore, the US-based National Task Group (NTG) has adapted and included most DSQIID items in their screening questionnaire *Early Detection Screen for Dementia* (NTG-EDSD) (Esralew *et al.* 2018), which is available in several languages including German. However, the DS-AD specific psychometric properties of the German DSQIID are unknown. Therefore, we prospectively evaluated a German version of DSQIID (DSQIID-G) in a well-characterised cohort of DS participants and their caregivers.

Participants and methods

Participant recruitment

Eighty-six participants with Down's syndrome and their caregivers were recruited from our specialist outpatient clinic for dementia in people with DS. Inclusion criteria were confirmed trisomy 21 through karyotyping, the availability of an informant and the willingness to participate in neuropsychological testing. Estimates of the level of intellectual disabilities before the onset of cognitive decline placed participants in the mild (52.6%) to moderate (46.1%) range, only one participant had severe intellectual disabilities.

The German version of the dementia screening questionnaire for individuals with intellectual disabilities (DSQIID-G)

The NTG-EDSD comprises 41 of the 53 items from the original DSQIID questionnaire (Esralew *et al.* 2018). The German version of the NTG-EDSD showed good face validity and utility (Zeilinger *et al.* 2016). We included these 41 items from the German NTG-EDSD in the DSQIID-G to maximise comparability of the two scales in future studies. The remaining 12 questions were translated via a two-step

process. First, three separate translations were conducted by neurologists (primary language: German). Subsequently, a multidisciplinary team of neurologists and neuropsychologists created a German consensus version. Finally, two independent back-translations were conducted and evaluated concerning their consistency with the original DSQIID by two native English speakers.

Data collection

DSQIID-G questionnaires were sent to caregivers in paper form before the clinic visit. To evaluate test–retest reliability, a subset of caregivers were asked to complete DSQIID-G a second time during the clinic visit (test–retest interval 6 weeks or less). When available, a second caregiver was asked to complete the DSQIID-G to assess inter-rater reliability. A detailed medical history was recorded, and a neurological examination was carried out in the informant's presence. All participants underwent a neuropsychological assessment using the German version of the *Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities* (CAMDEX-DS), which comprises a structured informant interview and a neuropsychological test battery (*Cambridge Cognitive Assessment*, CAMCOG-DS) (Nubling *et al*. 2020, Loosli *et al*. 2024). For the CAMDEX interview, all positive items from the ICD-10 diagnostic domains 'memory impairment', 'cognitive abilities and daily living skills' and 'emotional control, motivation or social behaviour' were added to a final score.

A diagnosis of mild cognitive impairment (MCI), DS-AD, 'secondary' or 'unclassifiable' cognitive decline was reached by consensus of two neurologists who individually applied a previously published diagnostic algorithm taking into account all clinical, neuropsychological and technical investigations (Nubling *et al*. 2022). Raters were blinded to DSQIID-G scores. The consensus approach was chosen based on findings that clinical judgement outperforms the sole application of diagnostic criteria such as ICD-10, and a similar approach had been successfully implemented in previous studies (Sheehan *et al*. 2015; Silverman *et al*. 2021). In brief, a diagnosis of DS-AD was arrived at when the following conditions were met: (a) Self and/or caregiver report of decline in cognitive function in at least one cognitive domain or decrease in CAMCOG total score if previous examinations were available; (b) conclusive report of a relevant decline in capabilities concerning activities of daily living; (c) exclusion of haematological, endocrinologic, psychiatric, or other co-morbidities with potential relevance to cognitive function and insufficient treatment at the time of investigation; (d) (if feasible) evidence of amyloid/tau pathology and/or neurodegeneration. A diagnosis of MCI was arrived at if criteria (a), (c) and (d) (if feasible) were fulfilled, but there was no relevant decline in activities of daily living. 'Secondary' cognitive decline (CD_{second}) was defined as cognitive decline due to diseases other than DS-AD. 'Unclassifiable' cognitive decline ($CD_{unclass}$) was defined as cognitive decline relevant to activities of daily living in cases where DS-AD was possible, but there was at least one co-morbidity, such as untreated hypothyroidism or insufficiently controlled epilepsy, that may equally have led to the cognitive decline observed. Current and pre-morbid levels of intellectual disability were assessed according to DSM V criteria (Falkai & Wittchen 2018). All participants received standard laboratory investigations (full blood count, liver and kidney function tests, vitamins D, B1, B12 and thyroid function parameters) to rule out relevant co-morbidity (data not presented). Additional investigations such as lumbar puncture, magnetic resonance imaging, amyloid ([^{18}F]-Florbetaben) or tau ([^{18}F]-PI-2620) positron emission tomography were performed in cases with suspected DS-AD/MCI whenever feasible.

Statistical analyses

Total DSQIID-G scores were used for analysis. Missing values were counted as '0' (maximum 10% missing values tolerated). Three questionnaires could not be analysed due to missing values. Normal distribution of data was examined using the Shapiro–Wilk test. Data are presented as mean ± standard deviation or median (range) in the case of non-normality. For multiple comparisons of demographic data, the Kruskal–Wallis test was used (data not normally distributed). Correlation analyses were performed using Spearman correlation (data not normally distributed). We used the receiver operating curve (ROC) to determine the best fit between

sensitivity and specificity of the DSQIID-G total score, as well as positive/negative likelihood ratios.

Convergent validity was assessed by correlation analyses of DSQIID-G and CAMDEX-DS interview total scores as well as Fisher's exact test on the diagnostic outcome of the respective test at predefined and/or determined cut-off values. Split-half reliability was analysed by consecutive

Table 1 Demographic data

	Total	No CD	MCI	DS-AD	$CD_{secondary}$	$CD_{unclassified}$	χ^2 (*P*-value)
n (%)	86	43 (50)	7 (8.3)	17 (19.8)	13 (15.1)	6 (7.0)	
Age (median (range))	32 (18–62)	28 (18–36)	51 (32–58)	56 (42–62)	29 (20–37)	49 (29–54)	<0.0001
Sex (female, %)	45.3	48.8	42.9	41.2	38.5	50	n.s.
DSQIID-G score (median (range)	8 (0–48)	3 (0–21)	7 (0–12)	25 (4–48)	23 (7–43)	18 (13–20)	
Psychiatric disorders*** (*n* (%))	29 (33.7)	14 (32.6)	2 (28.6)	2 (11.8)	9 (69.2)	4 (66.7)	0.017*
Depression***	12 (14.0)	4 (9.3)	1 (14.3)	1 (5.9)	5 (38.5)	2 (33.3)	n.s.
Adjustment disorder***	8 (10.5)	6 (13.9)	1 (14.3)	0 (0)	2 (15.4)	2 (33.3)	n.s.
Other***	12 (14.0)	7 (16.3)	0 (0)	1 (5.9)	4 (30.8)	1 (16.7)	n.s.
Other co-morbidities (*n* (%))							
Hypothyroidism	55 (63.9)	30 (69.8)	4 (57.1)	10 (58.8)	7 (53.8)	4 (66.7)	n.s.*
Hearing impairment	11 (12.8)	4 (9.3)	0 (0)	1 (5.9)	4 (30.8)	2 (33.3)	0.041*
Epilepsy	9 (10.5)	5 (11.6)	0 (0)	2 (11.8)	2 (15.4)	0 (0)	n.s.*
Co-morbidities causative for a classification of $CD_{secondary}$ or $CD_{unclassified}$							
Depression					3 (23.1)	2 (33.3)	
Adjustment disorder					2 (15.4)	0 (0)	
Regression syndrome					3 (23.1)	0 (0)	
Schizophrenia (suspected) Unspecified psychiatric					0 (0)	1 (16.7)	
Syndrome					2 (15.4)	1 (16.7)	
Obstructive sleep apnoea					2 (15.4)	2 (33.3)	
Hearing/vision impairment					1 (7.7)	1 (16.7)	
Epilepsy					1 (7.7)	0 (0)	
Hypothyroidism					2 (15.4)	0 (0)	
Side effects of medication					1 (7.7)	0 (0)	
Late puberty					1 (7.7)	0 (0)	
Medication							
AChE inhibitors	3 (3.5)	0 (0)	0 (0)	3 (17.6)	0 (0)	0 (0)	
Antidepressants	14 (16.3)	4 (9.3)	2 (28.6)	3 (17.6)	3 (23.1)	2 (33.3)	
Neuroleptics	8 (10.5)	2 (4.7)	0 (0)	4 (23.5)	0 (0)	2 (33.3)	
Anticonvulsants	7 (8.1)	4 (9.3)	0 (0)	2 (11.8)	1 (7.7)	0 (0)	
Benzodiazepines/Z-Substances****	3 (3.5)	3 (7.0)	0 (0)	0 (0)	0 (0)	0 (0)	
Pre-morbid intellectual disability							
Mild (*n* (%))	40 (52.6)	24 (61.5)	5 (71.4)	5 (45.5)	4 (30.8)	2 (33.3)	n.s.*/**
Moderate (*n* (%))	35 (46.1)	14 (35.9)	2 (28.6)	6 (54.5)	9 (69.2)	4 (66.7)	
Severe (*n* (%))	1 (1.3)	1 (2.6)	0 (0)	0 (0)	0 (0)	0 (0)	
A/T/N criteria (*n* (%))							
Aβ-PET pos.	10/14 (71.4)	1/1 (100)	3/3 (100)	6/6 (100)	0/4 (0)	n.d.	
Tau-PET pos.	3/8 (37.5)	0/1 (0)	0/1 (0)	3/4 (75)	0/2 (0)	n.d.	
Neurodegeneration	6/16 (37.5)	0/6 (0)	2/2 (100)	4/4 (100)	0/4 (0)	n.d.	

*For chi-square analyses, MCI/DS-AD and secondary/unclassified cognitive decline (CD_{second}/$CD_{unclass}$) were combined to meet the test's requirements.
**Comparison of the distribution of mild and moderate intellectual disability. Severe intellectual disability was omitted given that the group contained only one patient.
***Suspected or confirmed, current and previous diagnoses.
****On-demand medication.

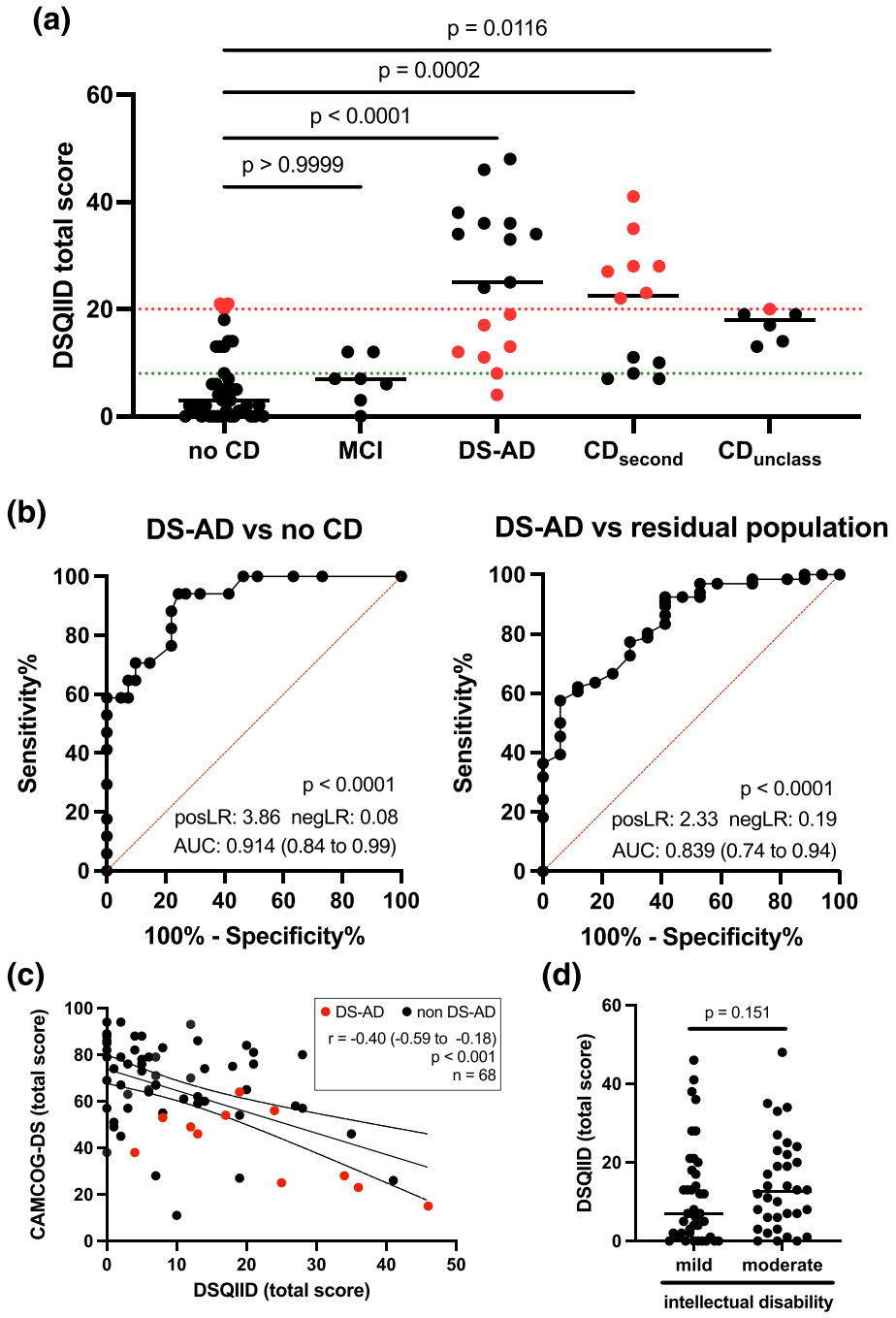

Figure 1. The DSQIID yielded elevated scores for all forms of cognitive decline except MCI when compared with cognitively normal controls (a). Notably, several patients with clinically confirmed DS-AD do not exceed the threshold of 20 points (red line), whereas some patients with other causes of cognitive decline (CD) as well as three participants without cognitive decline exceed this threshold. Still, ROC analyses yielded a high diagnostic accuracy when differentiating AD from both cognitively healthy controls (b, left panel; AD $n = 17$, no cognitive decline $n = 43$) and the entire population including MCI (b, right panel; AD $n = 17$, residual population $n = 69$). The DSQIID further showed a moderate correlation with the CAMCOG-DS (c), indicating that cognitive performance is not dependent on the presence of cognitive decline alone in DS. (d) Lastly, there was a tendency towards higher DSQIID scores in participants with moderate (2) as compared with mild (1) premorbid intellectual disability.

allocation of DSQIID-G questions to two groups in an alternating fashion and subsequent correlation analysis and correction according to the Spearman-Brown formula (Fisseni 1997). Internal consistency was examined by calculating Cronbach's alpha. Test–retest and inter-rater reliability of the DSQIID-G total scores were assessed using the Spearman correlation (data not normally distributed).

Ethical considerations

Written informed consent was obtained from legal representatives of all participants, and oral consent was obtained from all participants. The study was conducted in accordance with the declaration of Helsinki in its latest revision and was approved by a local Institutional Review Body (IRB) (application number 535-15).

Results

Prevalence of cognitive decline in the study population

Of the 86 participants in our study, cognitive decline was detected in 43 (50%) participants (for demographics, see Table 1). Seventeen individuals were diagnosed with DS-AD (19.8%) and seven with MCI (8.3%). Thirteen participants (15.1%) showed cognitive decline due to secondary, mostly psychiatric causes (see Table 1); these patients were markedly younger than the DS-AD/MCI group. In six patients DS-AD could not be diagnosed with sufficient certainty due to one or several significant co-morbidities (see Table 1). There was a tendency towards higher DSQIID-G scores in participants with premorbid moderate intellectual disabilities compared with mild intellectual disabilities (see Figure 1).

Table 2 DSQIID sensitivity and specificity analyses

		Sensitivity		Specificity			
Cut-off score	**Original publication**	**Current study**	**Original publication**	**Current study**	**Original publication**	**Positive LR**	**Negative LR**
No cognitive decline (n = 43) vs. DS-AD (n = 17)							
5	(Silverman *et al.* 2021) (English)	0.94	*0.87*	0.59	*0.8*	2.3	0.10
>7	Current study	0.94		0.76		3.9	0.08
13	(Takenoshita *et al.* 2020) (Japanese)	0.76	*1.0*	0.78	*0.97*	3.48	0.30
20	(Deb *et al.* 2007b) (English)	0.59	*0.92*	0.93	*0.97*	8.0	0.44
No cognitive decline (n = 43) vs. MCI (n = 7)							
1	(Silverman *et al.* 2021) (English)	0.86	*0.89*	0.27	*0.52*	1.2	0.53
5		0.71		0.68		1.7	0.49
>7		0.57		0.73		2.1	0.59
13		0		0.78		0	1.3
20		0		0.93		0	1.1
No cognitive decline (n = 43) vs. cognitive decline due to any cause (n = 43)							
5		0.93		0.59		2.2	0.12
>7		0.90		0.73		3.4	0.13
13		0.62		0.78		2.8	0.49
20		0.43		0.93		5.9	0.62

Direct comparison of different cut-off scores for the DSQIID from our current study as compared with previous validation studies. Sensitivity and specificity analyses concerning Alzheimer dementia in Down's syndrome (DS-AD), mild cognitive impairment (MCI) and cognitive decline of any cause are provided.

LR, likelihood ratio.

Sensitivity and specificity analyses

A cut-off score of >7 based on the total DSQIID-G score provided the best fit between a sensitivity of 0.94 (excellent) and a specificity of 0.58 (moderate) to differentiate DS-AD from the rest of the study population (see Figure 1). In Table 2, we present data on the specificity, sensitivity, positive and negative likelihood ratio based on different cut-off scores derived from the literature (5, 7, 13 and 20), comparing the participants without cognitive decline (n = 43) with DS-AD (n = 17), MCI (n = 7) and cognitive decline due to any cause (n = 43).

Psychometric properties of the DSQIID-G

To further characterise the psychometric properties of the DSQIID-G, we addressed convergent validity and reliability. Feasibility was not examined since this was already investigated in the German version of the NTG-EDSD, which comprises the majority of the DSQIID items (Zeilinger *et al.* 2016).

A correlation analysis in a subgroup of participants where CAMDEX interview data were available (n = 48; no cognitive decline: n = 23; DS-AD: n = 7) yielded a strong correlation between the two measures [r = 0.76 (0.59–0.86); $P < 0.001$], confirming convergent validity. When comparing whether the CAMDEX indicated the presence or absence of cognitive decline at DSQIID-G values of at least 20 points via Fisher's exact test (P = 0.010), a low sensitivity (0.50, 95% CI 0.25 to 0.75) and good specificity (0.89, 95% CI 0.74 to 0.95) was observed. Conversely, the lower cut-off value of >7 points yielded excellent sensitivity (0.92, 95% CI 0.65 to 0.996) and low specificity (0.54, 95% CI 0.38 to 0.70). DSQIID-G total scores further correlated with the CAMCOG-DS cognitive assessment (see Figure 1).

As a measure of internal reliability, split-half reliability yielded a high correlation (r = 0.96; $P < 0.001$). Similarly, Cronbach's alpha was excellent (0.96). Test–retest reliability (n = 25; r = 0.88 95% CI 0.73 to 0.95, $P < 0.001$) and inter-rater reliability (n = 31; r = 0.81, 95% CI 0.64 to 0.91, $P < 0.001$) were also excellent.

Conclusions

With the accelerating development of disease-modifying therapies for AD specifically targeting cerebral amyloid and tau deposits, confirming a diagnosis of DS-AD may soon result in therapeutic consequences beyond symptomatic therapy and care planning. Although people with Down's syndrome, even though representing the largest at-risk population for genetically determined dementia, are still systematically excluded from therapeutic development, the increasing body of knowledge gained from sporadic and autosomal-dominant AD will hopefully enable us to apply novel therapies to DS-AD as well. Therefore, there is a dire need for tools to easily and reliably identify potential candidates for treatment. To this end, this paper presents a detailed psychometric assessment of DSQIID-G specific to this population.

Overall, the DSQIID-G showed good to excellent internal validity and reliability values. A high correlation of DSQIID and CAMDEX-DS interview scores established the convergent validity of the DSQIID-G in the current study. However, a moderate correlation between the actual diagnosis of cognitive decline may reflect limited sensitivity and specificity of the CAMDEX-DS interview alone.

Criterion-related validity showed the best fit between an excellent sensitivity (0.94) against a moderate specificity (0.57) for a total DSQIID-G cut-off score of >7. However, in the past, different studies found different best fit cut-off scores (22, 20, 19, 13 and 5, see Table 2) for sensitivity and specificity. We do not anticipate that these differences are due to translation effects but are best explained by differences in participant selection and the diagnostic criteria applied. In the most recent, retrospective French validation study, DSM-IV criteria were used to diagnose DS-AD. However, an earlier study had shown a low sensitivity of both DSM-IV-TR (56.3%) and ICD-10 (70.3%) dementia diagnostic criteria (Sheehan *et al.* 2015). It is thus possible that less affected patients may not have been classified as having dementia in that study. In the original study that developed the DSQIID based on modified ICD-10 criteria for dementia, patients deemed as suitable for inclusion were mostly identified by local physicians and carers. This raises the possibility that

patients with a suspicion of secondary causes of cognitive decline such as depression may not have been approached in the first place, as well as patients with only subtle clinical features of dementia (Deb *et al.* 2007b).

On the other hand, our findings are in line with a recent validation study of the English version of the DSQIID-derived NTG-EDSD items, which found a similarly low sensitivity for DS-AD (0.421) and MCI (0.056) when applying a cut-off score of 20 points (Silverman *et al.* 2021). This study found a better fit between sensitivity (0.868) and specificity (0.802) when a cut-off score of 5 was used for the total NTG-EDSD DSQIID-adapted items (see Table 2). Similar to our investigation, this study was integrated within a framework to identify liquid and imaging biomarkers of DS-AD and comprised a comprehensive neuropsychological workup and a consensus conference to arrive at a diagnosis of DS-AD/MCI. Interestingly, this study did not report on secondary causes of cognitive decline, implying that such patients were probably not included although this is not explicitly stated in the inclusion criteria published. This difference in population composition may well explain the higher specificity of the DSQIID-derived NTG-EDSD items in the study by Silverman *et al.* as compared with our investigation of the DSQIID-G. In fact, the specificity to differentiate DS-AD from healthy controls only was 0.76 in our study.

Of note, in the five DS-AD patients with low DSQIID-G scores (4–13 points) in our study, liquid/imaging biomarkers aided in making a diagnosis of DS-AD in all but one case, arguing for a proactive diagnostic approach in mildly affected patients.

It is worth emphasising that DSQIID is a screening instrument and not a diagnostic tool. As a screening instrument, maximising sensitivity is preferrable, as the false-positive diagnoses detected because of low specificity will be excluded subsequently through a thorough clinical assessment. Therefore, we recommend a lower score of >7 or similar for screening purposes rather than a higher score of 20 or 22. It is also worth emphasising that DSQIID items were developed using the reporting of early symptoms of dementia by the caregivers of people with DS. Therefore, unlike other instruments, DSQIID does not measure cognitive decline itself or impairment in adaptive behaviour. This is reflected by the low sensitivity and specificity of DSQIID-G to detect MCI in the current study. DSQIID will not detect dementia until the early symptoms are manifested.

Excellent inter-rater and test–retest reliability scores are reassuring, given that one of the criticisms of observer-rated scales in general is the difference in reporting by different observers/caregivers. This is unlikely to happen with the DSQIID-G. An excellent internal consistency confirms DSQIID-G's efficacy.

Although current data are robust and the findings are promising, the readers have to be aware of certain limitations. First, the total number of people with confirmed DS-AD is small. We tried to address this issue by maximising diagnostic accuracy through thorough neuropsychological testing, routine exclusion of differential diagnoses, the addition of CSF, MRI and PET studies as tolerated and a consensus approach to the diagnosis of cognitive decline. Furthermore, DSQIID questionnaires were completed by caregivers before they visited our outpatient department, resulting in a relevant number of cases with (mostly singular) missing values. Thus, the application of the DSQIID investigated in this study was that of a screening tool, and the data have to be interpreted as such. Another issue is that from our dataset, possible unspecific age effects cannot be excluded given the expected older age of the DS-AD subset as compared with those without cognitive decline. However, at least within the latter group (age range 18–53) we found no correlation between age and DSQIID-G total score [$r = -0.11$ (-0.41 to 0.22), $P = 0.51$]. Therefore, we assume that a potential effect of age should not impede the tool's usefulness when screening for cognitive decline.

Furthermore, the number of participants with MCI is low. Given the difficulty of diagnosing the condition in people with intellectual disabilities, particularly in severely and profoundly affected patients, data have to be interpreted with caution. Given the small number of participants with severe/profound intellectual disability, the utility of DSQIID-G among these individuals remains unknown, as well as its efficacy in those with intellectual disabilities not caused by DS. A tendency towards higher DSQIID-G values in premorbid moderate as compared with mild intellectual disabilities was noted in this study, which may be explained by a higher percentage of participants with acquired cognitive decline in the

'moderate' group (60% vs. 40%). Of note, this difference was driven by secondary causes of cognitive decline (moderate vs. mild intellectual disabilities: 26% vs. 10%), while the number of DS-AD patients was similar in both groups (moderate vs. mild intellectual disabilities: 17% vs. 13%). Thus, our data do not indicate a higher prevalence of DS-AD in patients with moderate intellectual disability, although it has to be stated much larger cohorts would be required to confirm this finding.

In summary, the DSQIID-G proved to be an efficient screening tool for AD in the DS population, although other causes of cognitive decline such as psychiatric disorders must be considered especially in younger patients. Limitations apply in very early disease stages, underscoring the need for valid biomarkers for early detection in this population.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data availability statement

Data are available from the corresponding author upon reasonable request.

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