Title: Test accuracy of informant based cognitive screening tests for diagnosis of dementia and multi-domain cognitive impairment in stroke

Running title: Informant based cognitive screening

Word counts

Abstract:202 words

Paper:4,494 words

Keywords:cognitive impairment, dementia, informant assessment, sensitivity, specificity, stroke

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Background and purpose: Post stroke cognitive assessment can be performed using standardised questionnaires designed for family or care-givers. We sought to describe the test accuracy of such informant based assessments for diagnosis of dementia/multi-domain cognitive impairment in stroke.

Methods: We performed a systematic review using a sensitive search strategy across multidisciplinary electronic databases. We created summary test accuracy metrics and described reporting and quality using STARDdem and QUADAS tools respectively.

Results: From 1432 titles, we included 11 studies. Ten papers used the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Four studies described IQCODE for diagnosis of post-stroke dementia (n=1197); summary sensitivity:0.81 (95%CI:0.60-0.93); summary specificty:0.83 (95%CI:0.64-0.93). Five studies described IQCODE as tool for predicting future dementia (n=837); summary sensitivity:0.60 (95%CI:0.32-0.83); summary specificity:0.97 (95%CI:0.70-1.00). All papers had issues with at least one aspect of study reporting or quality.

Conclusions: There is a limited literature on informant cognitive assessments in stroke. IQCODE as a diagnostic tool has test properties similar to other screening tools, IQCODE as a prognostic tool is specific but insensitive. We found no papers describing test accuracy of informant tests for diagnosis of pre-stroke cognitive decline, few papers on post-stroke dementia and all included papers had issues with potential bias.

Introduction

International guidelines recommend that we assess all stroke survivors for cognitive disorders, however there is no consensus on the optimal method of assessment.[1,2] A usual first step is to assess with a direct cognitive screening tool such as the Montreal Cognitive Assessment (MoCA). These tools have utility but diagnostic accuracy is not perfect.[3] In the context of stroke, completion and assessment of such tools is complicated by stroke related impairments and physical illness.[4,5]

An alternative or complementary approach is to seek a history suggestive of cognitive problems from family or caregivers.[6] Using collateral information sources to describe medium to longer term cognitive change is particularly attractive for stroke settings as the informant view should be less subject to variation from stroke related impairments; should not be biased by educational level or cultural factors and offers potential for describing pre-stroke cognition in the acute phase of stroke.[7] Informant assessment can be operationalised using a validated questionnaire such as the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE).[8]

Taking IQCODE as an exemplar informant assessment, in the original validated versions of the scale, it asks a series of questions regarding how cognition and functioning have changed over a ten year period. Individual item scores are collated to give a summary score. Various IQCODE score cut-offs have been described to determine clinically important cognitive decline and there is no consensus on the optimal cutpoint.[7,8] Some have suggested that a high threshold, for example

IQCODE >3.6, should be used to determine dementia, while a more inclusive threshold should be chosen to define any cognitive impairment. This approach has been used in many important stroke-cognition epidemiological studies.[9-11]

Other informant assessments include the eight item interview to differentiate ageing from dementia (AD-8)[12], a shorter questionnaire that seems to have favourable properties compared to IQCODE[13], and the Blessed Dementia Scale (BDS); a multidomain assessment that describes change in functional ability, activities of daily living and personality.[14] Some assessments include an informant component. For example, the GP-Cog is a short screening test designed for use in primary care, comprising a direct to patient assessment complemented by six informant questions describing change over time.[15] None of these informant based tests have been specifically designed for use in stroke.

Informant based assessments can be used for three broad purposes in stroke care: a)the tools can be used to assess for pre-stroke cognitive decline; b)the tools can be used to assist in the process of diagnosing post-stroke cognitive impairment; or c)the tools can be used as a prognostic aid, identifying a period of cognitive decline that may predict future dementia. In situation c) the IQCODE is being used to detect early cognitive change not sufficient to warrant a label of dementia but that may predict risk of future dementia states.(Figure 1)

We sought to collate the published evidence describing test properties of informant based cognitive assessments when used in stroke settings.

Methods

We performed a systematic review of published literature following best practice guidance in conduct and reporting.[16,17] All aspects of searching, data extraction and quality assessment were performed by two independent researchers (AM, NM) with access to a third arbitrator (TQ) as needed. We created a protocol describing the search strategy and registered this with the PROSPERO database:PROSPERO 2014:CRD42014014554 (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014554).

Our primary aim was to describe the accuracy of informant based questionnaires for diagnosis of dementia or multi-domain cognitive impairment in stroke-survivors.

Our **index test** was any standardised informant based cognitive screening assessment. We did not specify how the assessment was performed. We pre-specified subgroup analyses based on possible uses of informant assessment: a)informant assessment (usually performed in the acute stroke period) for pre-stroke cognitive issues; b)informant assessment for contemporaneous assessment of post-stroke dementia; c)informant assessment (usually performed in the acute period) for predicting future cognitive issues (delayed verification).[18]

Our **target condition** was dementia or multi-domain cognitive impairment. This broad classification recognises that a diagnosis of clinically important cognitive issues can be made without necessarily assigning a dementia label. We accepted clinical diagnosis of dementia made using any recognised classification system and accepted a diagnosis of cognitive impairment based on multi-domain neuropsychological assessment.

Our **population** of interest was stroke-survivors. We operated no exclusions based on time since stroke or healthcare setting. In studies with mixed populations we included those with greater than 70% stroke survivors.

We developed search terms using a concepts based approach, combined with a validated “stroke” filter. We used Medical Subject Headings and other controlled vocabulary. We included search terms relating to commonly used informant based cognitive assessments (IQCODE, AD-8, GP-Cog, Blessed dementia scale) as well as generic terms relating to cognitive testing. We searched across multiple, cross disciplinary electronic databases from inception to April 2015. A collaborator (YF) performed a focussed search of Chinese literature databases. We hand searched conference proceedings from international stroke meetings, full search strategy is detailed in supplementary materials.

We screened all titles generated by initial searches for relevance. Abstracts were assessed and potentially eligible studies reviewed as full manuscripts against inclusion criteria. We checked reference lists of relevant studies and reviews for further titles, repeating the process until no new titles were found.

We extracted data to a study specific pro-forma. For informant scales with various cut-points we extracted data for all thresholds available, for studies where IQCODE was assessed at varying times post stroke we extracted data for each time point. We created tables describing characteristics of included studies, characteristics of informant assessments used and characteristics of patients included in studies. Where possible, for test accuracy data, we constructed two by two contingency tables to allow calculation of sensitivity, specificity and predictive values against a dichotomous outcome of cognitive impairment/no cognitive impairment. Where data were not immediately accessible for the paper we contacted lead authors.

Where data allowed, we calculated sensitivity, specificity, and corresponding 95% confidence intervals (95% CI) on test accuracy forest plots (RevMan 5.1, Cochrane Collaboration) and pooled test accuracy data using the bivariate approach with a bespoke macro.[19] We did not formally assess publication bias, as standard tests such as “funnel plots” are not appropriate and there is no consensus on the optimal measure of such bias in test accuracy review.

We assessed risk of bias and generalizability using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2)[20] tool. QUADAS-2 assesses domains of patient selection; application of index test; application of reference standard and patient flow/timing. We previously created and validated a series of anchoring statements for QUADAS-2 for test accuracy work with a dementia reference standard.[21] We assessed quality of reporting using the dementia specific extension to the Standards for Reporting of Diagnostic Accuracy STARDdem[16] tool.

STARDdem assesses reporting of key items for dementia test accuracy work across the introduction, methods, results, discussion sections of a manuscript. Full details of scoring criteria are given in supplementary materials.

Results

After deduplication, we screened 1,432 titles.(Figure 2) Following assessment of abstract or full paper we included 11 studies in our review.[22-32] Ten studies detailed the IQCODE, including n=1994 participants (n=465 [23%] with dementia).[22-31] One study detailed the BDS, including n=220 patients with data (n=93 [42%] with cognitive impairment).[32]

There was substantial study heterogeneity. Across the included studies informant assessments were used for a variety of purposes across various settings, with varying cut-points.(Table 1 and supplementary materials) The reporting around application of IQCODE was poor for several studies and it was not clear if a validated form of the questionnaire was used (n=3 studies); the time period over which IQCODE retrospective review was performed (n=4 studies) or which informants were used (n=3 studies).(supplementary materials) The generalisability of the patient populations used to assess IQCODE was variable. Where data were reported there were substantial baseline exclusions and included patient were young with relatively mild stroke.(supplementary materials)

Pre-stroke dementia: No study described test properties of assessments for the diagnosis of pre-stroke cognitive decline versus a reference standard for clinical diagnosis.(Table 1)

Contemporaneous diagnosis of post-stroke dementia: For IQCODE (4 papers, n=1197 participants)[23-26] summary test metrics were sensitivity:0.81 (95%CI:0.60-0.93; range:0.33-0.88) and specificity:0.82 (95%CI:0.64-0.92; range:0.63-0.98).(Figure 3 and Table 2)

Delayed verification/prognosis: For IQCODE (5 papers, n=837 participants)[26-30] summary test metrics were sensitivity:0.60 (95%CI:0.32-0.83; range:0.25-0.93) and specificity:0.97 (95%CI:0.70-1.00; range:0.66-1.00).(Figure 3 and Table 2) Where the approach to analysis was described, most papers assessed cognitive decline in the immediate period post-stroke and described the association with longer term dementia diagnosis.(supplementary materials)

The BDS had sensitivity 60% and specificity 76% (PPV:0.73; NPV:0.64) for diagnosis of any memory related impairment.[32]

No papers scored “low risk of bias” on all QUADAS-2 items. Areas of concern were around patient flow/loss to follow up (with substantial loss of IQCODE data, where reported) and the application of the IQCODE (risk of incorporation bias and using IQCODE in a non-validated way).(Figure 4 and supplementary materials) There were issues with reporting; no papers reported all details as recommended in STARDdem, particular problems were around reporting of results and details of statistical analyses. For example, two papers described blinding between those

applying the informant test and those performing clinical assessment; one paper described how missing or indeterminate results were handled in statistical analyses and no papers described test reliability or reproducibility.(supplementary materials)

Discussion

Although there are many informant based cognitive assessment tools available[6], few have been validated in stroke. Only the IQCODE had more than one paper describing stroke test properties and there was substantial heterogeneity in test accuracy reported. Across the included studies there were also issues with study quality and reporting and so we need to be cautious in the interpretation of these data.

Accepting these caveats we can draw some conclusions on properties of IQCODE in stroke. Across all studies IQCODE showed a pattern of specificity but high false negative rate. IQCODE for assessing post-stroke dementia had reasonable test accuracy. In practice, IQCODE or similar would often be used along with another direct to patient cognitive test, however we found no studies validating this approach.

IQCODE early after stroke has been used as a tool to predict future dementia. We accept that the use of retrospective assessment to predict future dementia is counter intuitive and it is interesting that a number of papers used this approach. When used for this purpose a positive IQCODE is likely to be associated with dementia but many that develop dementia will have an initial IQCODE assessment below the threshold

set for this purpose (specific but lacks sensitivity). This pattern of trade-off between sensitivity and specify changed when IQCODE was used at longer periods after the stroke event. The interpretation of these data is complicated by limited reporting around how the IQCODE was applied and this was apparent in our assessments of quality and reporting.

Informant assessments such as IQCODE are often used in practice and in research to assess pre-stroke cognition. There are many excellent examples of describing pre-stroke cognition using IQCODE.[33,34] While this approach makes intuitive sense, we found no published reports that validate the test accuracy of this use of IQCODE.

Our data adds to the literature on test properties of brief cognitive assessments in stroke. The accuracy of IQCODE for diagnosis of post stroke dementia was similar to summary metrics for other direct to patient cognitive assessments in stroke.[1] There is no ideal cognitive test for use with stroke populations. Choice of test needs to consider accuracy but also the purpose of the testing and issues such as feasibility.[35] Although based on a self-completion questionnaire, we should not assume feasibility and acceptability of IQCODE. We note the high non-completion rates of IQCODE in many of these studies, reminding us that IQCODE requires a suitable informant and that the informant has to understand and complete the questionnaire. There are some data in non-stroke settings to suggest that availability of an informant when accessing healthcare is associated with abnormal cognition.[36] IQCODE and other informant assessments may be complicated where a spouse or caregiver also has cognitive issues. In some centres, informants have a

brief cognitive screen to assess their suitability to complete questionnaires such as IQCODE. It is unfortunate that no assessment of informants was made in any of the papers included in this review.

Interpreting our data on IQCODE we should remember that IQCODE was developed for assessing dementia in community dwelling older adults and there are many reasons why the questionnaire may not work well in stroke. Certain IQCODE items may be difficult to score in the context of stroke, for example the IQCODE question on using gadgets may give false positives for stroke-survivors with physical disability but no cognitive deficit. The memory based focus of IQCODE may be less appropriate in vascular cognitive impairment syndromes, where executive function deficits may predominate. Finally, early physical recovery that can occur following stroke may be wrongly scored as positive cognitive change on IQCODE, a situation that would not be seen in Alzheimer's disease.

A particular issue in our "quality" assessment was around the application of the IQCODE. An issue with IQCODE is that it may be used in practice to inform the diagnostic formulation. There were included papers that risked such incorporation bias, comparing IQCODE to a reference standard of clinical diagnosis where the clinical diagnosis included IQCODE data. The generalisability of included populations was limited and certain studies excluded exactly those patients where IQCODE may be useful (aphasia, coma). Problems of selection bias in studies of post stroke cognition are not unique to IQCODE.[4]

It is interesting to note how the use of IQCODE in stroke deviates from that described in the original IQCODE derivation and validation work. The original IQCODE was designed to describe cognitive decline over a ten year period. This approach is better suited to assess a progressive neurodegenerative condition such as Alzheimer's disease, rather than an acute event such as stroke. In practice, assessors may use the IQCODE questions to explore cognitive change since a stroke event which may not necessarily be ten years past. Some papers also use repeated IQCODE assessments at endpoints. Altering the IQCODE in this way is not validated and so many papers were scored as potential risk of bias/poor external validity due to this issue. Where IQCODE covers a ten year period that includes a stroke event, the IQCODE result gives information on general cognitive decline but does not tell us that this decline relates purely to stroke. These concerns should not dissuade clinicians and researchers from using informant based assessments but suggest that more work is needed around tailoring informant assessments to fit post stroke populations. The data from our review do not allow us to give definitive guidance on when IQCODE should be applied. To avoid recall biases, we would suggest that informant assessment for pre-stroke dementia be performed close to the stroke event but with sufficient time to allow the informant to adjust to the diagnosis of stroke in their relative or friend.

Strengths of our study were the comprehensive literature search, including access to non-English language electronic databases. We acknowledge the between study heterogeneity and issues with risk of bias, generalisability and reporting. To allow for

data synthesis we accepted any clinical diagnosis of a cognitive syndrome as our reference standard. As a result of this, the summary estimates we offer are illustrative and should not be interpreted as definitive test accuracy metrics. Number of included papers was too small to allow meaningful sensitivity analyses around these issues.

Our data do not allow us to make a definitive statement on the “best” available informant assessment. While there are major limitations to the use of IQCODE, using this tool is probably better than no informant assessment at all. An important finding is the clinical-research gap around this form of cognitive testing. Future studies should consider the test properties of IQCODE and the other available informant assessments. A focus on use of informant assessments for pre-stroke cognitive states and on combining informant questionnaires with other direct to patient tests is needed.

Acknowledgements: We are grateful to authors who responded to queries or offered to share data and to Doctor Rachael MacIsaac, Stroke Trials Statistician, for running analyses.

Disclosures: None

Funding:TJQ is supported by a Joint Stroke Association/Chief Scientist Office Senior Clinical Lectureship. STP is supported by the Oxford NIHR Biomedical Research Centre.

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Figure 1. Describing three differing approaches to informant assessment in stroke care

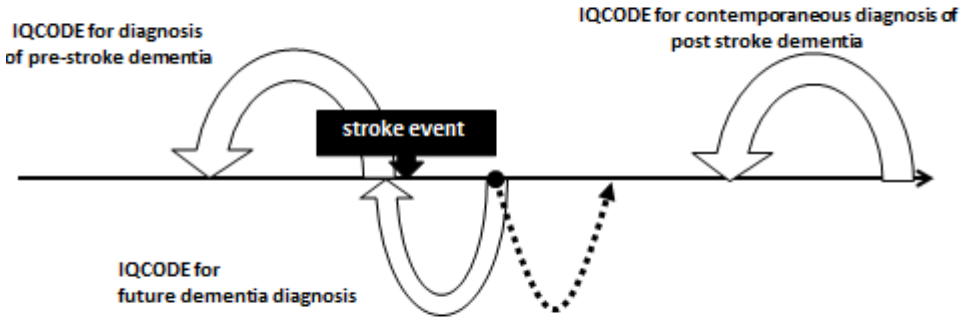


Figure describes potential uses of informant questionnaires for cognitive assessment in stroke. IQCODE can be used in the acute stroke period to assess for pre-stroke cognitive decline or at any period post-stroke to assess for cognitive impairment at that time. IQCODE has also been used to predict those likely to have a later dementia diagnosis.

Figure 2. Flow diagram detailing search strategy and results

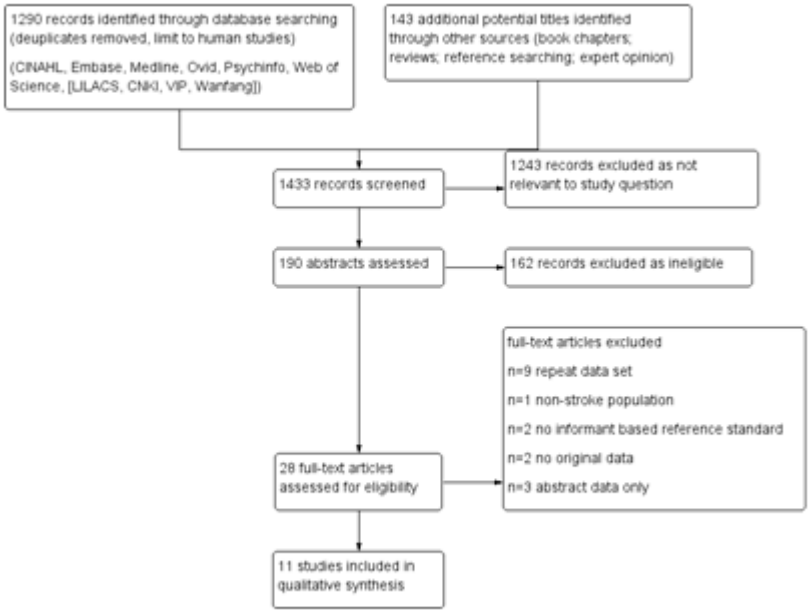
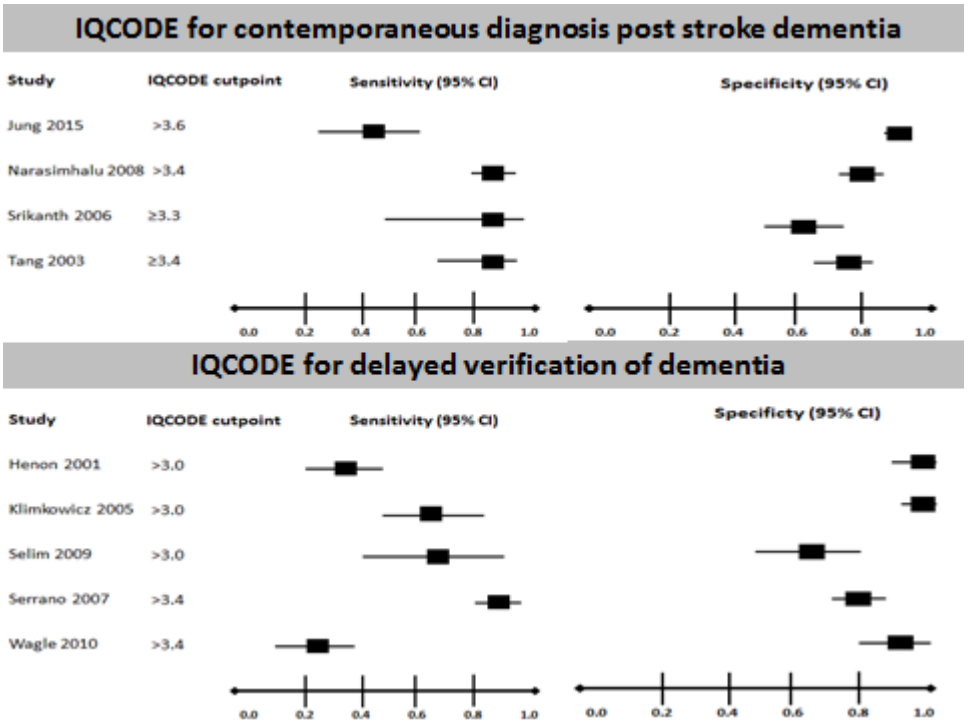


Figure 3. Forest plots of sensitivity and specificity in relation to IQCODE for diagnosis of dementia



Forest plots detail IQCODE for contemporaneous diagnosis (top) and IQCODE for "prognosis" (bottom). For the delayed verification studies (prognosis), where data were presented at varying time-points we used one year data or closest.

TP,FP,FN,TN:true positive,false positive,false negative, true negative

Figure 4.QUADAS-2 based assessment of bias and applicability

Explanations of QUADAS-2 domains are offered in supplementary materials

Study	Setting (recruitment)	Timing of diagnosis (post stroke)	Index test(s)	Diagnostic test(S)	Diagnostic test rater
Informant scale for contemporaneous diagnosis of dementia					
Jung* 2015[23]	Community	3 month	IQCODE (Korean)	VCI-HS	Neuropsychologist
Tang 2003[24]	ASU	3 month	IQCODE (Chinese)	DSM-IV	Stroke neurologist
Starr 2000[22]	Community	4.3 years	IQCODE	NPB	Neuropsychologist
Srikanth 2006[25]	Community	3 month	IQCODE16	DSM IV	Neuropsychologist
Narasimhalu 2008[26]	N/A	N/A	IQCODE16 (Chinese)	DSM IV	Adjudication panel
Informant scale for diagnosis of pre-stroke dementia					
No relevant papers found on systematic literature review					
Informant scale for prospective (delayed verification) diagnosis of dementia					
Henon 2001[27]	ASU	6, 12,24,36 months	IQCODE (French)	ICD-10	Adjudication panel
Klimkowicz 2005[28]	ASU	3 month	IQCODE (Polish)	DSM-IV	Stroke neurologist
Serrano 2007[30]	ASU	3, 12, 24 month	IQCODE16 (Spanish)	DSM NPB	Neurologist
Wagle 2010[31]	Rehab	13/12	IQCODE (Danish)	RBANS	N/A
Selim 2009[29]	ASU	<18/12	IQCODE (Egyptian)	ICD 10	Neurologist

Table 1. Summary of included studies

NPB=Neuropsychological battery, GCF=General Cognitive Factor; RBANS=Repeatable Battery for the assessment of neuropsychological status; DSM=Diagnostic and Statistical Manual; ICD=International Classification of Disease; VCI-HS=vascular cognitive impairment harmonisation standards

ASU=Acute Stroke unit; Rehab=Rehabilitation setting; N/A=not available(unknown/not reported

**Data from extended abstract and parent studies*

Table 2. Results of included studies

Study	"n" included	"n" (%) with dementia	"n" (%) not completing IQCODE	Index test (threshold)	Summary Results	
Informant scale for contemporaneous diagnosis of dementia						
Jung 2015[23]	353	45	?	IQCODE ≥3.6	Sens 45% Spec 96%	PPV:0.63 NPV:0.92
Tang 2003[24]	189	24	108 (36%)	IQCODE ≥ 3.40	Sens:33% Spec:98%	PPV:0.34 NPV:0.98
Starr 2000[22]	35	N/A	14 (29%)	N/A	Correlation with GCF (r=-0.42, p=0.016)	
Srikanth 2006[25]	79	8	20 (20%)	IQCODE ≥ 3.30	Sens: 88%; Spec:63%	PPV:0.21 NPV:0.98
Narasimhalu 2008[26]	576	169	?	IQCODE > 3.38	Sens:86% Spec:78%	PPV:0.62 NPV:0.93
Informant scale for diagnosis of pre-stroke dementia						
No relevant papers found on systematic literature review						
Informant scale for prospective (delayed verification) diagnosis of dementia						
Henon 2001[27]	127 at 6/12 104 at 36/12	36 at 36/12	56 (22%)	IQCODE ≥ 78	Sens:30%; Spec:100% (6/12)*	PPV:1.0 NPV:0.74
Klimkowicz 2005[28]	142	26	?	IQCODE ≥ 104	Sens: 66%; Spec:100%	PPV:1.0 NPV:0.92
Serrano 2007[30]	167 at 12/12 142 at 24/12	44 at 12/12 33 at 24/12	33 (10%)	IQCODE > 3.35	Sens:93% Spec:81% (12/12)	PPV:0.55 NPV:0.98
Wagle 2010[31]	104	52	8 (8%)	IQCODE > 3.44	Sens:25% Spec:92%	PPV:0.76 NPV:0.55
Selim 2009[29]	66	28	8 (9%)	IQCODE ≥ 78	Sens:69% Spec:66%	PPV:0.39 NPV:0.87

sens=sensitivity; spec=specificity; PPV/NPV=positive/negative predictive value

IQCODE thresholds are given as presented in primary paper (some are average score and some are raw-score); where more than one IQCODE threshold employed, the primary cutpoint is described.