# Development and Validation of the Alzheimer's Questionnaire

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# DEVELOPMENT AND VALIDATION OF THE ALZHEIMER'S QUESTIONNAIRE

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Abstract

This series of studies was carried in order to develop and validate the Alzheimer's Questionnaire (AQ). The underlying rationale for the creation of the AQ was to provide clinicians with a brief and easy-to-use informant-based assessment of symptoms associated with Alzheimer's disease (AD). Initial studies of the AQ found that it has both high sensitivity and high specificity for differentiating individuals with AD and its prodrome, amnestic mild cognitive impairment (MCI). The AQ's accuracy in identifying MCI was explored further in an additional study which sought to determine which items on the AQ were best predicted the presence of MCI. Four items were strongly associated with MCI which were: repetition of statements and/or questions [OR = 13.20 (3.02, 57.66)]; trouble knowing the day, date, month, year, and time [OR = 17.97 (2.63, 122.77)]; difficulty managing finances [OR = 11.60 (2.10, 63.99)]; and decreased sense of direction [OR = 5.84 (1.09, 31.30)]. Concurrent validity was established through another study which found that the AQ correlated moderately with the MMSE (r = -0.56) and MoCA (r = -0.46) while a strong correlation (r = 0.79) was found with the Clinical Dementia Rating Sum of Boxes (CDR-SOB). Additional work found that the AQ correlated well with formal neuropsychological measures of episodic memory and executive function. Longitudinal analyses found that was AQ was a significant predictor of clinically meaningful decline as measured by the changes in CDR Global Score (OR = 1.20, 95% CI: 1.09, 1.32; $p<0.001$). In addition, AQ identified clinically meaningful change among MCI cases at a greater rate (24%) than the MMSE (17%). This series of studies demonstrates that the AQ is an accurate instrument that correlates well with known measures of MCI and AD.

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**Author's Declaration**

I declare that all material contained in this thesis is my own work. Although this thesis is based on several peer-reviewed journal articles in which there were several co-authors, the compilation, integration, and interpretation of these studies represents my own work.

i. Preface – Author's Contributions to the Published Works

The published works contained in this thesis are the result of a collaboration and mentorship that developed between myself and Dr. Marwan Sabbagh in February 2010. In 2007, Dr. Sabbagh received a grant to conduct a pilot study of the Alzheimer's Questionnaire (AQ), an instrument he developed. Data from three clinical sites was collected, analyzed, written-up, and submitted for publication without success. Dr. Sabbagh challenged me to re-analyze the pilot data, significantly revise the manuscript, and attempt to submit it again for publication. With his mentorship and encouragement, we submitted a new version of the pilot study to *Journal of Alzheimer's Disease* in June 2010 which was subsequently accepted for publication in August 2010. Over the next year, we began working the on validation study in which we added additional cases to the pilot data to achieve a sample size of 300 (100 Normal Control, 100 Mild Cognitive Impairment, 100 Alzheimer's Disease). For this study, Dr. Sabbagh once again charged me with analyzing the data and writing the manuscript. After submitting the paper to four different journals, it was finally accepted for publication in *Age and Ageing*, the official journal of the British Geriatrics Society.

Concurrent to the work on this validation study, I thought of an idea for an additional analysis that would look at which items on the AQ best differentiated normal cognition from mild cognitive impairment. After putting together an abstract of the hypothesis with some preliminary analyses from the validation study data, Dr. Sabbagh enthusiastically supported me to follow through with the study. The analysis and writing of this paper was done concurrently with that of the validation study and the "item analysis study", as we referred to it, was accepted for publication in *BMC Geriatrics* at around the same time that the validation study was accepted for publication.

In 2012, after three successful publications with the AQ, Dr. Sabbagh was unsure about what direction to take regarding additional research on the instrument. The AQ had

recently been added to the battery of annual assessments in a large observational cohort study at our institute and after some thought, I proposed that we conduct a concurrent validity study to show how well the AQ correlated with established clinical measures of cognition and function in Alzheimer's disease. By this time, Dr. Sabbagh and I had developed a very strong rapport with each other so it was understood by both of us that I would again undertake the data analysis and drafting of the manuscript. The paper was accepted into the first journal we submitted it to, *Alzheimer's Disease and Associated Disorders*. It was at this point that Dr. Sabbagh allowed me a great deal of autonomy in terms of developing the hypotheses for further studies.

The next study was very straight-forward and looked at how well the AQ correlated with established neuropsychological measures. For this study, Dr. Sabbagh also gave me the opportunity to work with and mentor a medical school student, Katherine Budolfson. Katherine and I collaborated together on the text of the manuscript and I also demonstrated the statistical analyses to her. This study was accepted for publication in *Journal of Alzheimer's Disease*.

The final study in this thesis looked at the longitudinal change of the AQ in cognitively normal, mild cognitive impairment, and Alzheimer's disease cases. In this analysis, I collaborated with Dr. Kewei Chen of the Banner Alzheimer's Institute on the statistical approach. His guidance was crucial to the success of this study and his mentorship help me improve my statistical knowledge and skills immensely. In early 2015, this paper was accepted for publication in *Alzheimer's Research and Therapy*.

In general, the published works on this thesis are largely my own work which included collaborations from other clinicians and research coordinators who are listed as co-authors on these papers.

## 1. Introduction

### *1.1 Overview of Alzheimer's Disease*

Alzheimer's disease (AD) was first characterised pathologically in the early 20th century based on the neuropathological findings reported by Alois Alzheimer in a patient with significant cognitive and functional impairment. At autopsy, tissue samples from this patient's cortex showed significant cortical degeneration, neuronal loss, and dense tangles of argyrophyillic strands. This constellation of neuropathological findings is now known to be derived from the deposition of amyloid plaques and neurofibrillary tangles which are now considered the neurpathological hallmarks of AD[1]. Although the neuropathological definition of AD has been well-characterised through more specific refinements in the 1990's[2-4], the clinical characterisation of AD continues to evolve.

The initial clinical manifestation of AD is often characterised by deficits in short-term memory which can include symptoms such as repeating statements and questions and difficulty remembering statements and instructions within a short period of time[5]. Other symptoms include difficulty with naming common objects and disorientation in familiar areas. The severity of AD is commonly stratified into a three-stage scheme consisting of mild, moderate, and severe stages[6]. Although other standardised schemes use up to seven stages[7], the three-stage scheme may be more pragmatic for the purposes of diagnosis and treatment. The primary distinction between the mild, moderate, and severe stages is an individual's functional status, although cognitive status is also given equal consideration when determining the stage of AD[8]. Individuals with mild AD often have a relatively high level of functioning in terms of daily activities such as grooming and basic household tasks[6]. In the moderate stage more pronounced functional deficits are often noted and it is in this stage where individuals may begin to demonstrate significant difficulty with basic activities in the areas of bathing and grooming while more difficult tasks in the areas of finance and

transportation are taken over by a caregiver, usually a spouse, significant other, or child of the individual[6]. In the severe stage both cognitive and functional abilities are impaired to a degree that the individual is often completely dependent on others for grooming, bathing, and eating. It is in this stage that individuals often lose the ability communicate and become bed-ridden until the time of their demise[6].

In most industrialised countries, AD is now considered to be a major public health problem in terms of its impact on individuals, their caregivers, and society at large. Currently it is estimated that there are between 4.5 and 5.5 million cases of AD in the United States (US)[9] and 857,600 cases in United Kingdom (UK)[10]. By the year 2050 it is estimated that the prevalence of AD will be between 11 and 16 million in the US while prevalence in the UK is projected to be approximately one million by the year 2025. These estimates have significant implications for the utilisation of healthcare resources and pose a significant challenge for governments' abilities manage the extraordinary economic impact that caring for these individuals will require. In 2015, total healthcare costs for the treatment and care of AD in the US was 217 billion USD (177,158,800,000 GBP). In the UK for the year 2014, these costs amounted to 26 million GBP.

The implications of the societal and economic impact of AD will be staggering if more effective methods of diagnosis and treatment are not implemented. In the US, the most recent drug to receive regulatory approval for use was memantine which received its approval for the treatment of moderate to severe AD in 2004. Since then, no additional drugs have been approved for the treatment of AD by the US Food and Drug Administration (FDA). In fact, many therapies that demonstrated efficacy in early-phase clinical trials failed to show a clinically meaningful benefit in large-scale efficacy trials[11]. A variety of reasons have been put forth as to why so many of these clinical trials failed: lack of decline in the placebo group[12], lack of sensitivity to change in primary outcome measures[13], and significant

variability between clinical sites participating in the trials[14]. Others have noted that biological markers used in some of the trials indicated that AD pathology did decrease during the treatment phase despite the absence of clinically meaningful change[15]. This finding has prompted many to believe that treatment for AD must be initiated prior to the onset of clinical symptoms. As a result, the field has begun to shift its attention to a classification referred to as mild cognitive impairment (MCI) which is thought to represent the prodromal stage of AD.

*1.2 Overview of MCI*

Petersen et al[16] published the first set of clinical criteria to be used in the diagnosis of MCI. These criteria were derived from a finding derived in the Canadian Health Study[17] which found that individuals with a Global Deterioration Scale (GDS)[7] score of three were significantly more likely to develop AD than those with lower GDS scores. These individuals were thought to be in a transitional stage between normal age-related cognitive changes and AD. The MCI criteria proposed by Petersen et al[16] provided more specificity on the psychometric identification of these individuals using the following criteria: a) individuals demonstrate significant subjective changes in cognition via self-report or informant-report, b) have an absence of functional impairment, and c) demonstrate memory test scores that are 1.5 standard deviations below expected performance given their age and education and level. Petersen and colleagues also reported that the annual rate of conversion from MCI to AD was approximately 15%.

Since the publication of these criteria, several refinements have been made in order to provide more specificity with regard to those at risk for developing AD[18]. As a diagnostic entity, MCI is divided into two forms, amnestic (aMCI) and non-amnestic (naMCI). This subdivision was created in order to differentiate between individuals who demonstrate

impairments in memory as opposed to other cognitive domains such as attention, language, visuospatial perception, and complex reasoning/planning (also referred to as executive functions). The aMCI classification is used to represent individuals thought to be at the highest risk for developing AD while the naMCI classification is thought to represent cognitive dysfunction resulting from other non-AD dementia etiologies. Both the aMCI and naMCI classifications can be subdivided into single and multiple domain entities in order to further describe those who demonstrate impairment in only one cognitive domain or multiple cognitive domains.

*1.3 Epidemiology of MCI*

In a recent study by Knopman and colleagues[19] the prevalence of MCI was 21% in a subset (n = 6,471) of individuals who had been part of a larger longitudinal cohort. Of these MCI cases, AD was the primary or secondary etiology of impairment in 75% of these individuals. Additional evidence using pooled data from nine studies in varying geographical regions found a crude MCI prevalence of 5.9%, however the reported prevalence from each of the studies used in the analysis ranged from 5% to 37.6%[20]. In the same study, the prevalence of aMCI was 2% while the prevalence of naMCI was 3.9%[20]. Reported incidence rates of MCI have ranged from 27.7%[21] to 70%[22]. Chen et al[23] report that the progression rate from normal cognition to MCI is approximately 30% in a clinic-based sample while a substantially lower progression rate of 5% was found in a community-based sample. This difference in progression rates is likely the result a selection bias that is inherent in clinical populations as individuals with self-reported cognitive changes or a family history of AD more likely to be seek preventative or therapeutic interventions relative to the general population. Although individuals who receive a MCI diagnosis are more likely to progress to

AD, there is substantial evidence indicating that these individuals may revert to normal cognitive status in subsequent assessments[24].

A number of different biological, demographic, and environmental risk factors for MCI have been identified. Older age, fewer years of formal education, having at least one copy of the APOE ε4 allele, personal history of type II diabetes, and personal history of stroke have all been implicated as risk factors for MCI[25]. Other studies have also reported on several vascular risk factors for MCI such as history of heart failure[26], hypertension[27], hyperlipidemia[27], and coronary artery disease[27]. Others have also found that occupational exposure to pesticides associated with the development of AD[28] which has been supported by animal studies demonstrating that exposure to several different pesticides was associated with the development of AD pathology[29]. A recent systematic review by Killin et al[30] found that the evidence for pesticide exposure as a risk factor is strong while there is moderate evidence linking air pollution, aluminum, silicon, selenium, vitamin D deficiency, and electric and magnetic fields with an increased risk for AD.

Other studies have reported results for protective factors. Boyle et al[31] report that individuals reporting greater purpose in life had a substantially lower risk of developing MCI. In terms of occupational factors, there is evidence suggesting that individuals whose work demands included information processing and pattern recognition had a significantly lower likelihood of developing AD relative to individuals whose occupations had lower cognitive demands[32]. Along these lines, continual engagement in mentally stimulating activities as well as regular physical activity is also thought to confer a protective effect against cognitive decline[33].

*1.4 Evolution of MCI*

In the years that followed the publication of the MCI diagnostic criteria, clinicians and researchers alike began to acknowledge that the utility of these criteria must go beyond that of simply increasing the accuracy of a clinical diagnosis. Shortly after the publication of these criteria the idea that MCI represented a therapeutic target began to take hold[34] and during this time clinical trials involving MCI patients were initiated[15]. However, these trials also proved to be unsuccessful in showing a clinically meaningful benefit. In 2011, a consensus panel convened by the US National Institute of Health (NIH) made further refinements to the MCI classification[35]. In acknowledging the increased accuracy and utilisation of biological markers of AD pathology, the panel refined the criteria in which the classification of 'MCI due to AD' was proposed as a way to further increase the specificity of the MCI classification[35].

The impact that these criteria have had on the field of MCI/AD research has prompted a significant shift in how therapeutic interventions are being approached. The most notable impact has been that AD prevention trials are now being conducted which enroll cognitively normal individuals who are at risk for developing AD by virtue of genetic and biomarker classification[36,37]. The rationale for treating asymptomatic individuals is that disease-modifying therapies will yield the greatest therapeutic benefit when initiated early in the disease process so that the onset of clinical symptoms be delayed or halted completely.

Although the 2011 diagnostic criteria[35] were intended to be used for research purposes, they do provide a more specific diagnostic context for clinicians as amyloid imaging scans are now available and have obtained regulatory approval for clinical use[38]. This has the potential to significantly increase a clinician's confidence and accuracy in the clinical diagnosis of MCI due to AD. The inclusion of amyloid imaging within the formal workup for suspected cognitive impairment allows clinicians to begin making diagnoses of

inclusion as opposed to the typical diagnosis of exclusion. However, at the heart of the MCI/AD clinical diagnosis is the psychometric assessment of cognitive function which also continues to be refined[39].

*1.5. Cognitive Assessment of MCI*

In clinical settings, cognition is usually assessed using a battery of tests that measure performance in several different domains: memory, executive function, attention, visuospatial function, and language. This approach allows a clinician, usually a neuropsychologist, to discern patterns of performance among the tests to determine whether an individual's performance is consistent with a particular clinical diagnosis[40]. However, general practice and geriatric specialists are often the first to see individuals for suspected cognitive impairment and often lack the resources to perform a comprehensive cognitive assessment in the context of the general care visit which is usually very brief in duration[41,42]. The Mini Mental State Exam (MMSE)[43] was initially developed for hospital clinicians to conduct brief bedside assessments of cognition. The MMSE is comprised of 30 items that measure cognitive domains such as orientation, attention, memory, language, and visuoconstruction which yields a score with a range of 0 to 30. The MMSE was subsequently adopted and utilised by outpatient clinicians on a very large scale as its brief duration and simple administration procedures made it suitable for their clinical settings. As a result, the MMSE has been the most common and widely-known cognitive screening instrument among clinicians for some time.

However, as the focus of clinicians and researchers has shifted toward identifying people with more subtle cognitive deficits, the MMSE has shown to be relatively insensitive to milder levels of impairment[44]. In addition others have reported that performance on the MMSE is negatively impacted by lower levels of educational attainment and by floor and

ceiling effects[45] which may result in false-positive indications of cognitive impairment. The reliability of the MMSE is also questionable as individual scores can vary by as much as three points within a two-month testing interval[46]. When diagnostic classification groups are applied the percent of individuals who retained the same classification at a follow-up assessment ranged from 58% to 78%[46]. Previous studies have indicated that scores ranging from 24 to 30 indicate normal cognition[45], however more recent data using a very large sample size indicates that scores ranging from 26 to 30 are indicative of normal cognition[47]. In 2005, Nasreddine et al[48] published a validation study of the Montreal Cognitive Assessment (MoCA) which is purported to be more sensitive to milder degrees of cognitive impairment. The initial validation study of the MoCA yielded a cutoff score of 26 indicating that scores of 25 and below are indicative of cognitive impairment. The MoCA's administration procedures are similar to that of the MMSE where a variety of verbal and written tasks are administered to the individual in which the total score is based on the number of items correctly completed. As a result, the MoCA is now being widely-used in both research and clinical settings and has been translated into several different languages.

Previous research has demonstrated that the MoCA possesses greater accuracy in identifying MCI when compared to the MMSE. Damian et al[49] found that the MoCA was superior to the MMSE in terms of sensitivity and specificity, but noted that the cutoff score used to determine whether impairment is present is likely dependent upon whether the assessment takes place in a general care or memory disorder clinic setting. In clinical specialist settings a higher cutoff score may be utilised as these individuals are more likely to be diagnosed with a memory disorder. However, in general care settings a lower a cutoff score may be used in order to minimise the number of undetected cases of cognitive impairment. Specifically, Damian et al[49] suggest a lower cutoff score (24) than that indicated in the validation study[45] provided optimal diagnostic accuracy for MCI. Freitas et al[50] found

that diagnostic accuracy, as measured by area under the curve (AUC) value, for the MoCA in identifying MCI was 0.856 compared to the MMSE's AUC value of 0.745 which was found to be significantly different ($p < 0.001$). Roalf et al[51] found that the AUC values of the MoCA and MMSE were relatively similar with regard to differentiating MCI from normal cognition (MoCA AUC = 0.88; MMSE AUC = 0.84). However, these AUC values both increased to 0.97 when the MMSE and MoCA were used in conjunction with an informant-based assessment of cognition.

*1.6 Informant-Based Assessments of MCI*

In addition to objective, performance-based assessments of cognition, informant-based assessments of cognitive and functional ability are also used in clinical and research settings. One of the first informant-based assessments was introduced by Blessed et al[52] and consisted of a semi-structured interview with an informant who had adequate knowledge and history of the individual's cognitive and functional status. The questions contained in the assessment included items related to memory, daily functioning, and self-care. This assessment provided the impetus for many others to be developed, however the most ubiquitous has been the Clinical Dementia Rating (CDR)[53]. The CDR consists of a semi-structured interview with the caregiver and a small number of performance-based assessments of memory, judgment, orientation, and calculations for the patient. The CDR is comprised of six domains (Memory, Orientation, Judgment and Problem Solving, Home and Hobbies, Community Affairs, Personal Care) that are used to assess various aspects of cognition and daily function. Each of the domains is scored on a scale using scores of 0, 0.5, 1, 2, and 3 with higher scores indicating greater impairment in the domain. These scores are then added to create the Sum of Boxes score which is used as a summary score to indicate the degree of impairment. In addition to the Sum of Boxes score, the CDR Global Score is also

used in order to provide a categorical characterisation of cognitive status. The Global Score is derived from the individual domain scores and uses an algorithm to assign differing weights to each of the domain scores. The resulting categorisations are: 0 – Normal, 0.5 – Questionable Dementia, 1 – Mild Dementia, 2 – Moderate Dementia, 3 – Severe Dementia.

The CDR has been used as an outcome measure in placebo-controlled trials[54] as well as observational studies[55]. However, the amount of time need to administer the CDR ranges from 30 to 45 minutes which does not make it suitable for use in clinical settings. As a result, others have developed brief informant-based assessments of cognition that can be utilised in clinical settings. The AD8[56] and IQCODE[57] are among the most common informant-based cognitive assessments that are designed to be both brief and accurate. Although the AD8 and IQCODE require substantially less time to administer than the CDR, their ability to accurately identify MCI is unclear. One study found that the AD8 demonstrated good diagnostic accuracy for individuals classified as 0.5 (Questionable Dementia) on the CDR[56]. Although this CDR classification is often used as a proxy for the MCI diagnosis[58], it cannot be considered a fully equivalent proxy given that it lacks much of the information generally used when making the MCI diagnosis in a clinical setting. Published studies assessing the IQCODE's accuracy in identifying MCI are conflicting with one study reporting negative results[59] while another indicated relatively good diagnostic accuracy for MCI[60]. A direct comparison of the AD8 and IQCODE found that both measures accurately identified AD patients, but that the AD8 had higher accuracy for identifying MCI[60]. However, this study included only 13 MCI cases so these results require further study in order to fully validate their diagnostic accuracy for MCI. Based on these findings, it is unclear whether the AD8 or IQCODE can accurately differentiate clinically-diagnosed MCI individuals from those who are cognitively normal. As a result, there is a significant need for an informant-based

assessment of cognition has a short administration time and is accurate in identifying individuals with the earliest signs of cognitive impairment.

### *1.7 Overview of the Alzheimer's Questionnaire*

The Alzheimer's Questionnaire (AQ) is a clinician-administered and informant-based screening instrument that is designed to quickly and accurately detect cognitive impairment. The AQ consists of 21 yes/no questions that assess five domains of cognition function which are: Memory, Orientation, Functional Ability, Visuospatial and Language. Points for each question that are answered 'yes' are summed to give a total score which can range from 0 to 27 with higher scores indicating greater impairment.

Items for the AQ are similar to those contained in other widely used informant-based assessments[53,56,57], but have been adapted for ease and speed of administration. Items for the AQ were selected and approved by a group of clinicians with extensive experience in dementia assessment. The items were selected based on their face validity to assess each of the AQ domains. Six items are weighted in the AQ total score with positive responses receiving two points instead of one as it was agreed by the clinicians that these items would clearly differentiate an impaired individual from a cognitively normal individual.

## 2. Pilot Study

The initial pilot study[61] of the AQ was undertaken by three clinicians practising in separate memory disorder clinics in the southwestern United States. The AD and MCI cases were drawn from these three clinic populations while data from a group of cognitively normal (CN) individuals was also collected for use as a reference group. The CN individuals were drawn from the Banner Sun Health Research Institute Brain and Body Donation Program located in Sun City, Arizona[62]. The AQ was administered to the informants of these study

participants as part of a battery that includes performance-based cognitive assessments, physical and neurological examinations, and other informant-based assessments that are given annually.

The AD participants met NINCDS-ADRDA[8] criteria for a clinical diagnosis of probable and possible Alzheimer disease. The CN cases were defined as having no limitations of activities of daily living by informant report and were within normal limits on neuropsychological testing. Petersen criteria was used in the diagnosis of MCI[16]. For the CN subjects, consensus diagnosis with a neurologist, geriatric psychiatrist, and neuropsychologist was used to determine the clinical status of each participant. Rigorous criteria were used to exclude anyone with any type of symptomatic or severe brain related neurological or psychiatric illness. Excluded conditions included developmental delay/learning difficulties, epilepsy, cerebral infarction or hemorrhage, multiple sclerosis, brain tumour, major depressive disorder (unipolar or bipolar), schizophrenia, traumatic brain injury, and substance abuse. The clinical diagnoses for the MCI and AD cases were carried out in a similar fashion as described above with the exception that one clinician was responsible for the diagnostic decision. None of the individuals included in the study had a MMSE score less than 20 so that MCI and AD cases would be representative of individuals that would be seen by a clinician for early cognitive problems.

The sample consisted of 188 individuals (50 CN, 69 MCI, 69 AD) with an average age of 76.90±7.61 years and an average education level of 14.81±2.67 years. Gender distribution of the sample was of 45.7% (n = 86) females and 54.3% (n = 102) males. Initial psychometric analyses of the AQ showed that internal consistency was high as Cronbach's alpha was equal to 0.88 and that the majority of interdomain correlations were moderate ranging from r = 0.41 to r = 0.66. Interdomain correlations for Memory and Orientation, Memory and Functional Ability, and Orientation and Functional Ability were all high (r =

0.80, r = 0.82, r = 0.81, respectively). All correlation values were statistically significant ($p<0.001$). After accounting for the effects of age and education, statistically significant differences on mean AQ scores were present between all three clinical groups [$F = 177.85$ df = (2, 185), $p <0.001$]. Diagnostic accuracy of the AQ was excellent for both AD and MCI and is shown in Table 1 below. Additional analyses were carried out in which the additional point for the weighted items was removed and found that the AQ's diagnostic accuracy remained excellent for both MCI and AD (Table 2).

**Table 1. Pilot Study Diagnostic Accuracy Results for the AQ.**

| | **Sensitivity (95% CI)** | **Specificity (95% CI)** | **AUC (95% CI)** |
|---|---|---|---|
| **MCI** | 86.96 (*76.70 – 93.90*) | 94.00 (*83.50 – 98.7*) | 0.95 (*0.90 - 0.98*) |
| **AD** | 98.55 (*92.20 – 100.00*) | 96.00 (*86.30 – 99.50*) | 0.99 (*0.96 – 1.00*) |

CI – Confidence Interval; MCI – Mild Cognitive Impairment; AD – Alzheimer's Disease

**Table 2. Pilot Study Diagnostic Accuracy Results for the AQ Items Without Weightings.**

| | **Sensitivity (95% CI)** | **Specificity (95% CI)** | **AUC (95% CI)** |
|---|---|---|---|
| **MCI** | 87.14 (*77.00 – 93.90*) | 92.73 (*82.40 – 98.00*) | 0.94 (*0.89 - 0.98*) |
| **AD** | 95.65 (*87.80 – 99.10*) | 98.18 (*90.30 – 100.00*) | 0.99 (*0.96 – 1.00*) |

CI – Confidence Interval; MCI – Mild Cognitive Impairment; AD – Alzheimer's Disease

The primary finding of this study is that the AQ can differentiate both MCI and AD from cognitively normal individuals with a very high degree of accuracy. The simplicity of administration and scoring coupled with its relatively short length suggest that AQ could be implemented very easily into care settings where rapid and accurate and assessments of cognitive function are needed. Although several other informant-based dementia

questionnaires have been developed, they have not been validated as accurate instruments in detecting individuals with MCI. This is important as identifying individuals in the earliest stages of cognitive decline will be necessary as the development of disease-modifying therapies become available.

It is important to note that the AQ is not intended to replace a full diagnostic work-up that is typically administered when assessing individuals with memory problems. It should also be noted that the AQ was not used in a general practice setting so it is unclear whether the results of this study represent that of the general geriatric population. This study included patients who were seen by dementia specialists and as a result the sample used is biased to a certain extent. However, given its excellent diagnostic accuracy, ease of scoring, ease of administration, and short length of time needed for administration the AQ would be of great value to clinicians who have an extremely limited amount of time in order to assess individuals for memory and cognitive problems.

**3. Validation Study**

The pilot study of the AQ was followed by a subsequent validation study[63] that utilised the same sample, but added CN, MCI, and AD cases in order to achieve balanced group sizes that were sufficiently large. 50 CN, 31 MCI, and 31 AD cases were added so that the validation study had a final sample size of 300 (100 CN, 100 MCI, and 100 AD). The additional CN cases came from the Banner Sun Health Research Institute Brain and Body Donation Program[62] while the additional MCI and AD cases were derived from one of the three memory clinics used in the pilot study.

This validation study extended upon the work of the pilot study by utilising additional measures of diagnostic accuracy, in the form of likelihood ratios, and also by establishing cut-off scores for each clinical group. The results of the diagnostic accuracy analyses of the

validation study mirrored those of the pilot study as the AQ, again, demonstrated excellent diagnostic accuracy for both MCI and AD (Table 3).

**Table 3. Validation Study Diagnostic Accuracy Results of the AQ in MCI and AD.**

| | *Sensitivity (95% CI)* | *Specificity (95% CI)* | *AUC (95% CI)* | *LR+ (95% CI)* | *LR- (95% CI)* | *Cut-Off Score* |
|---|---|---|---|---|---|---|
| **MCI** | 89.00 (81.20 – 94.40) | 91.00 (83.60 – 95.80) | 0.95 (0.91 – 0.97) | 9.89 (9.00 – 10.80) | 0.12 (0.05 – 0.30) | 5≤14 |
| **AD** | 99.00 (94.60 – 100.00) | 96.00 (90.10 – 98.90) | 0.99 (0.96 – 1.00) | 24.75 (23.70 – 25.90) | 0.01 (0.001 – .09) | ≥15 |

CI – Confidence Interval; LR – Likelihood Ratio; MCI – Amnestic Mild Cognitive Impairment; AD – Alzheimer's Disease

The likelihood ratios provide further evidence of the AQ's diagnostic accuracy as they are independent of the underlying prevalence of MCI and AD. Both the positive and negative likelihood ratios indicate that the AQ differentiates MCI and AD from normal cognition with a high degree of accuracy. The cutoff scores reported in the validation study are of significant value to clinicians as they provide an initial indication of where a patient may fall on the spectrum of cognitive impairment. Internal consistency of the AQ remained high as Cronbach's alpha was 0.89 and the range of interdomain correlations was $r = 0.45$ to $r = 0.69$. The latter finding is very important as the moderate interdomain correlations indicate that each domain is measuring a unique construct and supports the argument that the AQ is capturing impairment in both cognitive and functional areas.

However, it is noted that the use of the cutoff scores are not intended to replace the typical diagnostic workup that is carried out to exclude other possible causes of cognitive impairment that may be aetiologically different from AD. Although the cutoff scores do reflect diagnostic accuracy with regard to a rigorously-supported clinical diagnosis, use of the AQ score without the proper clinical context would be erroneous and could lead to incorrect diagnoses which would be unhelpful to a patient. However, results of the AQ may provide

important information regarding whether an individual is showing early signs of cognitive impairment. Although the AQ does not provide a specific diagnosis, its use as an early indicator of impairment may help clinicians make referrals for further work-up more quickly which could lead to earlier treatment and better prognosis.

As the results of the pilot and validation studies showed that the AQ can differentiate MCI from normal cognition quite accurately, the next area of investigation sought to determine which individual AQ items drive its diagnostic accuracy.

**4. Item Analysis Study**

Concurrent to the validation study[63], a post-hoc analysis was carried out to determine which of the individual AQ items best differentiated MCI cases[64]. As additional data were being collected for the validation study, data from 47 MCI and 51 CN cases were used in this analysis. As expected, the majority of items had a greater proportion of positive responses for the MCI cases than the CN cases. However, more detailed analyses found that positive responses to four items were particularly strong predictors of MCI: repetition of statements and/or questions [OR 13.20 (3.02, 57.66)]; trouble knowing the day, date, month, year, and time [OR 17.97 (2.63, 122.77)]; difficulty managing finances [OR 11.60 (2.10, 63.99)]; and decreased sense of direction [OR 5.84 (1.09, 31.30)] (Table 4).

**Table 4. Analysis of Individual AQ Items as Predictors of MCI.**

| *AQ Item* | *Odds Ratio* | *95% CI* | *p-value* |
|---|---|---|---|
| Does the patient repeat questions or statements or stories in the same day? | 13.12 | (3.02, 57.66) | 0.001 |
| Does the patient frequently have trouble knowing the day, date, month, year, and time; or does the patient reference a newspaper or calendar for the date more than once a day? | 17.97 | (2.63, 122.77) | 0.003 |
| Excluding physical limitations, does the patient have trouble paying bills or doing finances; or are family members taking over because of concerns about ability? | 11.60 | (2.10, 63.99) | 0.005 |
| Does the patient have a decreased sense of direction? | 5.84 | (1.09, 32.30) | 0.04 |

Together, these four items demonstrated good accuracy in differentiating MCI as sensitivity was 80%, specificity was 82%, and area under the curve (AUC) was 0.94. In addition, these four items accounted for approximately 71% of the variance between MCI and CN cases.

Despite a relatively small sampling of MCI and CN cases, the results of this study provided quantitative evidence for specific cognitive symptoms that differentiate MCI from normal cognition. These results also provide clinicians with a degree of specificity and granularity that had not been previously reported in the context of the clinical presentation of MCI. However, the clinical presentation of MCI can be heterogeneous[65] and it is quite likely that individuals who eventually receive a diagnosis of MCI may present with a symptom profile that is different than the one presented with these four AQ items.

**5. Concurrent Validity**

After demonstrating the diagnostic accuracy of the AQ, assessing its concurrent validity with gold-standard assessments of cognition and function was necessary in to provide

additional clinical validation. The concurrent validity study[66] was carried out in a sample of individuals from the Banner Sun Health Research Institute Brain and Body Donation Program[62]. The sample of 146 individuals included 73 CN, 39 MCI, and 34 AD cases. The MCI and AD individuals were matched with a CN individual on age, gender, and education. The AQ was compared with the CDR Sum of Boxes, CDR Global Score, MoCA, and the MMSE. These particular measures were chosen because of their wide use in clinical and research settings so establishing the AQ's correlation with these measures would provide a thorough assessment of the AQ's validity. Concurrent validity was assessed primarily through Spearman correlations between the AQ and the reference assessments, however ROC analyses were also used to compare the diagnostic accuracy of the AQ with the other assessments.

The AQ correlated strongly with the CDR-Sum of Boxes (r = 0.79) while moderate correlations were noted with the MMSE (r = -0.56) and MoCA (r = -0.46). Table 5 displays the AUC values with 95% confidence intervals for each of the instruments for all clinical groups. The AQ, MoCA, and MMSE demonstrated comparable AUC values for both MCI and AD. When the MCI and AD groups were combined all instruments showed favourable diagnostic accuracy with AQ showing slightly better performance than the MoCA and MMSE. The CDR-SOB was superior to all of the instruments in terms of diagnostic accuracy, however this is likely because it was used as a component of the consensus diagnosis. This circularity likely resulted in an overestimate of its true diagnostic accuracy.

**Table 5: Diagnostic Accuracy Comparison of AQ, CDR-SOB, MMSE, and MoCA**

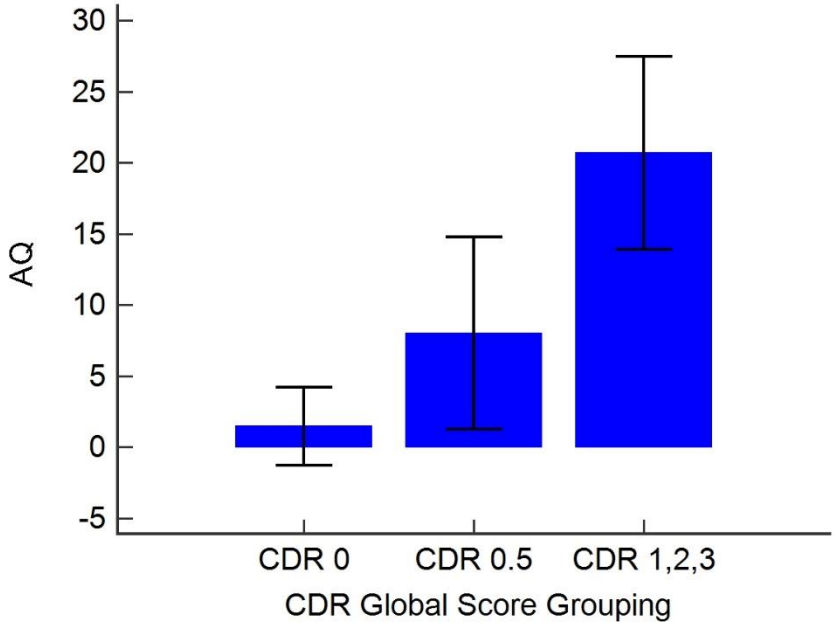
| | *CN vs MCI* | *CN vs AD* | *CN vs MCI+AD* |
|---|---|---|---|
| **AQ** | 0.74 (0.62, 0.83) | 0.99 (0.91, 1.00) | 0.81 (0.72, 0.87) |
| **CDR-SOB*** | 0.87 (0.77, 0.94) | 0.99 (0.92, 1.00) | 0.89 (0.82, 0.94) |
| **MMSE** | 0.76 (0.64, 0.85) | 0.97 (0.87, 1.00) | 0.80 (0.72, 0.87) |
| **MoCA** | 0.71 (0.60, 0.81) | 0.94 (0.82, 0.99) | 0.78 (0.70, 0.85) |

AUC (95% CI)

*CDR-SOB was used to make consensus diagnosis

An additional analysis was carried out to characterise the AQ's performance when participants were grouped according to their Global Score on the CDR (CDR 0 [n = 66]; CDR 0.5 [n = 49]; CDR 1, 2, 3 [n = 31]). Individuals with a CDR Global Score of 1, 2 and 3 were combined as these three subgroups were not significantly different from each other when compared separately on the AQ total score. A statistically significant difference for the AQ total score was noted between the three CDR Global Score groups (Kruskall-Wallis = 82.35 (df = 2) $p<0.001$; all groupwise comparisons $p<0.001$; Figure 1). Cohen's *d* was used to assess the effect sizes of these group differences and found large effect sizes for all of the group comparisons: CDR 0 vs. CDR 0.5 = 1.27; CDR 0 vs CDR 1, 2, 3 = 3.70; CDR 0.5 vs. CDR 1, 2, 3 = 1.87.

**Figure 1. AQ Performance for CDR Global Score Groupings.**




The results of the concurrent validity study demonstrated that the AQ is comparable to other commonly used informant-based and patient-based measures in terms of its ability to differentiate MCI and AD patients from those who are cognitively normal. The large group differences noted for the CDR Global Score comparison provide an additional level of clinical validation to the AQ since the CDR is intended to correspond to a clinical diagnosis. It was noted that the AQ's AUC value was lower than what was originally found in the validation study. This is likely due to the use of a smaller sample size in the current study, but also because clinical status was determined via consensus diagnosis rather than a clinical diagnosis. Although the consensus diagnosis is intended to correspond to a clinical diagnosis, since multiple clinicians are involved in a consensus diagnosis differing opinions and clinical interpretations among the clinicians may yield differing diagnostic categorisations than would have been obtained through a single clinician.

## 6. Neuropsychological Correlates

The next study extended upon the concurrent validity study and determined how well the AQ correlated with neuropsychological and cognitive screening tests[67]. Since neuropsychological tests are utilised in making differential clinical diagnoses of MCI and AD, determining the extent to which the AQ correlates with objective and specific measures of various cognitive domains is needed in order further validate its ability to detect cognitive changes associated with MCI and AD. Specifically, the study aimed to determine whether the AQ corresponds to the neuropsychological phenotype of MCI due to AD in which memory and executive functions are most often impaired[68].

This study utilised a larger sample of individuals (N = 300) from the Banner Sun Health Research Institute Brain and Body Donation Program[62]. Individuals diagnosed with MCI (n = 83) and AD (n = 67) were matched on age, gender, and education to a CN individual (n = 150). A large set of neuropsychological tests was used for the study which included: MMSE, MoCA, Mattis Dementia Rating Scale-2 (DRS-2), Clock Drawing Test, Rey Auditory Verbal Learning Test (AVLT), Brief Visuospatial Memory Test (BVMT), Trails A, Trails B, Digit Span (forward and backward), Controlled Oral Word Association Test (COWAT), Animal Fluency, Stroop Color/Word, Judgment of Line Orientation (JLO), Block Design, and the Boston Naming Test 30 Item (BNT-30).

Spearman correlation analyses were carried out to assess the linear associations between the AQ and the neuropsychological measures. Data for DRS-2 and Block Design were only available from smaller subsets of the study sample (DRS-2 n = 79, Block Design n = 55). In order to minimise the impact of floor and ceiling effects from the AD and CN groups on neuropsychological tests, the CN, MCI, and AD groups were analysed together. This also allowed for the relationship between the AQ and the individual cognitive tests to be assessed on a continuum of cognitive impairment.

The percentage of variance accounted for by each cognitive test in the AQ score was determined by using robust least median squares regression models with AQ score as the outcome and cognitive test as the predictor. Each test was modelled independently in order to obtain a $R^2$ value that was unique to each of the tests.

The additional predictive value of the AQ in MCI for a select subset of tests was assessed through a series of logistic regression models. The first series of models used only the cognitive test score as predictor with CN/MCI as the outcome. A second series of models included the AQ score along with the cognitive test. Area under the curve (AUC) values between the first and second models were compared in order to determine if the AQ added a significant amount diagnostic accuracy when combined with a cognitive test. All models included the GDS score in order to account for the effect of depressive symptoms on cognitive performance. Although measures of anxiety were not used in this study, the co-occurrence of depressive and anxiety symptoms in older adults is quite common[69] so it is possible that the presence of anxiety may have manifested in positive responses to the presence of depressive symptoms.

Correlations between the AQ and the individual cognitive measures are shown in Table 6. The AQ correlated strongly with DRS-2 Total (r = -0.72) and the MMSE (-0.71). The AQ showed a moderate correlation with the MoCA (r = -0.68) and a weak correlation with Clock Draw (r = -0.32). The AQ also demonstrated moderate correlations with measures of memory and executive function, as lower performance on the memory measures was associated with greater reported impairment on the AQ. For the measures of attention, the AQ correlated moderately with Trails-A, but demonstrated weak correlations with Digit Span Forward and Digit Span Backward. Both language measures also correlated moderately with the AQ. For visuospatial function, the JLO demonstrated a weak correlation with the AQ while Block Design demonstrated no correlation. Measures of general cognition, memory,

and executive function each accounted for a substantial proportion of variance in the AQ score. The latter finding is extremely important as the domains of memory and executive function are often affected most prominently in AD. In addition, the finding that measures of general cognition accounted for a large portion of the variance is important as these assessments are often given in general practice settings so it is important that the AQ correspond well with these measures.

**Table 6. Correlation Values for Neuropsychological Tests with the AQ**

| Domain | Test | Correlation with AQ | p-value | $R^2$ |
|---|---|---|---|---|
| General Cognition | | | | |
| | MMSE | -0.71 | <0.001 | 0.63 |
| | MoCA | -0.68 | <0.001 | 0.57 |
| | DRS-2 | -0.72 | <0.001 | 0.71 |
| | Clock Draw | -0.38 | <0.001 | 0.31 |
| Memory | | | | |
| | AVLT Total | -0.62 | <0.001 | 0.44 |
| | AVLT Delayed Recall | -0.61 | <0.001 | 0.43 |
| | BVMT-R Total | -0.61 | <0.001 | 0.41 |
| | BVMT-R Delayed Recall | -0.65 | <0.001 | 0.49 |
| Executive Function | | | | |
| | Trails B | 0.53 | <0.001 | 0.52 |
| | Stroop Color/Word | -0.51 | <0.001 | 0.32 |
| | COWAT | -0.27 | <0.001 | 0.11 |
| Attention | | | | |
| | Trails A | 0.52 | <0.001 | 0.41 |
| | Digit Span Forward | -0.21 | <0.001 | 0.06 |
| | Digit Span Backward | -0.37 | <0.001 | 0.18 |
| Language | | | | |
| | BNT | -0.44 | <0.001 | 0.14 |
| | Animal Fluency | -0.56 | <0.001 | 0.41 |
| Visuospatial | | | | |
| | Block Design | -0.24 | 0.08 | ---- |
| | JLO | -0.28 | <0.001 | 0.11 |

$R^2$ value derived from least median squares regression model; $R^2$ for Block Design could not be derived due to missing data among AD cases.

Analyses showing the added diagnostic value of the AQ with select cognitive tests are shown in Table 7. For these analyses, we selected measures of general cognition and delayed recall memory measures as they are often used independently to differentiate clinical groups while many of the other domain-specific cognitive tests are often used in a broader diagnostic framework and interpreted in relation to other tests. We chose to limit our analyses to CN versus MCI cases as they would provide the most informative classification data given that research has shifted toward identifying individuals in the pre-clinical stages of the disease. On its own, the AQ demonstrated good diagnostic accuracy for MCI [AUC = 0.83, 95% CI:

(0.77, 0.88)]. When used in combination with different cognitive tests, the only test which showed significant benefit of the AQ's addition was the MMSE as the AUC value significantly improved.

**Table 7. Additional Diagnostic Accuracy of Select Cognitive Tests with AQ in MCI Cases.**

| | Test Only | Test With AQ | p-value |
|---|---|---|---|
| AQ | AUC = 0.83<br>95% CI: (0.77, 0.88) | na | na |
| DRS-2 Total | AUC = 0.90<br>95% CI: (0.80, 0.96) | AUC = 0.94<br>95% CI: (0.86, 0.99) | 0.46 |
| MMSE | AUC = 0.79<br>95% CI: (0.73, 0.85) | AUC = 0.88<br>95% CI: (0.83, 0.92) | 0.02 |
| MoCA | AUC = 0.87<br>95% CI: (0.80, 0.92) | AUC = 0.90<br>95% CI: (0.85, 0.95) | 0.43 |
| AVLT Delayed Recall | AUC = 0.94<br>95% CI: (0.90, 0.97) | AUC = 0.97<br>95% CI: (0.94, 0.99) | 0.13 |
| BVMT-R Delayed Recall | AUC = 0.87<br>95% CI: (0.82, 0.91) | AUC = 0.91<br>95% CI: (0.86, 0.94) | 0.21 |

The results of this study demonstrate that the AQ correlates well with several performance-based neuropsychological and cognitive screening tests commonly used in clinical settings. The AQ demonstrated some weak correlations with several neuropsychological tests examining specific domains; however several moderate correlations were also noted, particularly with measures of memory and executive function. Given that decreased memory and dual processing skills are hallmark features that direct a clinician to a diagnosis of AD, these results suggest that the AQ is accurately assessing AD-specific

cognitive declines. Weak correlations between informant-reported measures and domain-specific neuropsychological tests may be expected to some extent given that informant-based measures often contain items spanning several cognitive domains. Thus, the lack of overlap in the constructs measured by broad informant-based and domain-specific neuropsychological measures may explain weak correlations between these assessment types.

Additionally, as some of these domains, such as visuospatial, are not typically expected to have significant involvement in AD, one would expect the AQ to have lower correlations with these domains than those with declines more strongly associated with AD, such as memory and executive function. It is noted that other measures such as, recognition memory, intrusions and repetitions on verbal memory, reduced primacy effect on verbal memory were not analyzed with the AQ. These measures are also thought to contribute to the neuropsychological profile of MCI and AD[70] and may have provided additional clinical validation of the AQ. In addition, specific subtests of the cognitive and neuropsychological measures were not correlated with the AQ. Orientation and memory subsections of the MMSE, MoCA, and DRS-2 may have contributed more to the correlations with the AQ given that these items on the AQ accurately differentiated MCI from normal cognition[64].

These findings provide further evidence to support the clinical validity of the AQ as an instrument for detecting cognitive impairment associated with MCI and AD. In particular, the AQ demonstrated moderate correlations with memory and executive function measures which shows that the AQ can reasonably assess cognitive impairment demonstrated on standard neuropsychological measures.

**7. Longitudinal Change**

Following the clinical validation studies, an examination of the AQ's ability to measure change over time was carried out[71]. A major issue that both clinicians and

researchers often contend with is the degree to which a particular instrument is sensitive to change over time. For clinicians the results yielded from an assessment are often used to make decisions regarding treatment and resource use (i.e., assisted living, in-home care, etc.). For researchers and clinical trial specialists, the issue of sensitivity to change for a particular instrument has significant ramifications for whether or not a meaningful treatment effect will be detected between placebo and treatment groups in a clinical trial.

The first aim of this study was to assess the sensitivity to change of the AQ in comparison to the MMSE, MoCA, and the Functional Activities Questionnaire (FAQ)[72]. The second aim of the study was to determine how well the AQ predicts global change as measured by the Functional Assessment Staging Test[73] (FAST), GDS, and the CDR Global Score. Data from the two most recent annual visits for 202 individuals from the Banner Sun Health Research Institute Brain and Body Donation Program[62] were utilised for this study. Of the 202 individuals, 101 were classified as cognitively normal (CN), 62 were classified as mild cognitive impairment (MCI), and 39 were classified as Alzheimer's disease (AD). Each MCI and AD individual was matched on age, education, and gender to a CN individual, without replacement.

The analyses investigating the sensitivity to change utilised a method similar to that of Costa et al[74] which was completed through the calculation of a Cohen's *d* effect size used for correlated designs[75,76]. Logistic regression analyses were used to assess the predictive value of the AQ, FAQ, and MMSE change scores on increases in FAST, GDS, or CDR Global Score. In the MCI group the AQ, FAQ, and MMSE all demonstrated small sensitivity to change in terms of their respective *d* values (0.33, 0.35, 0.24). In the AD group, the AQ demonstrated small sensitivity to change ($d = 0.43$), however the FAQ showed large sensitivity to change ($d = 0.84$) and the MMSE demonstrated moderate sensitivity to change ($d = 0.52$). In the CN group all three measures demonstrated small effect sizes (AQ: $d = 0.18$,

FAQ: $d$ = 0.15, MMSE $d$ = 0.02). Analyses that pooled the CN, MCI, and AD groups found that the AQ and FAQ demonstrated small, but significant associations with CDR Global Score increases (AQ [OR = 1.20 (1.09, 1.32), p<0.001]; FAQ [OR = 1.21 (1.11, 1.33), p<0.001]). The pooled analysis also yielded a small, but significant association for FAQ mean change and GDS increase [OR = 1.16 (1.06, 1.26), p = 0.001]. When clinically meaningful change was characterised with the reliable change index (RCI) the AQ was able to identify a higher percentage (24%) of MCI cases relative to the FAQ and MMSE (both 17%).

Although the effect sizes reported in this study are relatively small, they are consistent with the notion that cognitive changes associated with MCI and AD are often subtle and difficult to detect from a psychometric standpoint. This point is a major challenge for researchers and clinical trial specialists as the variability of cognitive tests is often numerically similar to the rate of change[77]. Informant-based instruments that assess functional ability are also prone to high degrees of variability due to varying pre-morbid levels of function and gender differences in the degree of participation for many functional activities that are assessed[77]. The degree to which a particular cognitive or functional measure is responsive to changes in disease status is extremely important, particularly in pre-symptomatic and MCI populations where cognitive decline is slower and more subtle[78].

The results of this study indicate that the AQ demonstrated small sensitivity to longitudinal cognitive changes associated with MCI and AD. The AQ's sensitivity to change in MCI was comparable to the FAQ while both instruments outperformed the MMSE in terms of effect size. The AQ was also significantly associated with longitudinal decreases in global cognition and function. Although the AQ's sensitivity to change was small, it is possible that its sensitivity to change may be enhanced when used in conjunction with sensitive objective cognitive tests and validated biomarkers of disease progression.

## 8. Discussion

This series of studies demonstrated that the AQ is an informant-based cognitive assessment that can accurately identify individuals with cognitive impairment that is consistent with MCI and AD. The initial validation studies of the AQ demonstrated high diagnostic accuracy for both MCI and AD (Sabbagh MN, Malek-Ahmadi M, Kataria R, Belden CM, Connor DJ, Pearson C, Jacobson S, Davis K, Yaari R, Singh U. The Alzheimer's Questionnaire: A proof of concept study for a new informant-based dementia assessment. *Journal of Alzheimer's Disease* 2010;22(3):1015-1021; Malek-Ahmadi M, Davis K, Belden CM, Laizure B, Jacobson SA, Yaari R, Singh U, Sabbagh MN. Validation and diagnostic accuracy of the Alzheimer's Questionnaire (AQ). *Age and Ageing* 2012;41(3):396-399; Malek-Ahmadi M, Davis K, Belden CM, Jacobson SA, Sabbagh MN. Informant-reported cognitive symptoms that predict amnestic mild cognitive impairment. *BMC Geriatrics* 2012;12:3) while subsequent studies provided ample evidence for its clinical validity through correlations with other established cognitive and informant-based instruments (Malek-Ahmadi M, Davis K, Belden C, Sabbagh MN. Comparative analysis of the Alzheimer's Questionnaire (AQ) with the CDR Sum of Boxes, MoCA, and MMSE. *Alzheimer's Disease and Associated Disorders* 2014;28(3):296-298). The AQ's correlations with standard neuropsychological tests provided additional evidence for its clinical validity by demonstrating specificity for the cognitive phenotype of MCI due to AD (Budolfson K, Malek-Ahmadi M, Belden C, Powell J, Davis K, Jacobson SA, Sabbagh MN. Neuropsychological correlates of the Alzheimer's Questionnaire (AQ). *Journal of Alzheimer's Disease* 2015;46(2):389-397). In terms of detecting longitudinal changes, the AQ demonstrated higher sensitivity to change relative to the MMSE and was also able to detect a higher proportion of individuals with clinically meaningful change (Malek-Ahmadi M, Chen K, Davis K, Belden CM, Powell J, Jacobson SA, Sabbagh MN. Sensitivity to change and

prediction of global change for the Alzheimer's Questionnaire. *Alzheimer's Research & Therapy* 2015;**7**:1).

The diagnostic and clinical value of the AQ has also been recognized at the policy/governmental level as it is listed as a recommended assessment for possible cognitive impairment in the British Columbia Ministry of Health Geriatric Assessment Guidelines[79]. The AQ's inclusion in these guidelines is a strong statement about the value it can provide to geriatric clinicians in terms of its speed of administration and diagnostic accuracy.

Additional work using the AQ was conducted by Salazar et al[80] who used the AQ to detect cognitive impairment in a Spanish-speaking population. The Spanish translation of the AQ was deemed to be a "culture fair" screening instrument for MCI and was a strong predictor of the CDR-SOB. This study also found that the AQ was able to accurately differentiate individuals with MCI from those who are cognitively normal and was also found to be biased toward the detection of memory impairment, which could be advantageous when used in pre-clinical AD populations. Given that research in the areas of MCI and AD has shifted toward identifying individuals in earlier stages of the disease[36,37,81] utilising an informant-based instrument that is sensitive to the subtle cognitive changes that differentiate normal cognition from MCI is important. Although the results of AQ studies demonstrate that it can accurately differentiate MCI and AD from normal cognition with a high degree of accuracy, it has also been reported that it can add predictive value when used with other performance-based neuropsychological assessments[67]. Others have also noted that the addition of informant-based assessments with neuropsychological assessments provide a significant amount of added predicted value[82] so it is likely that geriatric and memory disorder clinicians could benefit from using the AQ in conjunction with performance-based neuropsychological assessments such as the MMSE and the MoCA.

Clinicians often encounter cases where individuals with high educational and occupational attainment may perform within normal limits on objective cognitive tests, but are clearly demonstrating cognitive and functional deficits as reported by spouses and other informants. This dichotomy of cognitive and functional status is not uncommon and presents a significant diagnostic challenge to clinicians. In these instances, the AQ may be extremely useful to clinicians as informant-based reports of cognitive changes are less susceptible to the effects of cognitive reserve[84] where performance on objective cognitive tests may be within normal limits. In addition, the use of informant-based measures help alleviate biases of self-reported cognitive changes that may be due to factors unrelated to MCI and AD such as age-related changes, lifestyle changes, stress, and other factors. In some cases, the patient may deny having any cognitive problems. Although the latter is often associated with clinical AD, anosognosia can also occur in MCI patients[85]. When a patient denies the presence of cognitive decline, informant-based information can help the clinician to glean a more accurate picture of a patient's cognitive status.

In the context of identifying individuals with MCI, a number of other challenges remain which clinicians and researchers must contend with. One of the main challenges to obtaining an accurate MCI diagnosis is that the diagnosis itself has a high degree of temporal instability. Specifically, the occurrence of reversion from MCI to normal cognition has been documented in several longitudinal studies and was recently summarised in two meta analyses[24,86]. Malek-Ahmadi[24] summarised the reversion rates from 25 longitudinal studies and found that 24% of individuals who received a MCI diagnosis at their first assessment were classified as cognitively normal at their second assessment. A variety of factors appear to underlie this phenomenon, however the setting in which the study took place (community-based vs. clinic) is thought to be one of the biggest determinants of reversion as community-based studies had a substantially higher reversion rate (31%) relative to clinic-based studies

(14%). One possible explanation for this difference was proposed by Petersen et al[87] who point out that clinic-based samples tend to have greater cognitive impairment and greater likelihood of disease progression when compared to community-based samples which could explain the lower reversion rates in clinic-based studies. The underlying difference in the risk of progression to MCI and AD in clinic-based samples is referred to as Berkson's bias[88], which is one type of selection bias. Since individuals who are seen in memory clinics are likely to have a significant family history of AD or feel that that they are already symptomatic, this results in clinic-based samples consisting of individuals with a higher baseline risk for progression to MCI and AD than individuals in community-based studies. As result, clinic-based samples are likely to have lower rates of reversion to normal cognition due to the nature in which individuals are recruited. This point has significant implications for cognitive screening tests as it has been shown that their diagnostic accuracy can be substantially lower when administered in settings where the prevalence of MCI and AD is low[89]. Other factors such as recovery from illness, improvement of depressive symptoms, anxiety and/or lack of familiarity with cognitive testing at the initial assessment[90] are also thought to increase the likelihood of reversion. In addition, practice effects on neuropsychological tests may also contribute significantly to whether an individual reverts to a classification of normal cognition from MCI[91-94]. Since frequent neuropsychological assessments occur in both clinic-based and community-based studies, both types of studies are prone to the negative impact that practice effects have on discerning significant cognitive changes[94].

Although the instability of the MCI diagnosis is problematic for clinicians and researchers, this uncertainty can also have a profound impact on the patients themselves along with their families. Many clinicians are often reluctant to give a diagnosis of MCI as its ambiguity and uncertainty may cause unneeded worry and anxiety in their patients[95]. In

addition, there is often a negative stigma associated with MCI and in general, dementia diagnoses[96]. This stigma can occur at a public level where the general population may hold a negative view towards those with a particular diagnosis. However, the stigma for MCI and dementia also occurs at the personal level and may manifest as fear and anxiety which can lead an individual to decrease their socialization and to be more hesitant to seek specialised care for their condition[96]. Additional factors such as the inability of persons with more advanced AD to fully understand and remember the diagnosis, the potential for adverse psychological reactions, and the absence of effective treatments are reasons that many clinicians have cited as the rationale for not disclosing the AD diagnosis to their patients[97]. However, through the refinement of clinical diagnostic criteria, available treatments with modest efficacy, along with a societal emphasis on an individual's autonomy, the vast majority of clinicians now regularly disclose AD diagnoses to their patients[97].

Disclosure of a MCI diagnosis has also proven to be challenging in clinical settings. This is primarily because MCI was initially characterised as a research diagnosis to identify individuals who were thought be at high-risk for developing AD[97]. However, the use of MCI as a diagnostic entity in clinical practice has been established for some time now. This is evident by the Diagnostic and Statistical Manual 5$^{th}$ edition (DSM-5) which now includes mild neurocognitive disorder (mNCD)[98] and use of the mild cognitive disorder (MCD) diagnosis in the International Statistical Classification of Disease and Related Public Health Problems 10$^{th}$ edition (ICD-10)[99]. For the patient, the MCI diagnosis can still illicit a great deal of psychological discomfort although recent research suggests that proactive interventions directed toward depressive and anxiety symptoms may be helpful as well as addressing quality of life issues that may be impacted by a MCI diagnosis[100]. Furthermore, the diagnostic process for MCI allows clinicians the opportunity to implement cognitive

rehabilitation strategies while the patient is cognitively fit enough to understand and carry out the strategies.

As the field has shifted toward identifying individuals in the pre-clinical or asymptomatic stage of AD, many of the same ethical issues associated with the MCI and AD diagnoses are still present, but have an added layer of complexity given the lack of clinical symptoms and relative uncertainty about disease progression. Currently, pre-clinical AD is determined based on the presence of abnormal biomarkers[101] (fluid markers, protein markers, neuroimaging markers) that indicate the presence of disease pathology in the absence of overt clinical symptoms. Although these individuals are thought to be at an increased risk for developing MCI and AD, biomarker measurements currently in use do not have the prognostic certainty to definitively inform an individual that clinical disease progression is imminent. As a result, the disclosure of "biomarker positive" results puts clinicians and researchers in a very difficult position when attempting to explain the meaning of these results to patients and research participants[101]. In particular, disclosure of one's genotype for the apolipoprotein E (APOE) gene has been the source of significant debate among clinicians who treat MCI and AD patients[102]. Among the three APOE alleles (ε2, ε3, ε4) individuals who carry at least one copy of the ε4 allele are at an increased risk for developing AD[101]. Although the APOE ε4 genotype has shown the strongest and most consistent genetic risk for AD[103], it is not deterministic as many individuals who are ε4 carriers will not develop AD and individuals who are ε2 or ε3 carriers can also develop AD. The interpretation of APOE ε4 status as a risk factor for AD must be emphasized and communicated clearly to individuals who choose to find out their APOE genotype. Since the primary function of the APOE gene is cholesterol transport[103], it is very difficult to associate APOE's function directly with AD pathogenesis. In addition, the APOE ε4 allele is also associated with cardiovascular disease[104]

which further underscores the importance of communicating one's APOE genotype as a risk factor and not a determining factor.

However, even in this uncertain diagnostic context Caselli et al[105] found in their survey of 4,036 individuals that approximately 70% of the respondents would opt for being tested to know their APOE ε4 carrier status even in the absence of an effective intervention for AD. The vast majority (94.9%) reported that they would be comfortable learning of their APOE ε4 genotype for the purposes of research study participation. When respondents were posed with the hypothetical scenario of finding out that they had an increased genetic risk of AD, most of the respondents (90.5%) stated they would pursue a healthier lifestyle, however 11.6% reported that they would seriously consider suicide. The latter finding was explored further in an additional study by Caselli et al[106] and found that individuals endorsing suicidal ideation were not clinically depressed, did not have high degrees of neuroticism, and had no indication of cognitive impairment. However, these individuals did report a significantly higher degree of non-support relative to those who did not endorse suicidal ideation. In order to mitigate the risk of suicide in these individuals, Caselli et al[106] suggest that enrollment into a research study, participation in a support group, and close monitoring by a clinician may be helpful. The findings of these studies highlight the need to develop a framework for addressing the pre-clinical AD diagnosis from societal, legal, and socioeconomic perspectives[107].

In light of the ethical issues surrounding the MCI diagnosis, it should be mentioned that there is currently no standard pharmacological treatment for MCI available. Although cholinesterase inhibitors are the standard treatment for clinical AD, they do not appear to have a beneficial effect on cognition in individuals with MCI[108]. In recent years, non-pharmacological treatments have been tested in individuals with MCI and have had varying degrees of efficacy. A recent review by Horr et al[109] found that randomized trials using

physical activity and cognitive interventions provided modest benefits, however more definitive conclusions could not be drawn due to significant variability in study design, outcome selection, and diagnostic criteria used for MCI. Others have suggested that mindfulness-based therapies may be effective as well[110]. An earlier review by Cotelli et al[111] indicated that many studies found positive benefits for non-pharmacological interventions when used in conjunction with cholinesterase inhibitor therapy. However, it is unclear how long the benefits of non-pharmacological interventions last and to what extent they provide neuroprotective effects from future disease progression.

## 9. Conclusion

The series of studies that served to validate the use of the AQ demonstrate that it has a great deal of clinical value in terms of accurately identifying individuals with MCI and AD. In particular, its ability to accurately identify individuals with MCI is extremely important given that there is now an increased focus on identifying individuals in the earliest stages of the disease. In addition to the AQ's excellent diagnostic accuracy, this series of studies also demonstrated that it correlates well with established measures of cognition and functional status. In particular, the AQ was associated with longitudinal changes in global cognition and was able to detect a higher proportion of MCI cases relative to other instruments. Although these studies firmly established the clinical validity of the AQ, additional studies are needed to determine how well the AQ corresponds with AD biomarkers. Given that there is now tremendous focus on pre-clinical AD, characterising the AQ's performance in conjunction with AD biomarkers will be important in order to show that it can be used to detect the earliest cognitive changes so that therapeutic interventions can be initiated as quickly as possible to prevent or significantly delay disease progression.

## 10. References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## 11. Appendix

### Appendix 1. The Alzheimer's Questionnaire

| | | Yes | No | Weighted Score |
|---|---|---|---|---|
| | **Memory** | | | |
| 1 | Does the patient have memory loss? | | | 1 |
| 2 | If so, is their memory it worse than a few years ago? | | | 1 |
| 3 | Does the patient repeat questions OR statements OR stories in the same day? | | | 2 |
| 4 | Have you had to take over tracking events OR appointments? OR Does the patient forget appointments? | | | 1 |
| 5 | Does the patient misplace items more than once a month? OR Does the patient misplace objects so that he or she cannot find them? | | | 1 |
| 6 | Does the patient suspect others are moving, hiding or stealing items when they can not find them? | | | 1 |
| | **Orientation** | | | |
| 7 | Does the patient frequently have trouble knowing the day, date, month, year, time? OR Does the patient have to use cues like the newspaper or the calendar to know the day and date more than once a day? | | | 2 |
| 8 | Does the patient become disoriented in unfamiliar places? | | | 1 |
| 9 | Does the patient become more confused outside the home or when traveling? | | | 1 |
| | **Functional Ability** | | | |
| 10 | Excluding physical limitations (e.g. tremor, hemiparesis, etc) does the patient have trouble handling money (tips, calculating change?) | | | 1 |
| 11 | Excluding physical limitations (e.g. tremor, hemiparesis, etc), does the patient have trouble paying bills or doing finances OR Are family members taking over finances because of concerns about ability? | | | 2 |
| 12 | Does the patient have trouble remembering to take medications or tracking medications taken? | | | 1 |
| 13 | Is the patient having difficulty driving? OR Are you concerned about the patient's driving? OR Has the patient stopped driving for reasons other than physical limitations? | | | 1 |
| 14 | Is the patient having trouble using appliances (e.g. microwave, oven, stove, remote control, telephone, alarm clock)? | | | 1 |
| 15 | Excluding physical limitations, is the patient having difficulty in completing home repair or other home related tasks (house keeping) | | | 1 |
| 16 | Excluding physical limitations, has the patient given up or significantly reduced activities such as golfing, dancing, exercising, or crafts? | | | 1 |
| | **Visuospatial** | | | |
| 17 | Is the patient getting lost in familiar surroundings (own neighborhood)? | | | 2 |
| 18 | Does the patient have a decreased sense of direction? | | | 1 |
| | **Language** | | | |
| 19 | Does the patient have trouble finding words other than names? | | | 1 |
| 20 | Does the patient confuse names of family members or friends? | | | 2 |
| 21 | Does the patient have difficulty recognizing people familiar to him/her? | | | 2 |

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# The Alzheimer's Questionnaire: A Proof of Concept Study for a New Informant-Based Dementia Assessment

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**Abstract**. The aim of this pilot study is to determine the feasibility and clinical utility of a brief, informant-based screening questionnaire for Alzheimer's disease (AD) that can be administered in a primary care setting. The Alzheimer's Questionnaire (AQ) was administered to the informants of 188 patients in 3 dementia clinics (50 cognitively normal, 69 mild cognitive impairment (MCI), 69 AD). Total score for the AQ is based upon the sum of clinical symptom items in which the informant responds as being present. Clinical symptoms which are known to be highly predictive of the clinical AD diagnosis are given greater weight in the total AQ score. The mean time of administration of the AQ was $2.6 \pm 0.6$ minutes. Sensitivity and specificity were found to be high for detecting both AD (98.55, 96.00) and MCI (86.96, 94.00) with ROC curves yielding AUC values of 0.99 and 0.95, respectively. This pilot study indicates that the AQ is a brief, sensitive measure for detecting both MCI and AD and could be easily implemented in a primary care setting.

Keywords: Alzheimer's disease, instrument, questionnaire, primary care

## INTRODUCTION

Confidence in making the diagnosis of Alzheimer's disease (AD) and mild cognitive impairment (MCI) remains elusive. Evidence suggests that physicians, bombarded by demands of care by increasing numbers of medical conditions and available treatments, are not sufficiently sensitive to signs of cognitive impairment or early dementia.

Many physicians do not screen for cognitive problems in their practices unless they receive complaints from either patients or patients' families [1–3]. This is unfortunate since a majority of patients with a dementing illness do not report cognitive problems to their health care providers and, on average, family members do not seek medical attention for the patient until several years after the onset of symptoms. As a result, recognition of dementia by primary care physicians is poor until it is moderately advanced [3,4]. Providers cite a lack of confidence in diagnosing AD as a primary reason that nearly half of AD patients remain undiagnosed [1,5,6]. Delaying diagnosis results in increased likelihood of disease progression before intervention is attempted [7]. Screening has been proposed to help combat under-diagnosis but validated, structured, interview based instruments are lacking. The desirable characteristics for a clinician-administered screening instrument include high sensitivity, high specificity, short administration time, minimal training requirements for the instrument administrator and simplicity of scoring [7].

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We have developed the Alzheimer's Questionnaire (AQ), a clinician-administered and informant-based screening instrument as a way to quickly and accurately detect cognitive impairment. Scores for some items are weighted based on their ability to accurately predict the clinical AD diagnosis which is made based on the results from other validated instruments. The AQ offers the advantage of asking simple yes/no questions in a weighted format that gives an absolute score without requiring interpretation of individual domains. This will aid clinicians in asking the most pertinent questions when screening for cognitive decline in the primary care setting [2].

## METHODS

### *Development of the AQ*

Items for the AQ are based on those from other widely used informant-based assessments [8,10–12], but have been adapted for ease and speed of administration. Items for the AQ were selected and approved by a group of clinicians with extensive experience in dementia assessment. The items were selected based on their face validity to assess each of the AQ domains. Six items were selected to be weighted in the AQ total score as it was agreed by the clinicians that these items would clearly differentiate an impaired individual from a cognitively normal individual.

### *Study participants*

The AD and MCI subjects were drawn from the practices of three physicians (MS, RY, US). The cognitively normal (NC) subjects were administered the AQ as part of their annual assessment for a brain donation program as all are required to provide a collateral informant. Since this is a data gathering project, an IRB exemption was granted.

Included in the study were 188 subjects, 50 of which were designated NC, 69 were MCI cases, and 69 were AD cases. The AD subject met NINCDS-ADRDA [13] criteria for a clinical diagnosis of probable and possible AD. Our NC subjects were defined as having no demonstrable cognitively-based limitations of activities of daily living including employment by informant report. MCI cases were diagnosed as such based on Petersen criteria [14]. Consensus diagnosis with a neurologist, geriatric psychiatrist, and neuropsychologist was used to determine the clinical status of each subject. Rigorous criteria were used to exclude anyone with any type of symptomatic or severe brain related neurological or psychiatric illness. Excluded conditions included mental retardation, epilepsy, cerebral infarction or hemorrhage, multiple sclerosis, brain tumor, major depressive disorder (unipolar or bipolar), schizophrenia, traumatic brain injury, and substance abuse. This was done by prospective interview of the participant and careful scrutiny of the medical records. Each subject was asked to identify an informant to provide additional information on cognitive and functional changes.

### *Administration of AQ*

The AQ consists of simple yes/no questions in a weighted format pertaining to five domains which are: Memory, Orientation, Functional Ability, Visuospatial and Language (App 1). Points for each question that are answered "yes" are summed to give a total score. Each subject was accompanied by the informant to a clinic, where the AQ was administered to the informants of consecutive patients.

### *Statistical analysis*

The data were analyzed by first evaluating the sensitivity and specificity of the AQ with regard to identifying both MCI and AD cases. The accuracy of the AQ was then analyzed by using receiver operating characteristic (ROC) curves and their associated area under the curve (AUC) value. The psychometric properties of the AQ were then analyzed through a principal component factor analysis and by Cronbach's alpha which assessed the AQ's internal validity. In addition, correlations of the AQ domain scores were also derived in order to demonstrate internal validity. Analysis of covariance (ANCOVA) was also used to discern statistically significant group differences in AQ scores between the three clinical groups.

## RESULTS

The AQ was administered to the informants 188 subjects. Individuals with Mini-Mental Status Examination (MMSE) scores below 20 were excluded in order reduce the amount of overall variability in the data and so that the data better reflected a population that is likely to be seen in a primary care setting for cognitive complaints. The sample consisted of 45.7% ($n = 86$) females and 54.3% ($n = 102$) males. Detailed

Table 1
Demographic Characteristics of Study Sample

| | NC | MCI | AD | Total |
|---|---|---|---|---|
| N | 50 | 69 | 69 | 188 |
| Mean Age (sd) | 77.60 (7.33) | 74.61 (7.71) | 78.68 (7.21) | 76.90 (7.61) |
| Mean Education (sd) | 15.48 (2.85) | 14.61 (2.60) | 14.52 (2.57) | 14.81 (2.67) |
| Mean MMSE (sd) | 28.86 (1.31) | 27.28 (1.99) | 24.09 (2.50) | 26.53 (2.83) |
| Mean AQ Score (sd) | 2.12 (2.31) | 11.06 (5.12) | 17.64 (4.84) | 11.10 (7.53) |

NC – Normal Control; MCI – Mild Cognitive Impairment; AD – Alzheimer's Disease.

Table 2
Sensitivity, Specificity, and AUC of the AQ

| | Sensitivity (95% CI) | Specificity (95% CI) | AUC (95% CI) |
|---|---|---|---|
| MCI | 86.96 (76.70–93.90) | 94.00 (83.50–98.7) | 0.95 (0.90–0.98) |
| AD | 98.55 (92.20–100.00) | 96.00 (86.30–99.50) | 0.99 (0.96–1.00) |

MCI – Mild Cognitive Impairment;
AD – Alzheimer's Disease.

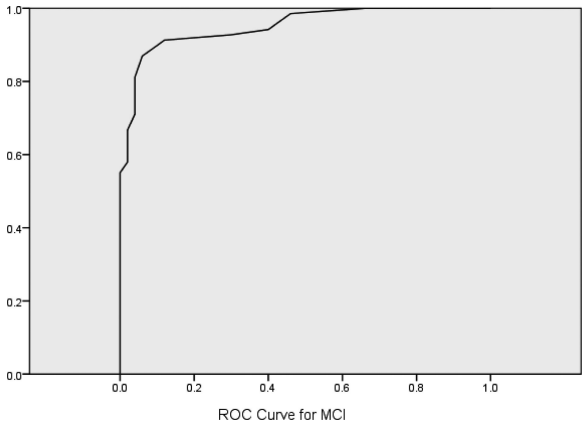


Fig. 1. ROC Curve for MCI (AUC = 0.95).

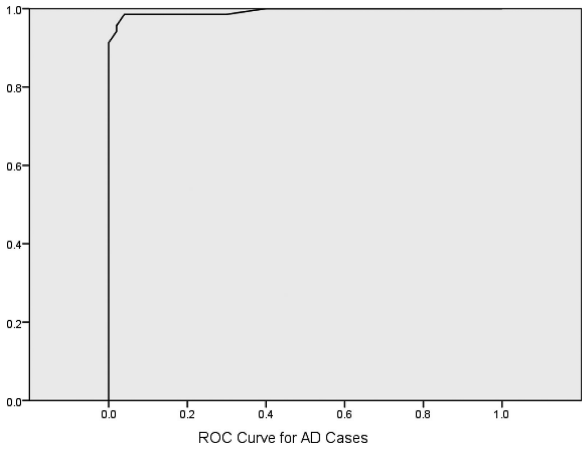


Fig. 2. ROC Curve for NC versus AD (AUC = 0.99).

demographic characteristics are displayed in Table 1. The mean time of administration of the AQ was 2.6 ± 0.6 minutes.

Sensitivity and specificity of the AQ were found to be high for detecting both MCI and AD. In addition, ROC curve analysis yielded high AUC values. Values for sensitivity, specificity, and AUC are displayed in Table 2. Graphical representations of the ROC analyses are displayed in Figs 1 and 2. Internal validity of the AQ was determined to be high as Cronbach's alpha was equal to 0.88. Factor analysis was conducted using the principal component analysis method and showed that all 21 items on the AQ loaded strongly onto one factor which accounted for 33.26% of the total variance with an Eigen value of 6.98.

Correlations between the domain scores of the AQ were also evaluated to further demonstrate internal validity and are shown in Table 3. All correlation values are significant at the $p < 0.0001$ level. Analysis of covariance (ANCOVA) was used to analyze group differences on the AQ. After accounting for the effects of age and education, statistically significant differences on mean AQ score were present between all three clinical groups [F = 177.85 df = (2, 185), $p < 0.0001$].

A separate analysis of the data was conducted with the weights removed from the weighted items. In general, removing the weights did not change sensitivity, specificity, and AUC values (Table 4). Correlations among the AQ domain scores were similar to those found with weighted scores (Table 5). However, the Language domain had notable increases in its correlations with Memory, Orientation, and Functional Ability in the unweighted analysis. In addition, the factor analysis results were almost identical to those of the weighted analysis and Cronbach's alpha was slightly higher (0.89) for the unweighted analysis.

In addition, several items on the AQ that appeared to be similar with respect to content and construct were

Table 3
Correlation of AQ Domain Scores

| Domain | Memory | Orientation | Functional ability | Visuospatial | Language |
|---|---|---|---|---|---|
| Memory | ——— | 0.80 | 0.82 | 0.55 | 0.64 |
| Orientation | 0.80 | ——— | 0.81 | 0.59 | 0.63 |
| Functional Ability | 0.82 | 0.81 | ——— | 0.59 | 0.66 |
| Visuospatial | 0.55 | 0.59 | 0.59 | ——— | 0.41 |
| Language | 0.64 | 0.63 | 0.66 | 0.41 | ——— |

p-value for all correlations is significant at the 0.0001 level.

Table 4
Sensitivity, Specificity, and AUC of the AQ With Unweighted Items

| | Sensitivity (95% CI) | Specificity (95% CI) | AUC (95% CI) |
|---|---|---|---|
| MCI | 87.14 (77.00–93.90) | 92.73 (82.40–98.00) | 0.94 (0.89–0.98) |
| AD | 95.65 (87.80–99.10) | 98.18 (90.30–100.00) | 0.99 (0.96–1.00) |

MCI – Mild Cognitive Impairment; AD – Alzheimer's Disease.

Table 5
Correlation of AQ Domain Scores with Unweighted Items

| Domain | Memory | Orientation | Functional ability | Visuospatial | Language |
|---|---|---|---|---|---|
| Memory | ——— | 0.80 | 0.81 | 0.63 | 0.66 |
| Orientation | 0.80 | ——— | 0.80 | 0.65 | 0.64 |
| Functional Ability | 0.81 | 0.80 | ——— | 0.62 | 0.68 |
| Visuospatial | 0.63 | 0.65 | 0.62 | ——— | 0.44 |
| Language | 0.66 | 0.64 | 0.68 | 0.44 | ——— |

p-value for all correlations is significant at the 0.0001 level.

identified and analyzed to determine if any of the items should be eliminated. These consisted of six questions among three of the domains. Each domain contained two questions that were identified for further analysis. Kappa statistics were calculated for each pair of questions to determine the extent to which they were answered similarly.

For the Orientation domain, "Does the patient become disoriented in unfamiliar places?" and "Does the patient become more confused when travelling outside the home?" yielded a Kappa of 0.34 (0.01, 0.67). For the Visuospatial domain, "Is the patient getting lost in familiar surroundings?" and "Does the patient have a decreased sense of direction?" yielded a Kappa of 0.34 (0.05, 0.62). For the Language domain, "Does the patient confuse names of family members or friends?" and "Does the patient have difficulty recognizing people who are familiar to him/her?" yielded a Kappa of 0.34 (0.01, 0.67).

## DISCUSSION

Two important and conclusive findings are highlighted within the present study. First, the AQ is a sensitive measure for detecting both AD and MCI. Second, the AQ is a time-efficient and easily administered tool with a simple scoring system. As the time taken to administer AQ is less than 3 minutes, making it easy to implement in a primary care setting to screen for cognitive problems. The simplicity of the AQ is reflected in that the total score is easily calculated by summing the number of items that have a "yes" response.

The rationale for weighting certain items on the AQ is that they reflect the presence of cognitive symptoms which are known to be highly predictive of the clinical AD diagnosis, such as disorientation to time (e.g., day of the week, month) and repeating statements and questions within a short period of time [15]. This differentiates the AQ from other informant-based instruments that give equal weight to all of their items as it is then problematic to accurately differentiate cognitive symptoms that are related to AD versus normal aging. The result of utilizing weighted scores for those items that are highly predictive of clinical AD is that high diagnostic accuracy, as demonstrated by the sensitivity, specificity, and ROC curves, is achieved which strongly supports the clinical validity of AQ. In addition, this study also demonstrated high internal validity of the AQ through factor analysis and also with a high Cronbach's alpha. Specifically, the factor analysis shows that the items of the AQ accurately assess memory and other cognitive components that are indicative of MCI and AD.

Table 6
Comparison of AQ Performance with AD8 and IQCODE in AD

| Instrument | Sensitivity | Specificity | AUC | Cronbach's alpha |
|---|---|---|---|---|
| AQ | 98.55 | 96.00 | 0.99 | 0.88 |
| AD8 | 85.00 [8] | 86.00 [8] | 0.83 [8] | 0.86 [25] |
| IQCODE | 79.00 [26] | 82.00 [26] | 0.85 [26] | 0.93–0.97 [9] |

**Appendix 1. The Alzheimer's Questionnaire**

| | Yes | No | Weighted Score |
|---|---|---|---|
| Memory | | | |
| Does the patient have memory loss? | | | 1 |
| If so, is their memory it worse than a few years ago? | | | 1 |
| Does the patient repeat questions OR statements OR stories in the same day? | | | 2 |
| Have you had to take over tracking events OR appointments? OR Does the patient forget appointments? | | | 1 |
| Does the patient misplace items more than once a month? OR Does the patient misplace objects so that he or she cannot find them? | | | 1 |
| Does the patient suspect others are moving, hiding or stealing items when they cannot find them? | | | 1 |
| Orientation | | | |
| Does the patient frequently have trouble knowing the day, date, month, year, time? OR Does the patient have to use cues like the newspaper or the calendar to know the day and date more than once a day? | | | 2 |
| Does the patient become disoriented in unfamiliar places? | | | 1 |
| Does the patient become more confused outside the home or when traveling? | | | 1 |
| Functional Ability | | | |
| Excluding physical limitations (e.g., tremor, hemiparesis, etc.), does the patient have trouble handling money (tips, calculating change?) | | | 1 |
| Excluding physical limitations (e.g., tremor, hemiparesis, etc.), does the patient have trouble paying bills or doing finances OR Are family members taking over finances because of concerns about ability? | | | 2 |
| Does the patient have trouble remembering to take medications or tracking medications taken? | | | 1 |
| Is the patient having difficulty driving? OR Are you concerned about the patient's driving? OR Has the patient stopped driving for reasons other than physical limitations? | | | 1 |
| Is the patient having trouble using appliances (e.g., microwave, oven, stove, remote control, telephone, alarm clock)? | | | 1 |
| Excluding physical limitations, is the patient having difficulty in completing home repair or other home related tasks (housekeeping)? | | | 1 |
| Excluding physical limitations, has the patient given up or significantly reduced activities such as golfing, dancing, exercising, or crafts? | | | 1 |
| Visuospatial | | | |
| Is the patient getting lost in familiar surroundings (own neighborhood)? | | | 2 |
| Does the patient have a decreased sense of direction? | | | 1 |
| Language | | | |
| Does the patient have trouble finding words other than names? | | | 1 |
| Does the patient confuse names of family members or friends? | | | 2 |
| Does the patient have difficulty recognizing people familiar to him/her? | | | 2 |

Analyses of the data without the weights showed no significant differences among the statistical measures; however the inclusion of weights on certain items appears to optimize sensitivity and overall diagnostic accuracy for AD. The unweighted analysis also showed an increase in correlation values among certain domains. Specifically, the Language domain showed increased correlations with Memory, Orientation, and Functional Ability. The reason for this is unclear, but it is possible that removing the weights simply made the data fit a more linear pattern. In addition, questions that appeared to be overlapping in construct measurement did not overlap as shown by the low rate of agreement within the question pairs in each domain. Although these items appear to be similar, they are measuring distinct phenomena.

Although several other informant-based dementia questionnaires have been developed, they have not been validated as accurate instruments in detecting individuals with MCI. This is important as identifying individuals in the earliest stages of cognitive decline will be necessary as the development of disease-modifying therapies become available. Currently-used instruments that are clinician administered such as the MMSE [16, 17], the neurobehavioral cognitive examination [18], the 7 minute screen [19], the time and change test [20], the memory impairment screen [21], the clock drawing test [22], and the mini-cog [23] have demonstrated rela-

tively good diagnostic ability in AD patients. However, the ability of these instruments to identify individuals with MCI is questionable.

In addition, currently used informant-based instruments have not been shown to accurately identify individuals with MCI. The most common clinician-administered [16–23] and informant-based [8–12,24–26] instruments have demonstrated specificities and sensitivities exceeding 80% in identifying AD cases and all take less than 10 minutes to administer. Relative to the most widely used of these instruments, the AQ has higher sensitivity and specificity with regard to identifying AD cases (Table 6), but also high sensitivity and specificity in identifying MCI. In addition, its administration time is comparable and in many cases takes less time to administer.

It is important to note that the AQ is not intended to replace a full diagnostic work-up that is typically done when assessing individuals with memory problems. It should also be noted that the AQ was not used in a general practice setting so it is unclear whether the results of this study represent that of the general geriatric population. This study utilized patients who were seen by dementia specialists and as a result the sample used is biased to a certain extent. Although the ultimate goal is to employ this instrument in general practice, it was employed in specialty practices during this pilot study. In spite of these shortcomings, the AQ may be an extremely useful tool to clinicians who require the use of a brief and accurate assessment of cognition in order to determine if a patient might require further evaluation. Given its diagnostic accuracy, ease of scoring, ease of administration, and short length of time needed for administration the AQ would be of great value to many clinicians who have an extremely limited amount of time in order to assess individuals with memory and cognitive problems.

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**SHORT REPORT**

# Validation and diagnostic accuracy of the Alzheimer's questionnaire

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## Abstract

**Background**: accurately identifying individuals with cognitive impairment is difficult. Given the time constraints that many clinicians face, assessment of cognitive status is often not undertaken. The intent of this study is to determine the diagnostic accuracy of the Alzheimer's questionnaire (AQ) in identifying individuals with mild cognitive impairment (MCI) and AD.
**Methods**: utilising a case–control design, 300 [100 AD, 100 MCI, 100 cognitively normal (CN)] older adults between the ages of 53 and 93 from a neurology practice and a brain donation programme had the AQ administered to an informant. Diagnostic accuracy was assessed through receiver-operating characteristic analysis, which yielded sensitivity, specificity and area under the curve (AUC).
**Results**: the AQ demonstrated high sensitivity and specificity for detecting MCI [89.00 (81.20–94.40)]; [91.00 (83.60–65.80)] and AD [99.00 (94.60–100.00)]; [96.00 (90.10–98.90)]. AUC values also indicated high diagnostic accuracy for both MCI [0.95 (0.91–0.97)] and AD [0.99 (0.96–1.00)]. Internal consistency of the AQ was also high (Cronbach's alpha = 0.89).
**Conclusion**: the AQ is a valid informant-based instrument for identifying cognitive impairment, which could be easily implemented in a clinician's practice. It has high sensitivity and specificity in detecting both MCI and AD and allows clinicians to quickly and accurately assess individuals with reported cognitive problems.

**Keywords:** *mild cognitive impairment, Alzheimer's disease, cognitive screening, informant-based assessment*

## Introduction

Given the expected increase in Alzheimer's disease (AD) prevalence in the USA [1] many clinicians will be faced with the prospect of evaluating many individuals for possible cognitive impairment. This problem may be further compounded by the possibility that screening for cognitive impairment may become mandatory under proposed healthcare reform [2]. Often, the first clinician a patient may see is a primary care physician who often has a limited amount of time to assess the individual. In addition to time constraints, many physicians do not screen for cognitive problems unless they receive complaints from patients or patients' families [3–5]. As a result dementia is not recognised by physicians until it is moderately advanced [6, 7]. Providers also cite a lack of confidence in diagnosing AD as a reason that nearly half of AD patients remain undiagnosed [3, 7, 8].

This necessitates the use of a brief and accurate screening instrument in order to determine, which patients require further assessment. The most common tool used to screen for dementia is the Mini-Mental Status Examination (MMSE) [9]; however, its scores can be biased by education level which can lead to false positive indications of impairment for individuals with low educational attainment and false negative indications of no impairment for highly educated individuals [10]. Informant-based questionnaires, such as the AD8 [11], IQCODE [12] and the DQ [13], have

been developed in order to quickly and accurately identify clinical AD and have demonstrated good sensitivity and specificity (please see Supplementary data available in *Age and Ageing* online, Table S3). Although the Clinical Dementia Rating (CDR) [14] is widely used in clinical research settings, its utility in clinical practice is questionable given the length of time necessary for administration.

The Alzheimer's questionnaire (AQ) was designed to be a brief and easily administered assessment for use with collateral sources. A recent pilot study of the AQ demonstrated high sensitivity and specificity for detecting mild cognitive impairment (MCI) and clinical AD [15]. The intent of the current study is to validate the AQ as an accurate informant-based instrument in detecting both MCI and clinical AD.

## Methods

### Study sample

Three-hundred individuals were included in this study (100 CN, 100 MCI, 100 AD). The AD and MCI cases were drawn from the practices of three physicians and were between the ages of 56 and 93. The cognitively normal (CN) cases were between the ages of 53 and 93 and were recruited from a brain and body donation programme [16] in which the AQ was administered as part of their annual assessment. An exemption was granted for this study by the institutional review board as it fell under the categorisation of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behaviour.

The AD cases met NINCDS-ADRDA [17] criteria for a clinical diagnosis of probable or possible Alzheimer's disease. MCI cases were diagnosed as such based on Petersen criteria [18]. These criteria require the presence of subjective memory complaints and objective memory test performance that falls 1.5 standard deviations below age- and education-corrected mean values. Both single and multiple domain amnestic MCI cases were included. The CN cases were defined as having a global CDR score of 0 and were not impaired in any cognitive domain measured by neuropsychological testing. Individuals with MMSE scores below 20 were excluded so that the data better reflected a population seen in a primary care setting for cognitive complaints.

Consensus diagnosis with a neurologist, geriatric psychiatrist and neuropsychologist was used to determine the clinical status of CN individuals. Consensus diagnoses were made based on neuropsychological testing, neurological and physical exam and interviews with an informant, which assessed global cognitive status, functional status and mood and behavourial status. Clinician's diagnosis consisting of medical history, social history, neuroimaging, clinical laboratory results and neuropsychological testing was used for MCI and AD individuals. Individuals with any type of brain-related neurological or psychiatric illness were excluded.

### The Alzheimer's questionnaire

The AQ [15] is a 21-item, informant-based dementia assessment. AQ items are divided into five domains including Memory, Orientation, Functional Ability, Visuospatial and Language. Items are posed in a yes/no format with the sum of points for 'yes' items equaling the total score that ranges from 0 to 27 with higher scores corresponding to greater impairment. Six items known to be predictive of a clinical AD diagnosis are weighted more heavily in the total score by being worth two points rather than one (please see Supplementary data available in *Age and Ageing* online, Appendix 1). The AQ was administered by a neurologist, geriatric psychiatrist and also by psychometrists trained by the neurologist and geriatric psychiatrist.

Items for the AQ are based on those from other informant-based assessments [11–14]. and were selected by a group of clinicians with extensive experience in dementia assessment. The items were selected based on their face validity to assess each of the AQ domains. Six items were selected to be weighted in the AQ total score as it was agreed that these items would clearly differentiate an impaired individual from a CN individual.

### Statistical analysis

One-way analysis of variance (ANOVA) was used to discern group differences on age, education, MMSE score and AQ total score. Receiver-operating characteristic (ROC) analysis was used to determine sensitivity, specificity, area under the curve (AUC), likelihood ratios and cut-off scores for MCI and AD. Correlations between the mean domain scores were derived in order to assess internal consistency along with Cronbach's alpha. Analysis of covariance (ANCOVA) was used to compare group differences on the AQ total score while using age, education and gender as covariates in order to account for their effects. Bonferroni adjustment was used to correct for multiple comparisons.

## Results

Demographic characteristics are displayed in Table 1. One-way ANOVA yielded statistically significant effects for age, education, MMSE score and AQ total score between

**Table 1.** Demographic characteristics of study sample with mean MMSE and AQ scores

| | CN | MCI | AD | Total | *P*-value |
|---|---|---|---|---|---|
| *n* | 100 | 100 | 100 | 300 | — |
| Age | 77.98 (7.11) | 74.82 (7.58) | 78.17 (7.23) | 76.99 (7.45) | 0.002 |
| Education | 15.46 (2.89) | 14.53 (2.50) | 14.50 (2.48) | 14.83 (2.63) | 0.01 |
| Gender (M/F) | 38/62 | 60/40 | 59/41 | 157/143 | 0.002 |
| MMSE | 28.62 (1.44) | 26.85 (2.50) | 24.15 (2.51) | 26.54 (2.76) | <0.001 |
| AQ score | 2.44 (2.54) | 11.23 (4.80) | 17.74 (4.78) | 10.47 (7.53) | <0.001 |

CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease, Mean (SD); MMSE normal range (26–30), AQ normal range (0–4).

Table 2. Diagnostic accuracy of the AQ in MCI and AD

| | Sensitivity (95% CI) | Specificity (95% CI) | AUC (95% CI) | LR+ (95% CI) | LR− (95% CI) | Cut-off score |
|---|---|---|---|---|---|---|
| MCI | 89.00 (81.20–94.40) | 91.00 (83.60–95.80) | 0.95 (0.91–0.97) | 9.89 (9.00–10.80) | 0.12 (0.05–0.30) | 5 ≤ 14 |
| AD | 99.00 (94.60–100.00) | 96.00 (90.10–98.90) | 0.99 (0.96–1.00) | 24.75 (23.70–25.90) | 0.01 (0.001–0.09) | 15≤[a] |

MCI, mild cognitive impairment; AD, Alzheimer's disease.
[a]Cut-off score derived through ROC analysis of MCI and AD cases with AD as outcome and MCI as the reference group; all other values for AD derived using CN as the reference group.

the clinical groups. An additional one-way ANOVA found a statistically significant difference for gender on the AQ total score. ANCOVA which adjusted for age, education and gender was then used to analyse clinical group differences on the AQ total score [$F = 327.68$, (df = 2, 294), $P < 0.001$].

Sensitivity, specificity, AUC, likelihood ratios (positive and negative) and cut-off scores for the AQ total score are displayed in Table 2. Two ROC analyses were carried out in order to derive AUC values. The first analysis used MCI as the outcome and CN as the reference while the other used AD as the outcome and CN as the reference. An additional ROC analysis was run with AD as the outcome and MCI as the reference in order to determine cut-off scores across a continuum. These analyses yielded high sensitivity and specificity for both MCI and AD.

Internal consistency was high (Cronbach's $\alpha = 0.89$). Correlations among the domain scores were moderate ranging from $r = 0.45$ to $r = 0.69$ (please see Supplementary data available in *Age and Ageing* online, Table S4).

## Discussion

The results of this study show that the AQ is a valid measure of cognitive status and accurately identifies individuals with AD and MCI. In addition, the AQ requires approximately 3 min to administer and is easily interpreted. The rationale for weighting certain items on the AQ is that they reflect the presence of cognitive symptoms which are highly predictive of the clinical AD diagnosis [19]. Given that subjective memory complaints are common among older adults [20] using weighted items may assist in more accurately identifying individuals who are impaired. The AQ is not intended to replace a full diagnostic work-up that is done when assessing cognitive problems. It is intended to be a screening instrument used to determine which individuals require further evaluation.

The data for this study came from patients who were seen by dementia specialists so these results may not represent the general geriatric population. Another problem is that the AQ requires the use of an informant. In many cases, individuals may see a clinician by themselves or may not have a reliable informant. Additionally, the study sample was ethnically homogenous as the majority of participants were Caucasian. One other problem is that the clinical groups were very specific and did not include other diagnostic groups, such as vascular or frontotemporal dementia. In addition, MCI is a heterogeneous condition that can occur from multiple aetiologies and does not necessarily progress to clinical AD. Therefore, screening for this clinical entity can be problematic if other medical and social information is utilised. However, given recent interest in MCI as treatable not entity [21], instruments that identify individuals early in the disease process may help lead to better outcomes.

Overall, the AQ may be a useful tool to clinicians who require the use of a brief and accurate cognitive assessment. As mandates for cognitive screening among older adults are implemented [2], the AQ would fill the need for a brief and simple cognitive screening instrument.

## Conflicts of interest

None declared.

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## Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

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RESEARCH ARTICLE Open Access

# Informant-reported cognitive symptoms that predict amnestic mild cognitive impairment

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## Abstract

**Background:** Differentiating amnestic mild cognitive impairment (aMCI) from normal cognition is difficult in clinical settings. Self-reported and informant-reported memory complaints occur often in both clinical groups, which then necessitates the use of a comprehensive neuropsychological examination to make a differential diagnosis. However, the ability to identify cognitive symptoms that are predictive of aMCI through informant-based information may provide some clinical utility in accurately identifying individuals who are at risk for developing Alzheimer's disease (AD).

**Methods:** The current study utilized a case-control design using data from an ongoing validation study of the Alzheimer's Questionnaire (AQ), an informant-based dementia assessment. Data from 51 cognitively normal (CN) individuals participating in a brain donation program and 47 aMCI individuals seen in a neurology practice at the same institute were analyzed to determine which AQ items differentiated aMCI from CN individuals.

**Results:** Forward stepwise multiple logistic regression analysis which controlled for age and education showed that 4 AQ items were strong indicators of aMCI which included: repetition of statements and/or questions [OR 13.20 (3.02, 57.66)]; trouble knowing the day, date, month, year, and time [OR 17.97 (2.63, 122.77)]; difficulty managing finances [OR 11.60 (2.10, 63.99)]; and decreased sense of direction [OR 5.84 (1.09, 31.30)].

**Conclusions:** Overall, these data indicate that certain informant-reported cognitive symptoms may help clinicians differentiate individuals with aMCI from those with normal cognition. Items pertaining to repetition of statements, orientation, ability to manage finances, and visuospatial disorientation had high discriminatory power.

## Background

The process of differentiating age-associated memory decline from those who might have a clinically significant disorder of memory and cognition is difficult. In particular, distinguishing individuals with amnestic mild cognitive impairment (aMCI) from those who are cognitively normal (CN) is challenging, as memory and cognitive complaints are often reported in both groups from both the patient and informants [1]. Given that the current diagnostic criteria for aMCI include subjective (patient and/or family report of decline) and objective (neuropsychological testing) evidence of memory decline, a clinician's initial impression from a relatively short office visit may not allow for an accurate assessment [2].

Amnestic MCI was first characterized as a syndrome consisting of memory performance at or below 1.5 standard deviations (SD) on age- and education-adjusted normative values on a verbal memory test along with subjective memory complaints, preserved global cognition, and preserved activities of daily living [3]. The diagnostic criteria for MCI have since been refined to differentiate between amnestic and non-amnestic forms, with the latter showing performance at or below 1.5 SD on a test or test(s) in one or more domains other than memory. Both amnestic and non-amnestic MCI can be further classified as single or multiple domain MCI depending upon the number of cognitive domains that show test performance(s) at or below 1.5 SD [4].

Several studies have investigated the clinical course and presentation of individuals who have self- and informant-reported memory complaints [5-8]. Some evidence suggests that individuals who are cognitively normal and have subjective memory complaints demonstrate MRI

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findings that are similar to those of aMCI individuals [9]. Other studies have demonstrated that an informant's report of an individual's cognitive status is valid and highly accurate in the very early stages of AD [6]. Although the diagnostic criteria for aMCI do not include functional impairment, previous studies have found that aMCI patients may have difficulty with higher level daily activities, such as balancing a checkbook, and may show mild, but not significant, difficulty in daily functioning [1,10].

Utilizing additional information with added discriminatory power can aid in identifying individuals at risk for developing Alzheimer's disease (AD), a task of greater interest now, with emerging early AD treatments [10,11]. To accomplish this, identifying certain cognitive symptoms that may yield greater diagnostic accuracy than subjective memory complaints alone is necessary. A recent pilot study found that the Alzheimer's Questionnaire (AQ), an informant-based questionnaire designed for use in primary care settings, has both high sensitivity [87.00 (77.00 - 94.00)] and specificity [94.00 (84.00, 99.00)] for aMCI [12].

The intent of this study is to determine which AQ items are predictive of aMCI. By identifying cognitive symptoms beyond subjective memory complaints, individuals at risk for developing AD may be identified more quickly so that further diagnostic testing and subsequent treatment may be initiated sooner in the disease process.

## Method

### Study Sample

Data from 98 individuals (47 aMCI, 51 CN) were taken from an ongoing validation study of the AQ. Both aMCI and CN individuals were drawn from the same geographic population (Sun City, AZ). A case-control design was used for this study as the aMCI participants were drawn from the practice of a neurologist specializing in dementia and memory disorders. The clinician's diagnosis was used as the gold standard for aMCI participants, based on cognitive and medical history, informant interview, and neuropsychological testing utilizing Petersen criteria [3]. Individuals whose performance was 1.5 standard deviations (SD) below age- and education-corrected means on a delayed recall measure of verbal memory were classified as aMCI. Individuals with both single and multiple domain aMCI were included in the analysis. Multiple domain aMCI cases were classified as those with memory performance 1.5 SD below age- and education-corrected means with performance in another cognitive domain (e.g., executive functions) also falling 1.5 SD below age- and education-corrected means.

CN participants were drawn from a brain and body donation program in which informants were given the AQ as part of the participants' annual assessment. Both aMCI and CN participants were recruited consecutively. CN participants were defined as having no demonstrable cognitively-based limitations of activities of daily living through an informant interview by a physician. In addition, all CN participants scored above 1.5 SD on age- and education-corrected means on a battery of neuropsychological tests and received global CDR rating of 0 [13]. Consensus diagnosis with a neurologist, geriatric psychiatrist, and neuropsychologist was used as the gold standard in determining CN status. The AQ was not utilized in the differential diagnosis for aMCI individuals and was not utilized in the consensus diagnosis for CN individuals. Interviews with the participant and informant and review of medical records were used to exclude those with symptomatic or severe brain-related neurological or psychiatric illness. Excluded conditions included mental retardation, epilepsy, cerebral infarction or hemorrhage, multiple sclerosis, brain tumor, major depressive disorder (unipolar or bipolar), schizophrenia, traumatic brain injury, and substance abuse. Collateral informants provided additional information on cognitive and functional changes.

IRB approval was waived by the Sun Health IRB as the study fell under their categorization of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior which is not subject to review and does not require informed consent. None of the authors on this paper served on the Sun Health IRB and the granting bodies that provided funding for this study did not require any type of ethics review.

### Neuropsychological Tests

#### *Rey Auditory Verbal Learning Test [14]*

A list of 15 words is read aloud to the individual after which they are asked to recall as many words as possible in any order. This is done 5 times. After the fifth trial, a new 15-word list is read aloud to the individual after which they are asked to recall as many words as possible in any order. They are then asked to recall the words they remember from the list that was read to them 5 times. After a 20 minute delay, they are again asked to recall words from the list that was read 5 times.

#### *WMS-R Logical Memory [15]*

A short fictional story is read to the individual after which they are asked to repeat as much of the story as they can remember. After a 20 minute delay, they are asked to recall the story again.

#### *Trails A [16]*

The individual is instructed to draw a line that connects circled numbers in consecutive order.

#### *Trails B [16]*

The individual is asked to draw a line that connects circled numbers and circled letters in consecutive order

while alternating between numbers and letters (1 - A - 2 - B - 3 - C, etc).

***Controlled Oral Word Association Test [14]***

Individuals are given one minute to verbally produce as many words as they can that begin a given letter. One minute per word is given.

***Animal Fluency [14]***

Individuals are given one minute to verbally produce as many names of animals as they can.

***Stroop Color/Word [17]***

The individual is presented with 5 columns of the words "blue", "red", and "green" presented in random order. The words are printed in an ink that is incongruent with the actual word itself (ie, the word "blue" is printed in red ink). The individual is then asked to identify the color of the ink the word is printed in. There is a 45-second time limit in which the individual must give as many correct responses as possible.

***Judgment of Line Orientation [18]***

Individuals are asked to match a set of two lines set at varying angles and lengths to a reference of lines placed below each stimulus card for each trial.

### The Alzheimer's Questionnaire (AQ)

The Alzheimer's Questionnaire (AQ) is a 21-item, informant-based dementia assessment designed for ease of use in a primary care setting. AQ items are divided into five domains including Memory, Orientation, Functional Ability, Visuospatial Ability, and Language. Items are posed in a yes/no format with the sum of 'yes' items equaling the total AQ score (0-27). Six items known to be predictive of a clinical AD diagnosis are weighted more heavily in the total score by being worth two points rather than one.

### Statistical Analysis

Data from the individual AQ items were first analyzed using the Chi-square statistic to determine if there were significant differences in positive response frequencies between aMCI and CN individuals for each item. Multiple forward stepwise logistic regression was carried out to determine the predictive ability of individual AQ items while adjusting for the effects of age and education. For this analysis, clinical status (aMCI) was the outcome and the individual AQ items were entered as predictors. Criteria for retaining predictor variables was set to alpha < .05. Nagelkerke's $R^2$ was used to determine the amount of variance accounted for by the logistic model.

Systat 13.0 was used to carry out all analyses.

## Results

Demographic characteristics of the study sample are displayed in Table 1. The CN group was older and slightly more educated than the aMCI group. Males and females had relatively equal representation across groups. Chi-square analysis showed significant differences in response frequencies for all but two AQ items (Table 2). Results from the multiple forward stepwise logistic regression analysis, which adjusted for age and education, are displayed in Table 3; only the AQ items that were included in the stepwise model are shown. This model yielded four AQ items as strong predictors of aMCI, which are listed in Table 3 with their associated odds ratios (OR), 95% confidence intervals, and *p*-values. The resulting stepwise logistic model yielded a Nagelkerke $R^2$ of 0.71 indicating that a large proportion of the variance between aMCI and CN individuals was accounted for by the four AQ items.

**Table 1 Demographic Characteristics**

| | *CN* | *aMCI* | *Total* |
|---|---|---|---|
| N | 51 | 47 | 98 |
| Male (%) | 43 | 57 | 50 |
| Female (%) | 57 | 43 | 50 |
| Age | 78.59 (6.72) | 74.36 (7.19) | 76.56 (7.23) |
| Education | 15.04 (3.03) | 14.43 (2.51) | 14.74 (2.79) |
| MMSE | 28.47 (1.27) | 26.89 (1.90) | 27.71 (1.78) |

Mean (sd)

In order to more accurately characterize the clinical validity of these findings, a second non-stepwise logistic regression analysis was carried out which used only the four significant AQ items while correcting for age and education. This model yielded sensitivity of 80.30 (67.00, 89.53) and specificity of 81.80 (69.67, 90.37) with an area under the curve (AUC) value of 0.94 (0.89, 0.99).

## Discussion and Conclusions

The results of the study indicate that the four informant-reported items listed immediately above are highly predictive of aMCI. These items are memory-related, and also suggest some degree of impairment in higher-level functional abilities. The use of informant-supplied information is a widely-used and highly valid method of assessing an individual's cognitive and functional abilities [5,7]. Relative to other informant-based instruments [19-22] the AQ takes substantially less time to administer [12], a fact of importance to clinicians with very limited time [23].

For clinicians who see patients with subjective memory complaints, accurate identification of those who need further evaluation is critical to cost containment and resource management. A significant proportion of older adults present with subjective memory complaints [24,25], and these complaints can precede the onset of clinical AD [26]. The large and growing number of older adults underscores the importance of utilizing brief and accurate screening measures. Additionally, as

**Table 2 Frequency of Informant-Reported Cognitive Symptoms for aMCI and CN Groups**

| *Item* | $\chi^2$ | *p-value* | *Yes - aMCI* | *Yes - CN* |
|---|---|---|---|---|
| Does the patient have memory loss? | 25.99 | < .0001 | 46/47 | 27/51 |
| If so, is their memory worse than a few years ago? | 6.30 | .01 | 33/47 | 23/51 |
| Does the patient repeat questions or statements or stories in the same day? | 37.60 | < .0001 | 33/47 | 5/51 |
| Have you had to take over tracking events or appointments, or does the patient forget appointments? | 21.77 | < .0001 | 30/47 | 9/51 |
| Does the patient misplace items more than once a month, or does the patient misplace objects so that he/she cannot find them? | 11.95 | .005 | 33/47 | 18/51 |
| Does the patient suspect others of moving, hiding, or stealing items when he/she cannot find them? | 3.53 | .06 | 7/47 | 2/51 |
| Does the patient frequently have trouble knowing the day, date, month, year, and time; or does the patient reference a newspaper or calendar for the date more than once a day? | 17.79 | < .0001 | 18/47 | 2/51 |
| Does the patient become disoriented in unfamiliar places? | 17.78 | < .0001 | 24/47 | 6/51 |
| Does the patient become more confused when travelling outside the home? | 9.87 | .0017 | 21/47 | 8/51 |
| Excluding physical limitations, does the patient have trouble handling money (tips, calculating change)? | 5.72 | .02* | 5/47 | 0/51 |
| Excluding physical limitations, does the patient have trouble paying bills or doing finances; or are family members taking over because of concerns about ability? | 19.91 | < .0001 | 21/47 | 3/51 |
| Does the patient have trouble remembering to take medications or tracking medications taken? | 16.76 | < .0001 | 19/47 | 3/51 |
| Is the patient having difficulty driving; or are you concerned about the patient's driving; or has the patient stopped driving for reasons other than physical limitations? | 0.50 | .48 | 11/47 | 9/51 |
| Is the patient having trouble using appliances? | 4.31 | .05* | 6/47 | 1/51 |
| Excluding physical limitations, is the patient having difficulty in completing home repair or housekeeping tasks? | 9.16 | .003 | 10/47 | 1/51 |
| Is the patient getting lost in familiar surroundings? | 4.31 | .04 | 6/47 | 1/51 |
| Does the patient have a decreased sense of direction? | 19.99 | < .0001 | 24/47 | 5/51 |
| Does the patient have trouble finding words other than names? | 6.81 | .009 | 24/47 | 13/51 |
| Does the patient confuse names of family members or friends? | 15.94 | < .0001 | 20/47 | 4/51 |
| Does the patient have difficulty recognizing people familiar to him/her? | 6.94 | .009 | 6/47 | 0/51 |

* Fisher's exact test p-value was used due to expected cell counts less than 5

new therapies for AD transition from being symptomatic to disease-modifying, identifying individuals who are at-risk or are in the earliest stages of the disease will be crucial in determining and improving disease outcome [1].

There are some limitations to this study. The first is that the confidence intervals for the odds ratios of the statistically significant AQ items were relatively wide, indicating decreased statistical power. Although the sample was large enough to yield robust odds ratios for the four AQ items, a larger sample size might provide a more accurate estimate of effect size. In addition, the $R^2$ value may not truly represent the amount of variance accounted for by the model. The reason for this is that $R^2$ values in logistic models are approximations of linear-based $R^2$ measures and are not fully equivalent. In addition, $R^2$ measures used in logistic models are prone to bias when used with small sample sizes and may

**Table 3 Multiple Forward Stepwise Logistic Regression Analysis of AQ Items**

| *AQ Item* | *Odds Ratio* | *95% CI* | *p-value* |
|---|---|---|---|
| Does the patient repeat questions or statements or stories in the same day? | 13.12 | (3.02, 57.66) | 0.001 |
| Does the patient frequently have trouble knowing the day, date, month, year, and time; or does the patient reference a newspaper or calendar for the date more than once a day? | 17.97 | (2.63, 122.77) | 0.003 |
| Excluding physical limitations, does the patient have trouble paying bills or doing finances; or are family members taking over because of concerns about ability? | 11.60 | (2.10, 63.99) | 0.005 |
| Does the patient have a decreased sense of direction? | 5.84 | (1.09, 32.30) | 0.04 |

result in an inflated estimate of the amount of variance accounted for [27]. Another limitation is that the AQ itself requires the use of an informant. In some cases, a patient may come to a physician's office alone or they may not have a reliable informant available to do the assessment. Although several patient-based cognitive assessments, such as the Mini Mental State Exam [28], can be used, they are subject to confounding factors such as cultural effects and low education [29-31]. Finally, the study sample was homogenous with respect to ethnicity, as all subjects were Caucasian, so it is unclear whether these results are applicable to an ethnically diverse population.

In addition, the ability of other widely-used informant-based instruments to accurately identify clinical aMCI has not been established. The validity and accuracy of the AD8 has been established in clinical AD and in individuals with a CDR global rating 0.5 which is considered "very mild dementia" [32]. It is important to note that this categorization (CDR = 0.5) does not necessarily equate to a clinical diagnosis of aMCI so it is uncertain whether the AD8 can accurately identify clinically-defined aMCI cases. In addition, a recent study demonstrated that the IQCODE does not have high sensitivity in the detection of aMCI [33]. As mentioned earlier, a previous pilot study of the AQ demonstrated high sensitivity and specificity for aMCI when compared to cognitively normal individuals. The results of the current study showed that four statistically significant AQ items accounted for large proportion of the variance between aMCI and CN individuals and also yielded high sensitivity and specificity in differentiating the two groups. Overall, the results of this study indicate that certain AQ items can differentiate individuals with aMCI from those experiencing age-associated changes in memory and cognition. As assessed by the AQ, difficulties with orientation to time, repetition of questions and statements, difficulties in managing finances, and visuospatial disorientation were all significant predictors of aMCI as diagnosed by an expert in memory disorders.

Given that memory complaints are commonly reported by elderly patients and their family members [7], a means to quickly and accurately identify individuals who may be in the early stages of AD and in need of further evaluation is critical to not only cost containment and resource management, but also to earlier diagnosis in order to improve disease outcome. These data indicate that problems with orientation to time, repeating statements and questions, difficulty managing finances, and trouble with visusospatial orientation may accompany memory deficits in aMCI. From a clinical standpoint, these findings are important as it will allow clinicians to more easily and accurately determine which individuals require further assessment of cognitive problems.

#### List of abbreviations

AD: Alzheimer's disease; AQ: Alzheimer's Questionnaire; aMCI: amnestic mild cognitive impairment; CN: cognitively normal; OR: odds ratio.

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#### Authors' contributions

All authors read and approved the final version of the manuscript. MM developed the study hypothesis, conducted the statistical analysis, drafted the manuscript, and administered the AQ. KD administered the AQ. CB aided in drafting the manuscript and administered the AQ. SJ aided in drafting the manuscript and administered the AQ. MS developed the research hypothesis, administered the AQ, and aided in drafting the manuscript.

#### Competing interests

None of the authors have competing interests to report. The AQ is copyrighted by Banner Health and is freely available by submitting a request to the authors via e-mail.

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# Comparative Analysis of the Alzheimer Questionnaire (AQ) With the CDR Sum of Boxes, MoCA, and MMSE

*Michael Malek-Ahmadi, MSPH, Kathryn Davis, BA, Christine M. Belden, PsyD, and Marwan N. Sabbagh, MD*

**Abstract:** The Alzheimer Questionnaire (AQ) has been established as a valid and accurate informant-based screening questionnaire for Alzheimer disease and amnestic mild cognitive impairment. Although the AQ's validity and diagnostic accuracy has been established, its performance in comparison with other instruments has not. Thirty-nine amnestic mild cognitive impairment cases and 34 Alzheimer disease cases were matched on the basis of age, education, and sex to 73 cognitively normal individuals. The sample had a mean age of 82.54 ± 7.77 years and a mean education level of 14.61 ± 2.61 years. The diagnostic accuracy of the CDR Sum of Boxes, Mini Mental State Exam (MMSE), and Montreal Cognitive Assessment (MoCA) were compared with the AQ. The AQ correlated strongly with the CDR Sum of Boxes ($r = 0.79$) and demonstrated similar diagnostic accuracy with the MoCA and MMSE. These results suggest that the AQ is comparable with other established informant-based and patient-based measures.

**Key Words:** cognitive screening, mild cognitive impairment, neuropsychological tests, dementia screening

(*Alzheimer Dis Assoc Disord* 2012;00:000–000)

The Alzheimer Questionnaire (AQ) has been established as a valid and accurate informant-based screening questionnaire for both Alzheimer disease (AD) and amnestic mild cognitive impairment (aMCI).[1] It is similar in content and structure to other informant-based dementia screening questionnaires,[2,3] but contains questions that probe several domains including memory, orientation, functional ability, visuospatial function, and language. Given the widespread use of measures such as the Clinical Dementia Rating (CDR),[4] Mini Mental State Exam (MMSE),[5] and the Montreal Cognitive Assessment (MoCA),[6] comparing the AQ's performance to them is important to further establish its validity. As the AQ is purely an informant-based instrument, comparing it to patient-based assessments (MoCA and MMSE) and with the CDR, which uses both informant-based and patient-based information, a broader assessment of the AQ's validity can be made from these comparisons.

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## METHODS

### Study Sample

Data from 146 individuals participating in a brain and body donation program[7] were used for this study. Participants in this program are recruited predominantly from the northwest region of the Phoenix, Arizona metropolitan area. Informed consent was obtained from all individuals before enrolling in the program. The age of the participants for this study ranged from 57 to 97 years with a mean of 82.54 ± 7.77 years and had a mean education level of 14.61 ± 2.61 years and included 82 females and 64 males. Of the 146 individuals, 73 were classified as cognitively normal (CN), 39 as aMCI, and 34 as AD. Demographic characteristics of the clinical groups are reported in Table 1. Each aMCI and AD individual was matched on the basis of age, education, and sex to a CN individual. Both single and multiple domain aMCI cases were categorized as aMCI and both possible and probable AD were categorized as AD. The AD cases met NINCDS-ADRDA[8] criteria for a clinical diagnosis of probable or possible AD. The aMCI cases were diagnosed as such based on Petersen criteria.[9] The CN cases were defined as having no limitations of activities of daily living by informant report and were within normal limits on neuropsychological testing.

Consensus diagnosis with a neurologist, geriatric psychiatrist, and neuropsychologist was used to determine the clinical status of each individual. Consensus diagnoses were made based on neuropsychological testing results, neurological and physical examination, and interviews with an informant that assessed global cognitive status, functional status, and mood and behavioral status. The AQ was not used in making the consensus diagnosis.

### Statistical Analysis

Diagnostic accuracy of the individual tests was assessed using ROC analysis through the use of area under the curve (AUC) values. The Shapiro-Wilk test was performed on the data to determine the normality of distribution for the continuous variables. Nonparametric tests for group comparisons and correlations were used as the data for all continuous variables were not normally distributed. The Kruskall-Wallis test was used to compare the AQ total score among participants when grouped by both clinical status (CN, aMCI, AD) and CDR Global Score (0; 0.5; 1, 2, 3). The Conover-Inman test was used to assess groupwise differences for the Kruskall-Wallis tests. A Bonferroni-adjusted *P*-value of 0.02 was used to determine statistical significance for the clinical group and CDR

**TABLE 1.** Clinical Group Demographic Characteristics

| | CN | aMCI | AD | *P* |
|---|---|---|---|---|
| Sex (M/F) | 40/33 | 21/18 | 21/13 | 0.75 |
| Age (y) | 82.59 (7.67) | 80.54 (8.43) | 84.74 (6.74) | 0.07 |
| Education (y) | 14.55 (2.41) | 14.77 (2.53) | 14.56 (3.15) | 0.76 |

AD indicates Alzheimer disease; aMCI, amnestic mild cognitive impairment; CN, cognitively normal; F, female; M, male.

Global Score group comparisons. Cohen's *d* was used to assess the effect size for each group comparison. Spearman correlation analysis was used to determine the degree of association between the AQ, CDR-SOB, MoCA, and MMSE. A false discovery rate[10] *P*-value of 0.008 was used to correct for multiple comparisons among the correlations. Statistical analyses were carried out using Systat 12.0 (Systat Inc., Chicago, IL) and MedCalc 12.2 (MedCalc Software, Mariakerke, Belgium).

## RESULTS

The Shapiro-Wilk test found that age, education, AQ, MoCA, MMSE, and CDR-SOB were not normally distributed. The distribution of males and females between clinical groups was not statistically significant ($\chi^2 = 0.57$, $df = 2$, $P = 0.75$) (Table 1). There were no significant differences in age (Kruskall-Wallis = 5.35, $df = 2$, $P = 0.07$) or education level (Kruskall-Wallis = 0.54, $df = 2$, $P = 0.76$) between the clinical groups (Table 1).

Table 2 shows the AUC values with 95% confidence intervals for each of the instruments for all clinical groups. The AQ, MoCA, and MMSE demonstrated comparable AUC values for both aMCI and AD, whereas the CDR-SOB demonstrated greater discriminatory power for aMCI than the other instruments. Groupwise comparisons from the Kruskall-Wallis test demonstrated that all 3 clinical groups were significantly different from each other on AQ total score (Kruskall-Wallis = 79.55, $df = 2$, $P < 0.001$; all groupwise comparisons $P < 0.001$). Effect sizes (Cohen's *d*) for AQ clinical group differences were as follows: CN versus aMCI = 0.98, CN versus AD = 3.51, aMCI versus AD = 2.04. The AQ correlated strongly with the CDR-SOB ($r = 0.79$) and correlated moderately with the MMSE ($r = -0.56$) and MoCA ($r = -0.46$). The MoCA was moderately correlated with the MMSE ($r = 0.63$) and CDR-SOB ($r = -0.62$). The MMSE and CDR-SOB were strongly correlated ($r = -0.76$). All correlations yielded *P*-values that were $P < 0.001$.

**TABLE 2.** Diagnostic Accuracy Comparison of AQ, CDR-SOB, MMSE, and MoCA

| | CN vs. aMCI | CN vs. AD | CN vs. aMCI + AD |
|---|---|---|---|
| AQ | 0.74 (0.62, 0.83) | 0.99 (0.91, 1.00) | 0.81 (0.72, 0.87) |
| CDR-SOB* | 0.87 (0.77, 0.94) | 0.99 (0.92, 1.00) | 0.89 (0.82, 0.94) |
| MMSE | 0.76 (0.64, 0.85) | 0.97 (0.87, 1.00) | 0.80 (0.72, 0.87) |
| MoCA | 0.71 (0.60, 0.81) | 0.94 (0.82, 0.99) | 0.78 (0.70, 0.85) |

AUC (95% CI).

*CDR-SOB was used to make consensus diagnosis.

AD indicates Alzheimer disease; aMCI, amnestic mild cognitive impairment; AQ, Alzheimer Questionnaire; AUC, area under the curve; CDR, Clinical Dementia Rating; CI, confidence interval; CN, cognitively normal; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment.

An additional analysis was carried out to characterize the AQ's performance when participants were grouped according to their Global Score on the CDR [CDR 0 (n = 66); CDR 0.5 (n = 49); CDR 1, 2, 3 (n = 31)]. Individuals with a CDR Global Score of 1, 2, and 3 were combined as these 3 subgroups were not significantly different from each other when compared separately on the AQ total score. A statistically significant difference for the AQ total score was noted between the 3 CDR Global Score groups (Kruskall-Wallis = 82.35, $df = 2$, $P < 0.001$; all groupwise comparisons $P < 0.001$). Cohen's *d* was used to assess the effect sizes of these group differences and found the following: CDR 0 versus CDR 0.5 = 1.27; CDR 0 versus CDR 1, 2, 3 = 3.70; CDR 0.5 versus CDR 1, 2, 3 = 1.87.

## DISCUSSION

This study demonstrated that the AQ is comparable with other commonly used informant-based and patient-based measures in terms of its ability to differentiate aMCI and AD patients from those who are CN. When the study sample was grouped according to the CDR Global Score, there were very large differences between the dementia (AD), questionable dementia (aMCI), and no dementia (CN) groups on the AQ total score.

The AQ's AUC value for aMCI was much lower than previously reported,[1] which is likely due to the smaller sample size of the current study. The validation study of the AQ[1] used a larger sample (100 CN, 100 aMCI, and 100 AD); however, its ability to differentiate aMCI in this study was similar to the MMSE and MoCA. The CDR-SOB yielded a higher AUC than the AQ, but this is likely because the CDR-SOB was used to make the consensus diagnoses, resulting in an inflated AUC value. Despite this weakness, the inclusion of the CDR-SOB AUC value does provide some frame of reference to compare with the other instruments. The AQ correlated moderately with the MMSE and MoCA, which is expected as the modalities of instrument administration (patient-based vs. informant-based) differ greatly.

One weakness of the study is that the sample was homogenous with respect to ethnicity as the majority of participants in this study were white. Therefore, it is unclear whether these results can be applied to a more ethnically diverse population. Another weakness is the relatively small sample size to assess diagnostic accuracy of the instruments used in the study. Despite these shortcomings, this study demonstrated that the AQ's performance is comparable with other widely-used informant-based and patient-based instruments.

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# Neuropsychological Correlates of the Alzheimer's Questionnaire

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**Abstract**. Informant-based assessments of cognition and function are commonly used to differentiate individuals with amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) from those who are cognitively normal. However, determining the extent to which informant-based measures correlate to objective neuropsychological tests is important given the widespread use of neuropsychological tests in making clinical diagnoses of aMCI and AD. The aim of the current study is to determine how well the Alzheimer's Questionnaire (AQ) correlates with objective neuropsychological tests. The study utilized data from 300 individuals participating in a brain and body donation program. Individuals diagnosed with aMCI ($n = 83$) and AD ($n = 67$) were matched on age, gender, and education to a control individual ($n = 150$). The average age for the entire sample was $83.52 \pm 6.51$ years with an average education level of $14.57 \pm 2.55$ years. Results showed that the AQ correlated strongly with the Mini-Mental State Exam ($r = -0.71$, $p < 0.001$) and the Mattis Dementia Rating Scale-2 ($r = -0.72$, $p < 0.001$), and moderate correlations were noted for the AQ with memory function (Rey Auditory Verbal Learning Test Delayed Recall, $r = -0.61$, $p < 0.001$) and executive function (Trails B, $r = 0.53$, $p < 0.001$). The findings of this study suggest that the AQ correlates well with several neuropsychological tests and lend further support to the validity of the AQ as a screening instrument for cognitive impairment.

Keywords: Alzheimer's disease, dementia, mild cognitive impairment, neuropsychology

## INTRODUCTION

As the prevalence of Alzheimer's disease (AD) continues to increase [1], so too does the need for a brief and accurate informant-based screening tool for the detection of AD and amnestic mild cognitive impairment (aMCI). Informant-based questionnaires are commonly used in both clinical and research settings for the purpose of differentiating aMCI and AD individuals from those who are cognitively normal (CN) [2, 3]. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and AD8 have demonstrated good diagnostic accuracy for AD and have been found to correlate well with other conventional cognitive screening tests, such as the Mini-Mental State Examination (MMSE) [4, 5]. However, these measures may not accurately identify aMCI individuals.

The Alzheimer's Questionnaire (AQ) is a 21-item, informant-based assessment designed for ease of use in the clinical setting that has demonstrated high sensitivity and specificity for both aMCI and AD [6, 7]. The concurrent validity of the AQ with other established measures of cognition was demonstrated by Malek-Ahmadi et al. [8] who found that the AQ correlates strongly with the Clinical Dementia Rating Sum of Boxes ($r = 0.79$) and moderately with the

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MMSE ($r = -0.56$) and Montreal Cognitive Assessment (MoCA) ($r = -0.46$).

Although the diagnostic accuracy and concurrent validity of the AQ have been established [6–8], the degree to which the AQ is associated with neuropsychological and cognitive screening tests has not been investigated. Since neuropsychological tests are utilized in making clinical diagnoses of aMCI and AD, determining the extent to which the AQ correlates with objective and specific measures of various cognitive domains is needed in order further validate its ability to detect cognitive changes associate with aMCI and AD. This study will determine the extent to which the AQ correlates with performance-based neuropsychological tests commonly used in clinical settings, as well as its correlation with other cognitive screening instruments.

## METHODS

### *Study sample*

Data from 300 individuals participating in the Banner Sun Health Research Institute (BSHRI) Brain and Body Donation Program were utilized for this study [9]. Participants in this program are recruited predominantly from the northwest region of the Phoenix, Arizona metropolitan area and are recruited from a variety of sources (clinic referral, community advertisement, talks in the community given by clinicians, word-of-mouth referral from current participants). Written informed consent, approved by the (BSHRI) Institutional Review Board, was obtained from all subjects. Each subject with aMCI or AD was matched on age, education, and gender to a CN individual, without replacement. When an exact match could not be found, a tolerance of $\pm$ 2 years was used for age and education in order to obtain an approximate match.

Both single and multiple domain aMCI cases were categorized as aMCI. Amnestic MCI cases were diagnosed using Petersen criteria [10] and were considered to be aMCI due to AD. The AD cases met NINCDS-ADRDA criteria for a clinical diagnosis of probable or possible AD [11]. The CN cases were defined as having no limitations of activities of daily living by informant report, were within normal limits on neuropsychological testing, and did not receive a clinical diagnosis of any cognitive disorder. Informants for all individuals were a spouse/significant other, a child, or a friend with frequent and close contact to the individual.

Consensus diagnoses were made by the study physician and neuropsychologist based on neuropsychological testing results, neurological and physical exam findings, and interviews with the subject and an informant that assessed global cognition, functional status, and mood and behavioral status. The AQ was not utilized in making the consensus diagnoses and is utilized as a measure independent of diagnosis for research purposes. The AQ was administered and scored in a manner that was blinded from neuropsychological assessments in order to avoid bias.

### *Instruments*

#### *Alzheimer's questionnaire [7]*

The AQ is a 21-item, informant-based dementia screening assessment designed for ease of use in a primary care setting. AQ items are divided into the following five domains: Memory, Orientation, Functional Ability, Visuospatial Ability, and Language. Items are posed in a yes/no format with the count of 'yes' responses equaling the total AQ score (0–27). For the AQ, higher scores indicate greater impairment. Six items known to be predictive of a clinical AD diagnosis are weighted more heavily and are worth two points each.

#### *Mini-mental state examination [12]*

The MMSE is a brief, 30-point cognitive screening instrument that includes items measuring Orientation, Memory, Language, Attention, and Visuospatial functions.

#### *Montreal cognitive assessment [13]*

The MoCA is a brief, 30-point cognitive screening instrument that assesses cognitive domains including Attention and Concentration, Executive Functions, Memory, Language, Visuoconstructional Skills, Conceptual Thinking, Calculations, and Orientation.

#### *Mattis dementia rating scale-2 (DRS-2) [14]*

The DRS-2 is a widely-utilized, structured assessment of cognitive function. The instrument has five subscales: Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory, with the subscales used to derive a total score. For this study, only the total score was used for the analyses.

#### *Clock drawing test [15]*

For this test, individuals are given a blank sheet of paper and asked to draw the face of a clock and to set the time to ten past eleven. A 10-point scoring system [15] was used which is based on three components: Integrity of Clock Face (0–2 points), Presence and Sequencing

of Numbers (0–4 points), Presence and Placement of Hands (0–4 points).

*Rey auditory verbal learning test (AVLT) [16]*

A list of 15 words is read aloud to the individual, after which they are asked to recall as many words as possible in any order, for a total of 5 repeated trials. After the fifth trial, a new, distractor, 15-word list is read aloud to the individual, from which they recall as many words as possible. They are asked to recall the words they remember from the initial list after the distractor list and once more after a 20-minute delay. AVLT Total is the sum of the number of correctly recalled words for Trials 1–5. AVLT Delayed Recall is the number of correct words recalled after a 20-minute delay.

*Brief visuospatial memory test-revised (BVMT-R) [17]*

The BVMT-R is a test of visuospatial memory in which subjects are presented with a page containing six unique designs for 10 seconds. After the 10-second presentation, subjects are asked to draw the shapes on a blank page. Three such 10-second learning trials are administered, and after a delay of 20 to 25 minutes, subjects are asked to draw the shapes again on a blank page. BVMT-R Total Score is the sum of points from the three learning trials while the BVMT-R Delayed Recall is the number of points from the delayed recall trial.

*Trails A [18]*

During this test, the individual is instructed to draw a line that connects circled numbers in consecutive order.

*Trails B [18]*

The individual is asked to draw a line that connects circled numbers and circled letters in consecutive order while alternating between numbers and letters (1 – A – 2 – B – 3 – C, etc.).

*Digit span forward [19]*

Number sequences of increasing length are read aloud to the participant, after which the number series is repeated back to the examiner.

*Digit span backward [19]*

Number sequences are read aloud to the participant, after which the number series is repeated back to the examiner in reverse order.

*Controlled oral word association test (COWAT) [20]*

Individuals are given one minute to say out loud as many words as they can that begin with a specified letter.

*Animal fluency [20]*

For this test, individuals are given one minute to say out loud as many names of animals as they can.

*Stroop color/word [21]*

The individual is presented with 5 columns of the words “blue”, “red”, and “green” presented in random order. The words are printed in an ink that is incongruent with the actual word itself (e.g., the word “blue” is printed in red ink). The individual is then asked to identify the color of the ink of the printed word. There is a 45-second time limit in which the individual must give as many correct responses as possible.

*Judgment of line orientation (JLO) [22]*

Individuals are asked to match a set of two lines, set at varying angles and lengths, to their respective reference lines located below each stimulus card.

*Block design [23]*

Subjects manipulate a set of colored blocks to create a design matching the stimulus design.

*Boston naming test 30-item (BNT) [24]*

The BNT consists of 30 line drawings of objects shown individually to the subject, who is asked to name the object.

*Geriatric depression scale (GDS) [25]*

The GDS is a 30-item depression screening questionnaire designed for older adults.

*Statistical analysis*

For the demographic variables, Chi-square analysis was used to examine the distribution of males and females among the three groups while the Kruskall-Wallis test was used to determine whether age and education differed significantly between groups. The Shapiro-Wilk test was used to determine whether the AQ and the individual neuropsychological variables were normally distributed. Since the neuropsychological variables and the AQ did not meet the assumption of normality, Spearman correlation analyses were carried out to assess the linear associations between the AQ and the neuropsychological measures. Correlation values were interpreted as weak (0.00–0.39), moderate (0.40–0.69), or strong (0.70–1.00). Data for DRS-2 and Block Design were only available from smaller subsets of the study sample (DRS-2, $n = 79$; Block Design, $n = 55$). In order to minimize the impact of floor and ceiling effects from the AD and CN groups

on neuropsychological tests, the CN, aMCI, and AD groups were analyzed together. This also allowed for the relationship between the AQ and the individual cognitive tests to be assessed on a continuum of cognitive impairment.

The percentage of variance accounted by each cognitive test in AQ score was determined by using robust least median of squares regression models with AQ score as the outcome and cognitive test as the predictor. Each test was modelled independently in order to obtain a $R^2$ value that was unique to each of the tests.

The additional predictive value of the AQ in aMCI for a select subset of tests was assessed through a series of logistic regression models. The first series of models used only the cognitive test score as predictor with CN/aMCI as the outcome. A second series of models included the AQ score along with the cognitive test. Area under the curve (AUC) values between the first and second models were compared in order to determine if the AQ added a significant amount diagnostic accuracy when combined with a cognitive test. All models included the GDS score in order to account for the effect of depressive symptoms on cognitive performance.

Statistical analyses were carried out using Systat 12.0 (Systat, Inc., San Jose, CA).

## RESULTS

The sample for this study ranged in age from 67 to 99 years, with a mean of $83.52 \pm 6.51$ and a mean educational level of $14.57 \pm 2.55$ years. The sample included 163 females and 137 males. Of the 300 subjects, 150 were classified as CN, 83 were classified as aMCI, and 67 were classified as AD. Demographic characteristics and results of the neuropsychological tests for each of the clinical groups are reported in Table 1. The groups were not significantly different in terms of age ($p = 0.99$) or education ($p = 0.33$). The Chi-square analysis indicated that there was no significant difference in the distribution of males and females among the three clinical groups ($p = 0.90$).

Correlations between the AQ and the individual cognitive measures are shown in Table 2. Each cognitive test was grouped according to its respective domain of assessment (General Cognition: DRS-2, MoCA, MMSE, Clock; Memory: AVLT and BVMT; Executive Function: Trails B, COWAT, Stroop Color/Word; Language: BNT and Animal Fluency; Attention: Trails A, Digit Span Forward, Digit Span Backward; Visuospatial: JLO and Block Design).

The AQ correlated strongly with DRS-2 Total ($r = -0.72$) and the MMSE ($-0.71$). The AQ showed a



Table 1
Demographic characteristics and neuropsychological data

| | CN | aMCI | AD | Total | *p*-value |
|---|---|---|---|---|---|
| n | 150 | 83 | 67 | 300 | – |
| Age | $83.45 \pm 6.49$ | $83.59 \pm 6.66$ | $83.56 \pm 6.44$ | $83.52 \pm 6.51$ | 0.99 |
| Education | $14.57 \pm 2.50$ | $14.88 \pm 2.62$ | $14.18 \pm 2.58$ | $14.57 \pm 2.55$ | 0.33 |
| Gender (M/F) | 82/68 | 44/39 | 38/29 | 164/136 | 0.90 |
| GDS | 4 [1, 7] | 3 [2, 7] | 5 [2, 8] | – | 0.18 |
| AQ | 0 [0, 2] | 10 [3, 13.75] | 22 [19, 27] | – | – |
| MMSE | 29 [27, 30] | 27 [24, 28] | 19 [14, 22] | – | – |
| MoCA | 26 [24, 28] | 21.50 [19, 23] | 14 [9.75, 18.25] | – | – |
| DRS-2 | 140 [134, 141] | 128 [126, 134] | 102 [70, 123] | – | – |
| Clock Draw | 10 [9, 10] | 9 [8, 10] | 8 [5, 9] | – | – |
| AVLT Total | 40.50 [33, 50] | 27 [21, 31] | 19 [15, 23] | – | – |
| AVLT Delayed Recall | 8 [5, 11] | 2 [0, 3] | 0 [0, 0] | – | – |
| BVMT-R Total | 16 [11, 22] | 8 [5, 10] | 4 [1, 5.25] | – | – |
| BVMT-R Delayed Recall | 7 [5, 9] | 3 [1, 4] | 0 [0, 1] | – | – |
| Trails B | 93 [73, 123] | 159 [119.25, 221] | 300 [219, 300] | – | – |
| Stroop Color/Word | 30 [23, 37] | 21 [15.25, 29] | 15 [8, 24.50] | – | – |
| COWAT | 36 [31, 45] | 29 [23, 39] | 24 [15, 37.25] | – | – |
| Trails A | 37 [30, 46.50] | 52 [40, 62] | 74.50 [55, 123] | – | – |
| Digit Span Forward | 8 [6, 9] | 8 [6, 9] | 7 [5.25, 8] | – | – |
| Digit Span Backward | 6 [5, 8] | 5 [4, 6] | 4 [3, 5] | – | – |
| BNT | 27 [25, 28] | 25 [23, 27] | 21 [17, 23] | – | – |
| Animal Fluency | 17 [14, 20] | 13 [11, 16] | 8 [6, 12] | – | – |
| Block Design | 29 [24, 34] | 26 [16, 32] | 20 [16, 24] | – | – |
| JLO | 24 [20, 27] | 21 [18, 23.75] | 20 [16, 24] | – | – |

Mean±standard deviation. Median [interquartile range].

Table 2
Correlation values for neuropsychological tests with the AQ

| Domain | Test | Correlation with AQ | *p*-value | $R^2$ |
|---|---|---|---|---|
| General Cognition | | | | |
| | MMSE | −0.71 | <0.001 | 0.63 |
| | MoCA | −0.68 | <0.001 | 0.57 |
| | DRS-2 | −0.72 | <0.001 | 0.71 |
| | Clock Draw | −0.38 | <0.001 | 0.31 |
| Memory | | | | |
| | AVLT Total | −0.62 | <0.001 | 0.44 |
| | AVLT Delayed Recall | −0.61 | <0.001 | 0.43 |
| | BVMT-R Total | −0.61 | <0.001 | 0.41 |
| | BVMT-R Delayed Recall | −0.65 | <0.001 | 0.49 |
| Executive Function | | | | |
| | Trails B | 0.53 | <0.001 | 0.52 |
| | Stroop Color/Word | −0.51 | <0.001 | 0.32 |
| | COWAT | −0.27 | <0.001 | 0.11 |
| Attention | | | | |
| | Trails A | 0.52 | <0.001 | 0.41 |
| | Digit Span Forward | −0.21 | <0.001 | 0.06 |
| | Digit Span Backward | −0.37 | <0.001 | 0.18 |
| Language | | | | |
| | BNT | −0.44 | <0.001 | 0.14 |
| | Animal Fluency | −0.56 | <0.001 | 0.41 |
| Visuospatial | | | | |
| | Block Design | −0.24 | 0.08 | – |
| | JLO | −0.28 | <0.001 | 0.11 |

$R^2$ value derived from least median of squares regression model; $R^2$ for Block Design could not be derived to a large number of missing AD cases.



moderate correlation with the MoCA ($r = -0.68$) and a weak correlation with Clock Draw ($r = -0.32$). The AQ also demonstrated moderate correlations with measures of memory and executive function, as lower performance on the memory measures was associated with greater reported impairment on the AQ. For the measures of attention, the AQ correlated moderately with Trails-A, but demonstrated weak correlations with Digit Span Forward and Digit Span Backward. Both language measures also correlated moderately with the AQ. For visuospatial function, the JLO demonstrated a weak correlation with the AQ while Block Design demonstrated no correlation as the correlation value was not statistically significant. Measures of general cognition, memory, and executive function each accounted for a substantial proportion of variance in the AQ score. Within-group correlations are shown in Table 3.

Analyses showing the added diagnostic value of the AQ with select cognitive tests are shown in Table 4. For these analyses, we selected measures of general cognition delayed recall memory measures as they are often used independently to differentiate clinical groups while many of the other domain-specific cognitive tests are often used in a broader diagnostic framework and interpreted in relation to other tests. We chose to limit our analyses to CN versus aMCI cases as they would provide the most informative classification data given that aMCI/AD research has shifted toward identifying individuals in the pre-clinical stages of the disease. On its own, the AQ demonstrated good diagnostic accuracy for aMCI (AUC = 0.83, 95% CI: (0.77, 0.88)). When used in combination with different cognitive tests, the only test which showed significant benefit of the AQ's addition was the MMSE as the AUC value significantly improved.

The association statistics for the GDS as it was used in the logistic regression models are shown in Table 5. For all of the models, no significant association was present.

## DISCUSSION

The results of this study demonstrate that the AQ, an informant-based assessment, correlates well with several performance-based neuropsychological and cognitive screening tests commonly used in clinical settings. The AQ correlates most strongly with the DRS-2, MMSE, and the MoCA. In the current study, the AQ demonstrated stronger correlations with the MoCA and MMSE than those reported previously (MMSE, $r = -0.56$; MoCA, $r = -0.46$) [8], possibly due to the larger sample size of the current study. The use of a larger sample size allows for more a precise interpretation of the AQ's correlation with

Table 3
Within-group correlation values for neuropsychological tests with the AQ

| Domain | Test | CN | aMCI | AD |
|---|---|---|---|---|
| General Cognition | | | | |
| | MMSE | 0.15 | −0.82 | −0.34 |
| | MoCA | −0.28 | 0.37 | −0.12 |
| | DRS-2 | −0.31 | −0.26 | −0.61 |
| | Clock Draw | 0.29 | 0.30 | −0.37 |
| Memory | | | | |
| | AVLT Total | −0.22 | 0.12 | −0.03 |
| | AVLT Delayed Recall | −0.04 | 0.46 | −0.02 |
| | BVMT-R Total | −0.48 | −0.17 | −0.34 |
| | BVMT-R Delayed Recall | −0.60 | 0.31 | −0.05 |
| Executive Function | | | | |
| | Trails B | 0.09 | −0.29 | 0.41 |
| | Stroop Color/Word | −0.34 | −0.55 | −0.31 |
| | COWAT | −0.39 | 0.20 | 0.03 |
| Attention | | | | |
| | Trails A | −0.01 | 0.35 | 0.23 |
| | Digit Span Forward | 0.03 | −0.19 | −0.36 |
| | Digit Span Backward | −0.13 | 0.06 | −0.30 |
| Language | | | | |
| | BNT | 0.10 | 0.20 | −0.30 |
| | Animal Fluency | −0.25 | −0.23 | 0.09 |
| Visuospatial | | | | |
| | Block Design | 0.05 | −0.20 | *** |
| | JLO | 0.04 | −0.06 | −0.20 |

Table 4
Additional diagnostic accuracy of select cognitive tests with AQ in aMCI cases

| | Test only | Test with AQ | *p*-value |
|---|---|---|---|
| AQ | AUC = 0.83 95% CI: (0.77, 0.88) | na | na |
| DRS-2 Total | AUC = 0.90 95% CI: (0.80, 0.96) | AUC = 0.94 95% CI: (0.86, 0.99) | 0.46 |
| MMSE | AUC = 0.79 95% CI: (0.73, 0.85) | AUC = 0.88 95% CI: (0.83, 0.92) | 0.02 |
| MoCA | AUC = 0.87 95% CI: (0.80, 0.92) | AUC = 0.90 95% CI: (0.85, 0.95) | 0.43 |
| AVLT Delayed Recall | AUC = 0.94 95% CI: (0.90, 0.97) | AUC = 0.97 95% CI: (0.94, 0.99) | 0.13 |
| BVMT-R Delayed Recall | AUC = 0.87 95% CI: (0.82, 0.91) | AUC = 0.91 95% CI: (0.86, 0.94) | 0.21 |

AUC, Area Under the Curve; 95% CI, 95% Confidence Interval; AQ, Alzheimer's Questionnaire; DRS-2, Dementia Rating Scale; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; AVLT, Auditory Verbal Learning Test; BVMT-R, Brief Visuospatial Memory Test.



performance-based neuropsychological and screening tests which strengthens its validity as an informant-based assessment that can be applied and utilized in clinical settings.

Other studies investigating the correlation between informant-based screening measures and objective cognitive tests have found that the AD8 is moderately correlated with the MMSE ($r = -0.41$, $r = -0.64$) [4, 26], while the reported correlation values for the IQCODE and MMSE have varied widely ($r = -0.37$ to $r = -0.78$) [5]. Galvin et al. [4] reported that the AD8 demonstrated weak correlations with neuropsychological tests of specific domains such as memory (WMS Logical Memory, $r = -0.38$ and 10-Item Word List, $r = -0.39$) and language (Animal Fluency, $r = -0.05$ and BNT, $r = -0.02$); however, executive function measures (Trails-B, $r = 0.47$ and Digit Symbol, $r = -0.52$) demonstrated moderate correlations with the AD8. Jorm [5] reported on the findings of several studies showing weak correlations between the IQCODE and several neuropsychological measures (WMS Logical Memory, $r = -0.42$; AVLT, $r = -0.35$; Block Design, $r = -0.28$; and Digit Span, $r = -0.27$).

Like the AD8 and IQCODE, the AQ demonstrated some weak correlations with several neuropsychological tests examining specific domains; however, several moderate correlations were also noted, particularly with measures of memory and executive function. Given that decreased memory and dual processing skills are hallmark features that direct a clinician to a diagnosis of AD, these results suggest that the AQ is accurately assessing AD-specific cognitive declines. Weak correlations between informant-reported measures and domain-

Table 5
Association statistics for the GDS covariate in the diagnostic accuracy models

| | Test only | Test with AQ |
|---|---|---|
| AQ | OR = 1.01<br>95% CI: (0.94, 1.09)<br>$p = 0.77$ | na |
| DRS-2 Total | OR = 1.08<br>95% CI: (0.86, 1.37)<br>$p = 0.49$ | OR = 1.06<br>95% CI: (0.82, 1.38)<br>$p = 0.65$ |
| MMSE | OR = 1.05<br>95% CI: (0.98, 1.11)<br>$p = 0.17$ | OR = 1.01<br>95% CI: (0.93, 1.09)<br>$p = 0.83$ |
| MoCA | OR = 1.00<br>95% CI: (0.92, 1.08)<br>$p = 0.98$ | OR = 0.99<br>95% CI: (0.90, 1.09)<br>$p = 0.79$ |
| AVLT Delayed Recall | OR = 0.98<br>95% CI: (0.90, 1.06)<br>$p = 0.61$ | OR = 0.93<br>95% CI: (0.84, 1.02)<br>$p = 0.13$ |
| BVMT-R Delayed Recall | OR = 1.05<br>95% CI: (0.98, 1.13)<br>$p = 0.14$ | OR = 1.02<br>95% CI: (0.94, 1.11)<br>$p = 0.59$ |

OR, Odds Ratio; 95% CI, 95% Confidence Interval; p, *p*-value; AQ, Alzheimer's Questionnaire; DRS-2, Dementia Rating Scale; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; AVLT, Auditory Verbal Learning Test; BVMT-R, Brief Visuospatial Memory Test.

specific neuropsychological tests may be expected to some extent given that informant-based measures often contain items spanning several cognitive domains. Thus, the lack of overlap in the constructs measured by broad informant-based and domain-specific neuropsychological measures may explain weak correlations between these assessment types. Additionally, as some of these domains, such as visuospatial, are not typically expected to have significant involvement in AD, one would expect the AQ to have lower correlations with these domains than the domains with declines more strongly associated with AD, such as memory and executive function.

There was considerable heterogeneity in the amount of variance accounted for in each neuropsychological test by the AQ as it accounted for most variability in the memory and executive function domains. Even with a relatively large amount of variance accounted for in these domains, a fair amount of variance remained unaccounted for. Since the AQ is an informant-based screening measure, it is inevitable that other sources of variability that underlie cognitive impairment, such as age and education, will not be captured. Within the context of screening one would not expect the AQ to fully predict impairment in specific domains nor would it be expected that the AQ be completely concordant with a specific diagnosis. The weak and moderate correlations with domain-specific neuropsychological tests may also be due to structure of the measure, as some AQ domains contain more items than others and are thus represented more heavily than others within the AQ total score. The AQ contains several items relating to memory, orientation, and functional ability, but only a few items relating to language and visuospatial domains. This might explain the moderate correlations found for the neuropsychological tests of memory and executive function and the weak correlations with visuospatial tests. However, the imbalance of items within the AQ is due to its initial conceptualization as an instrument designed to detect symptoms associated with aMCI and AD [6, 7], which tend to be concentrated in the areas of memory and executive function.

Another important consideration is that the AQ relies heavily on reported functional status in activities of daily life. Difficulties noted by family members may not emerge on neuropsychological instruments administered in a more controlled testing environment, which may impact the strength of the correlations between the AQ and neuropsychological measures. However, the moderate and strong correlations in this study provide evidence that informant-reported symptoms on the AQ correspond well to the results of performance-based cognitive assessments. It is interesting to note that the AQ did not significantly improve diagnostic accuracy when combined with other cognitive tests. The exception to this was the MMSE where the AUC value improved significantly when the AQ was added to the prediction model. Given that the MMSE is still one of the most widely-used cognitive screening instruments, using the AQ in conjunction with the MMSE may helpful in accurately identifying aMCI cases. Although the addition of the AQ did not significantly improve

the diagnostic accuracy of the other instruments, having information from the AQ may be helpful in cases where individuals are demonstrating impairment in daily function but are performing within normal limits on cognitive tests [27]. Rizk-Jackson et al. [28] found that functional decline among cognitively normal individuals may precede cognitive decline in the process of converting to aMCI. Juva and Sulkava [29] reported a case-study in which an individual demonstrated significant functional impairment, but whose cognitive testing was within normal limits. They also note that cognitive screening measures may be insensitive cognitive changes in atypical presentations of AD and that these measures may not be able to detect impairment in individuals with high levels of education.

While the large sample size was able to add strength to the correlations, one weakness of the study is the ethnically homogenous sample with a majority of participants in the study identifying as white. It is therefore unclear if these results are generalizable to more ethnically diverse populations. Another potential limitation lies in the cross-sectional design of the study as it is unclear whether longitudinal changes in the AQ correspond with longitudinal changes in the neuropsychological tests.

The results of this study provide further evidence to support the validity of the AQ as an instrument for detecting cognitive impairment associated with aMCI and AD. In particular, the AQ demonstrated moderate correlations with memory and executive function measures which shows that the AQ can reasonably assess cognitive impairment demonstrated on standard neuropsychological measures. Given the AQ's ease of use and short duration of administration, the results of this study also demonstrate that it could provide a great deal of value to general and geriatric practitioners who desire a screening instrument that is highly predictive of aMCI and AD.

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# Sensitivity to change and prediction of global change for the Alzheimer's Questionnaire

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## Abstract

**Introduction:** Longitudinal assessment of cognitive decline in amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) often involves the use of both informant-based and objective cognitive assessments. As efforts have focused on identifying individuals in pre-clinical stages, instruments that are sensitive to subtle cognitive changes are needed. The Alzheimer's Questionnaire (AQ) has demonstrated high sensitivity and specificity in identifying aMCI and AD; however its ability to measure longitudinal change has not been assessed. The aims of this study are to assess the sensitivity to change of the AQ and to determine whether the AQ predicts change in global cognition and function in cognitively normal (CN), aMCI, and AD subjects.

**Methods:** Data from 202 individuals participating in a brain and body donation program were utilized for this study (101 CN, 62 aMCI, 39 AD). AD and aMCI individuals were matched on age, education, and gender to CN individuals. Sensitivity to change of the AQ was assessed in addition to the AQ's ability to predict change in global cognition and function. The Mini Mental State Exam (MMSE) and Functional Activities Questionnaire (FAQ) were used as gold standard comparisons of cognition and function. Sample size calculations for a 25% treatment effect were also carried out for all three groups.

**Results:** The AQ demonstrated small sensitivity to change in the aMCI and CN groups ($d = 0.33$, $d = 0.23$, respectively) and moderate sensitivity to change in the AD group ($d = 0.43$). The AQ was associated with increases in the Clinical Dementia Rating Global Score (OR = 1.20 (1.09, 1.32), $P < 0.001$). Sample size calculations found that the AQ would require substantially fewer subjects than the MMSE given a 25% treatment effect.

**Conclusions:** Although the AQ demonstrated small sensitivity to change in aMCI and CN individuals in terms of effect size, the AQ may be superior to objective cognitive tests in terms of required sample size for a clinical trial. As clinicians and researchers continue to identify and treat individuals in earlier stages of AD, there is a need for instruments that are sensitive to cognitive changes in these earlier stages.

## Introduction

Longitudinal assessment of cognitive decline in amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD) often involves the use of both informant-based and patient-based assessments to measure the degree of change in cognition and function [1,2]. In both clinical and research settings, the two methods are often used in conjunction in order to glean a more accurate picture of an individual's current cognitive status relative to baseline or other prior time points. A major issue that both clinicians and researchers grapple with is the degree to which a particular instrument is sensitive to change over time. For clinicians, determining the significance of change from one time to the next has implications for decisions regarding treatment and resource use (that is, assisted living, in-home care, and so on.). Clinicians may also benefit from instruments that are sensitive to change over time in order to satisfy the Affordable Care Act's cognitive screening requirement for Medicare recipients. For researchers and clinical trialists, the issue of sensitivity to change for a particular instrument has significant ramifications for whether or not a meaningful treatment effect will be detected between placebo and treatment groups.

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The need to identify individuals as early as possible in the AD disease process has prompted researchers to begin conducting studies with individuals who are classified as having pre-symptomatic AD. Although no formal diagnostic criteria currently exist for this classification, it is used to classify individuals whose biological markers are consistent with the pathological presence of AD, but who are cognitively normal and are considered to be at risk for eventually developing clinical AD. An interesting study by Riley *et al.* [3] compared cognitively normal individuals who, at autopsy, met National Institute on Aging (NIA)-Reagan criteria for no- and low-likelihood of AD with cognitively normal individuals who met criteria for intermediate- and high-likelihood of AD. This study found that the intermediate- and high-likelihood groups had a steeper rate of decline on several cognitive measures across several domains, although all individuals in the study were within normal limits on cognitive testing. Riley *et al.* [3] suggest that rates of longitudinal cognitive decline may be informative in identifying individuals with pre-symptomatic AD, even when cognitive testing falls within normal limits. Gavett *et al.* [4] found that informant-reported cognitive symptoms on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) correlated well with longitudinal neuropsychological performance and that informant-reported changes in cognition were a robust predictor of cognitive decline in a high-functioning, cognitively normal group. Both of these studies demonstrate that cognitive decline in cognitively normal individuals can be reliably detected and may be used to predict subsequent development of clinical AD.

The Alzheimer's Questionnaire (AQ) was originally introduced in 2010 [5] and has been validated as an accurate informant-based measure of cognition and function for both aMCI and AD [5-7]. The AQ also correlates well with established measures of cognition and global function [8]. Although the AQ has demonstrated its validity in cross-sectional studies, its ability to accurately measure change in cognition over time has not been assessed. Instruments such as the Mini Mental State Exam (MMSE) [9] and the Functional Activities Questionnaire (FAQ) [10] are commonly used to assess changes in cognition and function in aMCI and AD. Clark *et al.* [11] report that although the MMSE may be sufficient to use as a screening instrument for cognitive impairment, its utility as an instrument to assess change over time accurately is limited by high measurement error and high variability of annual change between individuals. A recent study by Costa *et al.* [12] found that the Montreal Cognitive Assessment (MoCA) yielded small sensitivity to change in prodromal AD and moderate sensitivity to change in mild AD. Recent studies suggest that the FAQ is a significant predictor of conversion to AD from aMCI [13] and has also been associated with longitudinal decreases in glucose metabolism associated with aMCI and AD [14]. Rizk-Jackson *et al.* [15] found that the FAQ was able to detect functional decline in cognitively normal individuals prior to the presence of impairment on objective cognitive tests.

The first aim of this study was to assess the sensitivity to change of the AQ through the use of effect size and sample size calculations for a hypothetical placebo-controlled clinical trial. For comparison, the MMSE and FAQ were also used in order to gauge the AQ's performance against instruments that have been more widely used. The second aim of the study was to determine how well one-year change in AQ total score predicts global change as measured by the Functional Assessment Staging Test (FAST) [16], Global Deterioration Scale (GDS) [17], and the Clinical Dementia Rating Global Score (CDR-GS) [18].

## Methods

### Study sample

Data from the two most recent annual visits for 202 individuals participating in a brain and body donation program [19] were utilized for this study. Participants in this program were recruited predominantly from the northwest region of the Phoenix, Arizona metropolitan area. Approval for the brain and body donation program was granted by the Banner Health Institutional Review Board and informed consent was obtained from all individuals prior to enrolling in the program. The sample for this study ranged in age from 57 to 97 years with a mean of 81.70 ± 7.25 and had a mean education level of 14.74 ± 2.54 years and included 95 women and 107 men.

Of the 202 individuals, 101 were classified as cognitively normal (CN), 62 were classified as amnestic mild cognitive impairment (aMCI), and 39 were classified as Alzheimer's disease (AD) at the first visit. Each aMCI and AD individual was matched on age, education, and gender to a CN individual, without replacement. When an exact match could not be found, a tolerance of ± 2 years was used for age and education in order to obtain an appropriate match. Both single and multiple domain aMCI cases were categorized as aMCI and both possible and probable AD were categorized as AD. The AD cases met National Institute of Neurological and Communicable Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [20] for a clinical diagnosis of probable or possible Alzheimer's disease. aMCI cases were diagnosed as such based on Petersen criteria [21]. The CN cases were defined as having no limitations of activities of daily living by informant report and were within normal limits on neuropsychological testing.

Consensus diagnosis with a neurologist, geriatric psychiatrist and neuropsychologist was used to determine the clinical status of each individual. Consensus diagnoses were made based on neuropsychological testing results, neurological and physical exam, and interviews with an informant that assessed global cognitive status, functional status, and mood and behavioral status.

### Instruments

AQ [5,6] – A 21-item, informant-based dementia assessment designed for ease of use in a primary care setting. AQ items are divided into five domains including Memory, Orientation, Functional Ability, Visuospatial Ability, and Language. Items are posed in a yes/no format with the sum of 'yes' items equaling the total AQ score (0-27). Six items known to be predictive of a clinical AD diagnosis are weighted more heavily in the total score by each being worth two points rather than one.

FAQ [11] – An informant-based measure of instrumental activities of daily living (IADLs) which scores 10 items on a 0 to 3 scale, with higher scores corresponding to greater impairment.

MMSE [9] – A brief, 30-item cognitive screening instrument that includes items on Orientation, Memory, Attention, Language and Visuospatial functions.

FAST [16] – A dementia staging instrument that classifies individuals as Normal Aging, Possible Mild Cognitive Impairment, Mild Cognitive Impairment, Mild Dementia, Moderate Dementia, Moderately Severe Dementia and Severe Dementia using a 1 to 7 scale where higher ratings indicate greater severity.

GDS [17] – A dementia staging instrument divided into seven different stages with increasing impairment corresponding with higher stages (No Cognitive Decline, Age-Associated Memory Impairment, Mild Cognitive Impairment, Mild Dementia, Moderate Dementia, Moderately Severe Dementia, Severe Dementia).

CDR [18] –A semi-structured, informant-based clinical staging instrument that characterizes six domains of cognitive and functional performance: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. The CDR provides a global score which is a composite score based on an algorithm that gives different weights to the scores for each of the domains. The global score (GS) is used to grade the severity of dementia and is measured using 0, 0.5, 1, 2, and 3 to denote no impairment, very mild dementia, mild dementia, moderate dementia, and severe dementia, respectively.

### Statistical analysis

The Shapiro-Wilk test was performed on the data to determine the normality of distribution for the continuous variables. Non-parametric tests for group comparisons and correlations were used, as the data for all continuous variables were not normally distributed. The Kruskall-Wallis test was used to verify that the three groups were not significantly different in terms of age and education. Chi-square analysis was used to examine the distribution of men and women among the three groups.

The analyses investigating the sensitivity to change utilized a method similar to that of Costa *et al*. [11]. Middel and von Sonderen [22,23] described these methods and their rationale in detail. The sensitivity to change assessment was completed through the calculation of an effect size (ES) to quantify the magnitude of change. Since this study used a correlated design, the pooled standard deviation was used to calculate the ES which was taken from the individual standard deviation values for Year 1 and Year 2 for each measure (pooled standard deviation = $\sqrt{(((\text{Year 1 sd})^2 + (\text{Year 2 sd})^2)/2)}$; (ES = mean change score/pooled standard deviation)). The final effect size measure, $d$, included a correction for reliability ($d = \text{ES}/\sqrt{2(1-r)}$) where $r$ is the correlation between the scores at Year 1 and Year 2. The interpretation for $d$ utilized the following scheme proposed by Cohen [24]: <0.20 = trivial change; 0.20 to 0.50 = small change; 0.50 to 0.80 = moderate change; ≥0.80 = large change.

In order to provide a more practical interpretation of the sensitivity to change, a series of sample size calculations were carried out to show how many individuals would be needed for a clinical trial using a particular measure as its outcome. The sample size calculations assumed a 25% treatment effect on the mean change score for each measure at 80% power with a two-tailed significance level of 0.05 for a randomized clinical trial with a treatment arm and a placebo arm. These parameters were used as they have been utilized by several previous studies [25] and have also been used to estimate sample sizes for pre-dementia trials using data from the Alzheimer's Disease Neuroimaging Initiative [26]. Sample size calculations were carried out using G*Power 3 [27]. The reported sample sizes are the number per arm. For each of the clinical groups, varying trial lengths were used in the sample size calculations: AD = two years, MCI = three years, CN = five years.

To further examine the ability of each instrument to detect clinically significant change, a reliable change index (RCI) was calculated for each instrument. For this study, two different RCI methods were utilized as the AQ and FAQ are informant-based assessments and the MMSE is an objective performance-based assessment. For the AQ and FAQ, RCI calculations that corrected for inter-test reliability were used [28] while the MMSE RCI calculation utilized a method that corrects for both inter-test reliability and practice effects [29]. The most common convention for interpreting RCI scores is that scores that are ≥ ± 1.645 are interpreted as demonstrating clinically significant change [30]. This was used to

obtain 90% confidence intervals for estimates of clinically significant change for each instrument from Year 1 to Year 2. In this study, we report the percent of individuals who demonstrated annual score changes outside the range of the 90% confidence interval for each instrument.

An additional set of analyses were carried out to determine the extent to which the mean change scores of the AQ, FAQ and MMSE predicted global change as measured by increases in FAST, GDS and CDR-GS values. The CN, AD and aMCI groups were analyzed separately. An analysis with the entire sample was also carried out. All individuals were dichotomized based on whether their individual FAST, GDS and CDR-GS values increased from Year 1 to Year 2 (1 = increase, 0 = no increase) as increases on these scales represent clinically meaningful changes in disease severity. Logistic regression analyses were used to assess the predictive value of the AQ, FAQ and MMSE change scores on increases in FAST, GDS or CDR-GS. A False Discovery Rate (FDR) significance level of 0.006 was used to correct for multiple comparisons within each of the groups.

Spearman correlation analyses were carried out to assess the linear associations between AQ, FAQ and MMSE scores with the FAST, GDS and CDR-GS for Year 1 and Year 2 separately. Spearman correlation was also used to assess the associations between the change scores on the AQ, FAQ, MMSE and MoCA. The correlations used as the measures of test-retest reliability are also Spearman values. Statistical analyses were carried out using Systat 12.0 (Systat, Inc., San Jose, CA, USA).

## Results

Demographic characteristics of the entire study sample and each clinical group are shown in Table 1. The three clinical groups did not differ in terms of age or years of education and there was no significant difference in gender composition among the three groups.

The results from the sensitivity to change analysis are shown in Table 2. In the aMCI group the AQ, FAQ and MMSE all demonstrated small sensitivity to change in terms of their respective *d* values (0.33, 0.35, 0.24). However, both the AQ and FAQ yielded required sample sizes that were less than half of the sample size required by the MMSE.

In the AD group, the AQ demonstrated small sensitivity to change ($d = 0.43$),; however, the FAQ showed large sensitivity to change ($d = 0.84$) and the MMSE demonstrated moderate sensitivity to change ($d = 0.52$). In terms of required sample size the FAQ yielded the lowest value (n = 119) while the AQ yielded a value that was substantially higher (n = 232). This result may be explained by the reliability values for each instrument as the FAQ had a higher reliability value (r = 0.81) than the AQ (r = 0.64). The MMSE yielded a required sample size that was between that of the AQ and FAQ (n = 157).

In the CN group all three measures demonstrated trivial sensitivity to change. However, sample size calculations demonstrated that the MMSE would require substantially more subjects than both the AQ and FAQ.

Results from the RCI score calculations are shown in Table 3. For the aMCI group, the AQ yielded a higher percentage of individuals demonstrating clinically significant change when compared to the FAQ and MMSE. For the AD group, the AQ yielded a higher percentage of individuals demonstrating clinically significant change when compared to the FAQ, but demonstrated an equivalent percentage compared to the MMSE. Table 4 shows the results of the predictive ability of AQ, FAQ and MMSE mean change scores on increases in FAST, GDS and CDR-GS values. Within each of the clinical groups, no statistically significant effects were found after adjusting for multiple comparisons. When all three groups were pooled together, the AQ and FAQ demonstrated small, but significant associations with CDR-GS increases (AQ (odds ratio (OR) = 1.20 (1.09, 1.32), $P < 0.001$); FAQ (OR = 1.21 (1.11, 1.33), $P < 0.001$)). The pooled analysis also yielded a small, but significant association for FAQ mean change and GDS increase (OR = 1.16 (1.06, 1.26), $P = 0.001$).

Correlation values for first and second year scores for each instrument are shown in Tables 5 and 6. The AQ and FAQ correlated strongly with FAST, GDS and CDR-GS values in both years while the MMSE correlated moderately with FAST, GDS and CDR-GS values in Year 1. In Year 2, the MMSE correlated moderately with the FAST and GDS, but demonstrated a strong correlation with the CDR-GS.

The mean change score for the AQ correlated weakly with the mean FAQ change score (r = 0.22, $P = 0.002$)

**Table 1 Demographic characteristics**

| Characteristic | CN | MCI | AD | Total | *P*-value |
|---|---|---|---|---|---|
| Number | 101 | 62 | 39 | 202 | ----- |
| Age | 81.76 ± 7.23 | 81.57 ± 7.59 | 81.82 ± 6.92 | 81.71 ± 7.25 | 0.99 |
| Education | 14.69 ± 2.50 | 15.18 ± 2.56 | 14.15 ± 2.55 | 14.74 ± 2.54 | 0.12 |
| Gender (M/F) | 53/48 | 33/29 | 21/18 | 107/95 | 0.99 |

Mean ± standard deviation. AD, Alzheimer's disease; CN, cognitively normal; MCI, mild cognitive impairment; M/F, male/female.

**Table 2 Sensitivity to change comparison for the AQ, FAQ, and MMSE in amnestic mild cognitive impairment, Alzheimer's disease, and cognitively normal cases**

| Group | Instrument | Mean change | SD of mean change | 95% CI of mean change | Pooled SD | ES | Reliability | *d* | Required sample size[a] |
|---|---|---|---|---|---|---|---|---|---|
| aMCI | | | | | | | | | |
| | AQ | 1.66 | 4.96 | (0.40, 2.92) | 6.10 | 0.27 | 0.65 | 0.33 | 251 |
| | FAQ | 2.05 | 5.79 | (0.54, 3.56) | 3.29 | 0.30 | 0.63 | 0.35 | 224 |
| | MMSE | -0.55 | 2.54 | (-1.19, 0.10) | 2.47 | 0.22 | 0.56 | 0.24 | 597 |
| AD | | | | | | | | | |
| | AQ | 2.49 | 4.77 | (0.94, 4.03) | 6.75 | 0.37 | 0.64 | 0.43 | 232 |
| | FAQ | 3.59 | 4.91 | (2.00, 5.18) | 5.36 | 0.52 | 0.81 | 0.84 | 119 |
| | MMSE | -2.13 | 3.35 | (-3.23, -1.03) | 6.34 | 0.34 | 0.79 | 0.52 | 157 |
| CN | | | | | | | | | |
| | AQ | 0.47 | 2.73 | (-0.07, 1.00) | 3.37 | 0.14 | 0.69 | 0.18 | 340 |
| | FAQ | 0.33 | 1.80 | (-0.03, 0.69) | 3.29 | 0.11 | 0.73 | 0.15 | 300 |
| | MMSE | 0.05 | 1.71 | (-0.29, 0.39) | 2.47 | 0.02 | 0.41 | 0.02 | 660 |

[a]Number of subjects per arm based on a 25% treatment effect of the mean change at 80% power with a two-tailed significance level of 0.05; sample size estimates are based on a two-year study for AD, a three-year study for aMCI, and five-year study for CN; for AQ and FAQ positive mean change scores represent increased impairment over time and negative mean change scores for MMSE also represent increased impairment over time. Effect size values are reported in absolute values and represent the magnitude of the difference for Year 2 scores subtracted from Year 1 scores. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; AQ, Alzheimer's Questionnaire; 95% CI, 95% confidence interval; CN, cognitively normal; *d*, effect size corrected for reliability; ES; effect size using pooled standard deviation; FAQ, Functional Activities Questionnaire; MMSE, Mini Mental State Exam; SD, standard deviation.

while the MMSE mean change score demonstrated no correlation with the AQ mean change score (r = -0.02, $P = 0.83$).

## Discussion

Within the aMCI and AD groups the AQ demonstrated small sensitivity to change while its sensitivity to change in the CN group was trivial. In aMCI individuals the AQ, FAQ and MMSE all demonstrated small sensitivity to change. In the AD group, the MMSE and FAQ demonstrated greater sensitivity to change relative to the AQ. The AQ was also significantly associated with global change as measured by CDR-GS increase and correlated strongly with other established measures of global cognition and function. Although the effect sizes reported in this study are relatively small, they are consistent with the notion that cognitive changes associated with aMCI and AD are often subtle and difficult to detect from a psychometric standpoint. This point is a major challenge for researchers and clinical trialists as the variability of cognitive tests is often numerically similar to the rate of change [31]. Informant-based instruments that assess functional ability are also prone to high degrees of variability due to varying pre-morbid levels of function and gender differences in the degree of participation in many of the functional activities that are assessed [31]. The result is that when objective cognitive tests and informant-based instruments are used as endpoints in clinical trials the inherent variability of these measures often makes it difficult to detect true differences between placebo and treatment groups. However, others have suggested that lack of decline in placebo groups [32] and disease severity at baseline [31] can also significantly impact a trial's ability to detect a significant treatment effect. The degree to which a particular cognitive or functional measure is responsive to changes in disease status is extremely important, particularly in pre-symptomatic and aMCI populations where cognitive decline is slower and more subtle [33].

The sample size calculations in the aMCI group demonstrate that the AQ is superior to the MMSE in terms of sensitivity to change; however, the AQ required a larger sample size than the FAQ. The sample size calculations

**Table 3 Reliable change index results based on data from cognitively normal individuals**

| Instrument | Reliability | $SE_m$ | $SE_{diff}$ | 90% CI for RCI | Percent outside of 90% CI |
|---|---|---|---|---|---|
| AQ | 0.69 | 0.27 | 2.66 | ±4.37 | aMCI = 24%; AD = 16% |
| FAQ | 0.73 | 0.18 | 2.24 | ±3.67 | aMCI = 17%; AD = 12% |
| MMSE | 0.*41* | 0.17 | 1.73 | ±2.84 | aMCI = 17%; AD = 17% |

AD, Alzheimer's disease; AQ, Alzheimer's Questionnaire; CI, confidence interval; FAQ, Functional Activities Questionnaire; MMSE, Mimi Mental State Exam; RCI, reliable change index; $SE_{diff}$, standard error of the difference; $SE_m$, standard error of measurement.

**Table 4 AQ, FAQ, and MMSE mean change as predictors of global change in mild cognitive impairment, Alzheimer's disease, cognitively normal cases, and all groups combined**

| Group | Instrument | FAST increase | GDS increase | CDR Global score increase |
|---|---|---|---|---|
| aMCI | | | | |
| | AQ | 1.07 (0.96, 1.20); $P = 0.23$ | 1.09 (0.97, 1.22); $P = 0.15$ | 1.09 (0.97, 1.24); $P = 0.16$ |
| | FAQ | 1.07 (0.96, 1.19); $P = 0.25$ | 0.97 (0.87, 1.08); $P = 0.52$ | 1.08 (0.96, 1.22); $P = 0.22$ |
| | MMSE | 1.02 (0.83, 1.26); $P = 0.83$ | 0.81 (0.64, 1.02); $P = 0.07$ | 0.91 (0.72, 1.15); $P = 0.43$ |
| AD | | | | |
| | AQ | 1.17 (0.97, 1.29); $P = 0.14$ | 1.26 (1.05, 1.52); $P = 0.01$ | 1.16 (1.00, 1.35); $P = 0.06$ |
| | FAQ | 1.09 (0.95, 1.24); $P = 0.22$ | 1.17 (1.00, 1.38); $P = 0.05$ | 1.12 (0.97, 1.29); $P = 0.12$ |
| | MMSE | 0.93 (0.77, 1.14); $P = 0.50$ | 0.97 (0.79, 1.19); $P = 0.77$ | 0.91 (0.74, 1.11); $P = 0.35$ |
| CN | | | | |
| | AQ | 1.09 (0.93, 1.28); $P = 0.29$ | 1.04 (0.88, 1.23); $P = 0.67$ | 1.26 (1.00, 1.59); $P = 0.05$ |
| | FAQ | 0.91 (0.68, 1.22); $P = 0.52$ | 1.02 (0.77, 1.34); $P = 0.92$ | 1.61 (1.10, 2.36); $P = 0.02$ |
| | MMSE | 0.88 (0.66, 1.17); $P = 0.38$ | 0.94 (0.70, 1.25); $P = 0.66$ | 0.72 (0.35, 1.49); $P = 0.37$ |
| All Groups Combined | | | | |
| | AQ | 1.11 (1.03, 1.20); $P = 0.008$ | 1.08 (1.00, 1.16); $P = 0.05$ | 1.20 (1.09, 1.32); $P < 0.001$ |
| | FAQ | 1.09 (1.01, 1.18); $P = 0.03$ | 1.16 (1.06, 1.26); $P = 0.001$ | 1.21 (1.11, 1.33); $P < 0.001$ |
| | MMSE | 0.91 (0.81, 1.03); $P = 0.15$ | 0.84 (0.74, 0.95); $P = 0.006$ | 0.91 (0.74, 1.11); $P = 0.35$ |

Odds ratio (95% confidence interval); *P*-value; FDR significance level = 0.006; odds ratios indicate the association for a 1-point increase in AQ, FAQ, and MMSE change scores with FAST, GDS and CDR-GS score increase as the outcome. AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; AQ, Alzheimer's Questionnaire; CI, confidence interval; CDR, Clinical Dementia Rating; CN, cognitively normal; FAQ, Functional Activities Questionnaire; FAST, Functional Assessment Staging Test; GDS, Global Deterioration Score; MMSE, Mini Mental State Exam; MoCA, Montreal Cognitive Assessment.

highlight some important methodological issues in aMCI and AD studies that have been problematic. The first issue involves whether or not objective cognitive tests and informant-based instruments are sensitive enough to detect changes, particularly in earlier stages of aMCI and AD. Based on the results from the MMSE, our results suggest that the AQ may be superior to objective cognitive measures in detecting longitudinal change when compared on sample sizes required to detect a treatment effect. Although informant-based and objective cognitive assessments are often used in conjunction to assess drug efficacy, these results suggest that the MMSE is less sensitive to change over time than informant-based instruments.

Another issue these results highlight is that of instrument reliability as it relates to the required sample size needed to detect a treatment effect. There is a direct relationship between instrument reliability and sensitivity to change as instruments that are prone to higher variability between assessments may not detect significant longitudinal change as accurately as instruments with lower between-assessment variability. This imprecision ultimately leads to larger sample size requirements for clinical trials. Knopman and Caselli [34] point out that between-assessment variability is an inherent challenge when using patient-based objective cognitive tests to assess change, and longitudinal differences may be related to non-pathological factors, such as chance and regression toward the mean. Practice effects due to repeat administration of cognitive tests within relatively short periods of time also pose a significant threat to the ability to detect change associated with progression of

**Table 5 Correlation values for AQ, FAQ, MMSE, FAST, GDS and CDR Global Score for Year 1**

| Instrument | FAST Year 1 | GDS Year 1 | CDR-GS Year 1 |
|---|---|---|---|
| AQ Year 1 | 0.84 | 0.78 | 0.74 |
| FAQ Year 1 | 0.83 | 0.77 | 0.75 |
| MMSE Year 1 | -0.59 | -0.64 | -0.65 |

$P < 0.001$ for all correlations. AQ, Alzheimer's Questionnaire; CDR, Clinical Dementia Rating; FAQ, Functional Activities Questionnaire; FAST, Functional Assessment Staging Test; GDS, Global Deterioration Scale; MMSE, Mini Mental State Exam.

**Table 6 Correlation values for AQ, FAQ, MMSE, FAST, GDS and CDR Global Score for Year 2**

| Instrument | FAST Year 2 | GDS Year 2 | CDR-GS Year 2 |
|---|---|---|---|
| AQ Year 2 | 0.80 | 0.80 | 0.75 |
| FAQ Year 2 | 0.81 | 0.81 | 0.83 |
| MMSE Year 2 | -0.67 | -0.72 | -0.69 |

$P < 0.001$ for all correlations. AQ, Alzheimer's Questionnaire; CDR, Clinical Dementia Rating; FAQ, Functional Activities Questionnaire; FAST, Functional Assessment Staging Test; GDS, Global Deterioration Scale; MMSE, Mini Mental State Exam.

aMCI/AD [35]. Others have also suggested that some objective cognitive tests are inherently insensitive to cognitive changes [36] and that variability between examiners using these instruments [37] is also a detrimental factor that prevents treatment effects from being observed. Although informant-based measures are more robust to some of these challenges than objective cognitive tests, they are still prone to some degree of measurement error, particularly in the area of inter-rater reliability [38].

In this study, the issue of reliability and its relationship to effect size was demonstrated in the AD group where the AQ yielded moderate sensitivity to change and the FAQ yielded large sensitivity to change. In this case, the effect size (corrected for reliability) for the FAQ was almost twice as large as that of the AQ. Some of this difference may be attributable to the higher reliability value of the FAQ which underscores the importance of not only an instrument's psychometric ability to detect change, but also the ability of the examiner to administer the instrument in a way that can detect meaningful change. The importance of inter-rater reliability is highlighted by Kobak [39] who points out that reductions in inter-rater reliability, as measured by intra-class correlation, can result in significantly larger required sample sizes for clinical trials which stems from the increased measurement variability that reduces statistical power. This issue is also highlighted by Cummings *et al.* [40] who report that insufficient training and monitoring of examiners may lead to increased measurement variability which decreases the chance of detecting significant treatment effects. Connor and Sabbagh [41] also note that increases in measurement error may lead to decreases in instrument reliability, which results in a decreased ability to detect treatment effects.

The divergent sample size calculations for the AQ and FAQ may also be due to some of the inherent psychometric properties of each instrument. The FAQ captures not only the presence of impaired functioning, but also severity where the AQ only captures the presence of reported impairment in cognition and function. Thus, the inclusion of severity of impairment on the FAQ may account for the smaller required sample size calculation as a result of increased statistical power.

The results from the RCI calculations showed that the AQ identified clinically significant change in a larger percentage of individuals than did the FAQ and MMSE for aMCI individuals. The advantage that RCI scores provide is the ability to assess intra-individual change, which has been shown to have good predictive value in terms of cognitive decline [42]. The use of RCI scores in this context may provide a novel and more informative way to determine endpoints for aMCI and AD clinical trials. Since the majority of clinical trials for aMCI and AD rely on methods and analyses that simply assess group differences (for example, drug versus placebo) on a particular measure (for example, Alzheimer's Disease Assessment Scale – cognition (ADAS-Cog)), it might be possible for drug efficacy to be assessed based on the percent of individuals showing clinically significant change on a measure, rather than just demonstrating a certain amount of change (for example, 25%) on an outcome measure.

One drawback to the current study is the relatively small sample size. Given that clinical trials often enroll hundreds of individuals, replication of these findings in a larger sample is needed in order to strengthen the argument for the AQ's ability to detect longitudinal change. Autopsy confirmation of the clinical status for each individual would lend further support to the AQ's ability to detect longitudinal change. Although the individuals participating in this study have agreed to an autopsy, many of them were still living at the time of the analysis so neuropathological confirmation of their clinical status was not available.

## Conclusions

The results of this study indicate that the AQ demonstrated small sensitivity to longitudinal cognitive changes associated with aMCI and AD. The AQ's sensitivity to change in aMCI was comparable to the FAQ while both instruments outperformed the MMSE in terms of effect size and required sample size. The AQ was also significantly associated with longitudinal decreases in global cognition and function and was able to identify a greater proportion of aMCI individuals with clinically significant change when compared to other established measures. As clinicians and researchers continue to identify and treat individuals in earlier stages of AD, there is a need to utilize instruments that are sensitive to subtle cognitive changes over time. Although the AQ's sensitivity to change was small, it is possible that its sensitivity to change may be enhanced when used in conjunction with sensitive objective cognitive tests and validated biomarkers of disease progression. In addition, the recent changes in mandatory screening measures for Medicare recipients as part of the Affordable Care Act may provide the opportunity for the AQ to be used by clinicians in order to satisfy the requirement for cognitive screening and might be helpful in detecting change over time in clinical settings.

#### Abbreviations

AD: Alzheimer's disease; aMCI: amnestic mild cognitive impairment; AQ: Alzheimer's Questionnaire; CDR-GS: Clinical Dementia Rating Global Score; CN: cognitively normal; ES: effect size; FAQ: Functional Activities Questionnaire; FAST: Functional Assessment Staging Test; GDS: Global Deterioration Scale; MMSE: Mini Mental State Exam, Assessment; MoCA: Montreal Cognitive Assessment; RCI: reliable change index.

**Competing interests**
The authors declare that they have no competing interests.

**Authors' contributions**
MM contributed to the conception and design of the study, performed the statistical analysis, drafted the manuscript, and revised it for important intellectual content; KC aided in the analysis and interpretation of the data and drafted the manuscript; KD provided the data for the study, performed assessments used to collect data, and drafted the manuscript; CMB performed assessments used to collect data and drafted the manuscript; JP performed assessments used to collect data and drafted the manuscript; SJ performed assessments used to collect data and drafted the manuscript; MNS contributed to the conception and design of the study, drafted the manuscript, and revised it for important intellectual content. All authors read and approved the final manuscript.

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