eHealth in cardiovascular risk management to prevent cognitive decline
Jongstra, S.

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Are these tests really going to tell you if I have memory problems or even dementia? I will only have to name the things you said a minute ago!

(Quote of a participant during the MMSE test, December 2015)
Chapter 5

IMPROVING PREDICTION OF DEMENTIA IN PRIMARY CARE
THE INCREMENTAL VALUE OF THE VISUAL ASSOCIATION TEST TO THE MINI MENTAL STATE EXAMINATION – A COHORT STUDY

Susan Jongstra, Willem A. van Gool, Eric P. Moll van Charante, Jan-Willem van Dalen, Lisa S.M. Eurelings, Edo Richard, Suzanne A. Ligthart

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ABSTRACT

Background The Mini-Mental-State-Examination (MMSE) is one of the most widely used instruments to screen for cognitive defects. This instrument alone is not sensitive enough to recognise early symptoms of dementia in primary care. We aimed to investigate whether Visual Association Test (VAT) results improve the predictive value for the development of dementia of MMSE score changes in the course of two years.

Methods Participants were from the preDIVA-trial (n=2690). Using MMSE change scores over two years and VAT scores we assessed the predictive values of a diagnosis of dementia in the 4-6 years following. We performed logistic regression analysis adjusted for age and education.

Results Dementia developed in 157 (5.9%) participants. A decline of ≥2 in total MMSE score is associated with an odds ratio of 3.55 (95% CI 2.5-5.0) compared to a stable or improved MMSE. Participants with a ≥2 MMSE score decline over time and an additional imperfect VAT score had an odds ratio of 9.55 (5.9-15.4) for future dementia. A decline of one point in MMSE score is associated with an increased risk of dementia if the VAT score is imperfect.

Conclusion Administering the VAT in persons with only a small decline on the MMSE over a two year period has substantial incremental value for identification of those who are at increased risk of dementia. This simple test may help distinguishing older persons who need further cognitive examination and counselling from those in whom a watchful waiting policy is justified.
INTRODUCTION

Nowadays 47.5 million people worldwide suffer from dementia(1). Dementia is associated with increased disability, dependency and mortality(2) and has impact on different levels, affecting the wellbeing of the patient and posing a great burden on caregivers and society at large(1). A timely diagnosis of dementia is important as it will allow for tailored counselling of patients and caregivers, it enables access to specific information, resources and support, as well as early access to appropriate symptomatic treatment(s) (3-5). To screen for cognitive impairment, various diagnostic instruments are used. Although new screening instruments have been developed over the last years, the Mini Mental State Examination (MMSE)(6) is still widely used(7). In spite of its limitations, including limited sensitivity for early stages of cognitive impairment(8), many doctors use it on a regular basis and it is also widely used in clinical research. The MMSE has high test-retest reliability(9, 10), which has led researchers to using it for measuring changes in cognition over time, even though it was never developed for this purpose(11). However, when screening for dementia the meaning of a decline of only one or two points on the total MMSE score over a one to two year timeframe is unclear. This leads to the question whether such a decrease on the total MMSE score should invite further investigation and whether such a decrease heralds incipient cognitive decline. If further investigation would be warranted, non-invasive tests to distinguish between normal ageing and early signs of dementia are preferable(12-14).

The Visual Association Test(VAT) might be useful for this purpose. It is a test of associative memory and very sensitive to detect impaired anterograde memory(15), without bias based on language skills. It has particularly good test characteristics for the detection of early signs of Alzheimer’s disease, the most common form of dementia. It comprises a cued recall test using associations of pictorial material, to assess deterioration in episodic memory. The VAT is very quick (2-3 minutes) and easy to administer.

The preDIVA study(prevention of dementia by intensive vascular care) is the only study in which both the MMSE and the VAT have been administered repeatedly during long-term follow-up in cognitively intact older people, thus allowing for analysis of their discriminatory power for the early detection of dementia.

In this paper we aimed to investigate the predictive value of MMSE score changes in the course of two years for the development of dementia during the 4-6 years to follow and whether the score on the VAT improves the predictive value.
Chapter 5

METHODS

Participants
The study sample was drawn from the preDIVA trial(16). This was a cluster-randomized controlled trial with a mean follow-up of 6.7 years to assess the efficacy of nurse-led intensive vascular care on the prevention of dementia in a primary care population. Between May 2006 and March 2009, 3526 community-dwelling older individuals aged 70–78 years were included. Exclusion criteria at baseline were prevalent dementia and disorders or circumstances expected to hinder long-term participation and follow-up. Carefully instructed practice nurses carried out all measurements. A detailed description of the preDIVA study design and procedures has been published elsewhere(16, 17). For the present analyses the population is considered as a cohort, irrespective of randomization group. Since this study aimed to assess predictive values for future dementia during long-term follow up, participants were excluded from this analysis if they dropped-out in the first two years of the intervention, were diagnosed with dementia within the first two year of follow-up or within three months after the two-year follow-up assessment.

The Medical Ethics Committee of the Academic Medical Center in Amsterdam approved the study and all participants signed informed consent before enrolment.

Dementia diagnosis
For all participants, cognitive status was assessed during all follow-up measurements, supplemented by available clinical information from general practitioners’ electronic health records including reports on hospital admissions, outpatient diagnostic evaluations by geriatricians, neurologists, psychiatrists, neuroimaging, and/or neuropsychological examinations. For all participants (including dropped out participants) cognitive status was checked at the end of the study (after 6 to 8 years of follow-up). An independent outcome adjudication committee including neurologists, old age psychiatrists, geriatricians, cardiologists, and family physicians, evaluated dementia diagnoses blinded for treatment group. As a quality check and to minimise the risk of false-positive diagnoses, all dementia diagnoses were re-evaluated after one year(16).

MMSE and VAT
The Dutch version of the MMSE(18) was used in all measurements with a maximum obtainable score of 30 points. To determine change over time in MMSE scores, we compared the scores at baseline to the two-year follow-up measurement score.
The VAT test (version VAT A) consisted of six association cards showing two interacting objects (e.g. an ape holding an umbrella, Figure 1). The participants were asked to name both objects on the cards and they were not told to remember the objects (incidental learning). There are also six cue cards showing only one of the objects. Cued recall is tested without delay by showing the six cue cards and asking the participants to identify the missing object. One point is given if the response is sufficiently clear to distinguish the target object from the other objects used in the test. The maximum score is 6 points (one per card).

For the present analysis we used the VAT scores at the two-year follow-up assessment (and not the change in score over time).

**Figure 1.** Pictures used in the Visual Association Test. Ape with umbrella on the left and the cue card on the right.

**Statistical analysis**

Participants were included in the analysis if data were available for both the MMSE at baseline and at two-year follow-up, and VAT at two-year follow-up. MMSE score difference was calculated by subtracting the baseline total MMSE score from the two-year follow-up total MMSE score. We performed logistic regression analysis with diagnosis of dementia as dependent variable and with dichotomised MMSE difference (stable or improvement ≥-1 versus decline ≤-2 over time) and dichotomised VAT score (optimal score 6 versus imperfect score ≤5) as independent variables separately. This strict cut-off for the VAT score was chosen since...
the study concerned a healthy (older) population and therefore it was expected that the performance would be optimal if cognition was intact. We adjusted all analyses for age and educational level, since both factors are known possible confounders for the relationship between MMSE score and dementia. We have chosen for a logistic regression since we were interested in the cumulative risk over time rather than the specific timing of dementia onset. In addition, we performed logistic regression analysis for dementia predicted by combined MMSE difference and VAT scores, categorised into four groups (ΔMMSE≥-1 and VAT=6; ΔMMSE≥-1 and VAT≤5; ΔMMSE≤-2 and VAT=6; ΔMMSE≤-2 and VAT≤5).

Finally, we assessed the percentage of dementia cases per category of MMSE difference (from ≤-3 to ≥3), both overall and separately for participants with a maximum VAT score (6 points) and for participants with a lower VAT score (≤5 points).

For all analyses SPSS software (version 23) was used.

RESULTS

Study population

In total, 2690/3526 (76.3%) participants without dementia completed baseline and two-year follow-up measurements and were included in the present analysis. The most frequently occurring reasons for drop-out were withdrawal on own request or relocation, described in more detail elsewhere (16). Fourteen participants were excluded because they were diagnosed with dementia within the first two years of follow-up or within three months after the two-year follow-up visit. Baseline characteristics are summarized in Table 1. Mean age was 73.7 (SD 2.4) years and most of the participants (63.5%) had an intermediate education level (7 to 12 years).

Follow-up with respect to dementia diagnosis was available for 2648 participants (98.4%) after a median follow-up time of 6.7 years. Dementia developed in 157 (5.9% 95% confidence interval (CI) 5.0-6.8%) of this group.

The results of the logistic regression analysis are shown in Table 2. The odds ratio of the MMSE difference score (stable score versus decline) over two years is 3.55 (95% CI 2.5 to 5.0). The odds ratio of the dichotomized VAT score is comparable (3.28 95% CI 2.4 to 4.6). Adjusting for age or education did not significantly change these odds ratios.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Study population at baseline (N=2690)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>73.7(2.4)</td>
</tr>
<tr>
<td>Sex male, n (%)</td>
<td>1212 (45.6)</td>
</tr>
<tr>
<td>Educational level(^a)</td>
<td></td>
</tr>
<tr>
<td>Low (&lt;7 years), n (%)</td>
<td>591 (22.5)</td>
</tr>
<tr>
<td>Intermediate (7-12 years), n (%)</td>
<td>1672 (63.5)</td>
</tr>
<tr>
<td>High (&gt;12 years), n (%)</td>
<td>368 (14.0)</td>
</tr>
<tr>
<td>Race Caucasian, n (%)(^b)</td>
<td>2555 (96.2)</td>
</tr>
<tr>
<td>MMSE score at baseline, median (IQR)</td>
<td>29 (27-29)</td>
</tr>
<tr>
<td>VAT score at baseline, median (IQR)(^c)</td>
<td>6 (5-6)</td>
</tr>
</tbody>
</table>

\(^a\) 24 missings
\(^b\) 40 missings
\(^c\) 14 missings

Baseline characteristics of the study participants are reported as mean (standard deviation) or median (inter quartile range) for continuous variables and as number (percentage) for categorical variables.

Table 2. Risk of dementia

<table>
<thead>
<tr>
<th>ΔMMSE over 2 year(^1)</th>
<th>n/N</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>Adjusted(^*) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>57/402(^2)</td>
<td>3.55 (2.5 to 5.0)</td>
<td>&lt;0.001</td>
<td>3.45 (2.4 to 4.9)</td>
<td></td>
</tr>
<tr>
<td>VAT at 2 year FU(^2)</td>
<td>97/919(^3)</td>
<td>3.28 (2.4 to 4.6)</td>
<td>&lt;0.001</td>
<td>3.14 (2.2 to 4.4)</td>
</tr>
<tr>
<td>MMSE and VAT combined(^4):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE stable + perfect VAT(^3)</td>
<td>40/1466</td>
<td>1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MMSE stable + imperfect VAT(^3)</td>
<td>60/680</td>
<td>3.23 (2.1 to 4.9)</td>
<td>&lt;0.001</td>
<td>3.08 (2.0 to 4.7)</td>
</tr>
<tr>
<td>MMSE decline + perfect VAT(^3)</td>
<td>20/203</td>
<td>3.61 (2.1 to 6.3)</td>
<td>&lt;0.001</td>
<td>3.46 (2.0 to 6.1)</td>
</tr>
<tr>
<td>MMSE decline + imperfect VAT(^3)</td>
<td>37/142</td>
<td>9.55 (5.9 to 15.4)</td>
<td>&lt;0.001</td>
<td>9.14 (5.6 to 14.9)</td>
</tr>
</tbody>
</table>

\(^*\) Adjusted for age and educational level
\(^1\) Score: ≤-2 versus ≥-1
\(^2\) Score: ≤3 versus 6
\(^3\) ΔMMSE stable: improved or stable score (≥-1) on the MMSE total score over 2 year; ΔMMSE decline: declining score (≤-2) on the MMSE total score over 2 year; perfect VAT: score of 6 points; imperfect VAT: score of ≤5 points
\(^4\) Scores of ΔMMSE and VAT combined. Reference category is best performing group: participants with ΔMMSE≤-1 and VAT=6

For the analyses with participants categorised into four groups based on combined MMSE difference and VAT score (Table 2), the best performing group (ΔMMSE ≤-1 and VAT =6) was used as reference group. The group of participants that had lower scores on both tests
(ΔMMSE ≤-2 and VAT ≤5) had highest risk for incident dementia with an odds ratio of 9.55
95%CI 5.9 to 15.4 compared to those with a stable or improving MMSE change score or a
perfect score on the VAT.

Figure 2. a+b. On the left side of the x-axis are the participants who improved in total MMSE score
and the participants on the right side decreased in MMSE score over two years.
The percentage of participants diagnosed with dementia per MMSE change score is shown in Figure 2a. Of those who were stable or improved on the MMSE score, the risk of developing dementia varied (2.4% to 6.4%) around the average risk of 5.9%. A two or three points decline on MMSE score, however, was associated with an increased risk of developing dementia of 10.1% and 20.8% respectively (Figure 2a), significantly higher than the overall risk of developing dementia.

When comparing dichotomized VAT scores at the two-year assessment per MMSE change category (Figure 2b), groups with imperfect VAT scores (≤5) all had substantially higher percentages of incident dementia (Figure 2a). An imperfect VAT score increased the predictive value of a two or three points decrease on the MMSE substantially from 10.1% to 14.4% and from 20.8% to 29.3% respectively. Even in those who have a decline of 1 point on the MMSE score, an imperfect score on the VAT doubles the risk to 12.2% (95%CI 7.5 to 17.0). In contrast, the risk of developing dementia for participants with a two or three point decrease on the MMSE score and a perfect VAT score is not significantly different from the average risk of the cohort as a whole (Figure 2b).

**DISCUSSION**

Among non-demented community-dwelling older people, a decline of two or more points on the MMSE score over two years reflects an increased risk of all-cause dementia compared with those with a stable or improved score or lower decrease. This increased risk was not affected by age or educational level. VAT scores have additional value in discriminating persons with and without increased risk of dementia, especially in individuals with a (minor) decline in MMSE score. The VAT administered without the MMSE does not seem to have this additional value compared to the MMSE difference score alone in this population.

The clinical significance of changes over time in MMSE scores has been subject of debate, because a change in MMSE score over time can be explained by several causes. Small changes may result from various factors including measurement errors, learning effects, ageing and regression to the mean and therefore may not necessarily reflect true cognitive changes(13, 14). Our results are consistent with these findings. Although in our results two or more points decrease on the MMSE score does reflect an increased risk of dementia, still the vast majority of participants (about 80%) with such a score change did not develop dementia over the four years to follow. There are no studies that analysed the additional value of the VAT after performing the MMSE, while the MMSE seems unreliable in predicting and detecting (early) dementia(8),
whereas the VAT is especially developed for this purpose. Other studies show that the VAT has a higher specificity and positive predictive value to detect dementia compared to other cognitive tests\textsuperscript{(19)}, even in the preclinical phase\textsuperscript{(15)}. In our analyses, performing the VAT as an additional test in participants with a decline of only one point or more in MMSE score, was associated with a significant and clinically meaningful increased risk of dementia if the VAT score is imperfect.

A formal comparison with other methods that have been suggested for prediction of dementia is beyond the scope of the present study. However, a global comparison of the effect size (Cohen’s $d$ of 1.24, based on the odds ratio of 9.55 (table 2)(20) found in the present analysis for the combination of MMSE change with VAT compares quite well with effect sizes reported in a meta-analysis of levels in cerebrospinal fluid (CSF) of total tau, phosphorylated tau and amyloid-beta-42 ranging from 0.91 to 1.11 or the effect size of medial temporal lobe atrophy on magnetic resonance imaging (MRI) of 0.75\textsuperscript{(21)}. This approximate comparison based on studies with numerous methodological differences suggests that a direct comparison in a single cohort of the various predictive methods is warranted. Especially, because performing a VAT in individuals with a declining MMSE will be far more cost-effective and is associated with much less burden to patient and carer than doing a lumbar puncture for cerebrospinal fluid examination or making a MRI scan\textsuperscript{(22, 23)} which requires at least one extra visit.

**Strengths and limitations of this study**

This study has several limitations. Participants were only included in the analysis if they performed the MMSE at baseline and at two-year follow-up, and the VAT at two-year follow-up. This has led to a smaller sample than the original study and possibly to selection bias. For this paper, only version A of the VAT was used. Originally, the VAT consisted only of the VAT A version, with promising results in detecting dementia\textsuperscript{(15)}. VAT B (six extra association cards) could be added to further increase the sensitivity of the test in participants with a maximum score at the VAT A. The strengths of this study are the large sample size, the long follow-up period, the blinded adjudication of dementia diagnoses (including a one year follow-up after the diagnosis of dementia), completeness of follow-up on all-cause dementia\textsuperscript{(16)} and clinical perspective assessing instruments that can be administered easily in daily practice.
CONCLUSION

We have shown that administering the VAT in persons with a decline of only one point or more on the MMSE over a two year period has substantial incremental value for identification of those who are at increased risk of dementia. Administration of the VAT to those who decline on the MMSE in primary care may help distinguishing those who need a further cognitive examination, counselling or potentially referral to a memory clinic from those in whom a watchful waiting policy is justified.
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Declaration of competing interests
Nothing to declare.
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