Detection of Alzheimer's disease and dementia in the preclinical phase: population based cohort study

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Abstract

Objectives To evaluate a simple three step procedure to identify people in the general population who are in the preclinical phase of Alzheimer's disease and dementia.
Design Three year population based cohort study.
Setting Kungsholmen cohort, Stockholm, Sweden.
Participants 1435 people aged 75-95 years without dementia.
Assessments Single question asking about memory complaints, assessment by mini-mental state examination, and neuropsychological testing.
Main outcome measure Alzheimer's disease and dementia at three year follow up.
Results None of the three instruments was sufficiently predictive of Alzheimer's disease and dementia when administered separately. After participants had been screened for memory complaints and global cognitive impairment, specific tests of word recall and verbal fluency had positive predictive values for dementia of 85-100% (95% confidence intervals range from 62% to 100%). However, only 18% of future dementia cases were identified in the preclinical phase by this three step procedure. Memory complaints were the most sensitive indicator of Alzheimer's disease and dementia in the whole population, but only half the future dementia cases reported memory problems three years before diagnosis.
Conclusion This three step procedure, which simulates what might occur in clinical practice, has a high positive predictive value for dementia, although only a small number of future cases can be identified.

Introduction

Alzheimer's disease is characterised by a long preclinical period during which cognitive deficits are detectable.[1] Preclinical deficits have been shown in global indicators of cognition, such as the mini-mental state examination,[2 3] and for specific tasks assessing psychomotor speed, attention, verbal ability, and visuospatial skill.[1] Despite the seemingly global nature of cognitive impairment in preclinical Alzheimer's disease, studies indicate that the greatest deficit occurs in episodic memory,[1] especially when cognitive assessment is done several years before development of Alzheimer's disease. These findings raise questions concerning whether and how it is possible to identify demented subjects in the preclinical phase with high predictivity.

Different indicators have been investigated, such as neuropsychological tests,[4] subjective memory complaints,[5] non-cognitive symptoms,[6] and specific paraclinical examinations.[7 8] Studies have primarily focused on the strength of the association between an indicator and dementia in terms of risk ratios. Few studies have examined the predictivity of cognitive assessment, which provides the probability of developing a disease given the presence or absence of an indicator. Most studies have looked at cognitive impairment, defined as mild cognitive impairment,[9] cognitive impairment no dementia,[10 11] age associated cognitive decline,[12] or subclinical cognitive impairment.[13] Depending on the criteria used, 12-42% of cognitively impaired elderly people have been found to develop dementia after one to five years.[9–15] Many studies used clinic based populations, which probably have higher progression rates to dementia than the general population because they are at a more advanced stage of cognitive impairment. A general population study found an 11% conversion rate from mild cognitive impairment was detected over three years,[15] whereas one hospital study reported a yearly rate of 12%.[14]

In our population study, we showed that global cognitive impairment with no dementia is not, on its own, a sufficiently valid predictor of dementia.[11] People with global cognitive impairment with no dementia had a threefold higher risk of developing dementia over three years than unimpaired people, but one third of them improved in cognitive functioning or remained stable.[11] Few data are available concerning the clinical value of screening asymptomatic people for dementia.[16]

We hypothesised that a multistep procedure could be applied to the general population to identify with high predictivity people with cognitive impairment who will develop dementia. The steps were self reported memory complaints, performance on a global cognitive test, and performance on specific neuropsychological tests. These steps are analogous to a real life situation, in which an individual might first report symptoms to a general practitioner, would then be assessed globally by a non-specialised physician, and finally would have a more thorough examination in a specialised clinical setting. We assessed the feasibil-

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ity and predictivity of this strategy using data from the Kungsholmen project.

Methods

We used data from baseline, three, and six year follow up examinations in the Kungsholmen project, a longitudinal study of people aged 75 and older living in the Kungsholmen district of Stockholm, Sweden.[17] Informed consent was obtained from all participants at baseline. The Karolinska Institute ethics committee approved all phases of the project.

Among the 1700 baseline participants, 225 prevalent cases of dementia were identified by a two phase study design and diagnosed by specialists according to the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R). The mini-mental state examination was administered to all subjects to assess global cognitive functioning. Scores range from 0 to 30, with a higher score indicating better cognitive performance. We excluded 31 people because of low cognitive performance (score <20) and nine people because their educational background was unknown or they were older than 95. The remaining 1435 constituted the study population. Data on memory complaints were available for 1417 subjects.

A sample of the initial 1700 Kungsholmen project participants was selected for extensive neuropsychological testing. This sample comprised all participants with a mini-mental state examination score <24 (n=314) and a group of age and sex matched controls from participants scoring ≥ 24 (n=354). This sampling procedure meant that people with a score <24 were over-represented. As older women are more likely to be cognitively impaired or demented, the sample was older and included a higher proportion of women than the initial cohort. When we excluded participants with dementia, aged >95, or a mini-mental state examination score <20, 379 of the neuropsychological sample remained (60 with a score <24 and 319 with a score ≥ 24). The proportion of participants scoring ≥ 24 who developed dementia at follow up was similar in the neuropsychological sample (14%, 42/296) and the whole population (15%, 177/1205).

Baseline variables

We assessed memory complaints with a single direct question: "Do you currently have any problems with your memory?" Global cognitive impairment with no dementia was defined as scoring one standard deviation below the age and education specific mean on the mini-mental state examination, an easy to administer test of global cognitive functioning.[11]

Three domains of cognitive functioning were assessed in neurological testing: episodic memory, verbal fluency, and visuospatial skill. Impairment was defined as scoring one standard deviation below the age and education specific means on the following tests:

Recall, episodic memory—A composite score of four significantly correlated (r=0.54-0.59, $P<0.01$) word recall tasks were used: free recall of rapidly and slowly presented random words, and free and cued recall of organisable words.[18]

Verbal fluency—Participants were asked to produce as many grocery items as possible during 60 seconds. Scores were based on the number of grocery items produced.

Visuospatial skill—A composite score of three significantly correlated (r=0.24-0.40, $P<0.01$) tests was used to assess visuospatial skill: block design,[19] clock setting,[20] and clock reading.[20]

Diagnosis of dementia

The main outcome measure at follow up was presence of Alzheimer's disease or dementia in both survivors and those who had died. We diagnosed Alzheimer's disease and dementia according to DSM-III-R criteria, using a double diagnostic procedure.[17] All cooperating survivors had an extensive clinical examination using a similar protocol to that used at baseline, and we sought the death certificates and medical records of those who had died to determine the presence of dementia.

Analysis of data

We derived the relative risks of developing Alzheimer's disease and dementia from Cox regression models. We calculated the sensitivities and specificities for dementia for each measure, along with the positive predictive values and negative predictive values and 95% confidence intervals. Different combinations of the three measures were investigated. Firstly, we examined each measure separately in the whole population. Secondly, we calculated the predictive values of either global cognitive impairment with no dementia or domain specific cognitive impairment among participants with memory complaints. Thirdly, we assessed the predictive values of the cognitive tests in participants with both memory complaints and global cognitive impairment with no dementia. Due to the small number of people in this subgroup (n=83), we pooled data from the first and second follow up periods. At first follow up, 785 people without dementia were examined, and 67 (9%) were classified as having both memory complaints and global cognitive impairment with no dementia. The proportion of participants with memory complaints and global cognitive impairment who developed dementia was similar during first follow up (45%, 34/75) and second follow up (37%, 24/65). The predictive values of the cognitive tests for identifying future dementia were estimated from these two groups pooled together (83 and 67 people).

Results

Among the 1435 participants without dementia, 75% (1081) were female. At three year follow up, which took place on average 3.4 years (SD 0.6) after baseline, 291 (20%) had died and 170 (12%) either refused to participate or had moved. Those who refused were significantly younger ($P<0.01$) than participants but did not differ in level of education or sex distribution. Of the survivors, 189 (19%) had dementia diagnosed at follow up (146 (77%) Alzheimer's disease, 31 (16%) vascular dementia, 12 (7%) other dementia types). Of the 291 who had died, 18 (6%) had had Alzheimer's disease or dementia diagnosed. This figure is lower than the number of cases among the survivors because dementia is consistently under-reported in clinical records and death certificates. Table 1 shows the baseline characteristics for the 1417 participants in the whole sample and 352 in the neuropsychological test sample for whom we had information on memory

Table 1 Baseline characteristics and follow up status of whole study population and sample selected for neuropsychological testing according to presence of memory complaints

	Study population		Neuropsychological test sample	
	Memory complaints (n=457)	No memory complaints (n=960)	Memory complaints (n=128)	No memory complaints (n=244)
Baseline characteristic:				
Mean (SD) age (years)	81.3 (4.9)	81.3 (4.7)	84.0 (5.5)	84.3 (5.1)
No (%) of women	348 (76)	718 (75)	107 (84)	198 (81)
No (%) with high education (≥8 years)	183 (40)	400 (42)	54 (42)	89 (37)
Mean (SD) mini-mental state examination score	26.6 (2.0)*	27.9 (1.8)	25.7 (2.5)*	26.6 (2.3)
No (%) global cognitive impairment with no dementia	83 (18)*	126 (13)	37 (29)*	42 (17)
Status at follow up (No (%)):				
Demented	104 (23)*	100 (10)	38 (30)*	31 (13)
Dead	103 (23)	184 (19)	25 (20)	40 (16)
Refused or moved	38 (8)*	130 (14)	7 (5)	22 (9)

*Significant difference between people with and without memory complaints (χ^2 or *t* test, P<0.01).

complaints. In both groups, people with memory complaints had lower scores on the mini-mental state examination, were more likely to have had global cognitive impairment with no dementia at baseline, and were more likely to participate and to develop dementia at three year follow up than people without memory complaints.

At baseline, 457 participants (32%) had memory complaints and 212 (15%) had global cognitive impairment with no dementia. Among the participants who had neuropsychological testing for whom we had data, 51 (14%) had recall impairment, 53 (15%) had verbal fluency impairment, and 60 (17%) had visuospatial impairment. Table 2 shows the relative risks of developing Alzheimer's disease and dementia for the different indicators.

Table 3 shows the sensitivity and specificity of the three instruments for identifying dementia at three year follow up, and table 4 shows the positive and negative predictive values. When the instruments were used on the whole population without screening, the negative predictive values were similar for all three measures. The positive predictive value varied from 25% (95% confidence interval 21% to 29%) for memory complaints to 37% (23% to 51%) for recall impairment. Memory complaints had the highest sensitivity, identifying 51% (44% to 58%) of future dementia cases. After screening for memory complaints, the positive predictive value for global cognitive impairment with no dementia increased, with a slight decrease in negative predictive value. A similar pattern was seen for domain specific cognitive impairment. After we had screened for both memory complaints and global cognitive impairment with no dementia, the positive predictive value for recall impairment (75%, 51% to 99%) and impaired verbal fluency (85%, 62% to 100%) increased substantially.

When we included only survivors at follow up, the positive predictive value of the cognitive tests increased greatly. All of the participants with verbal fluency impairment had developed Alzheimer's disease and dementia at follow up (negative predictive value 57%, 35% to 79%) and 91% (72% to 100%) of participants with recall impairment had developed Alzheimer's disease and dementia at follow up (negative predictive value 64%, 43% to 85%). The positive and negative predictive values for visuospatial impairment increased slightly to 36% (3% to 69%) and 42% (20% to 63%), respectively. Among participants who screened positive for memory complaints and global cognitive impairment but no dementia, all those who had impairment on all three domains of the neuropsychological tests at baseline or impairment on both verbal fluency and episodic memory tasks had either developed Alzheimer's disease or dementia at follow up or died.

Discussion

We found a high positive predictive value for Alzheimer's disease and dementia with a three step procedure that simulates routine clinical practice: reporting memory complaints at primary care level, assessment of global cognitive functioning by a general practitioner, and, finally, domain specific cognitive testing in a specialised setting. Among participants who screened positive for memory complaints and global cognitive impairment with no dementia, 85% of those with impaired verbal fluency impairment and 75% of those with recall impairment developed dementia after three years, and the negative predictive value remained acceptable. However, the three step procedure was able to identify only 18% of those who developed dementia overall because of the low sensitivity of the measures. The low positive predictive value for all three instruments shows that no single measure is suitable for screening for dementia by itself in the general population.

When we measured dementia in survivors at follow up, the positive predictive value of the domain specific tests among participants with memory complaints and global cognitive impairment was higher than when we included those who had died. All participants with impaired verbal fluency and 91% with recall impairment at baseline developed Alzheimer's disease and dementia. This increased predictivity in survivors may

Table 2 Relative risk of developing Alzheimer's disease and dementia associated with possible indicators of impairment

Indicator	No (%) of people	Relative risk* (95% CI)
Memory complaint	457/1417 (32)	2.0 (1.5 to 2.6)
Global cognitive impairment with no dementia	212/1435 (15)	3.6 (2.6 to 4.8)
Domain specific cognitive impairment:		
Episodic/recall impairment	51/357 (14)	4.8 (2.7 to 8.5)
Verbal fluency impairment	53/357 (15)	3.8 (2.2 to 6.6)
Visuospatial impairment	60/360 (17)	2.1 (1.6 to 3.7)

*Estimated by using Cox regression models with adjustment for age, education, and sex.

Table 3 Sensitivity and specificity of memory complaints, global cognitive impairment with no dementia, and impairment on domain specific cognitive tests for predicting Alzheimer's disease and dementia* at three year follow up with three step screening

	Step 1: Tests in the general population		Step 2: Testing only people with memory complaints		Step 3: Testing only people with both memory complaints and cognitive impairment	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Memory complaint	0.51 (0.44 to 0.58)	0.70 (0.67 to 0.73)	—	—	—	—
Global cognitive impairment with no dementia	0.31 (0.25 to 0.38)	0.89 (0.87 to 0.91)	0.33 (0.24 to 0.42)	0.87 (0.83 to 0.91)	—	—
Domain specific cognitive impairment:						
Episodic/recall impairment	0.21 (0.11 to 0.32)	0.94 (0.91 to 0.97)	0.25 (0.10 to 0.40)	0.89 (0.82 to 0.96)	0.50 (0.29 to 0.71)	0.89 (0.75 to 1)
Verbal fluency impairment	0.30 (0.18 to 0.41)	0.89 (0.86 to 0.93)	0.40 (0.23 to 0.56)	0.85 (0.76 to 0.93)	0.48 (0.26 to 0.70)	0.92 (0.79 to 1)
Visuospatial impairment	0.27 (0.16 to 0.38)	0.90 (0.87 to 0.94)	0.25 (0.10 to 0.39)	0.84 (0.76 to 0.92)	0.26 (0.07 to 0.45)	0.46 (0.23 to 0.68)

*Progression to dementia versus remaining alive or dying without dementia.

Table 4 Positive and negative predictive values of memory complaints, global cognitive impairment with no dementia, and impairment on domain specific cognitive tests for Alzheimer's disease and dementia* at three year follow up with three step screening

	Step 1: Tests in the general population		Step 2: Testing only people with memory complaints		Step 3: Testing only people with both memory complaints and cognitive impairment	
	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Memory complaint	0.25 (0.21 to 0.29)	0.88 (0.86 to 0.90)	—	—	—	—
Global cognitive impairment with no dementia	0.35 (0.28 to 0.42)	0.87 (0.85 to 0.89)	0.45 (0.34 to 0.57)	0.80 (0.75 to 0.84)	—	—
Domain specific cognitive impairment:						
Episodic/recall impairment	0.37 (0.23 to 0.51)	0.87 (0.83 to 0.91)	0.41 (0.22 to 0.60)	0.80 (0.71 to 0.88)	0.75 (0.51 to 0.99)	0.73 (0.56 to 0.89)
Verbal fluency impairment	0.34 (0.21 to 0.46)	0.88 (0.84 to 0.91)	0.44 (0.25 to 0.64)	0.82 (0.74 to 0.90)	0.85 (0.62 to 1)	0.65 (0.47 to 0.82)
Visuospatial impairment	0.33 (0.20 to 0.45)	0.87 (0.83 to 0.91)	0.33 (0.15 to 0.50)	0.79 (0.70 to 0.87)	0.24 (0.01 to 0.47)	0.49 (0.29 to 0.68)

*Progression to dementia versus remaining alive or dying without dementia.

be due to two factors. Firstly, participants who died could have been in a stage of terminal decline at baseline.[21] Secondly, the under-reporting of dementia in hospital records could have led to underascertainment of dementia among those who died.[22] The actual predictive values for the three step procedure may fall between the estimated values from the whole population and those derived from the cohort of survivors.

Our results support previous studies showing the benefit of combining screening tools and specific cognitive tests to assess risk of dementia. Some studies found that the mini-mental state examination was better at identifying people who would progress to Alzheimer's disease when combined with a word recall task.[3 4] Bozoki et al found that over three years, 69% of people with memory impairment and deficits on at least one additional cognitive task developed dementia compared with 15% of people with memory impairment alone.[23]

Sensitivity

Unfortunately, some people who developed dementia were screened out at each step of the three stage procedure because of false negatives results. At the first stage, 12% of participants who reported no memory problems developed dementia during follow up. At the second stage, 20% of participants without global cognitive impairment with no dementia developed dementia during follow up. This high rate of false negatives results was due to the low sensitivity of the measures and has been found previously.[15]

The false negative rate at the last stage of our process could easily be decreased in a specialised clinical setting by using other diagnostic tools, such as neuroimaging or biological markers.[7 8] However, the low sensitivity at the first stages is cause for concern. Although memory complaints had the highest sensitivity, 49% of people who developed Alzheimer's disease and dementia did not report memory complaints in the preclinical phase. If this is translated into clinical practice, only half of future dementia cases will ask for help because of subjective memory problems three years before possible diagnosis. The sensitivity of memory problems might be higher if they were evaluated a shorter time before diagnosis. More studies concerning the temporal relation between subjective complaints and diagnosis of dementia may clarify this. Additionally, elderly people might regard memory deficits as part of normal ageing and thus not consider such problems as medically relevant.

Assessment of memory problems

Although some studies have used scales to assess subjective memory problems, a single, simple question is probably more indicative of a person's judgment of his or her memory. It would also have been interesting to investigate informants' reports, which are better indicators of dementia than self reports.[24] Finally, all subjects were asked whether they had problems with their memory, which is different from seeking medical advice. Those that consult a doctor probably have more severe memory deficits and represent a subgroup of those identified in this study. The positive predictive value among people actively seeking help for memory problems could be higher.

Applicability

Ritchie et al showed that criteria for mild cognitive impairment applied to the general population had low sensitivity and predictivity for dementia over three years.[15] Age associated cognitive decline, which includes all areas of cognitive functioning not specifically memory, had a much higher sensitivity and was more stable over time than mild cognitive impairment. We aimed to overcome these problems by including both global and domain specific cognitive

What is already known on this topic

Alzheimer's disease is characterised by a preclinical phase, during which cognitive deficits are seen before diagnosis

Elderly people with subjective memory complaints and objective global cognitive impairment have a high risk of developing Alzheimer's disease and dementia

What this study adds

This three step procedure (self report of memory complaints, test of global cognitive functioning, and then domain specific cognitive tests) has a positive predictivity of 85-100% for Alzheimer's disease and dementia at three years

However, only 18% of people in the preclinical phase can be identified using this procedure

About half of the people in the preclinical phase of Alzheimer's disease and dementia do not report problems with their memory three years before diagnosis

indicators and using a screening procedure that was simple and analogous to clinical practice. Our participants had impairment in cognitive domains other than memory, which is the only domain assessed by mild cognitive impairment. Consequently, our procedure can identify people that will develop Alzheimer's disease and other types of dementia. This is important because vascular and degenerative dementia often overlap in elderly people.

In conclusion, our study shows that a three step screening process similar to what might occur in real clinical practice can identify people in the general population who will develop dementia in three years with a high predictivity. The high predictivity is reached without using sophisticated examinations, such as neuroimaging or biological tests, and by using specific cognitive testing in only a subgroup of the population. This makes the procedure usable at the population level. The challenge for the future is to increase the sensitivity at the first step. This could include providing better information to elderly people concerning the importance of assessing cognitive functioning if they have memory problems.

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