

Chapter 13

VALIDATION OF TWO SHORT DEMENTIA SCREENING TESTS IN INDONESIA

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ABSTRACT

Background

Dementia is on the increase worldwide, and developing countries are expected to carry the burden of this. Relatively little is known about dementia prevalence in Indonesia. This chapter discusses two short screening tests to assess dementia in rural and urban Indonesian cohorts.

Method

At baseline in 2006/7, 719 elderly were included from rural and urban sites on Java. Large differences appeared in dementia prevalence in those over 60 years of age between urban (3%) and rural sites (7-16%) employing two dementia screening tests also used in Oxfordshire with the same cut-offs. An in depth study was performed on the rural sample from East Java to validate the cut-offs of the tests. For this study, Javanese Indonesian elderly from 4 villages around Borobudur were asked to participate. 113 agreed to

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participate and these were tested in a health center by medical experts and trained research assistants. The screening test cut-offs were validated against consensus based clinical dementia diagnoses by an expert psychiatrist, nurses and GP, which were based on a gold standard diagnostic instrument for dementia diagnoses from Cambridge. In addition, a sub sample of these participants was tested in depth by another psychiatrist using questions from our expert dementia diagnostic system developed at Oxford University.

Results

The adapted memory screening test was shown to have similar cut-offs for dementia (19.5 for controls and 14.5 for cases) as in Oxfordshire and the Mini Mental Status Examination (MMSE) had optimal sensitivity (100%) using a similar cut-off of 24. However, for optimal specificity, the MMSE was shown to require a lower cut-off of 21.5 and MMSE scores were also affected significantly by educational level. It was unclear how many of these cases had vascular dementia (VaD), as stroke, transient ischaemic attack and myocardial infarct assessed by self-report were rare ($n=1-2$) and were only reported by controls, suggesting a recall bias. There was also no difference in diabetes mellitus or (high) blood pressure between cases and controls which could have increased risk. Physical examination suggested no other morbidity driving the dementia (e.g. infectious or lung disease). The cut-offs were also tested by another expert psychiatrist on a sub sample of these participants using her clinical assessment and aided by questions from our expert dementia diagnostic system. Agreement between psychiatrists was high (79%) on diagnoses of these 28 participants, with only 6 disagreed on. Of these, only diagnoses of 2 participants were disagreed on whether these had dementia or were controls. Of 59 elderly patients from the villages who were tested in depth by the second psychiatrist, 17 were thought to have dementia, with most (53%) having Alzheimer's disease (AD) and 6 (35%) suspected of having VaD, with only one mixed (with stroke) case. There was no clear indication of other types of dementia, but two cases with dementia (12%) were thought to be related to systemic disease. The 19 preclinical cases (possible dementia) all had memory complaints, but scored significantly higher on the adapted memory test and MMSE than those with dementia and scored lower than controls (but not significantly so on the memory test), independent of age and gender. Optimal cut-offs for dementia on the memory test were again 19.5 for the total immediate recall (100% sensitivity and 78% specificity) and 24 for the MMSE (88% sensitivity and 96% specificity).

Discussion

This study showed that two short cognitive tests can be used for dementia screening in rural Java. It has been hypothesized that VaD is more prevalent than AD in East Asian countries, but we could not substantiate this. Future studies should investigate in more detail the prevalence of vascular and secondary dementias (due to thyroid or infectious disease, nutritional deficiency etc.). Use of this screening instrument in other ethnic groups in other developing countries also needs to be explored.

Keywords: Alzheimer's disease, dementia, screening, developing countries

INTRODUCTION

Dementia has high economic and human costs and its prevalence is predicted to increase substantially over the next decades. Currently it is estimated that 24 million people have dementia worldwide, a number predicted to double every 20 years. Of those afflicted with dementia, 60% is estimated to live in developing countries, with the proportion increasing to 70% by 2040 (Qui, 2007). An older age and low levels of educational attainment are strong risk factors for dementia (Launer, 1999; Karp, 2004). By 2050, 70% of older people will live in developing countries, who are burdened by lack of resources and a combination of non-communicable and communicable disease (Kalache 2003). This leads to increased risks of primary and secondary dementias, increased dependence and lower productivity, as many elderly still contribute to family finances (Kreager, 2006a.b). This combined with a predicted increase in migration from poorer countries (according to recent United Nations population division reports, see UN, 2007) to the North Western more prosperous regions, highlight the importance of cheap, short and cross culturally applicable screening tools for dementia assessment in multi-ethnic cohorts

The clinical diagnosis of dementia is based on neuropsychological testing, medical history and examination to rule out systemic, psychiatric, neurological and other causes of cognitive impairment, and to identify the pattern of progression (McKhann, 1984, APA, 1994). However, most clinical screening tools originate from developed countries and do not take into account some of the issues pertaining to many developing countries such as:

- i) a general lack of resources (e.g. a lack of trained staff, time and financial constraints)
- ii) high rates of illiteracy and cultural/linguistic differences which can affect the validity of neuropsychological tests.

While the brief Mini-Mental Status Examination (MMSE, Folstein, 1975) has often been criticised for its ceiling effects and modification by education, mood and age (Hogervorst, 2002, Iype, 2006), it is still the most widely used short screening test for dementia. The sensitivity of the MMSE is good (its ability to identify cases), but its specificity is low (Hogervorst, 2002, Iype, 2006). However, MMSE specificity can be much improved when used in an algorithm with the Hopkins Verbal Learning Test (HVLT, Brandt, 1991; see Hogervorst, 2002 for a review). Memory is usually one of the first functions to show a decline in Alzheimer's disease (AD), the most common form of dementia in Western countries and is, according to consensus based criteria, a key criteria for the assessment of dementia (APA, 1994). The HVLT, a short memory test, takes about 5 min to administer, is sensitive and well tolerated by patients. In a study (Hogervorst, 2002) of 82 patients with dementia and 114 healthy controls - equivalent in age, years of education and gender ratio - from the Oxford Project To Investigate Memory and Ageing (OPTIMA), the total immediate recall memory score of the HVLT had 87% sensitivity and 98% specificity for dementia, when using a cut-off score of 14.5. Sixty-eight patients had been diagnosed with AD using NINCDS/ADRDA criteria (McKhann, 1984). Using the 14.5 cut-off point, 91% sensitivity and 98% specificity for AD was found. There were no ceiling or floor effects. Regression analyses indicated that HVLT test results did not need to be adjusted for age, gender, education or depression.

These results were robust as a another OPTIMA study (De Jager, 2003) with a different patient group showed 98% sensitivity with 92% specificity, using a cut-off of 18.5 to discriminate between 60 AD cases and 51 controls. The cut-off was higher because in this study the control group did not include participants with mild cognitive impairment (MCI).

People with MCI may be at risk for dementia (Petersen, 1999) but, to simulate clinical reality, this group had been included with controls in our first study (Hogervorst 2002). The HVLT is adept at identifying people with MCI in an early stage. Using a cut-off of 21.5, 78% sensitivity and 80% specificity was detected at baseline between 51 healthy controls and 15 control participants who would develop MCI after a 2-3 year follow-up. A third study (Schrijnemakers, 2007) gave similar data on specificity and sensitivity for AD, MCI and controls, which were maintained at follow-up. To reduce slight learning effects in controls, six parallel versions exist, which have shown good inter-test reliability (Brandt, 1991). Several studies using the test in other cohorts have reported a similar discriminative capacity of the HVLT (see Hogervorst 2002 for a review), including the possibility to distinguish between vascular dementia (VaD) and AD. In our earlier study, 82% sensitivity and 75% specificity of AD versus VaD was found (De Jager, 2003).

On the basis of our prior research in Oxford (de Jager, 2003; Schrijnemakers, 2007; Hogervorst, 2002), the following algorithm was deemed to be most suitable for optimal sensitivity and specificity in screening:

- for dementia: HVLT total immediate recall less than 14.5 and MMSE less than 24.5;
- for controls: HVLT greater than or equal to 19.5, MMSE greater than or equal to 24.5.

Those who fall between cut-offs are questionable and require more in depth assessment. This algorithm was subsequently used for the initial screening in memory clinics in Oxfordshire.

However, it is unclear how cross culturally/ethnically applicable word learning tests are (Morris, 2001). For instance, in an impoverished rural cohort in Arkansas USA, Black Americans scored lower on similar word learning lists than White participants when controlled for age, education, socioeconomic status (SES), sex and mood (Hogervorst, 2004). Systematic distribution differences in education between Blacks and Whites may have confounded results, but were difficult to investigate.

Dementia prevalence is currently unknown in Indonesia, but it has one of the fastest growing aging multi-ethnic populations globally. Currently in Indonesia 8% (17 million) of the population is over 60 years old, which is expected to increase to 13.5% (35 million) by 2025 (Wibowo et al, 2004). Due to the similar demographic pyramid structure and life expectancy, similar dementia prevalence was expected in Indonesia as in India, which is 5% in those over 60 years of age (Biswas et al, 2005).

METHODS

Study of Elderly's Memory Impairment and Associated Risk Factors (SEMAR)

Our initial Indonesian cross-sectional study included 719 elderly who were between 52 to 98 years of age from two rural sites (West and Central Java) and an urban site (Jakarta). This study was described in more detail in Yesufu et al (2008). It was set-up as a baseline study in 2006/2007 to be followed-up by a more in depth study to also validate dementia status of participants in 2009. Briefly, prior to the study all village elders and staff at local community health centers or care institutes had been informed of the study and they subsequently forwarded this information to potential participants. Participants had been asked to bring their carers and to arrive in the morning at the local health centers at agreed dates if they were interested in participating. None of the elderly approached refused participation after they had been given information about the study by trained research assistants and all signed the informed consent forms. If a carer was present, they also signed the informed consent form. No incentive was offered. The study was carried out between April and June 2006 in Jakarta and between December 2006 and February 2007 in the rural areas of Borobudur and Sumedang. Ethical approval (University of Indonesia, Jakarta and Loughborough University, UK), governmental and local permits had all been obtained before study-onset, which included a follow-up study two years later.

In West Java, at the Sumedang site, all 207 Sundanese elderly who resided in the village of Citengah (a 1-2 hour drive from Bandung) were invited to come to the community health center and were tested there after they had given informed consent. At the Borobudur site (Central Java, a 2 hour drive from Yogyakarta) all 214 Javanese elderly covered by the Borobudur community health center were included and were asked to come to the local health center to be tested after they had given informed consent. Those with limited mobility were visited at home (n=2), when they had agreed to be visited there. For the urban area (Central, West and South Jakarta in North-West Java), a sample of 298 elderly with mixed ethnicity was included after giving informed consent (47% Javanese, 17% Sundanese, while other ethnic groups, such as Minangkebau, Chinese, etc., were less prevalent). This ethnic distribution for Jakarta reflected the Indonesian census of 2000. Most of these participants (n=164) were either attending the local community health centers, lived in local care homes for elderly (n=49), or were tested at home (n=1).

Assessment of Demographics and Cognitive Function

Testing was done by trained and supervised research assistants between 8-11am to avoid circadian interference and the effects of heat. Participants were surveyed for demographic and other variables (such as health and lifestyle) using standardized questionnaires. Answers were all substantiated by a carer when present (in about half of the suspected cases and half of controls). To assess memory function, the Hopkins Verbal Learning Test (HVLT, Brandt, 1991) was used. This is a word learning test measuring episodic memory, which consists of 12 words from 3 low frequency categories (for version A: 'human shelter'; 'animals' and

‘precious stones’). These words were all repeated 3 times to obtain a total immediate recall measure (‘learning ability’). After 20 min, a delayed recall without cues or prompting was done. Some items (of the precious stones category) were changed after a pilot study to adapt to local knowledge, creating a modified Indonesian version of this word list.

The Mini Mental Status Examination (MMSE, Folstein, 1975) consists of a series of questions designed to measure change in cognitive status and to differentiate between normal age-related cognitive decline and the pathological cognitive decline that occurs in dementia. It was slightly adapted for local circumstances (e.g. seasons of the year were scored as wet or dry season, which was similar to the Hindi version developed by Ganguli, 1995). To assess cognitive impairment/possible dementia, the combination of the two cognitive tests was employed, using the total immediate recall of the HVLT and the total score of the MMSE with previously established cut-offs (see above).

Assessment of Ability to Function on a Daily Basis By Carer Report

For carers’ confirmation of memory and other cognitive impairment and to identify progression of disease, questions based on the Dementia Questionnaire (Ellis 1998) were included, which is a semi-structured informant (carer) interview for the diagnosis of dementia. It has shown good validity and reliability and relates to the most commonly used consensus based (ICD-10 and DSM-IV, see APA, 1994) dementia criteria. However, according to Yesufu (2009) only the question ‘does the person you care for have memory problems and has this been getting worse?’ was sufficiently discriminative for cases and controls using factor analyses. None of the questions about other cognitive problems or etiology and course were therefore included in the subsequent analyses. The Barthel Activities of Daily Living (ADL, Barthel and Mahoney, 1965) and Instrumental Activities of Daily Living (IADL, Lawton and Brody, 1969) were used to assess functional capabilities of participants. For this study a slightly modified IADL was implemented using a cut-off of ‘9’ was used (see Appendix)

After pilots and revisions of some contents, the translated forms of cognitive tests and questionnaires encountered no further problems and back-translation from Bahasa Indonesia (in Jakarta), Javanese (in Borobudur) and Sundanese (in Sumedang) to English was also done successfully for all tests.

Consensus based DSM-IV criteria (APA, 1994) for dementia can be summarized as follows:

- A. Cognitive impairment including memory and at least one other cognitive function
- B. which are a decline from a previous level of function and impact on social and occupational function and activities of daily living, and
- C. have gotten progressively (gradually for AD, stepwise for VaD) worse over time,
- D. while there are no other medical or psychiatric (E) factors present that are judged to have caused the cognitive impairment.

This was operationalised in our study as:

- A. Performance below established cut-offs for cognitive dysfunction (see introduction);

- B. Performance below a cut-off of '9' to assess impaired Instrumental Activities of Daily Living (see Appendix)
- C. Carer's report of memory impairment (1), which affected IADL (2) and which had gotten (progressively or stepwise) worse over the last year.
- D. At this stage physical or mental morbidity affecting cognition could not be reliably investigated, but carers had been asked what they thought the etiology was of the memory problems (old age, stress, depression, sickness etc) and self reported health status (doctors visits, specialists visits, taking medication, perceived health etc) was measured.

RESULTS

Participants from rural areas (all participants covered by the health centres of Borobudur and Sumedang, in Central and West Java, respectively) had substantially higher risk of cognitive impairment/possible dementia using the cut-offs from Oxfordshire (around 43% in both areas scored below cut-offs of both tests using the established algorithm), when compared to the urban areas (with only 11% scoring below both cut-offs in Central and South Jakarta).

| | Jakarta 298 | Sumedang 207 | Borobudur 214 |
|----------------|----------------|-----------------|------------------|
| Below cut-offs | n=34 (11%) | n=88 (43%) | n=93(43%) |
| IADL <9 | n=28 (10%) | n=22 (11%) | n=40 (19%) |
| Cognition+IADL | n=9 (3-6%) | n=15 (7-9%) | n=34 (16%) |

The percentages given below for possible dementia take into account missing data of cognitive tests

| | Jakarta 288 | Sumedang 203 | Borobudur 214 |
|----------------|----------------|-----------------|------------------|
| Only 60+ | n=9 (3%) | n=15 (7%) | n=34 (16%) |
| Cognition+IADL | 175 | 143 | 164 |
| Only 65+ | n=8 (4.5%) | n=14 (9.8%) | n=34 (21%) |
| Cognition+IADL | | | |

Rural elderly were thus approximately 4 times more likely to score below cut-off scores. However, participants in Jakarta were on average younger and better educated than those in rural areas. In Central and South Jakarta, the average age of the elderly investigated was 68 years (SD 7.7, range 52 to 90 years). While 13% had obtained no education, 44% of elderly had at least obtained a high school diploma or more. In Sumedang, Citengah, the average age of elderly included was 69 years (SD 7.7 range 52 to 98 years), with 18% not having obtained any education, and only 3% having obtained high school education or more. In Borobudur, the average age of elderly included was 71 years (SD 7.9 range 60-90), and 46% of these elderly had obtained no education, while only 2% had obtained high school education or more. These differences in age and education explained the association of site (urban vs rural) in logistic regression analyses to predict cognitive impairment/possible dementia as

established by cut-offs. Ethnicity, socioeconomic status (occupation and house ownership) and gender were all not significantly associated with cognitive impairment/possible dementia in these analyses, although these variables were associated with performance on the word list, when this was investigated in separate analyses. Distributions of test performance were similar, but average MMSE and HVLT scores of Indonesian controls were slightly lower than those of our Oxfordshire cohort (Hogervorst, 2002; Yesufu, 2008).

Investigating IADL separately, which can be an indicator of dementia, showed regional differences with 1 in 5 of elderly over 60 years of age in Borobudur and 1 in 10 in Sumedang and Jakarta experiencing difficulties in instrumental activities of daily living. Overall, suspected dementia prevalence (taking into account both cognitive impairment and problems in activities of daily living) in those over 60 and 65 years of age was around 8%. This was slightly higher than expected, because of a very high percentage of possible dementia cases in Borobudur, Central Java (16-21%).

However, half of carers stated there were no memory problems in those elderly who scored below the cut-offs on the HVLT and MMSE. It is not clear whether this is an underestimate or whether the low cognitive test scores did actually not reflect deficiencies in every day memory and cognition. Overall, data of n=136 carers indicated that around n=40 (5.6% of the total cohort) of suspected cases had memory problems, of whom n=22 had gotten progressively worse over time and may have had Alzheimer's disease.

Taking these data together indicated that 6-8% of people, who were included in our sample and who were over 60 years of age could be afflicted with dementia. These suspected cases had an average MMSE of 15.5 (SD 9) compared to an MMSE of 23 (SD 6) in controls, as established by the cut-offs. Controls were all reported by carers not to have memory problems. Where activities of daily life and social functioning was affected by cognitive problems according to carers (n=22, 3%), average MMSE scores were 13 (SD 8). Similarly, in an Indian case control study (Iype, 2006), average modified MMSE scores were 23 (SD 5) for controls, and for mild to moderate dementia cases these were around 14 (SD 7). These differences between control cohorts on the MMSE may be related to systematic differences in culture or education between Western and developing countries cohorts.

DISCUSSION

The overall dementia prevalence estimate found in this study is in line with earlier estimates (Biswas, 2005) with around 6% (with a range of 3-8%) of people screened over 60 years of age suspected of having dementia. Taking Indonesian population growth into account (Wibowo, 2004), with a 5% prevalence of dementia, our estimate would render a total predicted 1.8 M dementia cases in 2025 in Indonesia. For the rural areas, our higher estimated prevalence in Borobudur than in Sumedang would be in line with reports from the village elderly and center for health staff when using focus groups and semi structured interviews to assess dementia prevalence.

In Sumedang, only aggression and paranoia (but not memory or any other cognitive impairment) was considered an issue as reported by village elders in perhaps 1 to 3 (of 100 elderly in the village), but this was not considered to be a problem in Borobudur. The most common issues reported in focus groups in Borobudur were those of memory (but not

attention), forgetfulness (e.g. forgetting that they had eaten already) and disorientation (getting lost). These problems were thought to fluctuate and were thought by Health Center staff in Borobudur to be mainly related to deafness, arthritis, and high blood pressure (which were all very common in the elderly). They were not thought to relate to dementia, thyroid disease (which is apparently endemic in the area and monitored in children, although in 100 elderly, only 1 goitre was identified), tuberculosis (only 1-2 known cases in the elderly and this was monitored by the centers and treated for free), or other infectious disease or anaemia (even though most elderly were reported to hardly ever eat meat). There were no tremors/motor problems indicative of Parkinson's disease (PD). There were 2 stroke cases, but one of these did not have dementia. About 1: 4 of elderly was reported to have wheezing (COPD (?), as all of these were smokers) but none of these cases had signs of 'Pikun' (dementia). Frontotemporal dementia (FTD, e.g. with personality changes, aggression, paranoia, problems in planning) and Lewy Body dementia (LBD, with hallucinations, fluctuations in attention etc) seemed either not to exist or were not recognized. However, according to staff, most elderly could still take care of themselves and memory (forgetting) and some planning problems were considered by them and the villagers to be a normal part of aging. When staff was pressed further, in Borobudur, 3-5 elderly (8-13% of 40 elderly villagers) were perhaps thought to have more than normal issues with memory problems and getting lost. Only 3 elderly had some (but significant) problems with planning and could not support themselves financially, but they still participated in community life (e.g. by sweeping etc). All but maybe 1 or 2 were reported to still be able to handle money and dress/feed themselves. The validity of this rural community consensus on identifying possible dementia cases who need support will be investigated further in a future study. So far, however, only half of the 5 reported cases actually had cognitive performance over the cut-offs of the screening tests, while others with very low scores were not included by the focus group. Whether this reflects poor every day life validity of the tests or a misrepresentation by village elders and center for health staff remains to be determined.

There are several limitations to the current study. Firstly, there was large variation between the sites and systematic demographic differences in the distribution of age, SES, ethnic differences and educational attainments between rural and urban samples may have acted as confounds and are difficult to investigate. In addition, the last APA criteria in our earlier study could not be systematically investigated (whether other medical (D) or psychiatric (E) factors were present that would be judged to have caused the cognitive impairment). It was thus unclear what percentage of those at risk could be counted as secondary preventable dementias or cognitive impairment due to other causes than dementia. According to a more detailed analyses of the course of disease and self reported health factors in this cohort (Yesufu, 2008), Alzheimer's disease (AD) was thought to be less common and vascular or secondary dementias were suspected to be more common. This is important as these may offer treatment possibilities, which are currently not a long term effective solution for AD. However, this was based on self-report data on health, which may be unreliable, particularly in suspected dementia cases due to the very nature of their impairment (see data second study on self report of stroke, etc). Furthermore, community workers (see above staff of Centers for Health) and carers were suspected to under-report (cognitive) problems of both cases and controls, to a somewhat similar magnitude. This may be part of a cultural attitude towards the elderly (one of respect), which needs to be taken into account when using carer report to corroborate patient's self report and cognitive test results. Lastly, in Indonesia, at the

time of testing life expectancy for men was 65 years and for women it was 69 years. People may thus not survive to be old enough to be at risk for dementia, leaving only healthy survivors (of heart disease, stroke etc.) to obtain an old age, who are also at a lower risk for dementia (Clifford, 2009). While our data suggested that this may be the case in Jakarta, with fewer than expected cases in the older age strata, rural areas showed more suspected cases based on cognitive cut-offs with increasing age, partly refuting these hypotheses. While access to health care (doctor and health centre visits) was not different between urban and rural areas, medication use and hospitalisation was lower in rural parts, particularly in Borobudur, which also had the oldest population. Confirmation of health and dementia status using a full medical exam was thus required to further investigate this and to validate our initial screening.

VALIDATION STUDY

In a follow-up study of our cohort in 2009 2 to 3 years after the discussed baseline study which was done in 2006/2007, Dr Fidiansjah Muirsjid and Dr Raden Irawati Ismael trained by dementia expert Dr Martina Nasrun (the 10/66 international dementia screening representative for Indonesia) set out to test whether the algorithm developed in Oxford was valid for the rural cohort in Central Java which had the highest dementia prevalence. The screening was based on the short neuropsychological test-battery consisting of the MMSE and HVLT and the above mentioned questionnaires. This outcome was compared against the judgement of Indonesian clinical dementia experts who used a standardized clinical examination based on the Cambridge Mental Disorders of Elderly Examination (CAMDEX, Roth, 1988) and also the questions from a validated dementia expert system from Oxford (Hogervorst, 2003).

This study was done to establish

- i) validity of the HVLT/MMSE algorithm against CAMDEX derived diagnoses
- ii) modification of diagnoses by demographic factors (age, education, sex, SES)
- iii) a short screening instrument, including a carer's report and questionnaires
- iv) to perform a preliminary investigation of prevalence ratios of different types of dementia in Indonesia (e.g. AD vs. VaD and other types of dementias).

METHODS

Rural community dwelling elderly of Central Java were included in this survey. All were over 56 years of age and were covered by the local health districts around Borobudur. Some were survivors of our earlier study (Hogervorst, 2008) conducted in 2006. Of these, an estimated 80% could still be contacted for follow-up from Borobudur and Salam districts after the 3 year follow-up in 2009. Follow-up data are discussed in another paper, as this paper concerns the rolling cohort data collected in 2009, which also included novel participants who were over 56 years of age in 2009.

Ethical approval from Loughborough University and the University of Indonesia, governmental permits and informed consent were obtained before data collection. Participants were informed of the research during their visits to the health clinics. They were made aware that non participation would in no way affect their treatment at the health center and that this was not obligatory. However, because of the excellent relationship between health center staff and the elderly, the willingness to participate was high. Participants were collected by car to travel to the research setting at an agreed date with their carer, who also signed the informed consent. This approach had a 96% response rate, as 7 participants (of n=177) could not be included on the day because of frailty or fatigue and a subsequent inability to travel. All others consented to participate. The research was carried out in 5 rooms of the home of one of the administrators in the integrated health unit (Pos Pelayanan Terpadu/Posyandu), which was quiet and which had no distractions.

Assessments

For the validation study, the same survey and test battery (using the same adapted versions of the HVLIT, MMSE etc. see above), which were used in the feasibility study were repeated (see above).

Weight, height, waist-hip circumference, non fasting glucose (finger prick) and blood pressure measurements were taken by research nurses. A medical examination and a health resume were conducted by a GP based on the questions from the Cambridge Mental Disorder of the Elderly Examination (CAMDEX, Roth, 1988). This examination consists of a full neurological exam (reflexes, tremors, problems vision/ hearing, gait, Parkinson's disease signs); a psychiatric assessment (interview and observation for depression, psychosis, anxiety, use of psychoactive medication, including those for insomnia, etc.); cognitive testing (orientation, calculation, memory (president Indonesia, family name, children's name), language etc.) and a carer report, which included a report of cognitive decline, mood, morbidity (cancer, dementia, Parkinson's disease (PD), stroke, myocardial infarct (MI), transient ischaemic attack (TIA), high blood pressure, diabetes), medication use and activities of daily living.

A consultant psychiatrist then made a clinical diagnoses of dementia on the basis of this assessment in consensus with the GP, assistants and health center nurses. The consultant psychiatrist who performed the dementia diagnoses using the CAMDEX questions had assessed 13 cases and controls in Jakarta using the CAMDEX and Kappa agreement on these cases was .81 with another expert psychiatrist and .83 with a GP.

The medical examination was routine and included, for instance, testing of heart rate, lungs, diabetes mellitus (fasting glucose > 7mmol/L or non fasting glucose > 11 mmol/L) and hypertension (systolic > 140 (stage I) or 160 mmHg (stage II) and/or diastolic > 90 (stage I) >100 (stage II) mmHg). Blood samples were taken to assess relevant biochemical variables for differential dementia diagnoses, as suggested by the CAMDEX (such as thyroid hormones, hematocrit, folate, cobalamin, electrolytes, etc) but these are also not included in this chapter as data were not yet assayed by the time of publishing.

Statistical Analyses

All data were checked for missing values and potential outliers. Where necessary, data were (log or square root) transformed to approach a normal distribution. Receiver Operating Characteristic (ROC) curve analyses were performed on the HVLТ and MMSE to investigate cut-offs for optimal specificity and sensitivity for clinically established dementia cases versus controls. This was also done by including MCI cases with controls to better mimic the clinic reality. MCI was defined as those elderly participants who had memory or other cognitive problems, but no IADL or social impairment.

Demographic characteristics (age, sex, education) were compared between cases and controls using ANOVA and Chi-square tests. Logistic regression analyses were carried out to investigate whether the diagnoses were associated with cut-off categorisation independent of age, education and gender. All analyses were performed in SPSS 17.0 using a p-value of 0.05.

RESULTS

Descriptive analyses of the cohort are given in the table below. Of the total cohort, of n=113 data on both cognitive tests as well as diagnoses were present. Of these n=113, 33% were considered to have dementia by using the clinical assessment based on the CAMDEX. The two self reported myocardial infarct (MI), the one self reported stroke and the one TIA were all controls. None of participants or carers reported having been diagnosed with dementia, Parkinson's disease, or cancer. 1 case and 1 control reported diabetes mellitus. Of those with high blood pressure, 31% were controls or MCI and 39% were dementia cases ($p=.74$). 5 controls were considered to show signs of depression, as well as 2 MCI, but only 1 dementia case ($p=0.07$). In none of these was depression considered to be severe enough to interfere with cognitive function. One dementia case with psychosis had been excluded from analyses. None of participants displayed symptoms of anxiety or other psychiatric morbidity or took medication for this (including medication for insomnia).

| | Controls N=31 | MCI/Preclin N=45 | Probable dementia N=37 | |
|----------------------|------------------|---------------------|---------------------------|------------|
| Age | 67 (6) | 74 (7) | 76(10) | $p<0.001$ |
| No education | 10% | 35% | 54% | $p<0.0001$ |
| High School or more | 80% | 20% | 0% | |
| Occupation (present) | | | | |
| Farmer | 21% | 27% | 51% | $p=0.03$ |
| Women (%) | 29% | 30% | 40% | $(p=0.06)$ |
| HVLТ | 23 (5) | 14 (5) | 9 (5) | $p<0.0001$ |
| MMSE | 28 (1) | 23 (1) | 18 (4) | $p<0.0001$ |

Average (and median) age of respondents was 73 (SD=8) years. The majority of these Javanese Muslim respondents were women (62%). Almost half (48%) had not obtained any schooling, and most others had only had primary schooling. Most (45%) worked as farmers or labourers and almost all were still actively involved in the community.

Those who were older and had received no education were more likely to be diagnosed with dementia, but there was no significant difference in the female:male distribution. Past occupation was not different between groups ($p=.53$), although those who were still working as farmers were twice more likely to be diagnosed with dementia ($P=0.03$). Education was significantly associated with occupation and to preserve power only education was entered in general linear models along with age and gender. However, the differences in test performance by diagnostic category were shown to be independent of age ($p=0.001$), education ($p=0.08$), and gender (ns) in general linear models with diagnoses (controls, MCI and dementia) as a main independent between subject factor [$F(2,108)=33.63$, $p<0.0001$] for the HVLTL. For the MMSE, there was also a similar significant main effect of diagnoses on performance [$F(2, 108)=8.56$, $p<0.0001$] with no effect of age ($p=.19$) or gender and only a trend for education ($p=0.06$) to be related to higher test scores.

To assess cut-offs for optimal sensitivity and specificity, Receiver Operating Characteristics analyses were performed. Including only dementia cases versus controls rendered 100% sensitivity and 91% specificity for the HVLTL total recall using a cut-off of 19.5. In addition, 100% sensitivity and specificity using a cut-off of 24.5 on the MMSE was found. These cut-offs were similar to those for the cohort in Oxford for both tests (Hogervorst, 2002).

When ROC were performed which included MCI with controls (which is more closely adapted to the clinical reality), results were as follows. A cut off of 19.5 for the HVLTL still gave optimal sensitivity, but now 14.5 gave a better balance between sensitivity and specificity, which is similar to Oxford data, when we also included MCI with controls against cases with dementia. The MMSE now also required a lower cut-off of 21.5 for optimal sensitivity and specificity. The sensitivity was still high at a cut-off of 24.5, possibly because the MMSE is part of the CAMDEX cognitive tests (CAMCOG).

| Test | Sensitivity | Specificity |
|-------|-------------|-------------|
| HVLTL | | |
| 19.5 | 100% | 43% |
| 14.5 | 92% | 70% (same) |
| 11.5 | 70% | 81% |
| MMSE | | |
| 24.5 | 100% | 54% |
| 21.5 | 81% | 92% (lower) |

This suggests that when identifying controls, a cut-off of >24.5 on MMSE should be used, together with a score of > 19.5 on the HVLTL. When screening for cases, cut-offs should be a score of < 21.5 on the MMSE and < 14.5 on the HVLTL. Thus, MMSE cut-offs for cases were lower in rural Central Java than in Oxford, but adapted HVLTL data were similar.

Logistic regression using the optimal cut-offs of 19.5 for the HVLTL showed that lower performance (< 19.5) was associated with diagnostic categorisation (OR=0.12, 95% CI=0.02 to 0.08, $p<0.0001$) independent of age (OR=0.89, 95% CI=0.78 to 1.01, $p=0.08$), gender ($p=0.53$) and education (ns, OR=1.38, 95% CI=.59 to 3.26). However, using similar analyses for the MMSE, showed that diagnostic category now was not entered in the equation and only education remained (OR=2.62, 95% CI=1.17 to 5.90), while age and gender also did not

significantly contribute to the analyses. This suggests that the MMSE should not be used by itself in screening for dementia particularly in those with a low educational background.

The SF-36 had been assessed to establish quality of life/overall health as an indicator of dementia. While there was a significant difference on the mean SF-36 scores between controls (70) and dementia cases (65) and MCI (73), it was not deemed suitable as a diagnostic (low combined sensitivity and specificity using ROC, $p=ns$). However, partial correlation analyses (controlled for age, education, gender and occupation) showed that the HVLT was related to the MMSE performance ($r=.56$, $p<0.001$) and that both were related to SF-36 ($r=.20$, and $r=.27$, respectively, $p<0.001$), showing worse quality of life with worse cognitive performance.

IN DEPTH STUDY OF A SUB SAMPLE OF RURAL BOROBUDUR

Dr Raden Irawati Ismail, aided by structured and post mortem validated questions from an expert dementia diagnostic system developed at Oxford University (Hogervorst, 2003), further tested validity of Dr Fidiyansha's diagnoses against the HVLT and MMSE performance in dementia cases and controls to further investigate the cut-offs in a separate study. She also assessed a random number of cases and controls in a more in depth examination to establish ratios of different types of dementia in this sample. For this study, the questions from the decision trees of our post-mortem validated computerized dementia diagnostic system (Hogervorst, 2003) were used. The computer expert system showed to improve inter-rater reliability (between a medical student and an expert neurologist) and improved diagnostic accuracy significantly (in particular specificity) when comparing this to over 200 post mortem confirmed cases and controls. The system can simultaneously diagnose different dementia types using most consensus and research derived criteria within 5 to 10 minutes per patient (Hogervorst, 2003).

This in depth study was carried out in a sub sample of the Borobudur sample of $n=59$ Javanese elderly who resided in two of the four villages tested. This rendered 17 cases clinically diagnosed with dementia by Dr Ismail. Of these, 2 were considered to be clear Vascular Dementia cases, there was one AD mixed with stroke and focal signs/symptoms and one control who had a stroke with focal and other neurological signs and symptoms, but no signs of dementia. However, carer's history of progression suggested that 6 people had stepwise decline, which may have been suggestive of vascular dementia (35%). Unfortunately, brain scan information was not available (except for the control), so more detailed information needed for the vascular dementia diagnoses was not available. There were no other signs of Binswanger's disease (incontinence, focal signs etc) suggesting that this specific cerebrovascular pathology was also not present. Blood pressure was the same in cases and controls. There was no clear indication of LBD or FTD (no fluctuations in attention, hallucinations, aphasia, or personality change), and it was also judged that there was no psychiatric co-morbidity or substance abuse. All dementia and MCI cases (but one of 19) had memory complaints. Of the 17 dementia cases, 9 were thought to have probable AD (53%) according to NINCDS-ADRDA criteria (memory complaints and at least one other cognitive problem, affecting ADL, no other morbidity explaining disease, gradual and progressive, McKhann, 1984). In addition, 1 patient initially diagnosed as MCI by the

psychiatrist was thought to have possible AD. Two cases with dementia were thought to be related to systemic disease (12%), they had (non Parkinson's disease) tremors, and were clearly ill with sweating and weakness. However, no further diagnostic assessment (blood screen) could be performed. Thyroid disease was suspected as it is endemic in the area (hyperthyroidism ?), but only one of the participants had a goitre. However, using blood samples, we earlier found (Hogervorst, 2009) that half of those afflicted with thyroid disease cases in those over 65 years of age are not detected medically even in developed countries. It was thought that clinicians often rely too much on the clinical signs of thyroid disease, which may not be present in half of the cases.

Controls were significantly younger than cases. However, diagnoses determined test performance on the adapted HVLT [$F(2,54)=6.35$, $p<0.003$], independent of age ($p<0.001$) and gender ($p=.59$). The 19 patients diagnosed as MCI or preclinical dementia all had memory complaints, but all scored significantly higher on the adapted memory test than cases with dementia (on average 5 more words immediately recalled for MCI, compared to the on average 6 more words recalled for the 23 controls). Although a key criteria for amnesic MCI (aMCI), MCI or preclinical dementia cases, as assessed by the psychiatrist scored not significantly different from controls on the memory test ($p=0.33$, on average 1.2 word recalled less by MCI). However, the MMSE showed independent main effects of diagnoses ($F(2, 54)=8.21$, $p=0.001$) and also effects of age ($p=.03$) and a trend for gender ($p=0.06$). Adapted scores (by age and gender) showed that MCI scored significantly lower on this test than controls (on average 2.2. points less) but more than dementia cases (on average 3.1 points more, with controls scoring 5.4 points more than dementia cases). This suggested that aMCI is perhaps less important than other non memory cognitive impairments (e.g. executive dysfunction or other more focal cognitive impairments, such as aphasia, caused by vascular incidents) in the MCI or preclinical group.

Using ROC, optimal cut-offs for dementia (excluding MCI) on the memory test were again 19.5 on the total immediate recall (with 100% sensitivity and 78% specificity, or, with a cut-off of 17.5, this was 76% with 91%, respectively). Optimal cut-offs for the MMSE were 24 (with 88% sensitivity and 96% specificity, or, with a cut-off of 21.5, it was 65% and 96%, respectively).

In the table below, demographics and test scores for different clinical categories are given.

| | Normal N=23 | MCI/Possible N=19 | Probable dementia N=17 | |
|-----------------------------|----------------|----------------------|---------------------------|------------|
| Age | 66.3 (5.1) | 70 (5.3) | 76.6(9) | $p<0.001$ |
| Women (%) | 70% | 74% | 65% | $p=.84$ |
| HVLT | 22.5 (4.1) | 20.0 (5.2) | 13.1 (5.8) | $p<0.0001$ |
| MMSE | 26.9 (2.4) | 24.0 (3.3) | 19.6 (5.4) | $p<0.0001$ |
| Adjusted for age and gender | | | | |
| HVLT | 21.1 (1) | 19.9 (1) | 15.2 (1.2) | |
| 95% CI | 19.1 to 23.2 | 17.8 to 22.0 | 12.7 to 17.6 | |
| MMSE | 26.1 (.8) | 23.8 (.8) | 20.7 (.9) | |
| 95% CI | 24.5 to 27.7 | 22.3 to 25.4 | 18.8 to 22.6 | |

Including MCI with controls versus dementia still gave a significant area under the curve (.83-.85, $p < 0.0001$) and test cut-off scores with their sensitivity and specificity are shown below.

| Test | Sensitivity | Specificity |
|------|-------------|-------------|
| HVLT | | |
| 19.5 | 100% | 64% |
| 17.5 | 77% | 72% |
| 15.5 | 53% | 93% |
| MMSE | | |
| 24.5 | 88% | 74% |
| 23.5 | 88% | 79% |
| 21.5 | 65% | 83% |

DISCUSSION

These studies showed that similar cut-offs for dementia on two cognitive screening tests could be used for screening relatively affluent, highly educated elderly in Oxfordshire UK and those living in a rural environments on Central Java, Indonesia and that this was independent of age, gender, education and ethnicity. However, this study has several limitations.

Firstly, this algorithm was only validated for elderly Javanese and data should be included on Sundanese, Mangankebau, etc., as Indonesia is a multi ethnic country. However, as cut-offs were the same between elderly in Oxford and those of rural Java, we do not expect much deviation from these findings in other ethnic groups. Similar to Ganguli's version of the MMSE (1995), our modified version also had to be altered to address those who were illiterate and also for the seasons of the year (to 'wet or dry'). However, this did not affect the distribution and ceiling and floor performance was not observed.

Other screening tests developed for multi cultural assessment have shown comparable results. For instance, the Rowland Universal Dementia Assessment scale (RUDAS, Storey, 2004) is another brief dementia screening test, originally developed for a multicultural setting in Australia, which was found to have 89% sensitivity and 98% specificity for dementia. In a study in India (with 58 dementia cases and 58 age and sex matched controls), the RUDAS was found to have similar sensitivity to the MMSE (88% and 90%, using cut-off scores of 23 and 24, respectively), but it also had an educational bias. On the other hand, the RUDAS had better specificity than the MMSE (76% versus 48%, Iype, 2006). In the present study, the MMSE and HVLT seemed to offer a reasonable comparable screening test, but a direct comparison against the RUDAS and also the frequently used (but lengthy) 10/66 algorithm would be useful. For Vascular Dementia and FTD more executive and other function tests, such as the CLOX should be included and future studies will also include the RUDAS executive components to investigate whether this increases resolution and allows better detection of other than AD dementias

A major limitation of the present study was that no blood screens were available and also that no brain scans could be performed to establish more in depth diagnostics. This mimics

the reality of dementia screening in developing countries. In fact, we experienced that even in USA memory clinics, blood screens were not always performed routinely as part of a dementia screening, physicians relying mainly on medical external examinations.

Using our limited data from rural Java suggested a similar profile to many European studies, in that the majority of people with dementia would have had AD followed by VaD, as the second most frequent dementia type. However, as said, this could not be confirmed using brain scans. Whether vascular cognitive impairment is more common than aMCI, AD or FTD/LBD in Indonesia and whether some dementia is secondary and treatable (e.g. related to thyroid and lung disease, infectious disease, nutritional deficiency, toxicity of pesticides etc.) remains to be further investigated and current studies are underway to assess this. It is of interest to include comments from rural health center staff who often view the cognitive impairments as a normal part of aging. They suggested that arthritis and deafness/vision impairments (sensorimotor function) as causing the impairments. These would cause issues in cognitive assessment, which could reflect the high prevalence of dementia in the rural Central Javanese cohort and this needs further confirmation. Visual impairment, for instance, can be an early sign in dementia (Kirby 2010) and we are currently investigating this as a diagnostic marker in both the UK and in Indonesia. When taking into account impaired instrumental activities of daily living, the more realistic prevalence figure for dementia was lower at 11% in this rural area (and 5-6% overall, see above).

Taking into account these discussions with rural health staff and village elders on Pikun (dementia), if an elderly person despite significant cognitive impairment can still maintain their daily life in these relatively uncomplicated settings with few instrumental (with little telephone contact, radios, computers, ATM banking, travel etc.) activities of daily life requirements and sufficient support, the question is whether there is a 'dementia' as such (as in 'impairments that affect daily life', see APA, 1994). According to staff of the center for health, dementia is rare in the rural communities investigated. This contrasts with our reported *higher* prevalence on the basis of cognitive test data which, importantly, was independent of age, occupation and education. So while dementia prevalence is currently low in Jakarta, it may be higher in rural areas but perhaps have less impact in these settings. However, with increasing Westernization, and more young people moving away from rural parts and perhaps even less public investment in health with less center for health staff support, dementia may be an issue for the future with more elderly being isolated in rural areas with little support. This support works both ways. Older people still contribute significantly to family finances (Kreager 2006a.b. Rahardjo, 2007,2008) and dementia means a loss of economic contribution of the person affected, but also of their carers, who need to give 24 hour surveillances in the late stages of the disease. With our estimates of almost 2 million elderly affected by dementia by 2025, this means that at least 4 million of people over 60 years of age, who could substantially contribute to Indonesian economy, can then no longer do so because of dementia.

Even more troubling is that our predicted prevalence estimates could be an underestimate. Data were from a cohort, a generation, who had survived wars, colonialism and famine without much health care and without availability of antibiotics in the vulnerable stages of childhood. This cohort is thus different from the next (perhaps more urbanized) generations who survived childhood disease with antibiotics. In addition, many urban young children from affluent parents in Indonesia now seem obese, eating fast foods and engaging in little physical activity. However, because the more affluent can benefit from good private

health care systems, despite increased risks of these lifestyles on early diabetes mellitus and heart disease also affecting cognition and independence (Clifford, 2009), this generation could be a longer non productive drain on community and health care resources. With increasing health risks at an earlier age, non communicable disorders (NCD) could be predicted to start occurring in very early midlife (the late third decade). Drastic lifestyle interventions are thus needed now for the younger generations. Otherwise, Indonesia could be hit by a double whammy of dementias of a primary nature associated with NCD risk factors (heart disease, diabetes etc) in the rich, and infectious-, nutritional deficient- and systemic disease leading to treatable secondary dementias in the poor.

Prevention of dementia is crucial as no treatment is effective in the longer term and both human and economic costs are high. For the West the current consensus based on longitudinal studies is that midlife is the latest when the most effective lifestyle interventions should be made (Clifford, 2009). If the current trend persists in Indonesia, the more affluent middle classes will experience typical old age disease (diabetes, vascular disease) much earlier, but will also experience this for much longer with improved health care, which is available for those who can afford it. This means that interventions in Indonesia must start earlier, e.g. with more physical activity promotion for middle-class obese children and with better and longer free education for the rural and poor urban children. High education in childhood protects the brain against an earlier onset of dementia and heart disease, possibly because of more reserve capacity (Whalley, 2002; Clifford, 2009) and availability of alternative coping and vocabulary once cognitive impairment sets in. Currently good education in Indonesia is very expensive, however, and more governmental investments need to be made to secure lower costs of poor health related to low education in the long run.

In sum, the studies described in this chapter have led to validation of a short and cheap screening instrument for dementia in rural and urban Java. The data from the validation study combined with those from our first study can give the Indonesian government some indication of the percentage of people afflicted with dementia and can aid in predictive analyses of costs and growth in some areas on Java. This is particularly important given the possible dark scenarios for the development of this disease, that will at least double in prevalence in the next decades, but which may start to occur even earlier for our current young cohort unless drastic lifestyle changes are implemented.

In a group discussion coordinated by Prof Rahardjo and Untung with local policy makers and the medical doctors in Jakarta at the end of this validation study, the consensus was that both validated instruments (the Modified MMSE and HVLT) should be used as screening tools to detect dementia in primary health centers. Subsequently, the implementation and training of the use of these tools was done in Borobudur, Palu and Banda Aceh by Dr Ismail and Dr Fidiansyah in 2010. Recently, it was proposed that from 2011 these tools are to be implemented in the whole of Indonesia, which was supported by the the Ministry of Health and the National Commission for Older Persons of Indonesia which advises directly to the Indonesian President on matters of aging. If this algorithm works in other developing countries and in multi-ethnic cohorts, it can be used by governments to track dementia prevalence, which is an increasing health concern affecting economies worldwide.

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Appendix

INSTRUMENTAL ACTIVITIES OF DAILY LIVING (IADL) BASED ON LAWTON AND BRODY (1969)

| No | Activities | Point | Criteria | Comment whether wife/maid does this |
|-------------|---|-------|--|-------------------------------------|
| Q1 | Extending message/using telephone (e.g. there will be meeting tomorrow at Mr. RT's at 10) | 0 | Unable to extend messages (doesn't have telephone included) | |
| | | 1 | Message extended partially (capable of answering phone but unable to operate it) | |
| | | 2 | Able to operate telephone/message extended completely | |
| Q2 | Shopping | 0 | Unable | |
| | | 1 | Capable of purchasing up to 3 items, otherwise need help. | |
| | | 2 | Independent | |
| Q3 | Preparing meal | 0 | Unable | |
| | | 1 | Able to cook if the ingredients are ready or can warm cooked food | |
| | | 2 | Independent | |
| Q4 | Housekeeping | 0 | Unable | |
| | | 1 | Able to do light tasks (sweeping, making the bed) only, otherwise needs help. | |
| | | 2 | Independent (capable of doing all household tasks including mopping and washing clothes) | |
| Q5 | Washing clothes | 0 | Unable | |
| | | 1 | Able to wash light clothes or ironing, otherwise needs help | |
| | | 2 | Independent (using washing machine included) | |
| Q6 | Utilization of transportation means | 0 | Unable to travel with any transportation | |
| | | 1 | Travels on public transportation/taxi or private car if helped/accompanied by other | |
| | | 2 | Independent travel | |
| Q7 | Responsibility of taking or preparing own medication | 0 | Needs help from others to prepare and consume medication. | |
| | | 1 | Able if medication is previously prepared | |
| | | 2 | Independent (able to prepare own medication according to prescribed dose and time) | |
| Q8 | Ability to handle finances | 0 | Incapable | |
| | | 1 | Able to arrange daily purchases, but needs help with banking/major purchasing | |
| | | 2 | Able to manage financial problems (household budget, pays the rent, receipt, bank matters) or to monitor income. | |
| Total score | | | | |

IADL score: 9 – 16 : Independent/doesn't need any help, 1 – 8 : Needs help, : Unable to do anything