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Essay

Operationalisation of Mild Cognitive Impairment: A Graphical Approach

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Despite intensive use of the term mild cognitive impairment (MCI) to describe an intermediate stage of cognitive decline between normal and pathological brain ageing, no formally agreed process of characterising this condition exists [1–3]. Various definitions have been proposed in the literature, each with differences in focus (e.g., age-associated change versus pathological decline) and non-uniform diagnostic criteria [4–18]. The degree of inconsistency is not trivial: current classifications define heterogeneous populations with different patterns of aetiology, cognitive decline, and clinical outcome [19].

As an opportunity for identifying individuals at risk of developing dementia, MCI is an important concept. Yet lack of consensus criteria has lead to debate about the utility of MCI, resulting in calls for abandoning its diagnosis and adopting an alternative nosology [20–22]. Consensus conferences are now being held, even though MCI diagnoses are already used in clinical trials for prevention of Alzheimer disease [23]. The aim of this paper is to develop a framework for mapping the different classifications of MCI using retrospective information, assessing variations in defining criteria.

Creating a Framework for Mapping MCI

The first step to coding MCI is to determine the necessary criteria and thresholds for operationalisation of each definition. We compiled a comprehensive list of those classifications which represent different aspects and definitions of MCI. The necessary components for each were abstracted and formulated into a diagnostic algorithm.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

The main problem encountered was that while some classifications have specific criteria for implementation (e.g., amnestic MCI [A-MCI] [13,14] and age-associated memory impairment [5]), others are vague descriptions that require interpretation as to the exact nature of the deficit (e.g., age-related cognitive decline [24]). Further complicating the problem is a lack of specification of screening tools and variability in: (1) the domain of impairment (memory versus non-memory, single- versus multi-domain deficits); (2) cut-off scores; (3) acceptable restriction on activities of daily living; and (4) exclusion criteria.

Eighteen current definitions of early cognitive impairment were identified in a systematic review of the literature and mapped using a flow diagram as shown in Figure 1. Mapping is completed in two phases: following exclusion of all individuals with dementia, each classification is then operationalised independently. Each classification could be constructed from a subset of 15 different criteria, with memory impairment required as an essential feature in almost all classifications. Surprisingly, no two classification systems map on the same path. Each classification is operationalised in the population and has been previously applied to the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) [19]. Table 1 outlines how each set of criteria was operationalised in CFAS. To facilitate cross classification comparisons, criteria were consistent in terms of level of impairment unless cut-off thresholds were uniquely specified.

In reading the flow diagram, the classification arrived at depends on the direction of decision at each criteria (*yes*, criteria required are fulfilled as indicated by a green arrow, or *no*, criteria are not fulfilled as indicated by a red arrow). If an individual fails to meet the specified outcome for a given criterion they are excluded from further mapping.

Two Examples: Benign Senescent Forgetfulness and A-MCI

For example, following the flow diagram to arrive at a classification of benign senescent forgetfulness (BSF) takes just three steps: from the *"START"* box you move to the *"Demented"* box. If the individual does not have dementia (as indicated by the red arrow), you next move to the *"Long-Term Memory Problem"* box, and if the

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Abbreviations: A-MCI, amnestic mild cognitive impairment; BSF, benign senescent forgetfulness; MCI, mild cognitive impairment; MRC CFAS, Medical Research Council Cognitive Function and Ageing Study

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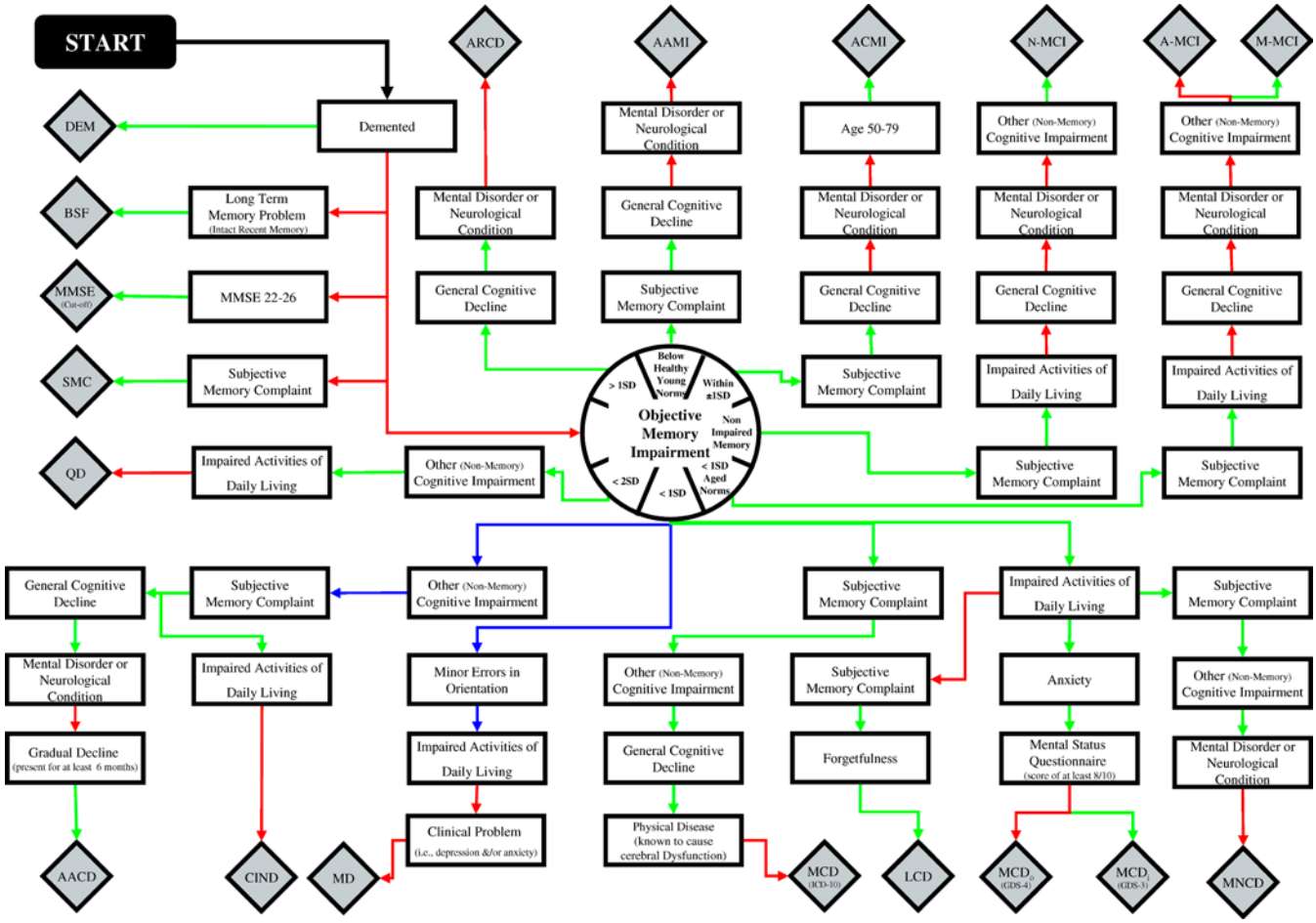

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Figure 1. Schematic Overview of the Approach Used to Classify MCI across Different Definitions in the Medical Research Council Cognitive Function and Ageing Study

AACD, age-associated cognitive decline; AAMI, age-associated memory impairment; ACMI, age-consistent memory impairment; ARCD, age-related cognitive decline; CIND, cognitive impairment no dementia; DEM, dementia; LCD, limited cognitive disturbance; MCD (ICD-10), mild cognitive disorder (International Classification of Diseases 10th Revision); MCD_i (GDS3), mild cognitive decline (Global Deterioration Scale Stage 3); MCD_o(GDS4), moderate cognitive decline (Global Deterioration Scale Stage 4); MD, minimal dementia; M-MCI, multiple mild cognitive impairment; MMSE, Mini Mental State Examination Cut-off Scores; MNCD, mild neurocognitive disorder; N-MCI, non-amnestic mild cognitive impairment; QD, questionable dementia; SD, standard deviation; SMC, self-reported memory complaint.

individual shows a long-term memory problem with intact recent memory (as indicated by the green arrow), you then arrive at a classification of BSF. (See Figure 2 for the BSF-specific path.)

In contrast, to arrive at a classification of A-MCI, seven steps are needed: (1) the individual is not demented (as indicated by the red arrow); (2) there is an objective memory impairment (one standard deviation below age-corrected norms, as indicated by the green arrow); (3) the individual or an informant complains of memory loss (as indicated by the green arrow); (4) there is no impairment in activities of daily living (as indicated by the red arrow); (5) there is no impairment of general cognitive functioning (as indicated by the red arrow); (6) the individual has no underlying medical or neurological condition (as indicated by the red arrow); and (7) there is no impairment in another non-memory domain (as indicated by the red arrow). (See Figure 3 for the A-MCI-specific path.)

Advantages and Disadvantages

The flow diagram details this process for each of the 18 different classification systems, allowing for reproduction across studies. Each concept has been detailed in turn with a criteria-specific graph and the appropriate references on the CFAS Web site (http://www.cfas.ac.uk/mciprogram/). The clinical utility of the concept of mild cognitive impairment depends on the validity of the diagnosis and the ability to predict higher rates of progression to dementia. The advantage of retrospective definition of these concepts is that they are not adjusted by current knowledge or changing criteria, an unfortunate downside of consensus criteria being that they can be influenced by changing knowledge over time. The disadvantage of mapping with retrospective information is that it removes clinical experience from the definition, and the information measured from all individuals must have enough scope to encompass the entire original definition.

A fundamental problem with a multiple system approach is the failure in consistency of classification. Prevalence estimates for each classification have been previously calculated in CFAS using the pathways

Table 1. Operationalisation of Components of Classification Systems in the Medical Research Council Cognitive Function and Ageing Study

Criteria	Operationalisation
Dementia	AGECAT organic symptom level ≥3. This corresponds to a diagnosis of dementia as defined by DSM-III-R [25].
Long-term memory intact/short-term memory impaired	CAMCOG remote memory score below the 16th centile score and recent memory score greater than the 16th centile score.
Subjective memory complaint	Self or informant report. Combined score created from three questions including: (1) Have you had any difficulty with your memory? (self report); (2) Have you tended to forget things recently? (self report); and (3) Has he/she had any difficulty with his/her memory? (informant report). Responses dichotomised into "non-complainers" or "complainers" (positive response to one or more questions).
Exclusions	Unique to each classification. Could include any combination of the following: history of heart attack, chest pain, angina, stroke, Parkinson disease, intermittent claudication, emotional problems, diabetes mellitus, asthma, arthritis, meningitis, head injury, thyroid problems, pernicious anaemia, depression, anxiety, chronic bronchitis, and high blood pressure.
General cognitive decline	Mini Mental Examination (MMSE) score ≤21.
Gradual decline (present for at least six months)	One or more positive responses to the following memory questions, with decline reported as being gradual: (1) Do you have to make more effort to remember things than you used to? What sort of things?; (2) When did you notice this beginning?; (3) Did it come on suddenly?; (4) Would you say there has been a deterioration of memory over a period of more than two years?; and (5) Did these problems with memory begin rapidly or gradually?
Minor errors in orientation	CAMCOG orientation subtest score below the 16th centile score.
Clinical problem (i.e., depression or anxiety)	Depression and anxiety both defined as AGECAT symptom level ≥3.
Other (non-memory) cognitive impairment	Below threshold on one or more of the following subtests of the CAMCOG: orientation, language, attention/calculation, praxis, abstract thinking, and perception.
Impaired activities of daily living	Modified Townsend Disability Scale, with an additional three items. Impairment defined as requiring help at least several times per week with washing, cooking, and dressing, or as being housebound.
Mental status questionnaire	Maximum score of 10 derived from the following questions: (1) What is the name of this place? Where is it located? (2 points); (2) What is the date today? (1 point); (3) What is the month? (1 point); (4) What is the year? (1 point); (5) How old are you? (1 point); (6) What is your date of birth (day/month)? (2 points); (7) What is the name of the prime minister? (1 point); (8) Who was the last prime minister? (1 point).
Objective memory impairment	Below threshold on one or more of the following memory subtests of the CAMCOG: learning, recent, or remote memory.
Forgetfulness	Positive response to one or more of the following questions: (1) Do you forget the names of your family and friends?; (2) Do you forget where you have placed things?

AGECAT, automatic geriatric examination for computer assisted taxonomy; CAMCOG, Cambridge Cognitive Examination; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; MMSE, Mini Mental State Examination Cut-off Scores.
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shown in Figure 1, and were found to be highly variable (range 0.1%–42%) [19]. Some of this difference results from the fact that not all criteria explain pathological ageing, but rather "normal" ageing. Although the distinction between those definitions associated with normal age-related change and those with pathological ageing is not apparent from prevalence estimates alone, it is seen with lower conversion to dementia in those groups defined by non-pathological classifications. Furthermore, the same individual could be classified as impaired on one system and normal on another, even within criteria that are supposedly investigating abnormal change. This makes the interpretation and comparison of results across studies very difficult, where not only the populations but additionally the criteria chosen to estimate MCI are different.

At first glance, a solution to the complexity of the diagram appears simple: reduce all classification

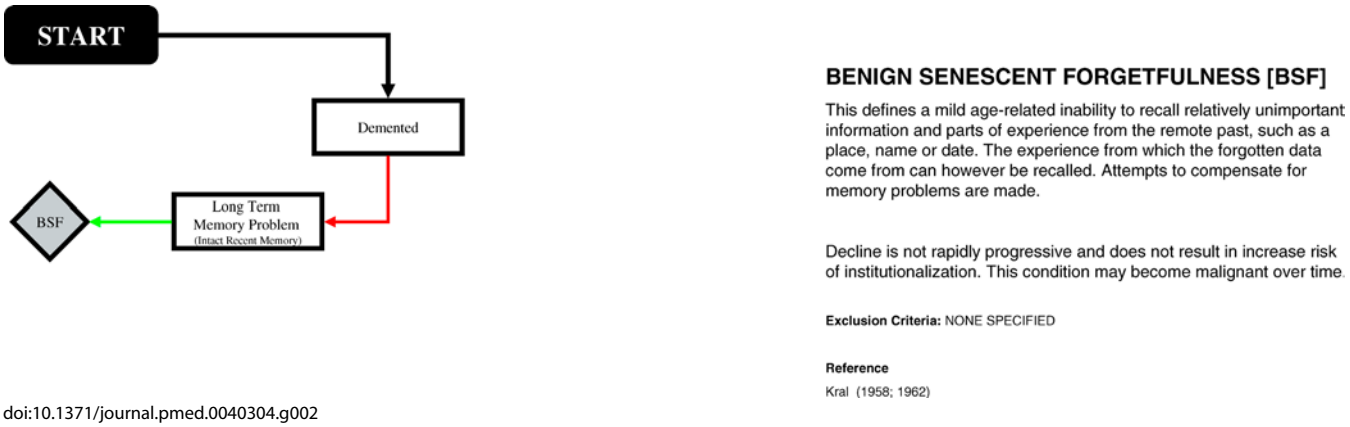

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Figure 2. Operationalisation of Benign Senescent Forgetfulness in the Medical Research Council Cognitive Function and Ageing Study

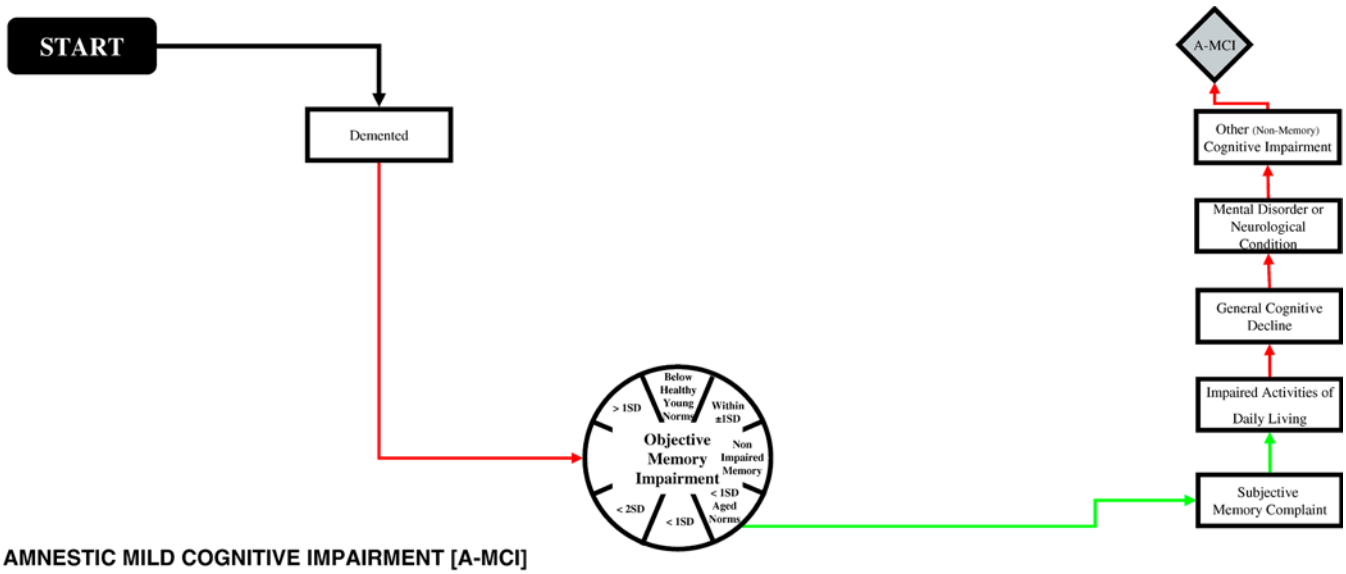

Figure 3. Operationalisation of Amnestic Mild Cognitive Impairment in the Medical Research Council Cognitive Function and Ageing Study
SD, standard deviation

systems to a single concept through the amalgamation of all defining criteria, particularly the measurement of objective memory and the medical (and disability) exclusion criteria. However, this solution assumes that within these criteria there is one that is the best for identification of at-risk individuals. Furthermore, definitions, particularly those of objective cognitive impairment, depend on arbitrary and varying thresholds, frequently with no reference to specific values, methods, or screening measures. In retrospective studies, the mapping of these thresholds will primarily be constrained by study design, though the use of different thresholds can be used to determine the most optimal threshold value to accurately distinguish those individuals at high risk of dementia from those with low dementia risk.

Conclusion

It is time to re-examine the concept of MCI. The diagnostic disparity and the lack of consistency in case definition calls into question what exactly is being captured in each classification. This is a fundamental weakness of research on MCI, as highlighted by the complicated nature of Figure 1. Using this flow diagram, MCI systems can be mapped in other population datasets to investigate: (1) what are the best boundaries for impairment; (2) which tests are most sensitive for measuring each criteria; (3) which criteria, if any, can adequately predict individuals at risk of developing dementia; and (4) would adopting multiple systems across different populations (specialist clinic versus population based) and age groups be more appropriate? It is hoped that graphical operationalisation of the criteria will aid in diagnostic consistency and assist in the visualisation of the current problem, with the aim of formulating a gold standard definition for both research and clinical practice. ■

References

1. Gauthier S, Touchon J (2005) Mild cognitive impairment is not a clinical entity and should not be treated. Arch Neurol 62: 1164–1166.
2. Kave G, Heinik J (2005) Issues to consider when using the new diagnosis of mild cognitive impairment. Isr Med Assoc J 7: 732–735.
3. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, et al. (2004) Mild cognitive impairment—Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256: 240–246.
4. Levy R (1994) Aging-associated cognitive decline. Working Party of the International Psychogeriatric Association in collaboration with the World Health Organization. Int Psychogeriatr 6: 63–68.
5. Crook T, Bartus RT, Ferris SH, Whitehouse PJ, Cohen GD, et al. (1986) Age-associated memory impairment: Proposed diagnostic criteria and measures of clinical change: Report of a National Institute of Mental Health Work Group. Developmental Neuropsychology 2: 261–276.
6. Blackford RC, La Rue A (1989) Criteria for diagnosing age-associated memory impairment: Proposed improvements from the field. Dev Neuropsychol 5: 295–306.
7. Kral VA (1962) Senescent forgetfulness: Benign and malignant. Can Med Assoc J 86: 257–260.
8. Kral VA (1958) Senescent memory decline and senile amnestic syndrome. Am J Psychiatry 115: 361–362.

9. Ebly EM, Hogan DB, Parhad IM (1995) Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging. Arch Neurol 52: 612–619.
10. Gurland BJ, Dean LL, Copeland J, Gurland R, Golden R (1982) Criteria for the diagnosis of dementia in the community elderly. Gerontologist 22: 180–186.
11. Reisberg B, Ferris SH, de Leon MJ, Crook T (1982) The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 139: 1136–1139.
12. World Health Organization (1992) The ICD-10 international statistical classification of diseases and related health problems. 10th Revision. Available: http://www.who.int/classifications/icd/en/. Accessed 27 September 2007.
13. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, et al. (1999) Mild cognitive impairment: Clinical characterization and outcome. Arch Neurol 56: 303–308.
14. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, et al. (2001) Practice parameter: Early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 56: 1133–1142.
15. Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, et al. (1986) A standarized instrument for the diagnoses of mental disorder in the elderly with special reference to the early detection of dementia. Brit J Psychiat 149: 698–709.
16. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. Br J Psychiatry 140: 566–572.
17. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, fourth edition [DSM-IV]. Washington (D. C.): American Psychiatric Association.
18. Morris JC, Edland S, Clark C, Galasko D, Koss E, et al. (1993) The consortium to establish a registry for Alzheimer's disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. Neurology 43: 2457–2465.
19. Stephan BCM, Matthews FE, McKeith I, Bond J, Brayne C, et al. (2007) Early cognitive change in the general population: How do different definitions work? J Am Geriatr Soc 55: 1534–1540.
20. DeCarli C (2003) Mild cognitive impairment: Prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2: 15–21.
21. Davis HS, Rockwood K (2004) Conceptualization of mild cognitive impairment: A review. Int J Geriatr Psychiatry 19: 313–319.
22. Dierckx E, Engelborghs S, De Raedt R, De Deyn PP, Ponjaert-Kristoffersen I (2006) Mild cognitive impairment: What's in a name? Gerontology 53: 28–35.
23. Jelic V, Kivipelto M, Winblad B (2005) Clinical trials in mild cognitive impairment: Lessons for the future. J Neurol Neurosurg Psychiatry 77: 429–438.
24. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, fourth edition, text revision [DSM-IV-TR]. Washington (D. C.): American Psychiatric Association.
25. Copeland JR, Dewey ME, Griffiths-Jones HM (1986) A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT. Psychol Med 16: 89–99.