Cognitive impairment without dementia has been commonly considered to be a normal consequence of brain aging. It has been of interest to clinicians because of the difficulties that it may engender in the performance of everyday activities. A number of clinical labels have been proposed to describe subclinical cognitive deficits. Earlier concepts such as “benign senescent forgetfulness,” “age-associated memory impairment,” (AAMI) “age-associated cognitive decline” (AADC), and “age-related cognitive decline” consider such mild cognitive deficits to fall within the limits of normal aging. More recently, the “normality” of these subclinical states has been called into question, because subjects with objectively demonstrated deficits have been shown to be at increased risk for neurodegenerative disease, show quantitative and qualitative differences in cerebral imaging, and share common biologic and environmental risk factors. A number of concepts have thus been proposed that link subclinical cognitive impairment to pathologic states: mild cognitive disorder, mild neurocognitive disorder, and mild cognitive impairment (MCI).

The concept of MCI has predominated in the United States, where large-scale research programs have recently been initiated, with an ultimate view of providing treatment, and therefore reducing the risk of progression to senile dementia. In Europe, reference is still more commonly made to AAMI and AADC—states linked rather to the normal biologic aging process. MCI is probably the more seductive concept for clinicians and researchers because, unlike AAMI and AADC, it is assumed to be pathology-based and therefore amenable to intervention. MCI at a nosologic level remains, however, problematic, and there is still no common consensus on diagnostic criteria.

A principal problem of research in this area is that it has been largely confined to small, selected clinical populations. In many cases, dementia screening tests are applied in the selection process, thus confounding observations of the relationship between MCI and AD. Population studies have largely focused on dementia syndromes, and therefore provide little information on subclinical levels of impairment. In 1991, a study of cognitive functioning in normal elderly individuals recruited from a representative sample of general practices was initiated in the Montpellier region in the south of France. This study, the Eugeria Project, involved the 3-year follow-up of a cohort of subjects with subclinical cognitive deficit, thus constituting a rare general population database on low-level cognitive impairments. The current study aims to examine the utility and
prognostic value of the concept of MCI by retrospec-
tively identifying the subjects in this study meeting
MCI criteria at each wave and examining their clin-
ical outcome and associated characteristics. Previous
clinical studies of MCI have suggested that subjects
with MCI may have smaller medial temporal lobe
volumes, and that risk factors for progression from
MCI to AD are higher age, the presence of the
APOE e4 allele, fine motor deficit, and lower premor-
bid IQ. These factors are considered in the current
general population validation study. The cognitive
tests used to investigate MCI thus far have often
been limited to those used to identify AD, or tests of
general ability. The current study examines poten-
tial cases of MCI using a comprehensive battery of
cognitive tests designed to assess all aspects of in-
formation processing as it is currently conceptualized
by cognitive psychologists. The clinical characteris-
tics and prognostic value of MCI is compared in this
study with those of AACD, with the latter represent-
ing an alternative formulation based on the underly-
ing theoretical supposition that subclinical cognitive
decline is a normal feature of the aging process and
not an early pathologic process.

Methods. The subjects for this study are taken from a
general practitioner research network created by the re-
search unit in collaboration with the regional medical asso-
ciation as part of the Eugeria longitudinal study of
cognitive aging. The network is representative of general
practice in the region, covering both urban and rural ar-
as. An intensive training course in psychogeriatric screen-
ing and application of criteria for senile dementia
was given to the 63 general prac-
titioners in the network. Eight hundred and thirty-three
subjects over 60 years of age without senile dementia were
recruited into the study in the first year. A proxy screening
questionnaire on cognitive functioning over the past year
was sent to all subjects. This screening instrument, Détérioration
Cognitive Observée (DECO), has been shown in
previous studies to be highly sensitive to early changes
in cognitive functioning due to various causes. It is based
on the degree of change in cognitive functioning over the
last year, as estimated by a proxy who has had at least
monthly contact with the subject over the past 3 years. Of
these subjects, 397 were found to have a score of less than
38, with this being the maximum total score. These per-
sons were thus considered by an observer to have shown
some degree of observable deterioration in at least one
area of cognitive functioning over the past year, and also to
have a subjective complaint of declining ability. These sub-
jects were followed over a further 2 years, along with a
random sample (n = 73) of the remaining subjects without
cognitive complaints.

A computerized neuropsychometric examination, Exa-
men Cognitif par Ordinateur (ECO), was given to all 833
subjects in the first year and annually to the subjects fol-
lowed over 2 more years. ECO assesses primary memory,
verbal and visuospatial secondary memory, language skills
(word and syntax comprehension, naming, verbal fluency),
visuospatial performance (ideational, ideomotor, and con-
structive apraxia; functional and semantic categorization
of visual data; visual reasoning; and form perception), and
focused and divided attention (visual and auditory modal-
ties). The development of ECO and the theoretical basis for
test selection is described elsewhere. Response latencies
were recorded using a tactile screen.

From the 159 ECO variables, 10 summary scores repre-
senting six cognitive domains were used in the analysis:

Attention: measured by response time on a dual task
(simultaneous visual selection and counting of auditory
stimuli)

Primary memory: assessed by immediate recall of first
names with and without cues which had the highest fre-
cuency in the French language 50 years ago

Secondary memory: measured by 1) delayed recall of
first names and 2) their associated faces

Visualspatial ability: measured by 1) reference to re-
sponse time on shape, functional, and semantic visual
matching tasks and 2) the number of elements correct in
the copying of meaningful and meaningless figures

Language: assessed by 1) mean reaction time on word
and syntax comprehension, 2) naming, and 3) verbal flu-
ergy using both phonetic and functional cues

Reasoning: assessed by completion of logical visual
series

A series of validated scales examining the capacity to
perform a wide range of activities of daily living, the Ech-
elle de Comportement et d’Adaptation (ECA) scale, was
completed in collaboration with both subjects and caregiv-
ers at each wave of the study. Information was also ob-
tained concerning depressive symptomatology according
to DSM III-R criteria. In the third year, a standardized
neurologic examination with SPECT for the diagnosis of
psychogeriatric disorder based on DSM III-R criteria was
performed by a neurologist who had no knowledge of the
results of the cognitive tests. Blood samples were collected
to establish APOE status. A consent form describing the
aims and methods of the study was signed by all subjects.
Authorization for the study was also obtained from the
National Data Protection and Ethics Committee.

At entry into the study (wave 1) and at yearly follow-up
(waves 2 and 3), subjects meeting MCI and AACD criteria
were identified. The criteria used for MCI initially pro-
posed by Petersen et al. specify 1) the presence of a
subjective memory complaint, 2) preserved general intel-
lectual functioning as estimated by performance on a
vocabulary test, 3) demonstration of a memory impairment
by cognitive testing, 4) intact ability to perform activities
of daily living, and 5) absence of dementia. More recently,
the same authors have stipulated that there should be
impairment on a memory task only and not on tests relat-
ing to other cognitive functions. Criteria for AACD are
consistent with previously established consensus guide-
lines of decline of more than one SD in any area of cogni-
tive functioning in comparison with age-matched controls.

Results. Among the 833 subjects recruited into the
study, 308 subjects were identified based on MCI criteria 1
and 2. These were all included in the cohort of 397 subjects
followed longitudinally. Of these, 103 subjects demon-
strated a decrement of more than one SD on a memory
task compared with ECO standardization data matched by
age and level of education (MCI criterion 3). Applying
the additional criterion, which excludes subjects with a diffi-
culty in any other area of cognitive functioning, led to the exclusion of all but 27 subjects. The application of MCI criterion 4 led to the inclusion of all remaining subjects, with a definition of disability as “persistent inability to perform activities of daily living without assistance.” All subjects classified as MCI or AACD were included in the follow-up.

Twenty-seven subjects were thus classified as MCI in wave 1, 23 in wave 2, and 15 in wave 3. One hundred and seventy-four were classified as AACD in wave 1, 170 in wave 2, and 144 in wave 3. The prevalence of MCI in the general population as estimated from the baseline examinations of all 833 subjects is 3.24%. The prevalence of AACD is 20.9%. Within the cognitive complaint cohort followed over 2 additional years, the prevalence of MCI is estimated to range from 6.8 to 8.5%, and AACD from 48.7 to 56.8%.

All persons classified as MCI were included in the AACD group in each wave, thus precluding the use of discriminant function analysis or similar methods to discriminate the characteristics of the two groups. The stability of each nosologic entity was then examined across time by examining the subjects originally classified as MCI who remained in this group during subsequent waves of the study (table 1). It can be seen that of the 27 subjects classified as MCI in wave 1, only two (7.4%) retained this diagnosis in wave 2. Twenty-one new incident cases of MCI appeared in wave 2, of whom only four (17.4%) are still considered to have MCI in wave 3.

Changes across time in group membership are also seen in subjects classified as AACD. Of the 174 cases identified in wave 1, 98 (56.3%) were again given this status in wave 2. Of the 170 subjects classified as AACD in wave 2, 101 (59.4%) were still in this group in wave 3. None of the subjects classified as MCI in wave 1 and only 11.1% of those who were classified as MCI in wave 2 received a diagnosis of senile dementia by wave 3. Chi-square values were not significant. Conversely, 17.5% of the subjects classified as AACD in wave 1 and 28.6% in wave 2 had a diagnosis of dementia by wave 3. Prediction of senile dementia across time to diagnosis as evaluated by logistic regression suggests only AACD to be a significant determinant of dementia (relative risk $= 21.2$) at wave 2. Receiver operating characteristics analysis has been used to evaluate the relative predictive power of MCI and AACD as diagnosed in wave 1 to predict dementia in the following 2 years (figure, table 2).

The curve lying along the diagonal indicates a total inability for the MCI diagnosis to predict dementia status (area under the curve [AUC] = 0.485; $p = 0.842$), whereas the curve for the AACD group, rising high above the diagonal to the left, is indicative of high discrimination (AUC = 0.744; $p = 0.001$). The mean summary cognitive test scores for the MCI and AACD groups in the second year of the

Figure. Receiver operating characteristic (ROC) curves showing the ability of age-associated cognitive decline and mild cognitive impairment criteria to diagnose dementia. (A) ROC curve for age-associated cognitive decline. (B) ROC curve for mild cognitive impairment.

<table>
<thead>
<tr>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Common subjects between waves 1 and 2 Wave 2</th>
<th>Wave 3</th>
<th>Common subjects between waves 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects initially classified as MCI/normal</td>
<td>Normal (n = 281) MCI (n = 23) 21</td>
<td>Normal (n = 285) MCI (n = 15) 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCI (n = 27) MCI (n = 23) 2</td>
<td>MCI (n = 23) MCI (n = 15) 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCI (n = 27) Normal (n = 285) 25</td>
<td>MCI (n = 23) Normal (n = 293) 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MCI (n = 27) AACD (n = 170) 18</td>
<td>MCI (n = 23) AACD (n = 144) 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects initially classified as AACD/normal</td>
<td>Normal (n = 123) AACD (n = 170) 66</td>
<td>Normal (n = 138) AACD (n = 144) 43</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AACD (n = 174) AACD (n = 170) 98</td>
<td>AACD (n = 170) AACD (n = 144) 101</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AACD (n = 174) Normal (n = 166) 76</td>
<td>AACD (n = 170) Normal (n = 166) 69</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AACD (n = 174) MCI (n = 23) 13</td>
<td>AACD (n = 170) MCI (n = 15) 10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
study (the point of highest predictive validity) are given in table 3.

AACD, MCI, and normal groups were compared on the following variables: age, sex, education, SPECT hypoperfusion in eight cortical regions and overall hypoperfusion index, DECO score, family history of cognitive impairment, medication use, exposure to anesthesia, illness over the past year, depressive illness, and APOE status. Discriminant function analysis was also used to compare the MCI and AACD groups with normal subjects. No significant difference was found between the groups on any of these variables either on univariate analysis or by discriminate function analysis. Two subjects with AACD showed significantly higher frontotemporal hypofusion on SPECT.

**Discussion.** We sought to determine whether MCI may be considered to constitute a separate, homogeneous syndrome. In his discussion of clinical validity in psychiatry, Kendell\(^\text{18}\) has stipulated that such an entity should meet two criteria: 1) there should be a cluster of related symptoms with a characteristic time course as demonstrated by clinical observation or cluster analysis; and 2) boundaries between the new syndrome and related syndromes should be demonstrated by discriminant function analysis. Application of currently used MCI criteria to a general population sample has shown that this clinical entity does not meet these criteria for the existence of a homogeneous syndrome, showing neither temporal stability nor clear boundaries from normal subjects apart from the cognitive deficit which defines it. MCI also has poor predictive validity for the onset of dementia within the general population. Conversely, AACD subjects appear to constitute a relatively stable group, with a high predictive validity for dementia onset. This, however, is contradictory to the underlying conceptual basis of AACD as a benign, stable impairment related to the normal aging process and unrelated to the pathologic processes of the senile dementias.

The study does confirm, however, that complaints of low-grade cognitive impairment verified by neuropsychological assessment are not benign and should not be dismissed as a normal feature of aging. Within our cognitive complaint cohort followed over 3 years, the conversion rate to senile dementia (18% incidence over 3 years) is much higher than that observed in the general population. Our results are in agreement with previous clinical observations of subclinical cognitive deficit,\(^\text{7-10,19}\) which report conversion rates of 15 to 53% over a similar time period. MCI criteria as currently defined have not, however, adequately captured this prodromal group in the general population. This may be due in part to differences in the neuropsychological tests used. At present, no specific tests have been stipulated, and this is a major shortcoming of current MCI criteria. Test differences are not, however, sufficient to explain the high rates of instability observed in our study, as our previous validation study of the ECO battery demonstrates high retest reliability for all tests. Furthermore, a high predictive value of AACD for dementia was found using the same battery, suggesting that a high-risk dementia group may be identified in the general population by means of the cognitive tests used in this study. Our findings suggest that certain modifications to current MCI criteria may greatly increase its predictive value.

Firstly, because the number of MCI cases found is small, and all are included within the AACD group, it would appear that current criteria for MCI are too stringent. The principal difference between MCI and AACD lies in the prerequisite that there be impairment in memory, but not in any other area of cognitive functioning. This point has already been the subject of much debate, as an increasing number of studies conclude that subjects with MCI, although having primarily memory complaints, also commonly show deficits on tasks of language,\(^\text{12,20}\) orientation,\(^\text{19}\) and praxis.\(^\text{12,20}\) Although there is some evidence that a purely mnesic syndrome may exist within a clinical context,\(^\text{7}\) this appears to be a rare occurrence when the full range of cognitive functions are examined.\(^\text{21}\)

Adhering to the strict criteria of isolated memory complaint in this study would have led to unacceptable levels of sensitivity, with the number of cases of isolated deficit falling well below the expected prevalence of AD itself. The isolation of a pure mnesic syndrome based on neuropsychometric testing methods is in itself highly questionable; even the so-called memory tests involve cognitive functions other than memory.

Comparative studies of MCI would be greatly facilitated if standardized cognitive testing procedures could be specified. The current study has used a much broader battery of cognitive tests than those used to date in current clinical studies, therefore providing information on the tests that are most likely to be sensitive to early dementia 1 and 2 years before diagnosis. From a previous analysis of the Eugenia data,\(^\text{22}\) we established that the following tests were able to differentiate normal subjects from those with preclinical senile dementia 2 years before

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**Table 2 Receiver operating characteristics analysis of the discriminability of AACD and MCI for the prediction of dementia after 2 years**

<table>
<thead>
<tr>
<th>Classification</th>
<th>AUC</th>
<th>SE</th>
<th>Asymptotic significance</th>
<th>95% CI</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AACD</td>
<td>0.744</td>
<td>0.051</td>
<td>0.001</td>
<td>0.644–0.844</td>
<td>94.73</td>
<td>54.08</td>
</tr>
<tr>
<td>MCI</td>
<td>0.485</td>
<td>0.071</td>
<td>0.842</td>
<td>0.346–0.625</td>
<td>5.26</td>
<td>91.83</td>
</tr>
</tbody>
</table>

AACD = age-associated cognitive decline; MCI = mild cognitive impairment; AUC = area under the curve.
diagnosis, and were also independent of education effects: simple reaction time, reaction time on a dual attention task, semantic category fluency, delayed free verbal recall, cued delayed verbal recall, recall of name–face pairs, narrative recall, and copying of a complex design. This concurs with previous studies, which have suggested delayed free and cued recall to be the most predictive of dementia onset, but also indicates that other tests may be useful in improving predictive validity.

The second difference between MCI and AACD criteria relates to performance of activities of everyday living. No guidelines have been given as to what constitutes activities of daily living restriction in MCI. Any number of activities might be proposed, which may be more or less culturally biased. The degree of disability is also not stipulated. This study is based on a definition of disability as persistent loss of ability to perform certain everyday activities. However, in previous analyses, it has been shown that very slight changes in activity performance (e.g., occasionally requiring assistance or needing to be reminded to perform an activity) are commonly observed in incipient AD up to 2 years before diagnosis. This suggests that activity changes may be seen in MCI if lower thresholds are used to define restriction. This difficulty has been overcome in studies using Clinical Dementia Rating 0.5 classification to define MCI, as this criterion refers to “usually intact” activities of daily living. We suggest that, in refining criteria for the identification of MCI in the general population, the predictive validity of introducing some mild difficulties in activity performance as positive inclusion criteria should also be examined.

Table 3 Cognitive test scores for normal, MCI, AACD, and dementia groups (wave 2)

<table>
<thead>
<tr>
<th>Task</th>
<th>Group</th>
<th>Normal (n = 64)</th>
<th>MCI (n = 23)</th>
<th>AACD (n = 170)</th>
<th>Dementia (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean reaction time on double task</td>
<td>19.94 (4.49)</td>
<td>21.03 (4.0)</td>
<td>25.42 (7.85)</td>
<td>31.43 (7.04)</td>
<td></td>
</tr>
<tr>
<td>Primary memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall of name list</td>
<td>5.42 (1.37)</td>
<td>3.34 (1.33)</td>
<td>4.07 (1.74)</td>
<td>3.36 (1.97)</td>
<td></td>
</tr>
<tr>
<td>Secondary memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed recall of names</td>
<td>5.48 (1.80)</td>
<td>3.0 (1.73)</td>
<td>3.37 (2.17)</td>
<td>2.57 (2.38)</td>
<td></td>
</tr>
<tr>
<td>Delayed recall of faces</td>
<td>7.96 (1.24)</td>
<td>7.30 (1.74)</td>
<td>6.77 (1.99)</td>
<td>5.84 (2.11)</td>
<td></td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean reaction time on total visual analysis</td>
<td>36.44 (6.60)</td>
<td>38.63 (7.47)</td>
<td>46.04 (11.09)</td>
<td>53.01 (10.34)</td>
<td></td>
</tr>
<tr>
<td>Copying tasks</td>
<td>23.95 (0.21)</td>
<td>23.82 (0.49)</td>
<td>22.38 (3.77)</td>
<td>19.37 (6.45)</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naming total correct</td>
<td>9.54 (0.68)</td>
<td>9.8 (0.38)</td>
<td>8.55 (1.68)</td>
<td>7.52 (1.71)</td>
<td></td>
</tr>
<tr>
<td>Fluency total</td>
<td>39.01 (10.98)</td>
<td>32.21 (7.76)</td>
<td>25.32 (11.33)</td>
<td>18.57 (8.02)</td>
<td></td>
</tr>
<tr>
<td>Reaction time word and syntax comprehension</td>
<td>17.81 (4.92)</td>
<td>19.05 (4.87)</td>
<td>26.56 (10.16)</td>
<td>33.16 (13.64)</td>
<td></td>
</tr>
<tr>
<td>Reasoning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical series total correct</td>
<td>1.45 (1.09)</td>
<td>1.52 (0.51)</td>
<td>0.76 (0.89)</td>
<td>0.42 (0.50)</td>
<td></td>
</tr>
</tbody>
</table>

Values expressed as mean (SD).

MCI = mild cognitive impairment; AACD = age-associated cognitive decline.

References
Cardiovascular risk factors and cognitive decline in middle-aged adults

D. Knopman, MD; L.L. Boland, MPH; T. Mosley, PhD; G. Howard, DrPH; D. Liao, MD, PhD; M. Szko, MD, DrPH; P. McGovern, MD; and A.R. Folsom, MD, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators

Article abstract—Objective: To perform serial neuropsychological assessments to detect vascular risk factors for cognitive decline in the Atherosclerosis Risk in Communities cohort, a large biracial, multisite, longitudinal investigation of initially middle-aged individuals. Methods: The authors administered cognitive assessments to 10,963 individuals (8,729 white individuals and 2,234 black individuals) on two occasions separated by 6 years. Subjects ranged in age at the first assessment from 47 to 70 years. The cognitive assessments included the delayed word recall (DWR) test, a 10-word delayed free recall task in which the learning phase included sentence generation with the study words, the digit symbol assessment from 47 to 70 years. The cognitive assessments included the delayed word recall (DWR) test, a 10-word delayed free recall task in which the learning phase included sentence generation with the study words, the digit symbol assessment. Results: In multivariate analyses (controlling for demographic factors), the presence of diabetes at baseline was associated with greater decline in scores on both the DSS and WF (p < 0.05), and the presence of hypertension at baseline was associated with greater decline on the DSS alone (p < 0.05). The association of diabetes with cognitive decline persisted when analysis was restricted to the 47- to 57-year-old subgroup. Smoking status, carotid intima–media wall thickness, and hyperlipidemia at baseline were not associated with change in cognitive test scores. Conclusions: Hypertension and diabetes mellitus were positively associated with cognitive decline over 6 years in this late middle-aged population. Interventions aimed at hypertension or diabetes that begin before age 60 might lessen the burden of cognitive impairment in later life.

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Vascular risk factors are typically thought to produce deleterious effects on brain function via overt strokes. However, it is more likely that the burden of brain lesions due to cerebrovascular disease actually accumulates subclinically over years or decades. Cross-sectional data in elderly demented individuals have shown that various cardiovascular risk factors are associated with a higher risk of dementia.1 How early these risk factors may begin to exert their influence is not well understood. Several studies have noted that blood pressure during middle age is associated with later cognitive dysfunction.2-8 None of
Classification criteria for mild cognitive impairment: A population-based validation study
Karen Ritchie, Sylvaine Artero and Jacques Touchon
Neurology 2001;56;37-42
DOI 10.1212/WNL.56.1.37

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