Risk profiles for mild cognitive impairment and progression to dementia are gender specific

S Artero,[1,2] M-L Ancelin,[1,2] F Portet,[1,2] A Dupuy,[1,2] C Berr,[1,2] J-F Dartigues,[3,4] C Tzourio,[5,6] O Rouaud,[5,6] M Poncet,[7] F Pasquier,[8,9] S Auriacombe,[3,4] J Touchon,[1,2] K Ritchie[1,2]

[1] Inserm, U888, Montpellier, France; [2] Université de Montpellier 1, Montpellier, France; [3] Inserm, U593, Bordeaux, France; [4] Université Victor Ségalen Bordeaux 2, Département de Neurologie, Bordeaux, France; [5] Inserm, U708, Paris, France; [6] Université Pierre et Marie Curie-Paris 6, Paris, France; [7] Hôpital de la Timone, Département de Neurologie et Neuropsychologie, Marseille, France; [8] Université de Lille, EA 2691, Lille, France; [9] CHU de Lille, Département de Neurology, Lille, France

Correspondence to: Dr K Ritchie, Inserm U888 Nervous System Pathologies: Epidemiological and Clinical Research, La Colombière Hospital, 34093 Montpellier Cedex 5, France; karen.ritchie@inserm.fr

Received 9 October 2007
Revised 20 February 2008
Accepted 26 February 2008

ABSTRACT

Objective: To examine risk factors for mild cognitive impairment (MCI) and progression to dementia in a prospective community-based study of subjects aged 65 years and over.

Methods: 6892 participants who were over 65 and without dementia were recruited from a population-based cohort in three French cities. Cognitive performance, clinical diagnosis of dementia, and clinical and environmental risk factors were evaluated at baseline and 2-year and 4-year follow-ups.

Results: 42% of the population were classified as having MCI at baseline. After adjustment for confounding with logistic regression models, men and women classified as having MCI were more likely to have depressive symptomatology and to be taking anticholinergic drugs. Men were also more likely to have a higher body mass index, diabetes and stroke, whereas women were more likely to have poor subjective health, to be disabled, to be socially isolated, and to suffer from insomnia. The principal adjusted risk factors for men for progression from MCI to dementia in descending order were ApoE4 allele (OR = 3.2, 95% CI 1.7 to 5.7), stroke (OR = 2.8, 95% CI 1.2 to 6.9), low level of education (OR = 2.3, 95% CI 1.3 to 4.1), loss of Instrumental Activities of Daily Living (IADL) (OR = 2.2, 95% CI 1.1 to 4.5) and age (OR = 1.2, 95% CI 1.1 to 1.2). In women, progression is best predicted by IADL loss (OR = 3.5, 95% CI 2.1 to 5.9), ApoE4 allele (OR = 2.3, 95% CI 1.4 to 4.0), low level of education (OR = 2.2, 95% CI 1.3 to 3.6), subclinical depression (OR = 2.0, 95% CI 1.1 to 3.6), use of anticholinergic drugs (OR = 1.8, 95% CI 1.0 to 3.0) and age (OR = 1.1, 95% CI 1.1 to 1.2).

Conclusions: Men and women have different risk profiles for both MCI and progression to dementia. Intervention programmes should focus principally on risk of stroke in men and depressive symptomatology and use of anticholinergic medication in women.

The identification of older people with cognitive impairment that is at high risk of evolving to Alzheimer's disease is important for early treatment. The concept of mild cognitive impairment[1] is now widely used to describe this high-risk group, and numerous research programmes have been undertaken with a view to therapeutic intervention aimed at reducing the incidence of dementia. As MCI is not by definition a very disabling condition, most people who have it do not consult specialists. The clinical characterisation of MCI and its related risk factors is thus best obtained from general population studies which cover the entire population at risk and not just the subset of patients with MCI who attend specialist centres. Epidemiological studies that have included specialist examinations have also shown that, whereas clinical cohorts show high rates of progression to dementia, application of criteria used in this context to the general population leads to the exclusion of many cases of MCI considered by clinicians to be high risk.[2–5] Furthermore, as population studies of MCI have shown that most people with MCI will not develop dementia even after 8 years of follow-up,[2 5–7] it is important to determine from epidemiological studies the clinical and environmental risk factors for progression from MCI to dementia in order to identify people likely to benefit from treatment and to target appropriate clinical intervention points.

Clinical studies of MCI characterise it principally as a decrease in performance on tests of delayed recall and executive functioning, linked to hippocampal atrophy mid-way between normal ageing and dementia.[8] Postmortem studies also indicate that the degree of cognitive impairment is proportional to the degree of neurofibrillary pathology in the medial temporal lobes.[9] A number of clinical and population studies have compared MCI and normal cohorts prospectively, and the principal conclusion has been that the risk factors for MCI and for MCI progression to dementia are principally the same as those for Alzheimer's disease (notably age, the presence of the ApoE4 allele and hypertension).[4 10] A major shortcoming of all of these studies is that the clinical measures and environmental risk factors examined in population studies have been largely limited to those for Alzheimer's disease, so that a more general characterisation of the clinical syndrome of MCI and its associated risk factors has not been possible. Clinical studies, on the other hand, have been based on subjects with MCI who have been referred to specialist centres rather than general practice, and are therefore unlikely to be representative of all cases of MCI. Finally, although most studies have adjusted by sex in multivariate analyses, they have not examined the possibility that MCI risk profiles may not be the same for men and women.

This study, based on a large multicentre prospective population study of brain ageing, aims to describe the MCI syndrome by reference to a much wider range of health and environmental variables than has previously been considered. Risk factors for MCI and for progression from MCI to dementia are examined separately for men and women.

Table 1 Differences between subjects classified as having mild cognitive impairment (MCI) at baseline and subjects without cognitive impairment both at baseline and follow-up (normal)

Characteristic	MCI (n = 2879)	Normal (n = 4013)	p Value*
Age (years)	74.6 (5.7)	73.1 (4.9)	<0.01
Sex (women)	64.6	56.6	<0.01
Education level			
Low	24.7	22.5	<0.01
Medium	62.2	54.2	
High	13.1	24.3	
Hypertension†	78.6	76.5	0.04
Hypercholesterolaemia‡	59.0	57.2	0.15
Diabetes mellitus	11.0	9.0	<0.01
Head trauma	7.5	7.2	0.21
All cardiovascular antecedents	10.0	7.7	<0.01
Stroke	5.1	2.8	<0.01
Asthma	8.5	7.5	0.13
Depression			
Current major depression	2.4	1.6	<0.01
Depressive symptomatology	16.0	10.3	<0.01
Subthreshold depression	9.2	4.6	<0.01
Antidepressive drugs	9.2	4.6	<0.01
ApoE4 genotype	20.6	19.5	0.29
NART	21.1 (6.5)	24.3 (5.4)	<0.01
Anticholinergic drugs	10.1	5.5	<0.01
At least 2 cups coffee/day	65.8	67.9	0.03
Tobacco use (packets/year)	7.4 (16.4)	8.6 (16.6)	<0.01
Alcohol use	78.8	81.4	<0.01
Physical activity	31.5	36.5	<0.01
Good subjective health	94.2	97.0	<0.01
Herpes	30.7	30.1	0.57
Insomnia	28.5	21.8	<0.01
BMI >27	35.4	31.0	<0.01
Appetite loss	14.2	10.7	<0.01
Social isolation	37.6	35.8	0.06
Difficulty with at least 1 IADL	12.0	7.8	<0.01
Anaesthesia	34.6	3.0	0.02
Hospitalisation for cancer	1.4	1.6	0.54
HRT (past or current)	30.2	33.0	0.06

All values are mean (SD) or percentage.
*Student t test or χ^2 test as appropriate.
†Blood pressure cut-off 140/90 or antihypertensive treatment.
‡Cholesterol concentration 6.2 mmol/l or treatment.
BMI, body mass index; HRT, hormone replacement therapy; IADL, Instrumental Activities of Daily Living; NART, National Adult Reading Test.

METHODS

Study population

Subjects for this study were recruited randomly from the electoral roles of three French cities (Bordeaux, Dijon and Montpellier) between 1999 and 2001 as part of a multi-site cohort study of community-dwelling people aged 65 years and over (the Three City Study also known as the 3C Study). Subjects were interviewed initially either at a study centre or in their own homes if disabled. The cohort was followed-up twice at 2-year intervals. Mortality over the 4-year follow-up was 6.8%. The study design has been described in detail elsewhere.[11] The study protocol was approved by the ethics committee of the University Hospital of Bicêtre (France), and written informed consent was obtained from each participant. This analysis was carried out on the 6892 subjects (74% of the subjects initially recruited at baseline) who did not have dementia and for whom 4-year follow-up data on all variables were available. The mean (SD) age of the sample was 74.0 (5.5) for men and 74.3 (5.6) for women.

Diagnosis of MCI and dementia

In a previous report, we observed difficulties with applying the original criteria for MCI, which were developed within a clinical setting, to community studies.[5] Subsequent revision of these criteria by an international consensus group[12] has led to the development of a diagnostic algorithm that has high discriminability in the general population.[13] The revised criteria (MCI-R) were thus applied in this study. They are (*a*) presence of a cognitive complaint from either the subject or a family member, (*b*) absence of dementia, (*c*) change from normal cognitive functioning, (*d*) decline in any area of cognitive functioning, and (*e*) preserved overall general functioning but maybe increasing difficulty in the performance of activities of daily living. Subjects were asked about their cognitive functioning as part of the general examination, and difficulties and decline in specific cognitive domains were noted. Each participant named a family member as proxy; cognitive difficulties reported by proxies were also recorded.

The cognitive tests used for the definition of MCI-R were the Benton Visual Retention Test,[14] the Trail Making Test,[15] the Isaacs' Set Test[16] and a word recall test with both delayed free recall and recall with semantic prompts.[17] These tests covered declarative verbal and spatial memory and central executive and semantic retrieval abilities. The National Adult Reading Test (NART)[18] was used as a marker of intelligence. Standardisation data were obtained by establishing quartile range by age (10-year age groups) and education (primary, secondary and tertiary levels) for the entire population. Cognitive impairment was defined as having a score (in at least one cognitive test) in the lowest quartile range in relation to the relevant age-matched and education-matched comparison group. A preliminary diagnosis and classification of dementia at each follow-up examination was made by the 3C Study local clinical investigators according to DSM-IV revised criteria,[19] and validated by a national panel of neurologists independently of the 3C Study investigators.

Sociodemographic and clinical variables

A standardised interview included questions on demographic characteristics, education level (classified into three groups corresponding to primary, secondary and tertiary levels),

Table 2 Principal sociodemographic and clinical characteristics differentiating subjects with mild cognitive impairment from those without at baseline, with adjustment for confounders (logistic regression)

Variable	p Value	OR (95% CI)
Men		
Anticholinergic drugs	<0.01	2.26 (1.44 to 3.56)
Depressive symptomatology	<0.01	1.69 (1.27 to 2.25)
Stroke	<0.01	1.54 (1.01 to 1.36)
Diabetes	0.01	1.45 (1.09 to 1.94)
BMI>27	0.01	1.40 (1.14 to 1.72)
Age (continuous)	0.02	1.02 (1.01 to 1.04)
Women		
Poor subjective health	0.04	1.55 (1.02 to 2.37)
Anticholinergic drugs	0.04	1.47 (1.12 to 1.91)
IADL deficit	0.01	1.40 (1.07 to 1.83)
Depressive symptomatology	0.04	1.26 (1.00 to 1.59)
Social isolation	0.01	1.21 (1.04 to 1.42)
Insomnia	0.03	1.21 (1.00 to 1.43)

Results are adjusted by centre.
BMI, body mass index; IADL, Instrumental Activities of Daily Living.

physical activities, weight and height. Information was also obtained on exposure to anaesthesia in the preceding year, subjectively evaluated health, sleep quality, herpes infections, subjective report of appetite loss, self-reported social isolation, current alcohol consumption, coffee and tea consumption (over two cups a day) and tobacco use (packets a year). Blood pressure was measured twice during the interview using a digital electronic tensiometer (Omron M4). Subjects were considered to be hypertensive if mean systolic blood pressure was 160 mm Hg or higher or mean diastolic blood pressure was 95 mm Hg or higher or they were taking antihypertensive drugs. Fasting blood samples were taken for evaluation of cholesterol and glucose concentrations and apolipoprotein E status. Hypercholesterolaemia was defined as cholesterol sulfotransferase ⩾6.2 mmol/l, and diabetes as treated diabetes or fasting blood glucose ⩾7.2 mmol/l. Cardiovascular antecedents included history of myocardial infarction, coronary surgery, coronary angioplasty, and arterial surgery of the legs for arteritis. Impairment in the performance of everyday activities was assessed with the Instrumental Activities of Daily Living (IADL) Scale, impairment being defined as increased difficulty in at least one IADL.[20]

Any history of head trauma, respiratory disease, cancer, hypertension, hypercholesterolaemia, diabetes, stroke, asthma, angina pectoris was established using standardised questions with additional information where necessary from general practitioners. For participants who reported the occurrence of vascular events during follow-up, further medical data were obtained from general practitioners, specialists and hospital records. The interview also included an inventory of all drugs used during the preceding month, and those with potential anticholinergic effects according to previously established criteria,[21] and past as well as present use of hormonal replacement therapy (HRT) were noted. Medical prescriptions and, where feasible, the drugs themselves were seen by the interviewer. Depressive symptomatology was assessed by the Center for Epidemiological Studies-Depression Scale (CES-D),[22] with a >16 cut-off point indicating a high level of symptomatology. Current major depressive episodes were assessed using the Major Depressive Episode module of the Mini International Neuropsychiatric Interview (MINI, French version 5.00) according to DSM-IV criteria.[23] Subclinical depression was defined as a high level of depressive symptomatology without current major depression.

Statistical analysis

Regression modelling procedures were carried out with SPSS for Windows NT, V15.0. Forward, stepwise logistic regression was carried out on variables found to be significant on univariate analysis. A correlation matrix was used to check collinearity ($r>0.80$). Interactions between variables were also examined. Significant interaction with sex on a large number of variables justified our decision to examine risk profiles separately for men and women. Using this stratification, we have developed additive models, which are easier to interpret. All models were adjusted by study centre.

RESULTS

After application of MCI-R criteria, 2882 subjects (42%) were classified as having MCI at baseline; 36% were over 75 years of age and 65% were women. Of these, 189 (6.6%) were given a diagnosis of dementia over the next 4 years, for 1626 (56.5%) the diagnosis remained MCI, and 1067 (37%) returned to normal levels of functioning. Significant ($p<0.02$) differences in outcome were observed for men and women, women being less likely than men to return to normal cognitive functioning (36% vs 39%) and more likely to have continuing cognitive disorder (58% vs 53%). Eight percent of men with MCI developed dementia compared with 6% of women. The types of dementia that developed were Alzheimer's disease (n = 122), vascular dementia (n = 19), Lewy body dementia (n = 4) and other forms of dementia (n = 44). Given the small numbers with dementia other than Alzheimer's disease, subgroups are mixed in subsequent analyses. Table 1 shows univariate comparisons of subjects with MCI at baseline with subjects without cognitive deficit (either at baseline or follow-up). Those with MCI were principally female, older, with lower levels of education, a history of diabetes, hypertension, cardiovascular antecedents, stroke, major and subclinical depression, recent anaesthesia, less physical activity, poorer subjective physical health, insomnia, higher body mass index (BMI), appetite loss, social isolation and IADL difficulties. Women with MCI were less likely to be HRT users.

Logistic regression was used to differentiate the principal characteristics of subjects with and without MCI. Compared with those without MCI, men with MCI were older, had more depressive symptoms, higher BMI, and were more likely to have had diabetes or stroke and to be taking anticholinergic drugs (table 2). Women with MCI were also more likely than women without MCI to have depressive symptomatology and to be taking anticholinergic drugs. In addition, they were more likely to be disabled, to be socially isolated, suffer from insomnia, and to rate their health as poor (table 2).

Table 3 shows the clinical and sociodemographic characteristics of subjects with MCI according to whether they developed dementia (group 1), remained MCI (group 2), or returned to normal cognitive functioning (group 3). The significant risk factors associated with progression from MCI to dementia were age, low level of education, hypertension, diabetes, stroke, subclinical depression, antidepressant use, ApoE4 genotype, low intelligence, use of anticholinergic drugs, poor subjectively evaluated health, appetite loss, social isolation and difficulties with at least one IADL, and women were less often HRT users.

Significant risk factors derived from the univariate analysis were then entered into a logistic regression model predicting MCI progression to dementia versus MCI remaining stable or a return to normal for men and women separately (table 4). For men, significant effects were observed for higher age, low level of education, IADL loss, ApoE4 allele and stroke. For women, significant effects were found for higher age, low level of education, IADL loss and ApoE4 allele. In women, significant effects are also observed for subclinical depression and use of anticholinergic drugs (principally psychotropics, 43%); stroke on the other hand was not found to be a significant risk factor for women. This difference is not due to differing prevalence of these conditions in men and women.

DISCUSSION

The principal strengths of this study are the examination of a much wider range of clinical characteristics and risk factors for MCI than has previously been studied and inclusion of a much more heterogeneous sample of MCI cases within this large prospective population study than would be expected from clinical studies. Prospective clinical examination by neurologists has permitted the identification of "true" MCI cases—that is, those progressing to dementia or remaining MCI as opposed to

Table 3 Sociodemographic and clinical characteristics of subjects with mild cognitive impairment (MCI) according to clinical status 4 years later (dementia, MCI, return to normal cognitive functioning)

Characteristic	Group 1 (n = 189)	Group 2 (n = 1626)	Group 3 (n = 1064)	1 vs 3*	1 vs 2*	2 vs 3*
Age (years)	78.5 (5.2)	74.1 (5.3)	73.3 (5.2)	<0.01	<0.01	<0.01
Sex (women)	58.7	66.7	62.3	NS	0.02	NS
Education level						
Low	41.5	23.7	23.2			
Medium	42.0	66.0	60.1	<0.01	<0.01	<0.01
High	16.5	10.3	16.7			
Hypertension	82.5	78.2	76.6	0.04	NS	NS
Hypercholesterolaemia	54.3	60.3	57.7	NS	NS	NS
Diabetes mellitus	17.2	11.0	10.0	<0.01	0.02	NS
Head trauma	7.0	7.8	7.0	NS	NS	NS
All cardiovascular antecedents	17.0	9.8	8.6	<0.01	0.02	NS
Stroke	11.7	5.1	3.8	<0.01	<0.01	NS
Asthma	10.6	9.2	7.1	NS	NS	0.04
Depression						
Current major depression	3.1	3.1	1.6	NS	NS	0.03
High depressive symptomatology	25.7	17.3	12.0	<0.01	<0.01	0.01
Subclinical depression	18.1	13.2	10.0	<0.01	<0.01	<0.01
Antidepressive drugs	19	9.7	7.0	<0.01	<0.01	0.01
ApoE4 genotype	32.1	21.0	16.7	0.01	<0.01	<0.01
NART	19.5 (7.3)	21 (6.3)	22.7 (5.8)	<0.01	<0.01	<0.01
Anticholinergic drugs	16.0	11.0	7.6	<0.01	0.04	0.01
At least 2 cups coffee/day	58.8	66.0	66.7	NS	NS	NS
Alcohol use	78.8	77.7	80.3	NS	NS	NS
Tobacco use (packet/year)	7.8 (19.2)	7.3 (16.5)	7.5 (15.8)	NS	NS	NS
Good subjective health	87.2	93.8	95.1	<0.01	<0.01	0.04
Herpes	29.1	32.0	29.2	NS	NS	NS
Insomnia	33.1	30.0	25.4	NS	NS	0.02
BMI >27	30.8	37.0	34.4	NS	NS	NS
Appetite loss	23.0	15.6	10.6	<0.01	<0.01	<0.01
Social isolation	43.8	38.6	35.2	0.05	NS	NS
Difficulty with at least 1 IADL	33.3	12.1	8.2	<0.01	<0.01	0.03
Anaesthesia	31.4	34.0	36.0	NS	NS	NS
Hospitalisation for cancer	1.6	1.3	1.5	NS	NS	NS
HRT (past or current)	18.6	0.6	33.0	<0.01	0.03	NS

All values are mean (SD) or percentage.
*Student t test or χ^2 test as appropriate.
Group 1, MCI to dementia; group 2, diagnosis remained MCI; group 3, MCI to normal.
BMI, body mass index; HRT, hormone replacement therapy; IADL, Instrumental Activities of Daily Living Scale; NART, National Adult Reading Test.

Table 4 Significant determinants of 4-year outcome (dementia) for subjects with mild cognitive impairment by logistic regression adjustment for confounders

Variable	p Value	OR (95% CI)
Men		
ApoE4 allele	<0.01	3.15 (1.74 to 5.70)
Stroke	0.02	2.84 (1.17 to 6.85)
Low education level	<0.01	2.26 (1.25 to 4.06)
IADL deficit	0.03	2.20 (1.07 to 4.49)
Age	<0.01	1.16 (1.10 to 1.21)
Women		
IADL deficit	<0.01	3.51 (2.09 to 5.89)
ApoE4 allele	<0.01	2.34 (1.38 to 3.96)
Low education level	<0.01	2.16 (1.31 to 3.56)
Subclinical depression	0.03	1.95 (1.06 to 3.58)
Anticholinergic drugs	0.04	1.78 (1.00 to 3.18)
Age	<0.01	1.14 (1.09 to 1.19)

Results are adjusted by centre.
IADL, Instrumental Activities of Daily Living.

those returning to normal functioning. Using MCI criteria revised for use for the general population, we estimate MCI prevalence at 42%, with relatively high consistency between centres (Bordeaux, 43%; Dijon, 47%; Montpellier, 28%). The lower rates of MCI in Montpellier, which is in the southern Mediterranean region of France, are consistent with a lower prevalence of dementia, hypertension, stroke and obesity in this region compared with Bordeaux and Dijon in the west and north.[11] The overall prevalence rates are higher than those reported by previous population studies using MCI revised criteria (3–25%),[2 6 7 13] but the catchment area is much wider and the sample much larger (6892 subjects compared with previous studies of 581–1790 subjects), thus methodologically likely to be more representative of the community-dwelling population and to be in naturalistic conditions of general practice, which explains the low annual rate of conversion to dementia.

The main finding is that MCI cases in the general population can be differentiated by a much larger number of

sociodemographic and clinical factors than previously observed and that risk factors for both a diagnosis of MCI and progression from MCI to dementia over 4 years are not the same for men and women. A comparison of subjects with and without MCI in this sample of the general population revealed similar differences to those found in previous studies: subjects with MCI were principally female, older, with lower education level, depressive symptoms and hypertension. We did not, however, find a higher prevalence of the ApoE4 allele in the MCI group. Our study also identified further environmental and clinical risk factors for MCI: a history of diabetes, cardiovascular antecedents, stroke, recent anaesthesia, major and subclinical depression, lower IQ, use of anticholinergic drugs, lower consumption of caffeine, tobacco and alcohol, less physical activity, poorer subjective physical health, insomnia, higher BMI, appetite loss, social isolation and IADL difficulties, and women were less often HRT users.

Multivariate analysis suggests, however, that, after taking into account all possible confounding variables and interactive effects, the principal characteristics that differentiate subjects with MCI from those without are not the same for men and women. These findings support the notion that MCI is a common end point to multiple aetiological pathways[24] which are not the same for men and women. These differences in MCI profiles may in part be modulated by endocrinological risk factors as well as differences in exposure to environmental hazards such as life events, diet and injury. Some studies report gender differences in dementia risk factors,[25–27] but large clinical trials have not yet been designed to include both women and men in numbers sufficient to assess gender effect in the field of MCI.

Four years after the baseline assessment, 62.7% of subjects classified as having MCI were found to remain either cognitively impaired or to progress towards dementia, suggesting that most of the subjects classified as having MCI did indeed have chronic cognitive problems. The rate of progression to dementia was low in this study (6.7%), perhaps because of the short follow-up period and non-inclusion at baseline of subjects living in institutions. The principal characteristics of subjects progressing from MCI to dementia over a 4-year period were consistent with previous findings: age, level of education, hypertension, antecedents of cardiovascular disease, stroke, depression, ApoE4 genotype, low IQ, and difficulties in the performance of everyday activities. This much broader study of health factors that influence cognitive performance has also identified diabetes, use of anticholinergic drugs, use of HRT for women, poor subjectively evaluated health, appetite loss, social isolation and increasing difficulty with at least one everyday activity as being significantly associated with poor prognosis (ie, continued MCI or progression to dementia). It is interesting to note that, although the presence of the ApoE4 allele does not differentiate normal from MCI subjects at the level of diagnosis, it does differentiate them in terms of prognosis. Many of these factors are clearly inter-related, such that, after confounding effects are taken into account, the principal risk factors for dementia emerge as being, in descending order of importance, ApoE4 allele, stroke, low level of education, IADL difficulties and age for men, and IADL difficulties, ApoE4 allele, low level of education, depressive symptomatology, use of anticholinergic drugs and age for women.

A large number of older people have stable MCI and it is interesting to note in terms of cognitive reserve theory that there are fewer subjects with low levels of education in this group compared with those who developed dementia within the 4-year period. Further follow-up of this cohort will allow us to differentiate people with pre-dementia from a probably more heterogeneous group of people with persistent non-dementing MCI and to examine more closely the causes of long-term cognitive impairment. Over a third of patients with MCI were observed to return to normal levels of functioning. The same proportion has been reported by a previous population study.[3] After adjustment for confounders, the principal factors determining a move in this direction were found to be lower BMI for men and absence of depression for women. In both men and women, the absence of an ApoE4 allele was also predictive of a return to normal cognitive functioning. As has previously been suggested by Forsell *et al*,[28] depressive symptomatology is an important risk factor for both MCI and progression to dementia; however, we note that, whereas depressive symptomatology increases the likelihood of a diagnosis of MCI for both men and women, it is only predictive of progression to dementia in women.

The study has a number of shortcomings. As already mentioned above, the time to follow-up may have been too short for slowly evolving cases of dementia. Analysis according to MCI subtype was not carried out, as it was felt that the valid diagnosis of an isolated domain-specific cognitive impairment would require a more sophisticated clinical battery.

In conclusion, this study highlights the high prevalence and heterogeneity of MCI. As most subjects identified at baseline were observed at follow-up to have persistent cognitive deficits or dementia, we conclude that the MCI-R algorithm has been relatively discriminating given the large number of potential confounders identified and the variable health status of subjects. Subjects returning to normal may, however, be considered to be false positives. It may be useful in future refinements of the MCI algorithm for population studies to take into account the characteristics of this group. The present study has not only identified a large range of characteristics of MCI that have not previously been taken into account, but has also shown gender differences—notably cerebrovascular and cardiovascular risk factors and diabetes for men, and poor subjective health, insomnia and social isolation, as well as lower rate of HRT use, for women. Depressive symptomatology is associated with a diagnosis of MCI for both sexes, but appears "benign" for men in that it is not associated with a poor prognosis. Finally, some potentially reversible risk factors for progression to dementia were identified, which were not the same for men and women (notably stroke in men and subclinical depression and use of anticholinergic drugs in women). These factors should be taken into account in the development of gender-specific clinical intervention programmes for MCI.

Acknowledgements: We thank the Génopôle of Lille, the Laboratories of Biochemistry of the University Hospitals of Dijon (Professor Gambert) and Montpellier (Dr Dupuy), the Town Council of Dijon and the Conseil Général of Côte d'Or, and the clinical case validation committee of the 3C Study.

Funding: The 3C Study is conducted under a partnership agreement between Inserm, the Victor Segalen–Bordeaux II University and Sanofi-Synthélabo. The Fondation pour la Recherche Médicale funded the preparation and first phase of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, the Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon and the Fondation de France, the Ministry of Research-Inserm Programme "Cohorts and collection of biological material". The Lille Génopôle received an unconditional grant from Eisai.

Competing interests: None.

REFERENCES

1. **Petersen RC,** Smith GE, Waring SC, *et al*. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;**56**:303–8.
2. **Busse A,** Bischkopf J, Riedel-Heller SG, *et al*. Mild cognitive impairment: prevalence and predictive validity according to current approaches. *Acta Neurol Scand* 2003;**108**:71–81.
3. **Fisk JD,** Merry HR, Rockwood K. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology* 2003;**61**:1179–84.
4. **Lopez OL,** Jagust WJ, Dulberg C, *et al*. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol* 2003;**60**:1394–9.
5. **Ritchie K,** Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology* 2001;**56**:37–42.
6. **Fischer P,** Jungwirth S, Zehetmayer S, *et al*. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology* 2007;**68**:288–91.
7. **Manly JJ,** Bell-McGinty S, Tang MX, *et al*. Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. *Arch Neurol* 2005;**62**:1739–46.
8. **Jack CR Jr,** Petersen RC, Xu YC, *et al*. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999;**52**:1397–403.
9. **Price JL,** Morris JC. Tangles and plaques in nondemented aging and ''preclinical'' Alzheimer's disease. *Ann Neurol* 1999;**45**:358–68.
10. **Tervo S,** Kivipelto M, Hanninen T, *et al*. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. *Dement Geriatr Cogn Disord* 2004;**17**:196–203.
11. **The 3C Study Group**. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology* 2003;**22**:316–25.
12. **Winblad B,** Palmer K, Kivipelto M, *et al*. Mild cognitive impairment: beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Internal Med* 2004;**256**:240–6.
13. **Artero S,** Petersen R, Touchon J, *et al*. Revised criteria for mild cognitive impairment: validation within a longitudinal population study. *Dement Geriatr Cogn Disord* 2006;**22**:465–70.
14. **Benton A.** *Manuel pour l'application du test de retention visuelle. Applications cliniques et experimentales*. Paris: Centre de Psychologie Appliqué, 1965.
15. **Reitan R.** Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 1965;**8**:271–6.
16. **Isaac B,** kennie AT. The Set test as an aid to the detection of dementia in old people. *Br J Psychiatry* 1973;**123**:467–70.
17. **Dubois B,** Touchon J, Portet F, *et al*. ["The 5 words": a simple and sensitive test for the diagnosis of Alzheimer's disease]. (In French.) *Presse Med* 2002;**31**:1696–9.
18. **Blair JR.** Predicting premorbid IQ: a revision of the National Adult Reading Test. *Clin Neuropsychol* 1989;**3**:129–36.
19. **American Psychiatric Association**. *Diagnostic and statistical manual of mental disorders* (4th edn) (DSM-IV). Washington, DC: APA, 1994.
20. **Lawton MP.** Scales to measure competence in everyday activities. *Psychopharmacol Bull* 1988;**24**:609–14.
21. **Ancelin ML,** Artero S, Portet F, *et al*. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ* 2006;**332**:455–9.
22. **Radloff L.** The CES-D Scale: a self report depression scale for research in the general population. *Applied Psychological Measurement* 1977;**1**:385–401.
23. **Lecrubier Y,** Sheehnan D, Weiller E, *et al*. The MINI International Neuropsychiatric Interview (MINI), a short diagnostic interview: reliability and validity according to the CIDI. *European Psychiatry* 1997;**12**:232–41.
24. **Ritchie K.** Mild cognitive impairment: an epidemiological perspective. *Dialogues Clin Neurosci* 2004;**3**:333–40.
25. **Azad NA,** Al Bugami M, Loy-English I. Gender differences in dementia risk factors. *Gend Med* 2007;**4**:120–9.
26. **Knopman DS,** Edland SD, Cha RH, *et al*. Incident dementia in women is preceded by weight loss by at least a decade. *Neurology* 2007;**69**:739–46.
27. **Fleisher A,** Grundman M, Jack CR Jr, *et al*. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. *Arch Neurol* 2005;**62**:953–7.
28. **Forsell Y,** Palmer K, Fratiglioni L. Psychiatric symptoms/syndromes in elderly persons with mild cognitive impairment. Data from a cross-sectional study. *Acta Neurol Scand* 2003;**179**(Suppl):25–8.