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

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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: Participants were 6892 persons over 65 without dementia 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 and 4 year follow-up.

Results: Forty two percent of the population were classified as MCI at base-line. Adjusting for confounding with logistic regression models we observed that men and women classified as MCI are more likely to have depressive symptomatology and to take medication with anticholinergic effects. Men are also likely to have higher BMI, diabetes and stroke whereas women are 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 are ApoE4 allele (OR=3.2, CI 1.7-5.7), stroke (OR=2.8, CI 1.2-6.9), lower education (OR=2.3, CI 1.3-4.1), IADL loss (OR=2.2, CI 1.1-1.2) and age (OR=1.2, CI 1.1-1.2). In women progression is best predicted by IADL loss (OR=3.5, CI 2.1-5.9), ApoE4 allele (OR=2.3, CI 1.4-4.0), low education (OR=2.2, CI 1.3-3.6), sub-clinical depression (OR=2.0, CI 1.1-3.6), anti-cholinergic medication use (OR=1.8, CI 1-3), and age (OR=1.1, CI 1.1-1.2).

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

INTRODUCTION

The identification of elderly persons with cognitive impairment at high risk of evolving towards 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 dementia incidence. As MCI is not by definition a very disabling condition, most cases do not consult specialists. The clinical characterization of MCI and its related risk factors are thus best obtained from general population studies which cover the entire population at risk and not just the sub-set of MCI patients coming to specialist centres. Epidemiological studies which have included specialist examinations have also shown that while clinical cohorts have high rates of progression to dementia, the 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 at high risk[2-5]. Furthermore, as population studies of MCI have shown that most persons with MCI will not develop dementia even after 8 years 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 cases likely to benefit from treatment, and to target appropriate clinical intervention points.

Clinical studies of MCI characterize it principally as a drop in performance on tests of delayed recall and executive functioning, linked to hippocampal atrophy mid-way between normal ageing and dementia [8]. Post-mortem 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, from which 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, ApoE4 allele and hypertension)[4, 10]. A major short-coming of all 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 characterization of the clinical syndrome of MCI or of its associated risk factors has not been possible. Clinical studies on the other hand have been based on MCI subjects referred to specialist centres rather than general practice, and therefore unlikely to be representative of all cases of MCI. Finally, although most studies adjust by sex in multivariate analyses, they have not examined the possibility that risk profiles in MCI may not be the same for men and women.

The present study, based on a large multi-centre 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.

METHODS

Study population

Subjects for the present 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 persons aged 65 years and over (the Three City Study). Subjects were interviewed initially either at a study centre or in their own homes if disabled. The cohort was followed up twice at two year intervals. The mortality rate over the four year follow-up was 6.8 %. The study design has been described in detail elsewhere[11]. The study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France) and written informed consent was obtained from each participant. The present analysis is carried out on the 6892 subjects (74% of the subjects initially recruited at

base-line) who did not have dementia and for whom four-year follow-up data was obtained on all variables. The mean age (SD) of the sample was 74.0 (5.5) for men and 74.3 (5.6) for women.

Diagnosis of Mild Cognitive Impairment and Dementia

In a previous report we observed difficulties with the application of the original criteria for MCI 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 which has high discriminability within the general population setting[13]. The revised criteria (MCI-R) are thus applied in this study. These are (i) presence of a cognitive complaint from either the subject or a family member (ii) absence of dementia (iii) change from normal cognitive functioning (iv) decline in any area of cognitive functioning (v) preserved overall general functioning but may be 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 in the study 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 (BVRT) [14], the Trail Making Test (TMTB)[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, central executive, and semantic retrieval abilities. The National Adult Reading Test (NART)[18] was used as a marker of intelligence. Standardization data was obtained by establishing quartile range by age (ten 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 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 investigators.

Socio-demographic and clinical variables

A standardized interview included questions on demographic characteristics, education level (classified into three groups corresponding to primary, secondary and tertiary levels of education), 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 2 cups per day) and tobacco use (packets per year). Blood pressure was measured twice during the interview using a digital electronic tensiometer OMRON M4. Subjects were considered as hypertensive if mean systolic blood pressure was 160mm Hg or higher or mean diastolic blood pressure was 95mm Hg or higher or they were on antihypertensive medication. Fasting blood samples were taken for cholesterol and glucose levels and apolipoprotein E status. Hypercholesterolemia was defined as CST $\geq$ 6.2 mmol/l) and diabetes as treated diabetes or fasting blood glucose $\geq$7.2 mmol/l. Cardiovascular antecedents included history of myocardial infarction, coronary surgery, coronary angioplasty, arterial surgery of the legs due to arteritis in inferior limbs. Impairment in the performance of everyday activities was assessed with the Instrumental Activities of Daily Living Scale (IADL), impairment being defined as increased difficulty in at least one IADL [20].

Past history of head trauma, respiratory disease, cancer, hypertension, hypercholesterolemia, diabetes, stroke, asthma, angina pectoris was established according to standardized questions with additional information where necessary from general practitioners. For persons 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, noting those with potential anticholinergic effects according to previously established criteria [21], and past as well as present use of hormonal replacement therapy (HRT). Medical prescriptions and, where feasible, the medications 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 episode (MDE) was assessed using the Major Depressive Episode module of the Mini International Neuropsychiatric Interview (MINI, French version 5.00) according to DSM-IV criteria [23]. Sub-clinical depression was defined by a high level of depressive symptomatology without current major depression

Statistical analyses

Regression modelling procedures were carried out with SPSS for Windows NT, version 15.0 . Forward, stepwise logistic regression was carried out on variables found to be significant on univariate analysis. A correlation matrix was used to check colinearity ($r>0.80$). 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 have been adjusted by study centre.

Results

Following application of MCI-R criteria, 2882 subjects (42%) were classified as having MCI at base-line. Thirty six percent of MCI subjects were over 75 years of age and 65% women. Of these 189 (6.6%) were diagnosed with dementia over the next four years, 1626 (56.5%) 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 to return to normal cognitive functioning (36% compared to 39% for men) and to have continuing cognitive disorder (58 %, compared to 53% for men). Eight percent of men with MCI developed dementia compared to 6% for women. With regard to type of dementia, 122 MCI subjects developed Alzheimer's disease (AD), 19 vascular dementia, 4 Lewy Body dementia and 44 other forms of dementia. Given the small numbers with non-AD dementia, sub-groups are mixed in subsequent analyses. Univariate comparisons of subjects with MCI at base-line with subjects without cognitive deficit (either at baseline or follow up) are given in Table 1. MCI subjects were principally female, older, with lower education levels, having a history of diabetes, hypertension, cardiovascular antecedents, stroke, major and sub-clinical depression, recent anaesthesia, less physical activity, poorer subjective physical health, insomnia, higher BMI, appetite loss, social isolation and IADL difficulties. Women with MCI were less frequently HRT users.

Table 1 here

Logistic regression was used to differentiate the principal characteristics of MCI and non-MCI subjects. Compared to the non-MCI population, men classified as MCI are older, have more depressive symptoms, higher BMI, are more likely to have had diabetes and stroke, and to take medication with anticholinergic effects. Women with MCI are also more likely than

women without MCI to have depressive symptomatology and to take medication with anticholinergic effects. Additionally they are more likely to be disabled, to be socially isolated, suffer from insomnia and to rate their health as poor (Table 2).

Table 2 here

Table 3 shows the clinical and socio-demographic characteristics of MCI subjects according to whether they evolved towards 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 are age, low education, hypertension, diabetes, stroke, sub-clinical depression, anti-depressant use, ApoE4 genotype, low intelligence, use of anti-cholinergic medication, poor subjectively evaluated health, appetite loss, social isolation and difficulties with at least one IADL and women were less frequently HRT users.

Table 3 here

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 returning to normal for men and women separately (Table 4). For men significant effects were observed for higher age, low education, IADL loss, ApoE4 allele, and stroke. For women significant effects were found for higher age, low education, IADL loss and ApoE4 allele. In women significant effects are also observed for sub-clinical depression and anti-cholinergic

medication use (principally psychotropics 43 %); stroke on the other hand is not a significant risk factor for women. This difference is not due to differing prevalence of these conditions in men and women.

Table 4 here

DISCUSSION

The principal strengths of the present study have been 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 those returning to normal functioning). Using MCI criteria revised for general population use we estimate MCI prevalence at 42%, with relatively high consistency between centres (Bordeaux 43%, Dijon 47% and Montpellier 28%). The lower rates of MCI in Montpellier, which is in the southern Mediterranean region of France, are consistent with lower prevalence of dementia, hypertension, stroke and obesity in this region compared to 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 to previous studies of 581 to 1790 subjects), thus methodologically likely to be more representative of the community-dwelling population and to be in naturalistic conditions of general practice, that explain the low annual conversion rate to dementia.

The main finding is that MCI cases within the general population may be differentiated by a much larger number of socio-demographic and clinical factors than have been previously observed and that risk factors for both a diagnosis of MCI and progression from MCI to dementia over four years are not the same for men and women. Comparing MCI and non-MCI subjects in this general population sample, similar differences to those found in previous studies were observed; MCI subjects being principally female, older, with lower education levels, having depressive symptoms and hypertension. We did not, however, find a higher prevalence of ApoE4 allele in the MCI group. Our study was able to identify further environmental and clinical risk factors for MCI ; namely a history of diabetes, cardiovascular antecedents, stroke, recent anaesthesia, major and sub-clinical depression, lower IQ, anti-cholinergic medication use, lower caffeine, tobacco and alcohol consumption, less physical activity, poorer subjective physical health, insomnia, higher BMI, appetite loss, social isolation, IADL difficulties and women were less frequently HRT users.

Multi-variate analysis suggests, however, that after taking into account all possible confounding variables and interactive effects the principal characteristics differentiating MCI and non-MCI subjects 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 reports gender differences in dementia risk factors[25-27], but large clinical trials have not yet be designed to included women and men in numbers sufficient for assessment of gender effect in the field of MCI.

Four years after the base-line assessment 62.7% of subjects classified as MCI are seen to either remain cognitively impaired or to progress towards dementia, suggesting that most of the subjects classified as MCI do indeed have chronic cognitive problems. The rate of progression to dementia is low in this study (6.7%), perhaps due to the short follow-up period and non-inclusion of subjects at base-line living in institutions. The principal characteristics of subjects progressing from MCI to dementia over a four year period were consistent with previous findings; namely age, education, hypertension, antecedents of cardiovascular disease, stroke, depression, ApoE4 genotype, low intelligence and difficulties in the performance of everyday activities. This much broader study of health factors influencing cognitive performance has also identified diabetes, use of anti-cholinergic medication, use of HRT for women, poor subjectively evaluated health, appetite loss, social isolation and increasing difficulties with at least one everyday activity as being significantly associated with poor prognosis. It is interesting to note that while the ApoE4 allele does not differentiate normal and 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 taking confounding effects into account the principal risk factors for dementia emerge as being in descending order of importance ApoE4 allele, stroke, low education, IADL difficulties and age for men and IADL difficulties, ApoE4 allele, low education, and depressive symptomatology, use of anticholinergic medication and age for women.

A large number of elderly persons 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 to those who developed dementia within the four year period. Further follow-up of this cohort will allow us to differentiate pre-dementia subjects from a probably more heterogeneous group of persistent non-dementing MCI and to examine more closely the

causes of long-term cognitive impairment. Over a third of MCI subjects were observed to return to normal levels of functioning. The same proportion has been reported by a previous population study [3]. Adjusting for confounders the principal factors determining a move in this direction were seen to be lower BMI for men and absence of depression for women. In both men and women 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 both for 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 short-comings. As already mentioned above, the time to follow-up may have been too short for slowly evolving cases of dementia. Analysis according to MCI sub-type 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 the majority of subjects identified at base-line 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 which were identified and the variable health status of subjects. Subjects returning to normal may, however, be considered as 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 which have not previously been taken into account, but has also shown gender differences; notably cerebro- and cardio-vascular risk factors and diabetes for men and poor subjective health, insomnia and social isolation for

women, as well as lower rate HRT use. 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 sub-clinical depression and anticholinergic medication use in women). These factors should be taken into account in the development of gender specific clinical intervention programs for MCI.

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References

1. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Archives of Neurology 1999;56(3):303-8.
2. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Mild cognitive impairment: prevalence and predictive validity according to current approaches. Acta Neurol Scand 2003;108(2):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(9):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. Archives of Neurology 2003;60(10):1394-9.
5. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. Neurology 2001;56(1):37-42.
6. Fischer P, Jungwirth S, Zehetmayer S, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. Neurology 2007;68(4):288-91.
7. Manly JJ, Bell-McGinty S, Tang MX, Schupf N, Stern Y, Mayeux R. Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. Archives of Neurology 2005;62(11):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(7):1397-403.
9. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 1999;45(3):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(3):196-203.
11. The3CStudyGroup. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. Neuroepidemiology 2003;22(6):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. Journal of Internal Medecine 2004;256(3):240-6.
13. Artero S, Petersen R, Touchon J, Ritchie K. Revised criteria for mild cognitive impairment: validation within a longitudinal population study. Dement Geriatr Cogn Disord 2006;22(5-6):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. British Journal of Psychiatry 1973;123(575):467-70.
17. Dubois B, Touchon J, Portet F, Ousset PJ, Vellas B, Michel B. ["The 5 words": a simple and sensitive test for the diagnosis of Alzheimer's disease]. Presse Med 2002;31(36):1696-9.
18. Blair JR. Predicting premorbid IQ: a revision of the National Adult Reading Test. Clin Neuropsychol 1989;3:129-36.
19. AmericanPsychiatricAssociation. 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.
21. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. Bmj 2006;332(7539):455-9.
22. Radloff L. The CES-D Scale: a self report depression scale for research in the general population. Applied Psychological measurment 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 in Clinical Neuroscience 2004;3:333-40.
25. Azad NA, Al Bugami M, Loy-English I. Gender differences in dementia risk factors. Gend Med 2007;4(2):120-9.
26. Knopman DS, Edland SD, Cha RH, Petersen RC, Rocca WA. Incident dementia in women is preceded by weight loss by at least a decade. Neurology 2007;69(8):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. Archives of Neurology 2005;62(6):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 Suppl 2003;179:25-8.

Table 1: Differences between subjects classified as MCI at base-line and subjects without cognitive impairment both at base-line and follow-up (normal group)

	MCI subjects (n=2879)	Normal subjects (n=4013)	Significance *
Age mean (SD)	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 (blood pressure cut off 140/90 or antihypertensive treatment) %	78.6	76.5	0.04
Hypercholesterolemia (cholesterol 6.2mmol or treatment) %	59	57.2	0.15
Diabetes mellitus	11	9	<0.01
Head trauma %	7.5	7.2	0.21
All cardiovascular antecedents	10	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	10.3	<0.01
Subthreshold depression %	9.2	4.6	<0.01
Antidepressive medication use %	9.2	4.6	<0.01
APOE4 genotype (%presence)	20.6	19.5	0.29
Nart (IQ) mean (SD)	21.1 (6.5)	24.3 (5.4)	<0.01
Anticholinergic medication %	10.1	5.5	<0.01
At least 2 cups coffee/day %	65.8	67.9	0.03
Tobacco use (packet/year) mean(SD)	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	<0.01
Herpes %	30.7	30.1	0.57
Insomnia %	28.5	21.8	<0.01
BMI >27 %	35.4	31	<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	7.8	< 0.01
Anaesthesia %	34.6	32	0.02
Hospitalisation cancer %	1.4	1.6	0.54
Hormonal Replacement Therapy (past or current) women %	30.2	33	0.06

* Student T Test or Chi-deux test as appropriate

Table 2: Principal socio-demographic and clinical characteristics differentiating normal and MCI subjects at base-line adjusting for confounders (logistic regression)

Men

Variables	Significance	OR	95 % CI
Anticholinergic medication	<0.01	2.26	1.44-3.56
Depressive symptomatology	<0.01	1.69	1.27-2.25
stroke	<0.01	1.54	1.01-1.36
Diabetes	0.01	1.45	1.09-1.94
BMI>27	0.01	1.40	1.14-1.72
Age (continuous)	0.02	1.02	1.01-1.04

Results are adjusted by centre

Women

Variables	Significance	OR	95 % CI
Poor subjective health	0.04	1.55	1.02-2.37
Anticholinergic medication	0.04	1.47	1.12-1.91
IADL deficit	0.01	1.40	1.07-1.83
Depressive symptomatology	0.04	1.26	1.00-1.59
Social isolation	0.01	1.21	1.04-1.42
Insomnia	0.03	1.21	1.00-1.43

Results are adjusted by centre

Table 3: Socio-demographic and clinical characteristics of MCI subjects according to clinical status four years later (dementia, MCI, return to normal cognitive functioning)

	group 1 MCI to dementia (n=189)	group 2 MCI to MCI (n=1626)	group 3 MCI to normal (n=1064)	1 vs 3	1 vs 2	2 vs 3
Age mean (SD)	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
Hypercholesterolemia %	54.3	60.3	57.7	NS	NS	NS
Diabetes mellitus %	17.2	11	10	<0.01	0.02	NS
Head trauma %	7	7.8	7	NS	NS	NS
All Cardiovascular antecedent %	17	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	<0.01	<0.01	0.01
Subclinical depression %	18.1	13.2	10	<0.01	<0.01	<0.01
Antidepressive medication use %	19	9.7	7	<0.01	<0.01	0.01
APOE4 genotype (% presence)	32.1	21	16.7	0.01	<0.01	<0.01
Nart (IQ) mean (SD)	19.5 (7.3)	21 (6.3)	22.7 (5.8)	<0.01	<0.01	<0.01
Anticholinergic medication %	16	11	7.6	<0.01	0.04	0.01
At least 2 cups coffee/day %	58.8	66	66.7	NS	NS	NS
Alcohol use %	78.8	77.7	80.3	NS	NS	NS
Tobacco use (packet/year) mean(SD)	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	29.2	NS	NS	NS
Insomnia %	33.1	30	25.4	NS	NS	0.02
BMI >27 %	30.8	37	34.4	NS	NS	NS
Appetite loss %	23	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	36	NS	NS	NS
Hospitalisation cancer %	1.6	1.3	1.5	NS	NS	NS
Hormonal Replacement Therapy (past or current) women %	18.6	29.6	33	<0.01	0.03	NS

* Student T Test or Chi-deux test as appropriate

Table 4: Significant determinants of four-year outcome (dementia) for MCI men and women by logistic regression adjusting for confounders

Men

Variables	Significance	OR	95 % CI
APOE4 allele	<0.01	3.15	1.74-5.70
Stroke	0.02	2.84	1.17-6.85
Low education level	<0.01	2.26	1.25-4.06
IADL deficit	0.03	2.20	1.07-4.49
Age	<0.01	1.16	1.10-1.21

Results are adjusted by centre

Women

Variables	Significance	OR	95 % CI
IADL deficit	<0.01	3.51	2.09-5.89
APOE4 allele	<0.01	2.34	1.38-3.96
Low education level	<0.01	2.16	1.31-3.56
Subclinical depression	0.03	1.95	1.06-3.58
Anticholinergic medication	0.04	1.78	1.00-3.18
Age	<0.01	1.14	1.09-1.19

Results are adjusted by centre