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Leisure Activities And The Risk of Amnestic Mild Cognitive Impairment In The Elderly

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Abstract

Objective: To study the influence of leisure activity participation on risk of developing amnestic Mild Cognitive Impairment (aMCI).

Methods: We examined the relationship between baseline participation in leisure activities and risk of aMCI in a prospective cohort of 437 community-residing subjects over age 75 years, initially free of dementia or aMCI, using Cox analysis adjusted for age, sex, education, and chronic illnesses. We derived Cognitive and Physical Activity Scales based on frequency of participation in individual activities.

Results: Over a median follow-up of 5.6 years, 58 subjects developed aMCI. A one-point increase on the Cognitive (Hazard ratio (HR) 0.95, 95% CI 0.91-0.99), but not Physical Activities Scale (HR 0.97, 95% CI 0.93-1.01) was associated with lower risk of aMCI. Subjects with cognitive-activity scores in the highest (HR 0.46, 95% CI 0.24-0.91) and middle thirds (HR 0.52, 95% CI 0.29-0.96) had a lower risk of aMCI compared to subjects in the lowest third. The association persisted even after excluding subjects who converted to dementia within two years of meeting criteria for aMCI.

Conclusions: Cognitive activity participation is associated with lower risk of developing aMCI, even after excluding individuals at early stages of dementia.

INTRODUCTION

The amnestic form of MCI (aMCI), which is considered a precursor state to Alzheimer's disease, has been defined as significant memory impairment with relatively preserved general cognition and functional status in older adults without dementia, with prevalence rates varying from 1 to 7 percent in population-based studies.¹⁻⁶ Preventive approaches to slow down cognitive decline are not well established. There is increasing interest in targeting interventions at the earliest stages of cognitive decline such as aMCI, as even small effects may translate into major public health gains.⁶⁻⁸

We reported that increased participation in leisure activities was associated with lower risk of dementia as well as reduced global cognitive decline in the Bronx Aging Study.⁹ Herein, we extend these findings to examine the influence of leisure activities on the risk of developing aMCI in the same cohort. Defining the role of leisure activities will help implementation of

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future primary and secondary prevention trials to reduce the incidence of MCI and dementia in older adults.

METHODS

Study Population: The study design of the Bronx Aging Study has been described previously.⁹⁻¹² Briefly, the study enrolled English-speaking community residing subjects between 75 and 85 years of age. Exclusion criteria included severe visual or hearing loss, idiopathic Parkinson's disease, liver disease, alcoholism, or known terminal illness. Subjects were screened to rule out presence of dementia, and included if they made eight or fewer errors on the Blessed Information—Memory—Concentration test,¹³ which has a high test—retest reliability (0.86), and correlates well with Alzheimer pathology.¹⁴ The inception cohort was middle-class, Caucasian (91%), and mostly women (64%). Written informed consent was obtained at enrollment. The local institutional review board approved the study protocol. The study enrolled 488 subjects between 1980 and 1983, of whom 437 (89.5%) who were free of dementia and aMCI (as defined below) were eligible for this analysis. The study period consisted of the 21-year span from 1980 to 2001.

Clinical evaluation: Subjects were interviewed with structured questionnaires and examined by study clinicians at enrollment and at 12 to 18 monthly follow-up visits.⁹⁻¹² A family member or caregiver accompanied most subjects, or was contacted to confirm the history. However, absence of informants was not used as an exclusion criterion. Functional limitations in ten basic and instrumental activities of daily living was assessed. An extensive neuropsychological test battery was administered at each visit including the Blessed test,¹³ Wechsler IQ scales,¹⁵ Fuld object-memory evaluation test,¹⁶ and the Zung depression scale.¹⁷ We created a summary illness index (range 0 to 10) based on presence of the following medical illnesses: diabetes, hypertension, angina, cardiac failure, myocardial infarction, chronic lung disease, depression, cancer, stroke, and Parkinsons disease (diagnosed after enrollment).

Leisure activities: Leisure activities may be defined as activities that individuals engage in for enjoyment or well being which are independent of work or activities of daily living. At baseline, subjects were interviewed about participation in six cognitive activities (reading, writing, crossword puzzles, board or card games, group discussions, or playing music) and ten physical activities (tennis, golf, swimming, bicycling, dancing, group exercises, team games, walking, climbing more than two flights of stairs, and babysitting).⁹ Although we examined housework in our previous study,⁹ it was not included in this analysis as it does not meet our present definition of leisure activity. We coded self-reported frequency of participation to generate a scale with one point corresponding to participation in one activity for one day per week. For each activity, subjects received 7 points for daily participation; 4 points for participating several days per week; 1 point for weekly participation; and 0 points for participating occasionally or never. We summed activity days for each activity to generate Cognitive Activity (range 0 - 42) and a Physical Activity Scales (0 - 70).

Dementia: At study visits, subjects with suspected dementia received a diagnostic work-up, including CT scan and blood tests.⁹⁻¹² Triggers for work-up included new cognitive complaints by subjects or caregivers, study staffs' observations, Blessed test scores change of four points or more than eight errors, and worsening neuropsychological test scores. Updated criteria for dementia and subtypes were introduced after the study launch. To ensure uniformity of diagnosis, all cases in the inception cohort were reconferenced in 2001 by a neurologist and a neuropsychologist who did not participate in diagnostic conferences from 1980 to 1998, as previously described.^{9,10} The diagnosticians had access to all available information for each subject at the conference, including results of any investigations done at or following the study

visit when dementia was diagnosed. Dementia diagnosis was assigned using the Diagnostic and Statistical Manual revised third edition criteria¹⁸ and subtyped using established criteria.^{9,10}

Amnesic mild cognitive impairment: Since the concept and definitions of aMCI evolved well after our study launch and not part of the original study diagnostic procedures, we adapted current aMCI criteria to diagnose cases.²⁻⁴ Our operational criteria were retrospectively applied to each subject at each follow-up visit using all available clinical and neuropsychological information routinely collected at study evaluations, irrespective of whether subjects had triggers for the diagnostic work-up or whether or not they were evaluated for dementia. Subjects were diagnosed with aMCI if they met the following criteria: 1) does not meet criteria for dementia;¹⁸ 2) objective memory impairment defined as three or more errors on the five-item Blessed test memory phrase.¹³ This cutscore corresponds to performance at or below 1.5 SDs from the mean (1.1 ± 1.4) in this age restricted sample. The same cutscore was reported to have comparable validity with the Mini Mental State Examination as a dementia screening test in other cohorts.¹⁹ The choice of memory tests or cutscores are not specified in current criteria.²⁻⁴ 3) subjective memory complaints by the subject, which was obtained as part of the structured medical history interview by research assistants. In addition, interviewers and the study clinician recorded any memory complaints reported by the subject during the course of their evaluation. History of memory problems was corroborated by an informant when available; 4) normal general cognitive functioning defined as verbal IQ scores greater than 84 (within one standard deviation from population mean)¹⁵ and a score of less than eight on the Blessed test.^{13,20} and 5) generally preserved activities of daily living defined as being able to independently perform basic and instrumental activities of daily from our list.⁹ Functional decline was ascertained independent of decline due to physical causes or in leisure activity participation.

Statistical Analysis: Continuous measures were compared with either independent-samples t-test or Mann Whitney U test, and categorical variables with Pearson chi-squared test.²¹ We studied the association of baseline cognitive and physical activity scores, both continuously and in tertiles, with risk of aMCI using Cox proportional-hazards regression analysis to estimate hazard ratios with 95% CI.²² Subjects with prevalent aMCI were excluded. Time to event was from date of enrollment to date at which subjects met aMCI diagnosis based on clinical and neuropsychological criteria described above, or to death or final contact for controls. All models included age at enrollment, sex, education (high school or less versus college), and illnesses index as covariates. Trends of association were assessed by the regression model assigning scores (0-2) to the levels of the independent variable. The proportional hazards assumptions of the models were examined analytically and graphically and were adequately met. To confirm reliability of our definition, we examined the association of leisure activities with MCI using age adjusted cutscores on the Fuld memory test¹⁶ to define objective memory impairment while retaining the remaining criteria. We examined the effect of individual leisure activities by comparing subjects who participated several days or more per week in an activity (frequent) with subjects who participated weekly or less (rare) in the full models, adjusted for participation in other leisure activities.

MCI is a transition stage between normal aging and Alzheimers disease.¹⁻⁴ Due to the intervals between visits, we may have missed identifying aMCI in some subjects who met dementia criteria first. We conducted secondary analyses including subjects who developed dementia without first meeting aMCI criteria as cases. Subjects who meet aMCI criteria may either be in the preclinical stages of dementia or have early dementia. To account for the possibility that our operational definition may mainly identify subjects with early dementia, we conducted analyses sequentially excluding subjects in whom dementia developed within five years of meeting criteria for incident aMCI.

RESULTS

Demographics: At enrollment 51 out of 488 subjects had aMCI; of these 23 (45.1%) converted to dementia (14 Alzheimer's disease, 4 mixed Alzheimer and vascular dementia, 3 vascular dementia, and 2 other dementias). The mean annual conversion rate to dementia in subjects with prevalent aMCI was 6.7% , which is comparable to mean annual conversion rates of 7.5% in other community-based studies but lower than clinic-based samples.⁵ During 2713 person-years follow-up (mean 5.6 ± 4.1 years), 58 of the 437 eligible subjects (89.5%) developed aMCI. The mean interval from entry to aMCI was 3.3 ± 2.2 years. There were no significant group differences between the 26 aMCI cases who converted to dementia and 32 non-converters in age (79.1 vs. 78.8y), sex (62.5% vs. 57% women), prevalence of medical illnesses, and overall study follow-up (7.2 vs. 7.4 years). However, converters had higher Blessed scores at entry (2.8 ± 2.0 vs. 1.8 ± 1.1 , $p = 0.03$). Of the 437 subjects, 26 developed dementia after meeting aMCI criteria (11 Alzheimer's disease, 8 mixed Alzheimer and vascular dementia, 4 vascular dementia, and 3 other dementias) and 84 first developed dementia (43 Alzheimer's disease, 15 mixed Alzheimer and vascular dementia, 23 vascular dementia, and 3 other dementias). There was no significant difference in follow-up between the normal controls (5.4 ± 4.1 years) and incident dementia cases (5.9 ± 4.2 years). By the end of the study period, 361 subjects died, 88 dropped out (mean follow-up, 6.6 ± 4.9 years), and 20 were still active in our current study.²³

There were no significant differences in age, sex, or education between the 58 incident aMCI cases and 295 normal controls (Table 1). The 58 incident aMCI cases had lower baseline Cognitive but not Physical Activity Scale scores. While neuropsychological test scores were in the normal range, subjects who developed aMCI had lower Fuld test ($p = 0.02$) and verbal IQ scores ($p = 0.004$). The frequency of various medical illnesses was not different. The 84 subjects who developed dementia without meeting MCI criteria had lower neuropsychological and Cognitive Activity Scale scores compared to the other two groups. As previously reported in this cohort,¹² women and subjects with myocardial infarction were over represented among those who developed dementia first.

None of the individual cognitive and physical leisure activities (adjusted for participation in other activities) showed independent associations with lower risk of aMCI in the fully adjusted models.

Table 2 shows that the adjusted hazard ratio of aMCI for a one-point increase on the Cognitive Activity Scale was 0.949 (95% CI 0.910 to 0.990). Subjects with Cognitive Activity Scale scores in the highest third did not have significant differences in age, sex, or illness index compared to the other two groups. However, they had lower Blessed scores at entry (1.9 ± 1.8) compared to subjects with scores in the lower third (2.9 ± 2.4 , $p < 0.001$) but not the middle third (2.4 ± 2.0 , $p = 0.12$) of the cohort. There were no significant differences in Blessed scores between the middle and lower third. A dose response effect was seen (test for trend $p < 0.001$); the adjusted hazard ratio of aMCI for subjects with scores in the highest third on the Cognitive Activity Scale was 0.462 (95% CI 0.235 to 0.910) and for the middle third was 0.523 (95% CI 0.286 to 0.958) compared with those with scores in the lowest third (Table 2 and Figure 1). Including baseline Blessed scores in the full models slightly attenuates the association with incident aMCI for subjects in the highest (HR 0.468, 95% CI 0.231 to 0.947) and middle third (HR 0.549, 95% CI 0.297 to 1.013) compared to the lowest third.

We have reported that low leisure activity participation was associated with depression.⁹ However, the observed association between cognitive leisure activities and incident MCI remains even after adjusting for baseline depressive symptoms¹⁷ (hazard ratio 0.935, 95% CI

0.884 to 0.994) or cognitive status using Blessed scores (hazard ratio 0.957, 95% CI 0.919-0.996) in the fully adjusted models.

Of the 33 subjects who met the alternate aMCI criteria at baseline using age adjusted cutscores on the Fuld test,¹⁶ 17 (51.5%) converted to dementia. Over 1785 person-years follow-up (mean 4.9 years), 77 subjects developed aMCI using this criteria. Baseline Cognitive Activity Scale scores were associated with lower risk of developing aMCI (adjusted hazard ratio 0.958, 95% CI 0.925 to 0.993).

The Physical Activity Scale was not associated with risk of developing aMCI either overall or in tertiles (Table 2). The Physical Activity Scale was also not associated with lower risk of aMCI (adjusted hazard ratio 0.986, 95% CI 0.955 to 1.019) defined using the Fuld test.¹⁶

Influence of diagnostic criteria: Subjects who develop dementia may pass through the stage of aMCI which may be missed due to the interval between visits. When we included the 84 subjects who developed dementia without first meeting aMCI criteria as cases, the association of baseline Cognitive Activity Scale scores overall and in tertiles was strengthened (Table 2; Model 2). To account for the possibility that our operational criteria may mainly identify subjects with early dementia, we conducted secondary analyses sequentially excluding subjects who developed dementia after meeting aMCI criteria. Table 3 shows that the association between the base-line Cognitive Activity Scale scores and aMCI is significant even after the exclusion of eight subjects who developed dementia within two years of meeting aMCI criteria (adjusted hazard ratio 0.953, 95% CI 0.911 to 0.997). The direction of the association was unchanged even after excluding subjects who converted to dementia three or four years after developing aMCI.

DISCUSSION

This prospective study demonstrates that high levels of participation in cognitive leisure activities is associated with reduced risk of aMCI in community-residing older adults, initially free of MCI or dementia. A one-point increase in the cognitive activity scale score was associated with a five percent reduced risk of aMCI. The observed association remains robust even after adjusting for potential confounders such as age, sex, education, chronic illnesses, depression, and baseline cognitive status. Our results suggest a dose response effect; subjects with scores in the highest third on the cognitive-activity scale had a 54% reduced risk of developing aMCI compared to those with scores in the lowest third. This result builds on our findings of the association between participation in cognitive leisure activities and reduced risk of dementia in the same cohort,⁹ and is corroborated by similar findings with respect to dementia in other cohorts.^{24,25}

The Bronx Aging study has several limitations, as previously acknowledged.^{9,10,26} This was a community-residing volunteer cohort; Caucasians and subjects over age 75 were over-represented. Though subjects were evaluated and diagnosed using standard criteria and well-established procedures, some misclassification is inevitable. Presence of informants was not a requirement. Subjects with aMCI who did not convert to dementia had longer follow-up than converters, suggesting that differential follow-up is less likely to bias estimates. Although only 17% of the dementia cases in our cohort went to autopsy our clinical pathologic studies support the accuracy of clinical diagnoses.²⁶⁻²⁸ There is ongoing debate about current operational criteria for aMCI,¹⁻⁴ and whether subjects who meet these criteria have very early dementia or are in a true preclinical stage of dementia. Our operational criteria were applied retrospectively as the study launch predated the MCI concept, and were developed specifically to address the relationship of leisure activities with this syndrome that has been studied widely in the context of both observational studies and clinical trials.¹⁻⁶ The absence of detailed leisure activity information or shorter follow-up period may preclude a similar analysis in some more

recently established cohorts. Our previous study showed that participation in leisure activities was associated with reduced risk of both Alzheimer's disease and vascular dementia.⁹ It is likely that presence of non-amnestic forms of MCI among our reference group may have led to underestimation of effects. We attempted to control in part for their presence by conducting analyses excluding incident dementia cases. In future studies we plan to prospectively study the effect of leisure activities on different subtypes of MCI.

There is no perfect solution when retrofitting diagnostic criteria. Nonetheless, the consistency of our findings using alternate memory definitions and conversion rates in our subjects with MCI suggests we are identifying subjects at high risk of meeting incident dementia criteria. Our results remained significant even when we employed an alternative memory definition. The annual conversion rate to dementia in this cohort (6.7%) was similar to the conversion rate (6%) we reported using a cutscore of eight or more errors on the Blessed test to define cognitive impairment in another community-based volunteer sample.^{5,20} The conversion rate was similar to other but not all studies.^{1,3,5} A recent systematic review of 19 aging studies reported that the average annual conversion rates to dementia in subjects with MCI was almost double in clinic based samples (15%) compared to community based samples (7.5%).⁵ Subjects with aMCI in clinic samples are likely to be enriched with patients with early dementia, resulting in higher conversion rates.¹ We did not examine the neurobiological basis of aMCI in this retrospective study. The study launch in 1980 also precluded examination with investigational techniques such as MRI. Most subjects with prevalent MCI (78.3%) in our study converted to pure or mixed AD suggesting Alzheimer pathology alone or in combination with other neurodegenerative processes has an important role in further cognitive deterioration.

The association of leisure activities with lower risk of aMCI may reflect causal effects or confounding by measured or unmeasured variables. It is debated whether MCI represents the early pathological stages of the dementing process before clinical symptoms appear (preclinical dementia) or the earliest clinical stages of dementia.¹ A reduction of leisure activities even years before a diagnosis of MCI may reflect the undetected pathological presence of AD, given that the pathological process begins years, perhaps decades, prior to the onset of clinically-evident symptoms. We conducted a number of sensitivity analyses to address these issues. Including subjects who met criteria for dementia first during follow up strengthens the associations. As suggested by baseline differences in cognitive test scores, subjects who went on to develop dementia may already have early signs of dementia. However, the results were significant even after we excluded subjects who converted to dementia within two years of developing aMCI. We have previously reported in the same cohort that excluding subjects who developed dementia within seven years of entry to account for the effect of preclinical dementia does not attenuate the relationship between baseline Cognitive Activity Scale scores and risk of dementia in the remaining sample. The relationship between baseline CAS scores and MCI may reflect the correlation between CAS and cognitive performance. At baseline there were no significant differences in general mental status and depression scores between subjects who went on to develop aMCI and controls. However, adjusting for these variables did not significantly influence our results. Furthermore, in our⁹ and prior work²⁵ increased participation in cognitive leisure activities was associated with lower global rates of cognitive decline as well as decline on specific cognitive domains, analyzed using mixed linear models which account for baseline differences in CAS and cognitive performance. This effect is especially strong for episodic memory,^{9,25} a core diagnostic feature of both aMCI and dementia.^{2-4,18}

The preclinical onset of dementia spans many years.²⁹ We have used Bayesian and profile likelihood change point methods, which use time of dementia diagnosis as a temporal referent, to retrospectively describe the preclinical course of dementia in this cohort.²⁹ Memory decline measured by the selective reminding test accelerates about seven years before dementia

diagnosis.²⁹ Leisure activities may act at various stages on this pathway including before memory decline starts, during preclinical stages of dementia where some subjects may meet aMCI criteria, or following dementia. While the exact biological mechanisms for leisure activities have not been established, possible explanations include building cognitive reserve, reducing chronic stress, or promoting a healthy lifestyle.^{9,30,31} Enhanced cognitive reserve may help mask the earliest clinical changes of dementia.^{30,31} Alternatively, cognitive leisure activities may slow down pathological disease processes.^{32,33} In rodent models, exposure to enriched environments promoted neurogenesis³² and reduced amyloid burden in a dose related manner.³³ Although leisure activity participation may reflect health-related behavior, this does not explain our results which was limited to cognitive activities and remained significant even after adjusting for chronic illnesses.

Physical activities were not associated with reduced risk of aMCI. These results are consistent with the lack of association between physical activities and reduced risk of dementia reported in our and other cohorts.^{9,24,25} The leisure activities reflect the interests of our elderly subjects. It is likely that physical activities other than the ones we studied may have cognitive beneficial effects.³⁴ While frequency and intensity of participation may be important, we did not observe a significant dose response effect when physical activities were examined in tertiles.

Like other observational studies, our results cannot establish causal relationships. However, our findings suggest that aMCI may be targeted as an endpoint in primary prevention trials employing leisure activities. This is important given the lack of potential primary preventions for dementia,^{7,30} and the limited success in the secondary prevention of dementia in older adults with aMCI using drugs.⁶ Irrespective of whether or not decline in participation in leisure activities represents an early feature of preclinical dementia, cognitive training may have a role in slowing down further decline and should be explored in the context of future clinical trials. This view is supported by recent randomized clinical trials in both cognitively normal adults as well as patients with dementia that have shown that participation in cognitively stimulating activities slows down further cognitive decline.^{35,36}

Our findings suggest that cognitive leisure activities are associated with lower risk of developing aMCI. Prospective observational studies and clinical trials are needed to define the causal role of cognitive leisure activities in delaying the progression of cognitive decline in the elderly, establish the specific nature of the cerebral responses to leisure activities, and demonstrate the relative benefits of different types of cognitive leisure activities.

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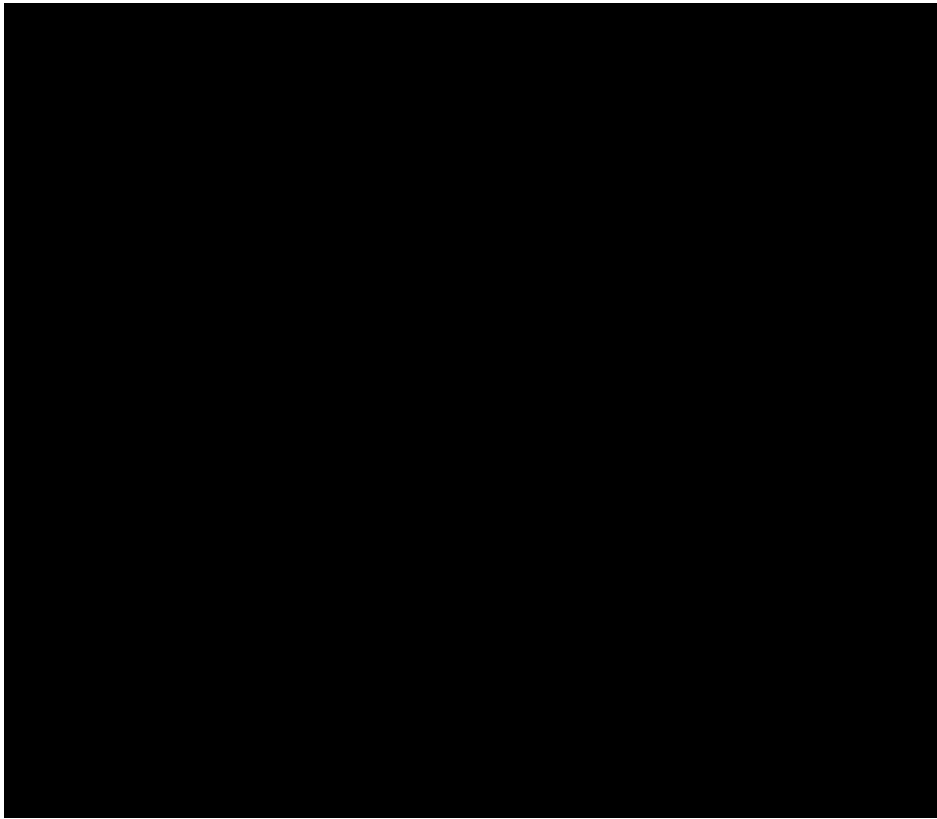


Figure 1. Kaplan-Meier curves for the cumulative risk of developing amnesic Mild Cognitive Impairment (aMCI) according to tertiles on baseline Cognitive Activity Scale (CAS) scores at enrollment; adjusted for age, sex, education, and chronic illnesses.

Table 1

Baseline characteristics as a function of cognitive outcomes. The incident dementia cases are subjects who developed dementia during follow-up without first meeting criteria for amnesic mild cognitive impairment (aMCI). Values are means with standard deviations unless otherwise specified. The p-values are for comparison of subjects who developed incident aMCI and incident dementia with normal controls.

Variable	No aMCI (n = 295)	Incident aMCI (n = 58)	Incident dementia (n = 84)
Age, years	79.0 ± 3.1	78.9 ± 2.8	79.9 ± 3.3
Women, %	64.7	58.6	69.0
Caucasian, %	89.2	89.3	89.1
High school or less education %	72.8	81.0	81.0
Functional rating (range, 10 - 30)	11.1 ± 2.2	11.1 ± 1.6	11.6 ± 2.1
Physical Activity Scale (0-77)	10.8 ± 7.5	9.8 ± 6.4	10.2 ± 7.7
Cognitive Activity Scale (0-42)	11.8 ± 6.7	9.3 ± 6.8 ^b	8.5 ± 6.1 ^b
Neuropsychological tests			
Blessed test	1.9 ± 1.8	2.3 ± 1.6	3.1 ± 2.4 ^b
Performance IQ	104.4 ± 11.7	104.4 ± 13.3	103.8 ± 12.2
Verbal IQ	112.2 ± 15.6	105.2 ± 14.4 ^b	104.2 ± 17.2 ^b
Fuld test	7.5 ± 1.2	7.1 ± 1.2 ^a	6.7 ± 1.6 ^b
Zung depression scale	46.4 ± 9.9	48.1 ± 10.9	49.7 ± 12.1
Medical illnesses (%)			
Hypertension	52.8	50.0	47.6
Myocardial infarction	13.5	8.6	17.9
Angina	26.7	22.4	27.4
Cardiac failure	28.1	32.7	25.2
Diabetes	11.5	12.1	14.3
Any cancer	12.8	12.1	9.3
Depression	7.5	8.6	7.1
Strokes	7.5	6.9	7.1
Parkinson's disease	0.7	0.0	1.2
Chronic lung disease	30.8	22.1	31.3

^a p<0.05

^b p<0.01

Table 2

Risk of amnesic Mild Cognitive Impairment (aMCI) according to the baseline scores on the Cognitive-Activity and the Physical-Activity Scales, examined for overall group as well as in tertiles. Model 1 excludes subjects who developed dementia without first meeting criteria for aMCI, and is adjusted for age, sex, education, and chronic illnesses. Model 2 includes the variables in Model 1, and also includes subjects who developed dementia without first meeting criteria for aMCI as cases.

Activity	Model 1		Model 2	
	No. of subjects with incident aMCI (total cases)	Hazard ratio for aMCI (95% CI)	No. of subjects with incident aMCI (total cases)	Hazard ratio for aMCI (95% CI)
Cognitive activity score				
One-point increment	58 (353)	0.949 (0.910, 0.990)	142 (437)	0.946 (0.921 - 0.972)
< 8 points	26 (107)	1 (reference)	73 (154)	1 (reference)
8 to 14 points	19 (146)	0.523 (0.286, 0.958)	41 (168)	0.446 (0.302, 0.660)
> 14 points	13 (100)	0.462 (0.235, 0.910)	28 (115)	0.391 (0.250, 0.609)
Physical Activity Score				
One-point increment	58 (353)	0.970 (0.933, 1.008)	142 (437)	0.985 (0.967, 1.008)
< 8 points	29 (161)	1 (reference)	71 (203)	1 (reference)
8 to 14 points	20 (114)	0.920 (0.520, 1.629)	43 (137)	0.934 (0.638, 1.387)
> 14 points	9 (78)	0.493 (0.227, 1.072)	28 (97)	0.754 (0.481, 1.183)

Table 3

Risk of amnesic mild cognitive impairment (aMCI) per 1-point increment in the baseline cognitive-activity score in 353 subjects, with the sequential exclusion of subjects in whom dementia developed during the first five years after incident mild cognitive impairment.

Analysis	Excluded subjects with aMCI No.	Subjects in whom aMCI developed	Hazard ratio (95% CI)	p-value
Overall	0	58	0.946 (0.903, 0.991)	0.022
With exclusion of subjects with aMCI who developed dementia				
Within first year	3	55	0.944(0.904,0.986)	0.009
Within two years	8	50	0.953 (0.911, 0.997)	0.035
Within three years	10	48	0.957 (0.915, 1.002)	0.059
Within four years	11	47	0.958 (0.915, 1.002)	0.063
Within five years	13	45	0.963 (0.920, 1.009)	0.110