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Subtypes of Mild Cognitive Impairment in Older Postmenopausal Women: The Women's Health Initiative Memory Study

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Abstract

Mild cognitive impairment (MCI) is a transitional state between normal cognitive functioning and dementia. A proposed MCI typology¹ classifies individuals by the type and extent of cognitive impairment, yet few studies have characterized or compared these subtypes. 447 women 65 years of age and older from the Women's Health Initiative Memory Study² were classified into the four MCI subgroups and a 'no impairment' group and compared on clinical, sociodemographic, and health variables.

82.1% of participants had a cognitive deficit in at least one domain with most (74.3%) having deficits in multiple cognitive domains. Only 4.3% had an isolated memory deficit, while 21.3% had an isolated non-memory deficit. Of the 112 women who met all MCI criteria examined, the most common subtype was amnesic multi-domain MCI (42.8%) followed by non-amnesic multiple domain MCI (26.7%), non-amnesic single domain (24.1%) and amnesic single domain MCI (6.3%). Subtypes were similar with respect to education, health status, smoking, depression and pre- and on-study use of hormone therapy.

Despite the attention it receives in the literature amnesic MCI is the least common type highlighting the importance of identifying and characterizing other non-amnesic and multi-domain subtypes. Further research is needed on the epidemiology of MCI subtypes, clinical and biological differences between them and rates for conversion to dementia.

Keywords

MCI; women; WHIMS; postmenopausal; cognition; dementia; hormone therapy

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Introduction

The prevalence of age-associated cognitive decline and dementia are increasing in developed countries as the number of older adults rises. To improve identification and treatment of dementing diseases like Alzheimer's, attention to early detection and identification of pre-dementia syndromes has intensified. Different definitions of milder forms of acquired cognitive loss in late life have been proposed including age-associated cognitive decline³, cognitive impairment-not dementia (CIND)⁴ and mild cognitive impairment (MCI)⁵, which has been the focus of much research.

MCI is considered a transitional state between normal, age-appropriate cognitive decline and dementia^{1, 6, 7}. The original Mayo MCI criteria are: a subjective report of a memory problem, an objective memory performance deficit, preserved functioning in activities of daily living (ADL), generally normal global cognitive functioning, and no dementia^{5, 8-10}. MCI so defined is associated with impaired learning and memory¹¹, hippocampal atrophy^{12, 13}, a greater than normal rate of cognitive decline,⁵ death¹⁴ and an increased risk of Alzheimer's dementia (AD)¹⁵.

One limitation of the original Mayo MCI criteria is that they fail to describe non-memory deficits or deficits occurring in multiple cognitive domains. Recently a more comprehensive typology of MCI has been proposed that classifies individuals by the type or domain of their cognitive deficit (memory vs. non-memory such as language, visuospatial, speed of processing or executive function) and the extent of their deficits (single domain vs. multiple domains). Four MCI subtypes have been proposed: Amnesic MCI-Single Domain (a-MCI-sd), Non-Amnesic MCI Single Domain (na-MCI-sd), Amnesic MCI-Multiple Domain (a-MCI-md), and Non-Amnesic MCI-Multiple Domain (na-MCI-md).^{1, 16, 17} However, there has been very limited research into the epidemiology of these subtypes in non-clinical populations and their clinical and demographic characteristics.

The Women's Health Initiative Memory Study 2 (WHIMS) is an ancillary study to the WHI Hormone Trial, a randomized, placebo-controlled, double-blind clinical trial of estrogen supplementation therapy, with or without a progestin.¹⁸ WHIMS enrolled 7,479 postmenopausal women who were 65 years of age or older. The primary outcome of WHIMS is adjudicated all-cause probable dementia (PD) with secondary endpoints of 'mild cognitive impairment' and global cognitive function. At the time WHIMS began in 1996, the Mayo criteria were not available so a classification of 'mild cognitive impairment' in WHIMS (WHIMS MCI) was applied by adjudicators to evident cognitive impairment that was less than levels considered to be indicative of PD and greater than normal aging. All WHIMS participants were screened annually for cognitive impairment with the Modified Mini Mental State (3MS) exam¹⁹ and women who scored below the pre-designated cut-point received a comprehensive clinical neuropsychiatric evaluation² and were classified as PD, WHIMS MCI or No Impairment. The data from these evaluations is used here to algorithmically classify women into one of the four MCI sub-groups or a No Impairment. Groups are then compared on sociodemographic, neurocognitive and clinical variables including hormone therapy treatment assignment. Lastly we compare our algorithmic classification to the clinical classification made in the main study.

Methods

Participants

Eligible participants were 7,479 postmenopausal women recruited into WHIMS from the 39 sites participating in the Women's Health Initiative Hormone Trials²⁰. Four hundred and

eighty-three women received the comprehensive neuropsychiatric evaluation as described below. Thirty-six women did not provide supplemental data for adjudication: 33 refused further testing, 2 were too ill to return and 1 died before testing could be conducted. A WHIMS adjudicated classification of either No Impairment or WHIMS MCI was assigned to 447 women. Probable dementia cases were excluded for this analysis. All women were between 65 and 79 years old at enrollment.

Procedures

WHIMS methodology—The WHIMS methodology has been described in detail elsewhere.^{2, 21, 22} Briefly, all WHIMS participants were administered the 3MS annually. Women scoring below pre-set standard cut points (≤ 88 for ≥ 9 years of education, ≤ 80 for ≤ 8 years) were given a complete neuropsychiatric evaluation that included the Consortium for the Establishment of a Registry for Alzheimer's Disease (CERAD) battery of neuropsychological tests^{23, 24} and standardized questions about acquired cognitive and functional impairments administered to participants and a knowledgeable friend or family member^{23–25}, and a complete clinical evaluation by a board certified dementia specialist (i.e., neurologist, geropsychiatrist, or geriatrician) plus lab tests (computerized tomography of the brain without contrast and selected blood tests). The local dementia specialists then classified each woman into one of three groups: Probable Dementia based on criteria from the Diagnostic and Statistical Manual of the American Psychiatric Association-3rd Edition²⁶, WHIMS MCI or No Impairment. All data including the clinicians' classifications were then submitted to a centralized adjudication committee consisting of dementia experts at the WHIMS Coordinating Center at Wake Forest University School of Medicine for final classification (PD, WHIMS MCI, and No Impairment). Criteria for WHIMS MCI included cognitive deficits insufficient for a classification of PD yet greater than expected for normal age-appropriate functioning

Algorithmic Classification of MCI Subtypes

For this analysis participants had to meet four MCI criteria identified by Winblad et al.¹: objective cognitive deficit(s), observed cognitive problems, the absence of an ADL impairment attributable to cognition and no dementia. Evidence of cognitive deficits was defined as a score at or below the 7th percentile (1.5 standard deviation units below the mean) of age- and education-matched norms²⁷ on the CERAD subtests measuring episodic memory (Word List Delayed Recall or Constructional Praxis Recall), verbal fluency (Category Fluency-Animals), language (Boston Naming Test-15 item version), visuo-constructive skills (Constructional Praxis), speed of mental processing (Trail Making Test, Part A), and executive functioning (Trail Making Test, Part B). Based on their cognitive test scores, participants first were placed into one of five groups characterizing their cognitive deficits: amnesic single domain (a-sd); non-amnesic single domain (na-sd); amnesic multiple domains (a-md); non-amnesic multiple domains (na-md); and no cognitive deficits (No Deficit). For a-sd group, a deficit on at least one of the memory tests and no other test was required. For na-sd group, a deficit in verbal fluency, language, visuospatial skills, speed of mental processing or executive function was required and no memory deficit. For a-md group, at least one deficit in memory plus at least one additional domain was required, and for na-md group deficits in two or more domains other than memory were required. Participants whose scores were all $> 7^{\text{th}}$ percentile were classified as No Deficit.

Observed cognitive impairment was considered present if the participant's friend or family member reported at least one of the following problems during the preceding six months: "difficulty remembering things that happened recently, in the past few hours or days;" "forgotten conversations that occurred a few hours or days earlier;" "asked the same questions repeatedly;" "forgotten to turn off the stove;" and "repeated herself more".

Participants and proxies were independently asked nine Yes/No questions about ADL deficits (bathing, grooming, feeding, dressing, preparing meals, simple household tasks, operating simple household appliances, shopping, handling money) occurring over the preceding six-month period related to their cognitive functioning. We considered ADL impairment absent if both participant and her proxy agreed that these nine functions were not impaired.

The MCI criterion that global cognitive functioning must be within the normal range was not applied in this analysis, since all women receiving a comprehensive evaluation in WHIMS had to have scored below the 3MS cut-point for normal cognitive functioning.

Other Variables

Standardized questions were used to assess other demographic (age, education), medical (perceived health status, history of stroke, hypertension or diabetes), and lifestyle variables (smoking, alcohol use) that could be related to cognitive function as well as pre-trial use of hormone therapy and WHI HT treatment assignment (HT vs. No HT). The 15-item Geriatric Depression Scale-Short Form was administered to assess depressive symptom severity.

Analysis

Women were first grouped into one of five groups by the presence and type of a cognitive deficit: a-sd, na-sd, a-md, na-md and No Deficit. The other two criteria (observed cognitive problems, the absence of ADL impairments) are reported by cognitive deficit group. To evaluate the ability of observed cognitive problems to identify women with an underlying cognitive deficit, we calculated its sensitivity, specificity and predictive power. The positive predictive power (PPP; $[\text{true positives} / (\text{true positives} + \text{false positive}) \times 100]$) is the probability that observed cognitive problems accompanies a cognitive deficit. Negative predictive power (NPP; $[\text{true negatives} / (\text{true negatives} + \text{false negatives}) \times 100]$) is the probability that the absence of observed cognitive problems is accompanied by the absence of a cognitive deficit. These indices could help clinicians decide how to weigh reports by family members regarding observed cognitive impairments. Women who met all four MCI criteria were grouped into one of four algorithmically-defined MCI subtypes: aMCI-sd, naMCI-sd, aMCI-md, or naMCI-md. A comparison No Impairment group was formed of women with no cognitive deficits, no observed cognitive problems and no ADL impairment. MCI subtypes were compared on demographic, health, lifestyle HT study group assignment and cognitive tests scores using chi-square or Fisher's Exact tests for categorical variables or Kruskal-Wallis tests for continuous variables. The significance level for pairwise comparisons, conducted with Wilcoxon tests when the overall p-value was < 0.05 , was 0.01 to adjust for multiple pairwise comparisons.

Results

Sample characteristics

The characteristics of the entire WHIMS sample have been described in detail elsewhere 21, 22, 28. The sub-sample of 447 woman with neurocognitive and clinical exam data has a mean age of 72.5 (4.0) yr., is well-educated (51 % had post-high school education), and is in good health (83% rated their health as "Good", "Very Good" or "Excellent"). Two hundred thirty-five (53 %) women of the WHIMS sample participated in the E-alone trial (54% in E-alone group, 46% placebo) and 212 women (47%) were in the E+P trial (52% in E+P group, 48% placebo).

Frequencies of each MCI criterion

All women were free of dementia meeting one of the MCI criteria¹. Table 1 shows the frequencies of women meeting each of the other MCI criteria. Of 447 women, 82.1% had a

cognitive deficit defined as scoring at or below the 7th percentile of the normative group on one or more of the neurocognitive tests. Of women with any cognitive deficit, 74.4% had deficits in multiple domains with more women (44.4%) having deficits that included memory than women with non-memory deficits (30.0 %). Only 4.4% of women with a deficit had an isolated memory deficit, while 21.3% had a single, non-memory deficit. Almost one fifth of the women (17.9%) were without deficits despite having a positive screener score.

More women (58.4%) had cognitive problems that were observable by a close friend or family member than women who did not (41.6%; 38 of the 447 women with missing proxy data were excluded). Only 60.4% (203/336) of women with a cognitive deficit were also observed to have cognitive problems (sensitivity) and 50.7% (37/73) of women without cognitive deficits also were without cognitive problems (specificity). Having an observed cognitive problem was strongly predictive of underlying deficits: PPP = 84.9% (203/239) while not having an observed cognitive problem was a poor predictor of the absence of cognitive deficits: NPP = 21.8% (37/170).

Two hundred and ninety seven women in the sample (73.7%) had no significant ADL impairments as required for a diagnosis of MCI while 106 (26.3%) had at least one reported by either the participants or a friend/family member (44 with missing ADL data were excluded). Normal ADL functioning was more common among women with a single cognitive deficit (a-sd = 86.7%, na-sd = 83.6%) than among women with multiple deficits (a-md = 66.2%, na-md = 70.2%). In the No (cognitive) Deficit group 80.3% had no ADL deficit. Women with memory deficits were about as likely to have normal ADL functioning as women with non-memory cognitive deficits (Table 1).

Frequencies of algorithmically-derived MCI subtypes

Of the 447 women, 393 had complete data and could be classified into one of the four MCI groups or the No Impairment group based on the cognitive deficit (see Table 1). One hundred and twelve women (28.5%) met all four MCI criteria and were classified into one of the four MCI groups and 32 women (8.1%) met none of the criteria and were classified as No Impairment. Of the 112 algorithmically-defined MCI cases seven women (6.3%) met criteria for the aMCI-sd subtype, 27 (24.1%) met criteria for the naMCI-sd subtype, 48 (42.9%) were classified as the aMCI-md subtype and 30 (26.8%) met criteria for the naMCI-md subtype. Thus, the proportions of women meeting criteria for each MCI subtype from the full WHIMS sub-sample of 393 were 1.8%, 6.9%, 12.2%, and 7.6%, respectively.

Agreement between Clinicians and algorithm

The overall agreement between WHIMS clinicians' classification of WHIMS MCI and the algorithm-derived classification (see Table 2) was 68.8% [(71 MCIs + 28 No Impairments / 144) × 100]. Almost all (94.7%; 71/75) of MCIs identified by clinicians were also identified by our algorithm while only 40.6% (28/69) of non-MCIs identified by clinicians were similarly classified by the algorithm. Most (91.1% = 41 of 45 cases) of the disagreements occurred when the clinician classified the individual as No Impairment while the algorithm classified her as MCI.

Neurocognitive measures at the index visit

Table 3 shows scores on the neurocognitive measures at the index visit by MCI subtype. Since classification into MCI subgroups depended in part on scores on these tests, it was expected that there would be group differences and that the No Impairment group would outperform the MCI groups. Women in the multi-domains MCI groups had significantly poorer performance ($p < 0.01$) than women with no impairment for all tests except for the Word List Delayed Recall where there were no differences between the No Impairment and the na-MCI-md group. When

compared to the No Impairment group, women in the a-MCI-sd group had significantly poorer performance ($p<0.01$) on recall tasks (Word List Delayed Recall, Constructional Praxis Recall) while those with singular, non-amnestic deficits scored significantly worse ($p<0.01$) on the Boston Naming and Trail Making Tests. Women in the a-MCI-md performed significantly worse than those in the na-MCI-md on the Word List Delayed Recall, Constructional Praxis Recall tests and better on the Boston Naming test ($p<0.01$). The scores on the WHIMS screening measure (3MS) at the index visit were not different across all groups perhaps because it was the criterion test for inclusion so thus it had a limited distribution.

Demographic and clinical characteristics of the MCI subtypes

Table 4 compares the MCI subgroups and No Impairment group on demographic and selected clinical variables. Significant group differences were found for age at randomization ($p<0.0001$) and age at the index visit ($p=0.0002$)---women in the a-MCI-md group were slightly younger than women in all other groups ($p<0.01$). A greater proportion of women in the MCI single domain subgroups drank alcohol (≥ 1 drink/day) than women in the multi-domain MCI subgroups and No Impairment group ($p=0.01$). There were no significant group differences for depressive symptoms; self-reported health status; incidence of cerebrovascular events, hypertension or diabetes; frequency of smokers, or either pre-trial or on-trial HT exposure (all $ps >0.05$).

Discussion

The recent development of a four-group MCI typology that includes amnestic and non-amnestic and single and multiple domain sub-types highlights the need for epidemiological, clinical and biological studies to characterize each subtype. This study examined the prevalence of each subtype in a sample of older women participating in a clinical trial of hormone therapy using criteria proposed by Winblad et al.¹ and compared them on demographic and clinical variables. In this sample of older women preselected on the basis of a 3MS score below study cut-point, 4 out of every 5 women had at least one cognitive deficit measured by more sensitive cognitive tests, with three quarters having deficits in multiple cognitive domains. Just over half of the sample had observable cognitive problems while over two thirds were free of ADL impairments. Of the women with cognitive deficits, 30.5% (112/367) met all three criteria and were classified into one of the MCI subgroups, while 8% of the sample met none of the criteria.

Despite its prominence in the MCI literature, the aMCI-sd subtype represented only 6% of the algorithmically defined MCI cases. This proportion is similar to estimates from other community-based samples which range between 0.05% and 6%^{29–32}. Estimates may vary across studies because of differences in samples, measures, cut-points, criteria or whether single and multiple domain amnestic groups are combined; however, prevalence estimates for the aMCI-sd subtype are consistently low. Thus, our data also reveal that most women with MCI do not meet criteria for pure amnestic MCI highlighting the importance of better characterizing other MCI subtypes and supporting the development of a multi-group MCI typology. Amnestic, multi-domain MCI was the most prevalent of all four subtypes accounting for 43% of cases. Though the number of cases is too small for sub-analyses, this subtype may offer an opportunity to pair specific cognitive deficits with underlying neuropathologies. For example, APOE epsilon4 genotype was associated only with amnestic MCI and with impaired memory function³³. Also, Jicha et al. recently reported that MCI associated with Lewy body dementia (MCI-LBD) shows a different pattern of cognitive deficits than MCI associated with Alzheimer's dementia (MCI-AD). Scores on a letter fluency task were poorer and scores on a memory task were higher in the MCI-LBD group compared with the MCI-AD³⁴.

Forty-nine percent of the women in our sample had memory deficits and over half had deficits in multiple domains rather than a single domain. Lopez et al. reported almost three times as

many multi-domain MCI cases compared with a-MCI-sd cases in the Cardiovascular Health Study Cognition Study³⁵. As we did, Manly et al. found a larger proportion of non-amnestic MCI (17%) compared to amnestic MCI (11%) and in particular to single domain amnestic MCI (5%). On the other hand, Busse et al. reported that single domain subtypes were more frequent than multiple domain subtypes in their community based sample and the prevalence of amnestic and non-amnestic subtypes did not differ³⁶. Taken together, these studies show that multiple domain MCIs appear more prevalent than single domain MCI subtypes. Given the greater emphasis in the clinical literature on the aMCI-sd subtype, multi-domain and non-amnestic single domain subtypes may be under-detected and under studied.

While 82% of our sample had cognitive deficits only 60% had cognitive problems significant enough to be observed by a friend or family member. This cannot be explained by demographic or clinical variables or exposure to HT. It suggests that these women are using a variety of cognitive, behavioral, environmental or social resources to prevent cognitive deficits from becoming cognitive impairments. Some have argued that individuals who are able to utilize a wider range of neural networks and cognitive processes possess greater *cognitive reserve* (CR) which may explain why some individuals are able to maintain cognitive function despite having neuropathologies such as Alzheimer's disease.^{37–40} Educational attainment, a common proxy for CR, was relatively high in our sample which suggests that CR may explain why some women showed no functional problems despite having cognitive deficits.

Some have argued that the inclusion of subjective reports of cognitive problems are unnecessary for identifying MCI in population-based samples²⁹ but our data suggest that it may be helpful. A high proportion (82%) of women with observed cognitive problems also had an underlying cognitive deficit. Among older post-menopausal women with some mild, global cognitive deficits (lower 3MS score) observed cognitive problems help to identify those who need a thorough clinical evaluation.

Minimal or no ADL impairments are required for a diagnosis of MCI. Since most (72%) women met this criterion it is a weaker discriminator than cognitive problems perhaps because ADLs are routine and therefore less subject to interference than more novel tasks. Nevertheless ADL problems were more common among women with more pronounced cognitive deficits, whereas the type of cognitive deficit was not associated with differential ADL impairments. This implies that a heavier overall cognitive deficit load may be more critical to ADL functioning, perhaps because ADL functioning depends on a variety of cognitive abilities.

There was moderately good agreement (69%) between clinicians and the MCI algorithm. It was not surprising that there were fewer algorithmically-determined cases of MCI than there were clinically-determined cases because the latter relied on additional sources of information and used less stringent criteria more closely resembling the CIND classifications⁴ than current MCI criteria 1. Moreover, almost all of the disagreements indicated a more lenient or less severe classification by clinicians which is in line with the more lenient WHIMS MCI criteria. The nature of the disagreements points to the significance of applying differing MCI criteria and supports efforts to refine and define MCI syndromes. Future studies will examine the comparative rates of cognitive decline and progression to dementia.

The 3MS showed very good sensitivity for identifying women with cognitive deficits documented by our neurocognitive battery—82% of WHIMS participants with a 3MS score below the cut-point had cognitive deficits in single or multiple domains based on the more sensitive measures found in the CERAD neurocognitive battery. However it did not distinguish between the four MCI subtypes, thus supporting its use only for screening but not as a diagnostic tool. Also, given the high level of education in our sample, which may reflect greater cognitive reserve, there is a likelihood that the 3MS failed to identify preclinical cases of dementia---

women with underlying AD or other neuropathologies but who do not manifest cognitive deficits sufficient to be adjudicated PD or MCI (i.e., false negatives).

The primary outcome in WHIMS was incident dementia associated with HT vs. placebo. In our original report we found a non-significant treatment effect for WHIMS MCI though there was a significant adverse effect on incident PD. Similarly in this analysis we did not find an association between HT and algorithmically-defined MCI. This suggests that HT in post-menopausal women may exert its greatest adverse effect on women with more advanced underlying neuropathology than MCI. The significant group differences for age and alcohol consumption are based on small cell sizes and are therefore difficult to interpret.

This study has several limitations. WHIMS included women participating in a clinical trial, thus the generalizability of these results is uncertain. Our findings may be limited to women with characteristics similar to those in our sample. As noted, in WHIMS only women who score below the 3MS cut-point received a full neurocognitive evaluation. Thus the MCI criteria used in this analysis are different from conventional criteria.¹⁷ It is noteworthy that at least one other study used modified criteria similar to ours and reported similar findings.¹⁰ Nevertheless this may explain why such a high proportion of women (82%) in the present sample had specific cognitive deficits. Also we relied on norms for the CERAD test battery derived from a population (i.e. Cache County, Utah residents) of unknown comparability to the WHIMS sample. However to guard against overestimates of MCI subtypes we chose conservative cut-points for cognitive tests ($\leq 7^{\text{th}}$ percentile). Strengths of the study include the use of a standardized and validated neurocognitive battery and clinical procedures, a large sample of post-menopausal women who are geographically diverse and a prospective study design.

This study examined the cognitive and behavioral deficits of a sample of non-demented, post-menopausal women who were classified into one of four MCI subgroups or a no impairment group according to newly proposed criteria. This is one of the earliest and few studies to characterize the four-group MCI typology. We documented that among women pre-screened for mild global cognitive deficits most had clinically meaningful deficits when assessed with sensitive, domain-specific neurocognitive tests and that the deficits most often involved multiple cognitive domains. Consistent with other studies, we identified only a relatively small proportion of women with the pure amnesic MCI syndrome highlighting the importance of more research into non-memory and multi-domain MCI subtypes. Future studies are needed to identify clinical and biological characteristics that distinguish subtypes, to define the epidemiology of MCI in populations of interest, and to estimate the rate of conversion to dementia.

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Reference List

1. 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 Intern Med* 2004 September;256(3):240–246. [PubMed: 15324367]
2. Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Controlled Clin Trials* 1998 December;19(6):604–621. [PubMed: 9875839]
3. Levy R. Aging-associated cognitive decline. *International Psychogeriatrics* 1994;6:63–68. [PubMed: 8054494]
4. Tuokko H, Frerichs RJ. Cognitive impairment with no dementia (CIND): longitudinal studies, the findings, and the issues. *Clin Neuropsychol* 2000 November;14(4):504–525. [PubMed: 11262720]
5. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999 March;56(3):303–308. [PubMed: 10190820]
6. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001 May 8;56(9):1133–1142. [PubMed: 11342677]
7. Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* 2005 July;62(7):1160–1163. [PubMed: 16009779]
8. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangalos EG. Aging, memory, and mild cognitive impairment. *Int Psychogeriatr* 1997;9 Suppl 1:65–69. [PubMed: 9447429]
9. Lopez OL, Becker JT, Jagust WJ, et al. Neuropsychological characteristics of mild cognitive impairment subgroups. *J Neurol Neurosurg Psychiatry* 2006 February;77(2):159–165. [PubMed: 16103044]
10. 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 October;60(10):1394–1399. [PubMed: 14568809]
11. Negash S, Petersen LE, Geda YE, et al. Effects of ApoE genotype and mild cognitive impairment on implicit learning. *Neurobiol Aging*. 2006 May 13;
12. Jack CR Jr, Petersen RC, Xu YC, et al. Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999 April 22;52(7):1397–1403. [PubMed: 10227624]

13. Pennanen C, Kivipelto M, Tuomainen S, et al. Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. *Neurobiol Aging* 2004 March;25(3):303–310. [PubMed: 15123335]
14. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology* 2002 July 23;59(2):198–205. [PubMed: 12136057]
15. Grundman M, Petersen RC, Ferris SH, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol* 2004 January;61(1):59–66. [PubMed: 14732621]
16. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001 December;58(12):1985–1992. [PubMed: 11735772]
17. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004 September;256(3):183–194. [PubMed: 15324362]
18. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Controlled Clin Trials* 1998;19:61–109. [PubMed: 9492970]
19. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry* 1987 August;48(8):314–318. [PubMed: 3611032]
20. Tractenberg RE, Patterson M, Weiner MF, et al. Prevalence of symptoms on the CERAD behavior rating scale for dementia in normal elderly subjects and Alzheimer's disease patients. *J Neuropsychiatry Clin Neurosci* 2000;12(4):472–479. [PubMed: 11083164]
21. Shumaker SA, Legault C, Rapp SR, et al. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial. *JAMA* 2003 May 28;289(20):2651–2662. [PubMed: 12771112]
22. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004 June 23;291(24):2947–2958. [PubMed: 15213206]
23. Welsh KA, Butters N, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology* 1994 April;44(4):609–614. [PubMed: 8164812]
24. Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A. Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol Bull* 1988;24(4):641–652. [PubMed: 3249766]
25. Tariot PN. CERAD behavior rating scale for dementia. *Int Psychogeriatr* 1996;8 Suppl 3:317–320. [PubMed: 9154581]
26. Diagnostic and Statistical Manual of Mental Disorders. Fourth ed.. Washington, DC: American Psychiatric Association Press; 1994. American Psychiatric Association.
27. Tschanz JT, Welsh-Bohmer KA, Skoog I, et al. Dementia diagnoses from clinical and neuropsychological data compared: the Cache County study. *Neurology* 2000 March 28;54(6):1290–1296. [PubMed: 10746600]
28. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of Estrogen Plus Progestin on Global Cognitive Function in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial. *JAMA* 2003 May 28;289(20):2663–2672. [PubMed: 12771113]
29. Fisk JD, Merry HR, Rockwood K. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology* 2003 November 11;61(9):1179–1184. [PubMed: 14610117]
30. Jungwirth S, Weissgram S, Zehetmayer S, Tragl KH, Fischer P. VITA: subtypes of mild cognitive impairment in a community-based cohort at the age of 75 years. *Int J Geriatr Psychiatry* 2005 May;20(5):452–458. [PubMed: 15852463]
31. Lopez OL, Kuller LH, Fitzpatrick A, Ives D, Becker JT, Beauchamp N. Evaluation of dementia in the cardiovascular health cognition study. *Neuroepidemiology* 2003;22(1):1–12. [PubMed: 12566948]
32. 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. *Arch Neurol* 2005 November;62(11):1739–1746. [PubMed: 16286549]

33. Knopman DS, Roberts RO, Geda YE, et al. Association of prior stroke with cognitive function and cognitive impairment: a population-based study. *Arch Neurol* 2009 May;66(5):614–619. [PubMed: 19433661]
34. Jicha GA, Schmitt FA, Abner E, et al. Prodromal clinical manifestations of neuropathologically confirmed Lewy body disease. *Neurobiol Aging*. 2008 November; %19.
35. Lopez OL, Jagust WJ, DeKosky ST, et al. Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. *Arch Neurol* 2003 October;60(10):1385–1389. [PubMed: 14568808]
36. Busse A, Hensel A, Guhne U, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology* 2006 December 26;67(12):2176–2185. [PubMed: 17190940]
37. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 2002 March;8(3):448–460. [PubMed: 11939702]
38. Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord* 2006 July;20 3 Suppl 2:S69–S74. [PubMed: 16917199]
39. Scarmeas N, Stern Y. Cognitive reserve: implications for diagnosis and prevention of Alzheimer's disease. *Curr Neurol Neurosci Rep* 2004 September;4(5):374–380. [PubMed: 15324603]
40. Roe CM, Xiong C, Miller JP, Morris JC. Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology* 2007 January 16;68(3):223–228. [PubMed: 17224578]

Table 1

Frequencies of MCI criteria.

Criterion 1: Cognitive Deficit	No	Yes				Total
		a-sd	na-sd	a-md	na-md	All
N	80 (17.9)	16 (3.6)	78 (17.4)	163 (36.5)	110 (24.6)	367 (82.1)
447						
Criterion 2: Observed Cognitive Problems						
N	73	15	74	150	97	336
409						
No (%)	37 (50.7)	5 (33.3)	36 (48.6)	52 (34.7)	40 (41.2)	133 (39.6)
170						
Yes (%)	36 (49.3)	10 (66.7)	38 (51.4)	98 (65.3)	57 (58.8)	203 (60.4)
239						
Missing	7	1	4	13	13	31
38						
Criterion 3: ADL impairment						
N	76	15	73	145	94	327
403						
No (%)	61 (80.3)	13 (86.7)	61 (83.6)	96 (66.2)	66 (70.2)	236 (72.2)
297						
[% of Total]	[15.1]	[3.2]	[15.1]	[23.8]	[16.3]	[58.4]
Yes (%)	17 (19.7)	2 (13.3)	12 (16.4)	49 (33.8)	28 (29.8)	91 (27.8)
106						
Missing	4	1	5	18	16	40
44						
MCI classification (meeting all criteria)						
	No Impairment	MCI				Total
		a-MCI-sd	na-MCI-sd	a-MCI-md	na-MCI-md	All
Overall N	73	14	72	143	91	320
393						
N	32	7	27	48	30	112
144						
(%)	(43.8)	(50.0)	(37.5)	(33.6)	(33.0)	(35.0)
[% of Total]	[8.1]	[1.8]	[6.9]	[12.2]	[7.6]	[28.5]
% of MCI cases		6.3	24.1	42.9	26.8	

Criterion 1: Cognitive Deficit	No	Yes					Total
		a-sd	Na-sd	a-md	na-md	All	
Missing	7	2	6	20	19	47	54

Notes: MCI = mild cognitive impairment; a = amnesic, na = non-amnesic. sd= single domain, md = multiple domain. Denominator for ‘% of Total’ is 447.

Table 2

Comparison of clinician and algorithm classification of MCI subtypes

Clinician Classification	Algorithm Classification		
	MCI	No Impairment	Total
MCI	71 (94.7)	4 (5.3)	75 (52.1)
No Impairment	41(59.4)	28 (40.6)	69 (47.9)
Total	112 (77.8)	32 (22.2)	144

Note: MCI = mild cognitive impairment. The percents for the second and third columns are row percents and the percents in the last column are column percents.

Table 3

Scores of neurocognitive measures at index visit, Median (Min-Max).

Cognitive test	Possible Range	No Impairment (n=32)	a-MCI-sd (n=7)	na-MCI-sd (n=27)	a-MCI-md (n=48)	na-MCI-md (n=30)	p-value ¹
3MS at index visit ²	0-88	86 (77-88)	86 (79-88)	85 (71-88)	85 (73-88)	85 (69-88)	0.94
CERAD Word List-Delayed	0-10	6 (2-10)	1.5 (0-2)	5 (2-9)	4 (0-10)	5.5 (2-8)	<0.0001
CERAD Constructional Praxis-Recall	0-11	9 (3-11)	4 (0-7)	7 (2-11)	6 (0-11)	7 (2-11)	<0.0001
CERAD Category Fluency	unlimited	14 (10-26)	14 (12-16)	12 (7-21)	12 (3-20)	11 (6-19)	0.0007
Boston Naming Test-15 item	0-15	15 (13-15)	14 (13-15)	14 (11-15)	13 (7-15)	12 (8-15)	<0.0001
Constructional Praxis	0-11	10 (9-11)	10 (9-11)	10 (6-11)	9 (4-11)	9 (7-11)	.004
Trail Making Test-Part A	0-300	45 (26-87)	43 (27-70)	53 (30-140)	60.5 (32-140)	71 (32-300)	<0.0001
Trail Making Test-Part B	0-300	113 (55-201)	128 (86-254)	148.5 (42-300)	199 (71-300)	300 (79-300)	<0.0001

Notes: MCI = mild cognitive impairment; a-MCI-sd = amnesic MCI-single domain; na-MCI-sd = non-amnesic MCI-single domain; a-MCI-md = amnesic-MCI-multiple domain; na-MCI-md = non-amnesic MCI-multiple domain.

¹ Kruskal Wallis test. Pairwise comparisons (Wilcoxon test) were performed when overall p-value is < 0.05. Significance level for pairwise comparisons is 0.01 to control for multiple comparisons.

² log-transformed

Table 4
Demographic, cognitive and clinical characteristics of algorithmically-defined MCI subtypes and No Impairment group

Variable	No Impairment (n=32)	a-MCI-sd (n=7)	na-MCI-sd (n=27)	a-MCI-md (n=48)	na-MCI-md (n=30)	p-value ^f
Age at randomization Median (min-max)	75 (65–80)	75 (66–80)	75 (66–80)	70 (65–78)	72 (66–80)	<0.0001
65–69 yr. Freq.(%)	8 (25)	1 (14)	5 (19)	25 (52)	8 (27)	
70–74	9 (28)	3 (43)	7 (26)	21 (44)	15 (50)	
75+	15 (47)	3 (43)	15 (56)	2 (4)	7 (23)	
Age at index visit Median (min-max)	78 (66–84)	79 (69–82)	77 (67–83)	73 (67–81)	75 (69–85)	0.0002
Years after enrollment of index visit Median (min-max)	2 (1–7)	3 (1–6)	2 (1–6)	2 (1–6)	3 (1–7)	0.19
> High School (Frequency, %)	12 (38)	5 (71)	15 (56)	25 (53)	15 (52)	0.43
GDS-SF total score ² Median, (min-max)	1 (0–6)	2 (0–4)	1 (0–10)	1 (0–13)	2 (0–7)	0.24
Health status (Good, Very Good or Excellent) (Frequency, %)	29 (91)	7 (100)	26 (96)	43 (90)	23 (77)	0.20
Cerebrovascular Accident (Frequency, %)	1 (3)	0	0	3 (6)	1 (4)	0.83
Hypertension (Frequency, %)	12 (39)	1 (20)	9 (35)	25 (52)	18 (60)	0.18
Diabetes (Frequency, %)	3 (9)	0	2 (7)	10 (21)	4 (15)	0.43
Alcohol use (Freq. ≥ 1 drink / day, %)	1 (3)	2 (29)	3 (11)	0	1 (3)	0.01

Variable	No Impairment (n=32)	a-MCI-sd (n=7)	na-MCI-sd (n=27)	a-MCI-md (n=48)	na-MCI-md (n=30)	p-value ¹
Smoking currently (Frequency, %)	4 (13)	0	2 (7)	1 (2)	2 (7)	0.38
Pre-trial HT use (Frequency, %)	13 (41)	3 (43)	9 (33)	17 (35)	10 (33)	0.96
On-trial HT (Frequency, %)	16 (50)	3 (43)	10 (37)	24 (50)	19 (63)	0.39

Notes: MCI = mild cognitive impairment; a = amnesic, na = non-amnesic. sd= single domain, md = multiple domain;

¹ Kruskal Wallis test. Pairwise comparisons (Wilcoxon test) were performed when overall p-value is < 0.05. Significance level for pairwise comparisons is 0.01 to control for multiple comparisons.

² The min-max possible total scores for the GDS-SF are 0–15.