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Cognitive impairment in non-1 demented oldest-old: Prevalence and relationship to cardiovascular risk factors

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Abstract

Objective—To determine the prevalence and types of cognitive impairment in a sample of non-demented aged 90 and older (the oldest-old) and to examine the relationships between cognitive impairment and cardiovascular risk factors.

Participants—420 non-demented participants from *The 90+ Study*, a study of aging and dementia in the oldest-old. Participants were categorized into four non-overlapping groups: normal cognition, amnesic mild cognitive impairment (aMCI), non-amnesic MCI (naMCI), and other cognitive impairment (OCI). History of cardiovascular risk factors was assessed through self-report.

Results—The overall prevalence of cognitive impairment in non-demented was 34.0% (95%CI: 29.5–38.5). The prevalence of OCI was highest (17.4%; 95%CI: 13.9–21.4) followed by aMCI (8.3%; 95%CI: 5.9–11.4) and naMCI (8.3%; 95%CI: 5.9–11.4). Normal cognition was present in 66.0% (95%CI: 61.2–70.5) of participants. History of hypertension and stroke were the only risk factors that varied between the groups, occurring more frequently in participants with naMCI ($\chi^2=3.82$; $p<0.05$) and OCI ($\chi^2=5.51$; $p<0.05$).

Conclusions—This study found a high prevalence of cognitive impairment in a sample of non-demented oldest-old. We did not find a strong relationship between cardiovascular risk factors and the cognitive impairment groups other than between hypertension and naMCI and stroke and OCI. Future studies comparing the incidence of dementia in these groups will ultimately determine their predictive utility in the oldest-old.

Keywords

mild cognitive impairment; oldest-old; cardiovascular risk factors

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1. Background

The prevalence and incidence of dementia are extremely high in the oldest-old, people aged 90 and older¹, with approximately twenty percent of non-demented people aged 90 or over becoming demented every year². Although the oldest-old are the fastest growing age group in the United States³ and are at the greatest risk of developing dementia, little is known about oldest-old who are not demented but have cognitive impairment.

In recent years, researchers have focused on categorizing non-demented but cognitively impaired participants into groups based on cognitive performance in order to help predict which people are most likely to develop dementia. Terms such as cognitive impairment not demented (CIND) and others have been used for this purpose^{4, 5}. However, the definitions of CIND, etc., often vary widely between studies, leading to markedly different prevalence estimates and calculations of dementia incidence^{6, 7}. Mild cognitive impairment (MCI) is perhaps the most widely used of the cognitive groupings^{8, 9}. MCI has been defined by Petersen and colleagues as: a subjective memory complaint, an objective memory impairment, preserved general cognitive function, intact activities of daily living, and no dementia¹⁰. Many researchers have further divided people with MCI into subgroups based on the specific cognitive impairment present^{11–13}. Participants with memory deficits are labeled amnesic MCI (aMCI) and those with other types of cognitive deficits are called non-amnesic MCI (naMCI). It has been suggested that participants with aMCI may be more likely to develop Alzheimer's disease whereas participants with naMCI may be more likely to develop other types of dementia (vascular, fronto-temporal dementia, etc)^{12, 14}.

The purpose of this study is to examine the prevalence and types of cognitive impairment in a sample of non-demented individuals aged 90 and older. Few studies have calculated the prevalence of cognitive impairment in this age group. Specifically this paper will present prevalence values for aMCI, naMCI, other cognitive impairment (OCI)^{13, 15}, and normal cognition. We will also examine the relationships between types of cognitive impairment and age, gender, and cardiovascular risk factors.

2. Methods

2.1 Study Population

In 1981, all residents of Leisure World, a southern California retirement community, were mailed a health survey. The residents who completed the survey (n=13,978) comprised the Leisure World Cohort study¹⁶. These participants were followed longitudinally through several follow-up surveys. All Leisure World Cohort study participants who were alive and aged 90 and older on January 1, 2003, and again on January 1, 2008, were invited to join *The 90+ Study*, a prospective study of aging and dementia in the oldest-old. As of December 31, 2008, *The 90+ Study* consisted of 1153 participants (77% female) aged 90 and older (average=94 years). Consistent with the demographics of the community from which they were recruited, *The 90+ Study* participants are predominantly Caucasian (99%) and are well educated (63% have at least some college education).

2.2 Assessments

There are several levels of participation in *The 90+ Study*: people assessed in-person, people assessed over the telephone, and people assessed through a friend or relative (by informant). Demographics, medical history, and medication information are collected from all participants or their informants. Only people who participated in-person with complete neuropsychological and neurological evaluations were eligible for the current study. A flow-chart detailing the participant inclusion criteria is shown in Figure 1. Participants in *The 90+*

Study who agree to longitudinal in-person follow-up receive a semiannual visit by trained neuropsychological testers and neurological examiners (physicians or nurse practitioners) to evaluate health, functional, and cognitive status. A self-report medical history is compiled at each visit to assess past and current medical conditions. The neurological examiners determine if the participant has any functional impairment in activities of daily living (ADLs)¹⁷ or instrumental activities of daily living (IADLs)¹⁸ due to physical or cognitive difficulties using selected items from the Functional Activities Questionnaire¹⁹. During the examination, participants receive a neuropsychological test battery including the Mini-Mental State Examination, a measure of general cognitive function²⁰ (MMSE), tests of memory (California Verbal Learning Test-II Short Form²¹; CVLT), language (Category Verbal Fluency^{22, 23}), praxis (Constructions²³), and executive function (Digit Span Backwards²⁴) among others, previously described²⁵. Sensory deficits are assessed before testing, amplifiers are provided for participants who are extremely hard of hearing, and visual stimuli are presented in size 90 boldface font to increase visibility. All procedures are approved by the Institutional Review Board at the University of California, Irvine and all participants give informed consent.

2.3 Determination of Cognitive Status

The neurological examiners determined dementia status at each visit according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria²⁶. The neurological examiners also determined functional status. For this study, requiring assistance with the task from another person due to cognitive impairment was considered “functional impairment due to cognition”. Having difficulty with the item, but still being able to perform the task independently was considered no functional impairment. Modified Petersen’s criteria for MCI¹⁰ were applied to all non-demented participants’ first visit with a complete neurological examination and neuropsychological battery. Participants were considered aMCI if they had: 1) objective memory impairment (CVLT long-delay > 1.5SD below age- and gender-specific norms), 2) normal general cognitive function (MMSE \geq 24), and 3) no functional impairment in ADLs or IADLs due to cognition. Participants categorized as aMCI could have impairment in additional cognitive domains such as language, executive function, and praxis as well. Participants were considered naMCI if they had: 1) impairment in one or more non-memory domains such as language, executive function, or praxis (animal fluency, digit span backwards, or constructions > 1.5SD below age-specific norms), 2) normal general cognitive function (MMSE \geq 24), 3) no functional impairment in ADLs or IADLs due to cognition, and 4) no memory impairment (as defined above). Although normative data for *The 90+ Study* were previously published²⁵, they were not gender specific. Therefore, the gender-specific normative data used to determine the 1.5SD cut-off scores was calculated from all non-demented participants in the current study (n=420). Subjective memory complaints were not required for MCI group inclusion in the current study. Participants were considered OCI if they had a MMSE < 24 or functional impairment in ADLs or IADLs due to cognition, or both, and thus, did not meet aMCI or naMCI criteria. Participants with OCI could have impairment > 1.5SD below age-specific norms in one or more cognitive domains. Participants were considered normal if they did not meet any of the above criteria.

2.4 Determination of Cardiovascular Risk Factors

All cardiovascular risk factor data were acquired from a self-report medical history questionnaire completed at the same visit as the neurological examination and neuropsychological testing. Participants responded “yes” or “no” to ever being diagnosed with hypertension, coronary artery disease, myocardial infarction, atrial fibrillation, congestive heart failure, stroke, transient ischemic attack, or diabetes.

2.5 Statistical analysis

All non-demented participants with a complete neurological examination and neuropsychological test battery were included in the prevalence analysis.

Demographic comparisons between the groups were made using one-way ANOVAs for continuous variables and χ^2 analyses for categorical variables. Contrasts for specific group comparisons were only performed on variables with a significant main-effect. Prevalence of cognitive impairment and normal cognition in non-demented participants was calculated by gender and age group (90–94 and 95+). Binomial 95% confidence intervals (CI) were obtained for each prevalence calculation. Logistic regression models were used to determine the effects of age and gender on the prevalence of the cognitive groups. Logistic regression models were also used to determine differences in cardiovascular risk factors between the cognitive groups. All analyses were adjusted for age, gender, and education.

3. Results

There were 420 participants who had complete in-person visits and were included in the final analysis. Basic demographic information for the participants is shown in Table 1. Gender ($\chi^2=7.65$; $p=0.05$) and MMSE total score ($F=133.44$; $p<0.01$) were the only variables that significantly differed between the groups. There was a lower proportion of women in the aMCI group than in the normal group ($\chi^2=7.52$; $p<0.01$) and a trend in the same direction in the OCI group ($\chi^2=3.94$; $p=0.06$). The MMSE total score significantly differed between all cognitive groups except aMCI and naMCI (all $p < 0.01$). While there was no significant difference between the groups by presence of an apolipoprotein E (APOE) e4 allele ($\chi^2=3.45$; *n.s.*), there was a trend towards a higher proportion of aMCI participants having an APOE e4 allele than both normal participants ($\chi^2=2.71$; $p=0.10$) and participants with OCI ($\chi^2=3.12$; $p=0.08$).

Table 2 shows the prevalence values for all cognitive groups. Two-thirds (66.0%; 95%CI=61.2–70.5) of non-demented participants were normal. The prevalence of aMCI was 8.3% (95%CI=5.9–11.4) and the prevalence of naMCI was 8.3% (95%CI=5.9–11.4). OCI was twice as common as either sub-type of MCI (17.4%, 95%CI=13.8–21.4). The majority of the 73 participants included in the OCI group had MMSE scores too low for MCI criteria (82%); the remainder had normal MMSE scores but had functional impairment due to cognitive deficits. Among OCI participants, 21.9% had impairment $>1.5SD$ in memory, and 8% had impairment $>1.5SD$ in both memory and non-memory domains.

Age-specific prevalence values and 95%CI for each cognitive group are shown in Table 2. No significant differences were found by age. We also examined prevalence by gender for each cognitive group (Table 3). There was a trend towards men being more likely to have cognitive impairment than women (OR=1.54, 95%CI: 1.00–2.38; $p=0.052$). In addition, men were more likely to have aMCI (OR=2.86, 95%CI: 1.38–5.91; $p<0.01$).

We compared self-reported cardiovascular risk factors between the cognitive groups (Table 4). Compared to participants with normal cognition, participants with aMCI, naMCI, and OCI were not significantly more likely to have a history of hypertension. However, posthoc comparisons showed that participants with naMCI were more likely to have a history of hypertension than participants with OCI ($\chi^2=3.94$; $p<0.05$) and aMCI ($\chi^2=2.82$; $p=0.09$). Participants with OCI were more likely to have a history of stroke compared to participants with normal cognition (OR=2.40, 95%CI: 1.11–5.21; $p<0.05$). There were no other differences in cardiovascular risk factors between any of the cognitive groups. Adjusting the cardiovascular analysis for presence of an APOEe4 allele reduced the number of participants

available for analysis. The significant relationship between hypertension in OCI and naMCI became non-significant, but no other results were affected.

Not included in the study were 253 non-demented participants who were not seen in-person and 67 non-demented participants who were seen in-person but did not complete the neuropsychological testing. Compared to study participants, the 253 people not seen in-person were older (93.3 years versus 95.0 years; $p<0.001$), more likely to be women (66% women versus 77% women; $p<0.01$), and more likely to have a history of congestive heart failure (9% versus 27%; $p<0.001$), stroke (10% versus 17%; $p<0.01$), and TIA (16% versus 25%; $p<0.01$). Participants not included due to lack of in-person visit did not differ from study participants in education. Compared to study participants, the 67 non-participants with an incomplete visit were older (93.3 years versus 94.3 years; $p<0.01$), more likely to be women (66% women versus 78% women; $p=0.06$) and had a lower MMSE score (26.3 versus 25.0; $p<0.01$). This group of non-participants did not differ from the study participants in education or history of any cardiovascular risk factors.

4. Discussion

In this study, we found that 34.0% of non-demented oldest-old had impaired cognition. The most common type of cognitive impairment was OCI, which was more common than both aMCI and naMCI combined. Participants with OCI were too impaired for MCI criteria (MMSE < 24, functional impairment due to cognition, or both), yet did not meet criteria for dementia. There was no significant relationship between age and cognitive impairment group. Men were more likely to have aMCI than women. We did not find many differences in cardiovascular risk factors between the cognitive groups although history of hypertension occurred more frequently in participants with naMCI and history of stroke was found more frequently in participants with OCI.

A few studies have investigated the prevalence of MCI in the oldest-old and have reported varying results. These studies had different definitions of MCI, as well as variable subject populations and sample sizes. A community-based cohort study in Italy found that 55% of non-demented nonagenarians and centenarians had MCI, but only 20 people were included in the study and the criteria for their MCI definition were not specified in the article²⁷. Researchers using data from the Mayo Oldest-Old Study, a population-based study, found that 18% of 69 non-demented participants had aMCI²⁸. Although the researchers used MCI criteria similar to the current study, a neurologist made the determination of memory impairment after a neurological examination. This is in contrast to the current study, which used a 1.5SD cut-off score on a verbal memory test to define memory impairment.

Other studies examined cognitive impairment in “older” elderly, although not specifically those over 90, but generally had relatively few people in the oldest age groups^{29–31}. Nonetheless, the prevalence of cognitive impairment in these studies was similar to the prevalence of cognitive impairment found in the current study sample. Results from these studies comparing prevalence of aMCI and naMCI have been mixed; some found higher prevalence of naMCI than aMCI^{12, 32} whereas others found the opposite^{33, 34}. In the current study, one of the first studies to report the relative prevalence of aMCI and naMCI in the oldest-old, we found aMCI and naMCI to be equally prevalent.

The other cognitive impairment group, OCI, was the largest group and included 17.4% of non-demented participants making it larger than the two MCI groups combined. While we were hesitant to define a new group of cognitively impaired individuals in the cognitive impairment literature, this group is the largest in the current study and we feel it represents a group of participants distinctly different from those with normal cognition or MCI. Other

studies have reported data from cognitive groupings similar to OCI. One population study in France used a similar definition of OCI and found a prevalence of 12.5% in a younger sample. They found that OCI was more prevalent than MCI (3.5%) and equally as predictive of future dementia¹³. Another study, which modified MCI criteria to include participants with low general cognitive functioning, found higher prevalence rates compared to traditional MCI criteria and higher dementia incidence rates¹⁵. Therefore, OCI is an important cognitive grouping in non-demented elderly in both prevalence and likelihood of developing dementia.

In the current study, we found that aMCI was more prevalent in men than in women. Studies in younger elderly subjects have found similar results. In a cross-sectional analysis of a population-based epidemiological study³⁵, researchers found that men were nearly twice as likely to have MCI than women. Another study found that men were 1.5 times as likely as women to have MCI, even after controlling for potential confounding variables such as number of comorbidities³⁶. It has long been known in the neuropsychology literature that men score lower on verbal memory tests than women^{37, 38}. This difference was accounted for in the current study by using both gender- and age-specific norms to determine the 1.5 SD cut-off scores on the CVLT. Thus, the gender difference in aMCI prevalence does not appear to merely be an artifact of the normative data. One possible explanation for the sex difference is that the duration of aMCI may be longer in men than women. This seems unlikely, however, because the incidence of dementia among non-demented oldest-old participants in our study is equal in men and women². Future studies are necessary to determine if duration differences in aMCI in the oldest-old exist between men and women. Another possible explanation for the gender difference is diagnostic bias. The only criterion in the current study that does not rely on objective test scores is the determination of functional status. Although the prevalence rates of OCI in men and women are identical (indicating that women were not placed in the OCI group rather than the aMCI group due to functional impairment), women have been shown to have a higher prevalence of overall functional disability than men in *The 90+ Study* and other studies^{39, 40}. If a gender bias exists in determination of functional status then dementia diagnoses could also be gender biased, as functional impairment is included in the DSM-IV criteria for dementia. Future studies with larger populations of participants with aMCI are needed to more completely examine these gender differences.

Previous studies hypothesized that participants with aMCI are at a higher risk of Alzheimer's disease and participants with naMCI are at a higher risk of vascular dementia^{12, 14}. Thus, we predicted that oldest-old participants with naMCI would be more likely than participants with aMCI to have a history of cardiovascular risk factors. History of hypertension was more common in naMCI than aMCI. However, other cardiovascular risk factors did not significantly differ between the groups. Several other studies have found associations between naMCI and hypertension. Data from a sample of seniors (aged 65 and older) in Manhattan found that both a history of hypertension and current hypertensive status were related to incidence of naMCI but not aMCI⁴¹. Researchers from the Canadian Study of Health and Aging found that naMCI participants with current hypertension were more likely to develop dementia in five years than those without hypertension⁴². Although we examined prevalence rather than incidence in our participants, our results concerning hypertension and naMCI converge nicely with the results of studies in younger elderly.

Although the current study did not find relationships between naMCI and most cardiovascular risk factors in the oldest-old, studies in younger elderly subjects have noted this relationship. Two studies with large groups of participants with MCI (average age 75 and 80) found that heart disease was more common in naMCI than aMCI^{34, 43}. A history of stroke has also been linked to naMCI⁴⁴ in younger age groups. Interestingly, these

relationships between naMCI and cardiovascular risk factors were not found in this study of oldest-old. One hypothesis is that the mortality associated with these risk factors is very high and the oldest-old who survive these challenges represent a different population than those who possess the risk factors at younger ages. This hypothesis is supported by the fact that we did find a relationship between naMCI and hypertension, a risk factor with a relatively low mortality rate and a risk factor that exerts its effects over many decades. However, other possibilities exist for the lack of a strong relationship between cardiovascular risk factors and naMCI, including problems associated with the use of self-report variables rather than using a medical record search. Future investigations of cardiovascular risk factors in the oldest-old and their significance to cognitive impairment and other health factors will shed more light on the current findings.

In addition to comparing cardiovascular risk factors between aMCI and naMCI, we examined cardiovascular risk factors in the OCI and normal groups as well. The only significant difference was that OCI participants were more likely to have a history of stroke compared to normal participants. This result is not surprising considering that strokes can cause cognitive impairment, sometimes severe, as well as physical impairment. Participants with low general cognitive function made up the majority of the OCI group.

A risk factor for Alzheimer's disease, APOE, was also examined in this study. Although the association between APOE e4 and dementia in the oldest-old is not clear in the literature^{45–48}, we found that the proportion of participants with an APOE e4 allele was greater in aMCI than in the other groups. The difference trended towards significance when comparing the rates in aMCI (30%) to both normal cognition (18%) and OCI (15%). The small sizes of the aMCI and naMCI groups likely kept us from finding a significant difference between these groups, however, 30% of participants with aMCI have an APOE e4 allele compared to 16% of naMCI participants. Controlling for factors related to Alzheimer's and vascular dementia such as APOE status and education in future analyses examining incident dementia in these cognitive groups will be important.

This study of cognitive impairment and cardiovascular risk factors in the oldest-old has several strengths. Given the extreme age of the participants, the size of the current study is an advantage. Previous studies with oldest-old participants estimated prevalence of cognitive impairment with much smaller populations^{27–28}. Additionally, we applied well-defined criteria for the different cognitive groupings (aMCI, naMCI, OCI). Frequently these criteria are not specified well, making comparing studies challenging.

There are several limitations of this study. First, this study did not require a subjective memory complaint for inclusion in the aMCI group. Previous studies have shown that subjective memory complaints are useful for predicting cognitive impairment and decline, especially in the oldest-old^{15, 49}. Unfortunately, a large portion of participants included in the current study did not have data concerning subjective memory complaints so this criterion was not used in the aMCI definition. Second, the participants in this study had very high levels of education. It is very likely that our sample of oldest-old is more highly educated than average for this age group, which may lead us to underestimate the level of cognitive impairment in the overall population of non-demented oldest-old. Third, while we made considerable effort to compensate for any sensory losses in vision and hearing that might compromise performance, it is possible that some participants who were classified as cognitively impaired performed poorly due to sensory loss rather than cognitive decline. Lastly, this study's requirements included an in-person visit with a complete set of neuropsychological test scores and a full neurological examination. Compared to study participants, the 253 people who were not included because they did not have an in-person visit were older, more likely to be women, and more likely to have a history of cardiac

events. Based on the information known about these non-participants, they likely would have had a greater prevalence of cognitive impairment than the participants included in the study. Also, people with an incomplete battery of tests were not included in the study. The reasons varied but frequently listed were fatigue and participant time constraints (such as requesting a short visit or having another appointment). The participants with incomplete testing were older and had lower MMSE scores. Because the people not included in this study likely had worse cognition than people included in the study, it is possible that this study has a non-participation bias causing an underestimation of the prevalence of cognitive impairment in the oldest-old.

For research purposes cognition is generally categorized into discrete states (such as normal, cognitively impaired, and demented), but the process is actually a continuum. Although none of the participants in the current study met DSM-IV criteria for dementia, it is possible that some of the participants with OCI were actually in early stages of dementia. Supporting this notion, 82% of participants in the OCI group were categorized because of low MMSE score and 18% had functional impairment due to cognition. Additionally, of the OCI participants, approximately half had cognitive impairment $>1.5SD$ in any domain. Consequently, although none of the OCI participants met DSM-IV criteria for dementia, they were more impaired than participants with aMCI and naMCI. It is likely that some of the 82% of participants with low MMSE but without function decline would have met criteria for dementia had functional decline been found. This highlights the difficulty of determining functional status in the oldest-old due to the overlap of physical and cognitive disabilities. These challenges make it possible that oldest-old participants with OCI and physical disability but without diagnosed functional decline due to cognition may represent mis-diagnosed dementia. Future studies on incidence of dementia in the oldest-old with cognitive impairment will likely reveal that participants with OCI are indeed closer to a dementia diagnosis than participants with naMCI or aMCI.

In this study, we found a very high prevalence of cognitive impairment in this sample of non-demented oldest-old. Although other studies have found associations between naMCI and cardiovascular risk factors, we found that hypertension was the only risk factor more prevalent in naMCI. We also found that participants with OCI were more likely to have a history of stroke than normal participants. Further studies of cardiovascular risk factors in the oldest-old will help elucidate the potential risks or benefits⁵⁰ to the very elderly. In order to further examine cognitive impairment in the oldest-old, future research may examine longitudinal change in neuropsychological performance. The oldest-old age group is the fastest growing in the US³. Given this statistic, the high prevalence of dementia in the oldest-old¹ combined with the high prevalence of cognitive impairment in non-demented presented in this study have wide implications for public health. The results of studies such as this one will be useful in making public health decisions regarding cognitively impaired individuals in this age group.

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REFERENCES

1. Corrada MM, Brookmeyer R, Berlau D, Paganini-Hill A, Kawas CH. Prevalence of dementia after age 90: results from the 90+ study. *Neurology*. 2008; 71(5):337–343. 7/2008. [PubMed: 18596243]

2. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest-old: The 90+ Study. *Ann Neurol*. 2010; 67(1):114–121. [PubMed: 20186856]
3. U.S. Census Bureau. [Accessed September 21, 2009] U.S. Interim Projections by Age, Sex, Race, and Hispanic Origin. 2004 Mar 18. <http://www.census.gov/ipc/www/usinterimproj/>
4. Graham JE, Rockwood K, Beattie BL, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet*. 1997 Jun 21; 349(9068):1793–1796. [PubMed: 9269213]
5. Tuokko H, Frerichs RJ. Cognitive impairment with no dementia (CIND): longitudinal studies, the findings, and the issues. *Clin Neuropsychol*. 2000 Nov; 14(4):504–525. [PubMed: 11262720]
6. DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *Lancet Neurol*. 2003 Jan; 2(1):15–21. [PubMed: 12849297]
7. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am J Geriatr Psychiatry*. 2009 May; 17(5):368–375. [PubMed: 19390294]
8. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999; 56(3):303–308. [PubMed: 10190820]
9. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001; 58(12):1985–1992. [PubMed: 11735772]
10. Petersen RC. Mild cognitive impairment: current research and clinical implications. *Semin Neurol*. 2007 Feb; 27(1):22–31. [PubMed: 17226738]
11. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Subclassifications for mild cognitive impairment: prevalence and predictive validity. *Psychol Med*. 2003 Aug; 33(6):1029–1038. [PubMed: 12946087]
12. Busse A, Hensel A, Guhne U, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology*. 2006 Dec 26; 67(12):2176–2185. [PubMed: 17190940]
13. Larrieu S, Letenneur L, Orgogozo JM, et al. Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. *Neurology*. 2002 Nov 26; 59(10):1594–1599. [PubMed: 12451203]
14. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. *Arch Neurol*. 2009 Dec; 66(12):1447–1455. [PubMed: 20008648]
15. Palmer K, Backman L, Winblad B, Fratiglioni L. Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. *Am J Geriatr Psychiatry*. 2008 Jul; 16(7):603–611. [PubMed: 18591580]
16. Paganini-Hill A, Ross RK, Henderson BE. Prevalence of chronic disease and health practices in a retirement community. *J Chronic Dis*. 1986; 39(9):699–707. [PubMed: 3734024]
17. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *JAMA*. 1963; 185:914–919. [PubMed: 14044222]
18. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc*. 1983 Dec; 31(12):721–727. [PubMed: 6418786]
19. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982 May; 37(3):323–329. [PubMed: 7069156]
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12(3):189–198. [PubMed: 1202204]
21. Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test. 2nd ed.. San Antonio, TX: Psychological Corporation; 2000.
22. Benton, AL.; Hamsher, K.; Sivan, AB. Multilingual Aphasia Examination. 3rd ed.. Iowa City, IA: AJA Associates; 1983.

23. Morris JC, Mohs R, 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; 24:641–652. [PubMed: 3249766]
24. Wechsler, D. WAIS-III Administration and Scoring Manual. San Antonio, TX: The Psychological Corporation - Harcourt Brace & Company; 1997.
25. Whittle C, Corrada MM, Dick M, et al. Neuropsychological data in nondemented oldest-old: The 90+ Study. *J Clin Exp Neuropsychol.* 2007; 29(3):290–299. 4/2007. [PubMed: 17454349]
26. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th. ed.. Washington, DC: American Psychiatric Association; 1994.
27. Pioggiosi PP, Berardi D, Ferrari B, Quartesan R, De Ronchi D. Occurrence of cognitive impairment after age 90: MCI and other broadly used concepts. *Brain Res Bull.* 2006 Jan 15; 68(4):227–232. [PubMed: 16377428]
28. Boeve B, McCormick J, Smith G, et al. Mild cognitive impairment in the oldest old. *Neurology.* 2003 Feb 11; 60(3):477–480. [PubMed: 12578930]
29. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria. Results of the Leipzig Longitudinal Study of the Aged (LEILA75+). *Br J Psychiatry.* 2003 May; 182:449–454. [PubMed: 12724250]
30. 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 Oct; 60(10):1385–1389. [PubMed: 14568808]
31. Meguro K, Ishii H, Yamaguchi S, et al. Prevalence and cognitive performances of clinical dementia rating 0.5 and mild cognitive impairment in Japan. The Tajiri project. *Alzheimer Dis Assoc Disord.* 2004 Jan-Mar; 18(1):3–10. [PubMed: 15195457]
32. Fischer P, Jungwirth S, Zehetmayer S, et al. Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology.* 2007 Jan 23; 68(4):288–291. [PubMed: 17242334]
33. He J, Farias S, Martinez O, Reed B, Mungas D, Decarli C. Differences in brain volume, hippocampal volume, cerebrovascular risk factors, and apolipoprotein E4 among mild cognitive impairment subtypes. *Arch Neurol.* 2009 Nov; 66(11):1393–1399. [PubMed: 19901172]
34. Roberts RO, Knopman DS, Geda YE, Cha RH, Roger VL, Petersen RC. Coronary heart disease is associated with non-amnesic mild cognitive impairment. *Neurobiol Aging.* 2008 Dec 15.
35. Ganguli M, Dodge HH, She C, DeKosky ST. Mild cognitive impairment, amnesic type: an epidemiologic study. *Neurology.* 2004 Jul 13; 63(1):115–121. [PubMed: 15249620]
36. Petersen RC, Roberts RO, Knopman DS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. *Neurology.* 2010 Sep 7; 75(10):889–897. [PubMed: 20820000]
37. Bleecker ML, Bolla-Wilson K, Agnew J, Meyers DA. Age-related sex differences in verbal memory. *J Clin Psychol.* 1988 May; 44(3):403–411. [PubMed: 3384968]
38. Lewin C, Wolgers G, Herlitz A. Sex differences favoring women in verbal but not in visuospatial episodic memory. *Neuropsychology.* 2001 Apr; 15(2):165–173. [PubMed: 11324860]
39. Berlau DJ, Corrada MM, Kawas C. The prevalence of disability in the oldest-old is high and continues to increase with age: findings from The 90+ Study. *Int J Geriatr Psychiatry.* 2009; 24(11):1217–1225. [PubMed: 19259982]
40. von Strauss E, Aguero-Torres H, Kareholt I, Winblad B, Fratiglioni L. Women are more disabled in basic activities of daily living than men only in very advanced ages: a study on disability, morbidity, and mortality from the Kungsholmen Project. *J Clin Epidemiol.* 2003 Jul; 56(7):669–677. [PubMed: 12921936]
41. Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. *Arch Neurol.* 2007 Dec; 64(12):1734–1740. [PubMed: 18071036]
42. Oveisgharan S, Hachinski V. Hypertension, executive dysfunction, and progression to dementia: the canadian study of health and aging. *Arch Neurol.* 2010 Feb; 67(2):187–192. [PubMed: 20142526]

43. Mariani E, Monastero R, Ercolani S, et al. Vascular risk factors in mild cognitive impairment subtypes. Findings from the ReGAI project. *Dement Geriatr Cogn Disord*. 2007; 24(6):448–456. [PubMed: 17975314]
44. 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]
45. Skoog I, Hesse C, Aevansson O, et al. A population study of apoE genotype at the age of 85: relation to dementia, cerebrovascular disease, and mortality. *J Neurol Neurosurg Psychiatry*. 1998 Jan; 64(1):37–43. [PubMed: 9436725]
46. Gessner R, Reischies FM, Kage A, et al. In an epidemiological sample the apolipoprotein E4 allele is associated to dementia and loss of memory function only in the very old. *Neurosci Lett*. 1997 Jan 24; 222(1):29–32. [PubMed: 9121715]
47. Juva K, Verkkoniemi A, Viramo P, et al. APOE epsilon4 does not predict mortality, cognitive decline, or dementia in the oldest old. *Neurology*. 2000 Jan 25; 54(2):412–415. [PubMed: 10668704]
48. Bathum L, Christiansen L, Jeune B, Vaupel J, McGue M, Christensen K. Apolipoprotein e genotypes: relationship to cognitive functioning, cognitive decline, and survival in nonagenarians. *J Am Geriatr Soc*. 2006 Apr; 54(4):654–658. [PubMed: 16686878]
49. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. *Int J Geriatr Psychiatry*. 2000 Nov; 15(11):983–991. [PubMed: 11113976]
50. Corrada, MM.; Berlau, D.; Peltz, CB.; Kawas, C. Hypertension and its association with prevalent dementia in the oldest-old. Paper presented at: Poster presentation at the 62nd Annual American Academy of Neurology Meeting; April 10 – April 17 2010; Toronto, ON, Canada.

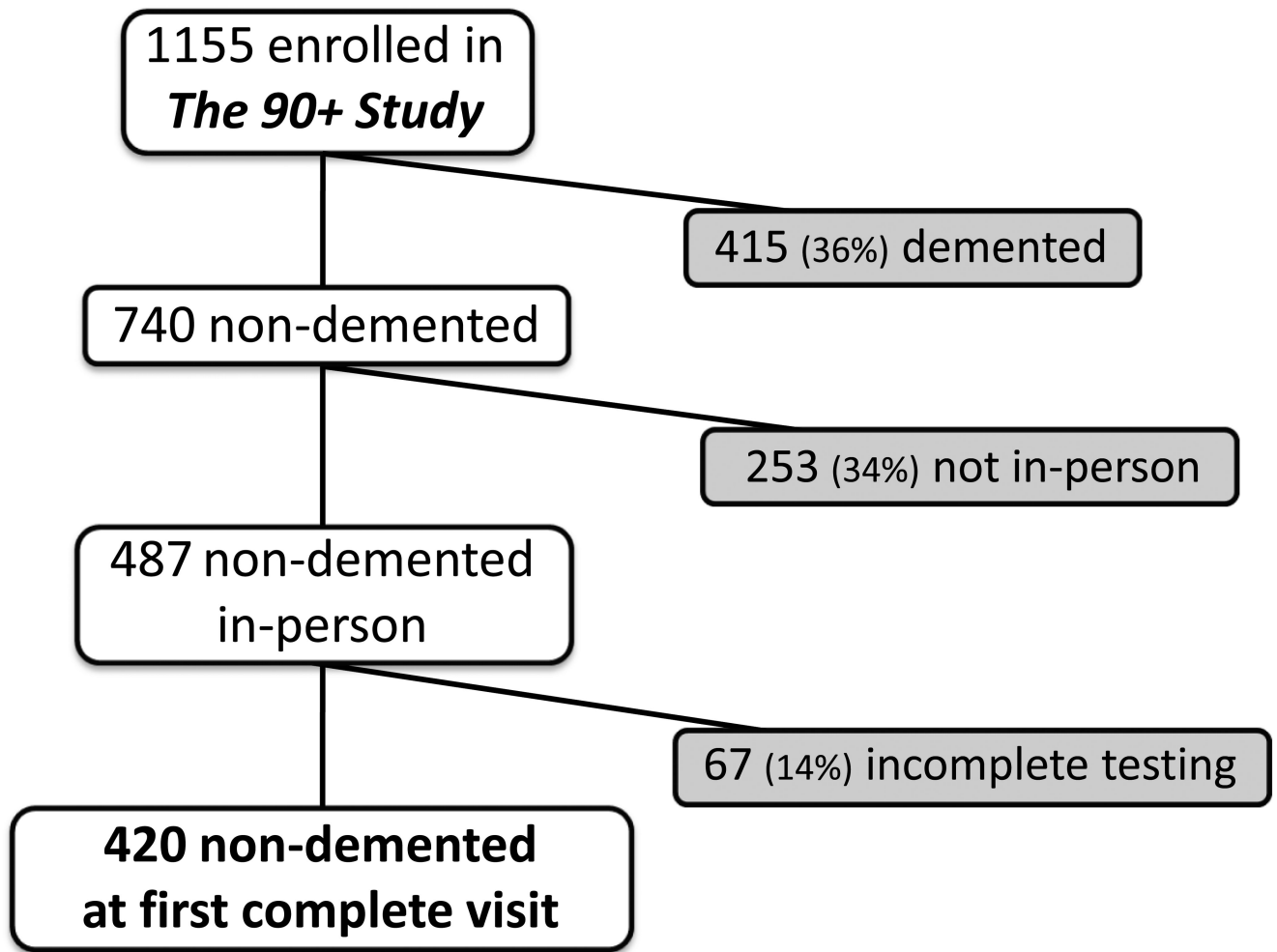


Figure 1.
Peltz: Flow Chart of Participants Included in Prevalence Study

Table 1

Participant Demographics (n=420)

Characteristics	Cognitive Groups				Total (N = 420)
	Normal (N = 277)	aMCI (N = 35)	naMCI (N = 35)	OCI (N = 73)	
Age (yrs): mean (range)	93.0 (90–101)	93.7 (90–102)	93.6 (90–100)	93.7 (90–103)	93.2 (90–103)
Women: N (%)	191 (69.0)	16 (45.7) [†]	22 (62.9)	48 (65.8)	277 (66.0)
Education: N (%)					
high school	57 (20.6)	5 (14.3)	14 (40.0)	21 (28.8)	97 (23.1)
< college graduate	91 (32.9)	16 (45.7)	9 (25.7)	20 (27.4)	136 (32.4)
college graduate	129 (46.6)	14 (40.0)	12 (34.3)	32 (43.8)	187 (44.5)
MMSE: mean (SD) [‡]	27.4 (1.7)	26.1 (1.6)	26.5 (1.9)	22.2 (2.9)	26.3 (2.8)
Genotype* APOE 4+: N (%)	45 (17.6)	9 (30.0)	5 (15.6)	10 (14.7)	69 (17.9)

aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, OCI = other cognitive impairment, MMSE = Mini-Mental State Examination, SD = standard deviation, APOE 4+ = apolipoprotein E e4 allele present

* = genotype data available on a subset of participants, n = 380; Overall APOE distribution (N's): e2e2=2, e2e3=61, e2e4=7, e3e3=248, e3e4=60, e4e4=2

[†] = $p < 0.01$ between Normal and aMCI

[‡] = $p < 0.01$ between all cognitive groups except aMCI and naMCI

Table 2

Age-Specific Prevalence of Cognitive Groups

Cognitive Group	Age Category (years)					
	90-94 (N = 308)		95+ (N = 112)		All Participants (N = 420)	
	N	Prevalence (95% CI)	N	Prevalence (95% CI)	N	Prevalence (95% CI)
Normal	208	67.5 (62.0-72.7)	69	61.6 (51.9-70.6)	277	66.0 (61.2-70.5)
aMCI	24	7.8 (5.1-11.4)	11	9.8 (5-16.9)	35	8.3 (5.9-11.4)
naMCI	26	8.4 (5.6-12.1)	9	8.0 (3.7-14.7)	35	8.3 (5.9-11.4)
OCI	50	16.2 (12.3-20.8)	23	20.5 (13.5-29.2)	73	17.4 (13.9-21.4)
All Cognitively Impaired	100	32.5 (27.3-38.0)	43	38.4 (29.0-47.0)	143	34.0 (29.5-38.5)

aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, OCI = other cognitive impairment

Table 3

Gender-Specific Prevalence of Cognitive Groups

Cognitive Group	Gender			
	Women (N = 277)		Men (N = 143)	
	N	Prevalence (95% CI)	N	Prevalence (95% CI)
Normal	191	69.0 (63.1–74.4)	86	60.1 (51.6–68.2)
aMCI	16	5.8 (3.3–9.2)	19	13.3 (8.2–20.0)*
naMCI	22	7.9 (5.0–11.8)	13	9.1 (4.9–15.0)
OCI	48	17.3 (13.1–22.3)	25	17.5 (11.6–24.7)
All Cognitively Impaired	86	31.0 (25.6–36.5)	57	39.9 (31.0–47.0)

aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, OCI = other cognitive impairment

* = $p < 0.05$ between prevalence of aMCI in men and women

Table 4

Percentage of Cardiovascular Risk History by Cognitive Group

Cardiovascular Variable	Cognitive Groups				Total
	Normal	aMCI	naMCI	OCI	
Hypertension	57.8	44.1	67.6 ^{*†}	47.9	55.8
Coronary Artery Disease	14.8	17.6	17.1	12.7	14.9
Myocardial Infarction	13.9	20.0	20.0	12.5	14.7
Atrial Fibrillation	30.7	37.5	37.5	21.3	30.1
Congestive Heart Failure	10.1	8.6	2.9	11.4	9.6
Stroke	7.8	5.7	14.0	16.7 [‡]	9.5
Diabetes	5.4	5.7	5.7	1.4	4.8
Transient Ischemic Attack	16.0	14.7	15.2	16.2	15.9

aMCI = amnesic mild cognitive impairment, naMCI = non-amnesic mild cognitive impairment, OCI = other cognitive impairment

^{*} = $p = 0.09$ between naMCI and aMCI

[†] = $p < 0.05$ between naMCI and OCI

[‡] = $p < 0.05$ between OCI and Normal