# Spectrum of Cognition Short of Dementia: Framingham Heart Study and Mayo Clinic Study of Aging

## ON LINE SUPPLEMENT / APPENDIX

## Clinical Methodology

## Mayo Clinic Study of Aging

**Participants**. The MCSA was established in 2004. Many of the details of the study design and methodology have been previously published[1-4]. This report is based on the 1969 non-demented individuals who were evaluated at the baseline visit. After the baseline assessment, participants were invited to return for follow-up evaluations every 15 months. After excluding 371 participants because of lack of follow-up or incomplete data, the analytic dataset consisted of 1598 individuals. The study protocol was approved by the Institutional Review Boards of Mayo Clinic and the Olmsted Medical Center. Each participant provided written informed consent.

**Participant evaluation.** All participants received a neurological examination and a brief mental status examination, the Short Test of Mental Status[5, 6] by a physician. Second, all participants, together with an informant whom they designated, underwent a Clinical Dementia Rating (CDR) interview[7] by nurses who had been certified on the procedure. The Functional Activities Questionnaire[8] was also completed by the informant but because this assessment was not performed in the FHS, it was not used in the current analysis. Third, all participants had neuropsychological testing.

**Neuropsychological battery.** The neuropsychological test battery consisted of subtests from the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[9] and the Wechsler Memory Scale-Revised (WMS-R)[10]. Four domains of cognitive function were evaluated: 1) **Attention/Executive function** - Trail Making Test B[11], Digit Symbol Substitution test from the WAIS-R; 2) **Language** - (Boston Naming Test[12], Category Fluency[13]; 3) **Memory** - Logical Memory-II (delayed recall) and Visual Reproduction-II (delayed recall) from the WMS-R, Auditory Verbal Learning Test [14]; and 4) **Visuospatial** - (Picture Completion and Block Design from the WAIS-R).

**Clinical diagnoses.** The consensus diagnostic process that was used allowed access to current data only; prior examination and diagnostic results were unavailable to evaluators at follow-up visits. The data for each participant were reviewed by an expert panel of physicians including the examining physician, the nurse who evaluated the participant and a neuropsychologist. The study neuropsychologists had access to raw test scores, as well as population-based, age-corrected normative values[14-16]. Diagnoses of CN, MCI or dementia were reached first individually and then by consensus[1]. A diagnosis of *normal cognition* was assigned according to published criteria[14, 17]. A consensus diagnosis of MCI was made according to published criteria: cognitive concern by a physician, patient, or nurse; impairment in 1 or more of the 4 cognitive domains; essentially normal functional activities; and not demented[17] as previously described[2-4]. A diagnosis of dementia was made according to *Diagnostic and Statistical Manual of Mental Disorders IV* criteria[18]. The distinction between MCI and dementia was influenced by performance on the objective cognitive assessments, but the principal basis for the diagnosis of dementia was whether there was "significant interference in the ability to function at work or in usual daily activities"[19]. For the present analyses, consensus diagnoses of incident dementia at follow-up visits constituted the main study endpoint. Etiological diagnoses are not the subject of the current report.

## Framingham Study

**Participants.** The Framingham Heart Study (FHS) is a longitudinal community based cohort study initiated in 1948 with the enrollment of the Original cohort of 5209 participants aged 28 to 62 years[20]. In 1971, adult children of the Original cohort and spouses of these children were invited to enroll as the Offspring cohort[21]. Participants have had serial examinations every 2-4 years, including standardized interviews, physician examinations, and laboratory testing. Surveillance for cardiovascular events, including stroke, has been in place since the study's inception, and rigorous tracking of cognitive function, including onset and diagnosis of dementia, was added in 1975. Participants who attended an examination between 1997 and 2001 (Original cohort examination 25 or 26, and Offspring cohort examination 7) were invited to return for a brain MRI study at which time they were also administered a 35-45 minute neuropsychological test battery[22, 23]. Non-demented participants aged 70-89 who were administered the neuropsychological battery between 1999 and 2005 (within 5 years of their baseline examination) comprise this study sample. The Institutional Review Board of the Boston University School of Medicine approved this study and all participants provided written informed consent.

**Neuropsychological Battery.** The neuropsychological battery administered to FHS participants has been previously described[24]. It included subtests from the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[9] and the Wechsler Memory Scale (WMS)[24]. We selected tests from this battery that permitted exploration of the four cognitive domains defined in the MCSA, using the same tests used in the MCSA where feasible. Thus we defined: 1) **Attention/Executive function** - Trail Making Test B[11] 2) **Language** - (Boston Naming Test[12] and 3) **Memory** - Logical Memory-II (delayed recall) and Visual Reproduction-II (delayed recall) from the WMS original version. The Digit-Symbol test and the Category Fluency Test are only available in subsamples of FHS participants who have been selected for annual, more intensive cognitive screening or who are enrolled as potential brain donors. None have had the Rey Auditory-Verbal Learning Test. Hence these tests were not included in the assessment of executive function, language and memory cognitive domains. Similarly, we had data on Block Design performance on only a subset of FHS participants and none had taken the Picture Completion test. Hence to assess 4) **Visuospatial** function, we used an alternative test, the Hooper Visual Organization Test[24].

**Clinical Diagnoses.** All FHS participants have been under continuous, ongoing surveillance for incident dementia and AD, and participants suspected to have cognitive decline are referred to the FHS Neurology/Dementia tracking team for further testing. There are multiple reasons for such referral including performance on the Folstein Mini-Mental Status Examination (MMSE) and functional status questionnaires that are administered at every baseline examination or on neuropsychological testing, a description of subjective memory loss or acetylcholinesterase inhibitors/memantine use, referral by self, family, FHS or participant's outside physicians, hospital and emergency room record linkage, and through annual telephone health history updates, which include a question regarding memory problems and dementia. All referred participants undergo further neuropsychological and neurological evaluation including a CDR. This is supplemented with health records, brain imaging and a structured family interview administered to one or more family members/caregivers related to the participant. Embedded in the family interview are measures of instrumental and basic activities of daily living. Records of FHS participants with clear or questionable deficits in one or more cognitive domains who were suspected to have MCI or dementia were brought to Dementia Review. Here, a panel consisting of at least 1 neurologist and 1 neuropsychologist reviews all available information to arrive at a final determination regarding the presence or absence of dementia, the date of onset of dementia, and the type of dementia. All individuals identified as having dementia satisfy DSM IV criteria. Dementia etiology was not utilized in the current analyses.

**Table e-1. Description of Participants as defined by scores < -1.5 SD, Mayo Clinic Study of Aging and Framingham Heart Study.**

| Group | All CI | All amnestic | SD amnestic | MD amnestic | All non-amnestic | SD non-amnestic | MD non-amnestic |
|---|---|---|---|---|---|---|---|
| **Mayo Clinic Study of Aging** | | | | | | | |
| **Number of Ppts** | 305 | 107 | 61 | 46 | 198 | 135 | 63 |
| **Age at visit date mean (range)** | 83.0 (79.6, 86.8) | 84.1 (80.9, 87.5) | 83.8 (81.4, 86.6) | 84.7 (80.9, 89.2) | 82.6 (78.5, 86.0) | 82.3 (77.2, 86.0) | 83.0 (80.0, 86.7) |
| **Male Sex, N (%)** | 147 (48.2) | 65 (60.7) | 40 (65.6) | 28 (54.9) | 82 (41.4) | 58 (43.0) | 24 (38.1) |
| **Education** | | | | | | | |
| **< HS Degree** | 78 (25.6%) | 25 (23.4%) | 9 (14.8%) | 17 (33.3%) | 53 (26.8%) | 34 (25.2%) | 19 (30.2%) |
| **HS Degree** | 104 (34.1%) | 35 (32.7%) | 15 (24.6%) | 22 (43.1%) | 69 (34.8%) | 46 (34.1%) | 23 (36.5%) |
| **Some College** | 54 (17.7%) | 15 (14.0%) | 11 (18.0%) | 5 (9.8%) | 39 (19.7%) | 26 (19.3%) | 13 (20.6%) |
| **College Degree** | 69 (22.6%) | 32 (29.9%) | 26 (42.6%) | 7 (13.7%) | 37 (18.7%) | 29 (21.5%) | 8 (12.7%) |
| **STMS Median (IQR)** | 31 (29, 33) | 31 (28, 33) | 32 (30, 33) | 29 (27, 32) | 31 (29, 33) | 31 (29, 34) | 29 (27, 32) |
| **CDR Global Median (IQR)** | 0 (0, 0.5) | 0.5 (0, 0.5) | 0.5 (0, 01.0) | 0.5 (0.5, 0.5) | 0 (0, 0.5) | 0 (0, 0.5) | 0 (0, 1) |
| **Framingham Heart Study** | | | | | | | |
| **Number of Ppts** | 139 | 57 | 29 | 28 | 82 | 69 | 13 |
| **Age at Visit Date, median (IQR)** | 81.4 (78.7, 84.4) | 81.2 (75.9, 85.0) | 79.9 (74.8, 83.4) | 82.5 (80.7, 85.1) | 81.6 (79.9, 84.2) | 81.2 (79.1, 84.2) | 82.7 (81.7, 86.2) |
| **Male Sex, N (%)** | 58 (41.7) | 22 (38.6) | 10 (34.5) | 12 (42.9) | 36 (43.9) | 30 (43.5) | 6 (46.2) |
| **Education** | | | | | | | |
| **< HS Degree** | 36(26%) | 21 (37%) | 8 (28%) | 13 (46%) | 15 (18%) | 12 (17%) | 3 (23%) |
| **HS Degree** | 63 (45%) | 22 (39%) | 10 (34%) | 12 (43%) | 41 (50%) | 33 (48%) | 8 (62%) |
| **Some College** | 25 (18%) | 10 (18%) | 7 (24%) | 3 (11%) | 15 (19%) | 15 (22%) | 0 (0%) |
| **College Degree** | 15 (11%) | 4 (7%) | 4 (14%) | 0 (0%) | 11 (13%) | 9 (13%) | 2 (15%) |
| **MMSE Median (IQR)** | 28 (27,29) | 27 (26,29) | 27 (27,29) | 27 (26,28) | 28 (27,29) | 29 (27,29) | 27 (26,27.5) |
| **CDR Global Median (IQR)** | 0 (0,0) | 0 (0,1) | 0 (0,0) | 0 (0,1) | 0 (0,0) | 0 (0,0) | 0 (0,0) |

single (SD); multi-domain (MD) patterns

**Table e-2. Numbers of participants with baseline low scores and numbers of incident dementia.**

| | FHS N with low scores baseline | FHS N Incident DEMENTIA | MCSA N with low scores baseline | MCSA N Incident DEMENTIA |
|---|---|---|---|---|
| Z= -0.5 | 453 | 67 | 861 | 147 |
| SD amnestic | 44 | 4 | 106 | 13 |
| MD amnestic | 199 | 47 | 389 | 102 |
| SD non-amnestic (all) | 133 | 6 | 247 | 15 |
| SD Language | 39 | 3 | 57 | 6 |
| SD Attn/Exec | 38 | 3 | 97 | 7 |
| SD Vis-spat | 56 | 0 | 93 | 2 |
| MD non-amnestic | 77 | 10 | 166 | 20 |
| Z=-1.0 | 271 | 55 | 552 | 128 |
| SD amnestic | 43 | 7 | 93 | 19 |
| MD amnestic | 78 | 30 | 162 | 61 |
| SD non-amnestic (all) | 96 | 8 | 195 | 24 |
| SD Language | 26 | 3 | 47 | 7 |
| SD Attn/Exec | 28 | 3 | 75 | 13 |
| SD Vis-spat | 42 | 2 | 73 | 4 |
| MD non-amnestic | 54 | 10 | 115 | 27 |
| Z=-1.5 | 139 | 42 | 305 | 91 |
| SD amnestic | 29 | 14 | 61 | 19 |
| MD amnestic | 28 | 11 | 46 | 24 |
| SD non-amnestic (all) | 69 | 11 | 135 | 28 |
| SD Language | 6 | 1 | 26 | 5 |
| SD Attn/Exec | 36 | 10 | 60 | 18 |
| SD Vis-spat | 27 | 0 | 49 | 5 |
| MD non-amnestic | 13 | 6 | 63 | 21 |
| Z= -2.0 | 66 | 25 | 134 | 55 |
| SD amnestic | 17 | 9 | 15 | 6 |
| MD amnestic | 7 | 4 | 12 | 9 |
| SD non-amnestic (all) | 38 | 11 | 62 | 24 |
| SD Language | 0 | 0 | 27 | 12 |
| SD Attn/Exec | 35 | 11 | 16 | 7 |
| SD Vis-spat | 3 | 0 | 19 | 5 |
| MD non-amnestic | 4 | 1 | 23 | 9 |

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