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Spatial navigation and risk of cognitive impairment: prospective cohort study

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Abstract

INTRODUCTION—Spatial navigation deficits are reported in dementia, but their temporal relationship to cognitive decline is not established.

METHODS—Prospective cohort study in 442 non-demented adults (mean age 79.9 years). Spatial navigation measured with the Floor Maze Test, and reported as immediate maze time (IMT) and delayed maze time (DMT). Pre-dementia syndromes, Mild Cognitive Impairment (MCI) and Motoric Cognitive Risk (MCR) syndromes, were primary outcomes.

RESULTS—Over a mean follow-up of 16.5 ± 13.7 months, 41 participants developed MCI and 30 MCR. In Cox models adjusted for age, sex, education, cognitive status, comorbid illnesses, and maze errors, a 10-second increment on IMT predicted incident MCI (adjusted hazard ratio [aHR] 1.25; 95% CI 1.06 to 1.48) and MCR (aHR 1.53; 95% CI 1.23 to 1.90). DMT predicted MCR but not MCI.

DISCUSSION—Spatial navigation performance predicted pre-dementia syndromes in aging, and implicates navigational impairments as an early feature in dementias.

Keywords

Incidence studies; Mild cognitive impairment syndrome; Motoric cognitive risk syndrome; cognitive tests; dementia; navigation

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Conflict of interests

Dr. Verghese and Ms. Ayers reports no disclosures. reports no disclosures. Dr. Lipton serves on the editorial board of *Neurology*, has reviewed for the NIA and NINDS, holds stock options in eNeura Therapeutics; serves as a consultant, advisory board member, or has received honoraria from Allergan, the American Headache Society, Autonomic Technologies, Boehringer-Ingelheim Pharmaceuticals, Boston Scientific, Bristol-Myers Squibb, CogniMed, CoLucid, Eli Lilly, eNeura Therapeutics, Merck, Novartis, Pfizer, Teva, and Vedanta Research.

INTRODUCTION[1]

Spatial navigation is a complex skill that involves the integration of visual, proprioceptive and vestibular inputs, and engages multiple cognitive processes such as visual perception, spatial orientation, learning, and memory.[1] Two navigational styles based on the navigator's perspective are described, egocentric and exocentric (allocentric). Egocentric navigation is body centered, relies on landmarks, and is dependent on the parietal lobes and caudate nuclei.[2] Exocentric navigation relies on mental spatial maps and activates brain networks including hippocampal regions, which are vulnerable to normal aging as well as Alzheimer pathology.[3]

Patients with dementias such as Alzheimer's disease (AD) frequently lose their way in familiar as well as unfamiliar surroundings. Spatial navigational difficulties are seen in early clinical stages of AD, and are even reported in pre-dementia syndromes such as Mild Cognitive Impairment syndrome (MCI).[4–7] Navigational impairments, especially those involving exocentric navigation, have a similar pattern in patients with MCI and AD.[7, 8] These observations suggest that spatial navigation skills may be impaired early in the course of brain diseases such as AD, and could be a marker of future clinical progression of dementias. However, longitudinal studies of the relationship of navigational skills with cognitive decline are rare.

We developed the Floor Maze Test (FMT) as a test of spatial navigation with real world applicability.[1] We reported that FMT was feasible in healthy older adults.[1] The FMT performance was correlated with cognitive status in another memory clinic sample; patients with MCI or early AD performed worse on the FMT compared to those with only subjective cognitive complaints.[8] Building on these cross-sectional FMT studies,[1, 8] we conducted a prospective cohort study in non-demented community-dwelling older adults participating in the Einstein Aging Study (EAS). Our objective was to examine the validity of spatial navigation performance on FMT for predicting future risk of developing pre-dementia syndromes or cognitive decline in nondemented older adults.

METHODS

Study Population

We undertook a prospective cohort study in the EAS.[9–12] The objective of the EAS was to identify risk factors for dementia.[9–12] Study design and methods have been reported.[10–13] In brief, potential subjects (age 70 and over) identified from population lists of Bronx County were first contacted by mail explaining the purpose and nature of the study, followed by a telephone interview that included verbal consent, medical history, and cognitive screeners.[10–12] Following the telephone interview, an age-stratified sample of subjects who matched on a computerized randomization procedure was invited for further evaluation at our research center.[10–13] Subjects returned at yearly intervals. Informed consents were

[1]**Abbreviations:** FMT: Floor maze test; IMT: Immediate maze time; DMT: Delayed maze time; MCI: Mild Cognitive Impairment syndrome; MCR: Motoric Cognitive Risk syndrome; EAS: Einstein Aging Study

obtained from participants. The local institutional review board approved the study protocols.

The FMT was implemented in EAS in June 2011. Of the 565 EAS participants seen between June 2011 and May 2015, 442 (78%) completed the FMT. Reasons for not obtaining FMT included tester unavailability (11), participant ill or non-ambulatory (75), refused (19) or missing data (2). One participant had Parkinson's disease at baseline and was excluded from this analysis. Another 5 participants with dementia 10 with MCI and MCR at baseline were excluded from the analysis. We report the 48-month study period till July 2015. Subjects who did and did not receive FMT were similar in terms of sex and education; but those who did not receive FMT were older (83.7 vs. 79.8 years, $p < 0.001$) and had worse Blessed test[14] scores (2.98 vs. 1.76, $p < 0.001$) than those who completed FMT.

Floor Maze test

As previously described,[1] we constructed a 7'x10' floor maze using yellow tape on a blue background on the floor in a large well-lit room in our research center. The maze was based on the pen and paper Porteus Maze test (extension VIII),[15] and our previous publication includes an illustration of the maze.[1] Besides the maze, the only equipment required for administering the FMT is a stopwatch. The research assistant positioned subjects at the entry point and instructed them to find their way to the exit point. A fixed 15-second planning period was given to all participants to plan their route. Using the stopwatch, the research assistant recorded the time elapsed from the end of the planning period to successful exit (Immediate Maze Time, IMT, seconds). The planning period was not included in IMT. In our previous study the planning time was the only FMT metric that was influenced by age.[1] Moreover, in our pilot studies most participants did not require unlimited planning time. The same research assistant who did the first segment timed participants as they repeated the maze after a delay of at least 10 minutes (Delayed Maze Time, DMT, seconds). No planning period was allowed for DMT. During the interim period, participants did other assessments in a separate room to avoid continued exposure to the maze. Participants received as much time as they needed for each segment of the test. Participants were instructed that they could correct any wrong turns or errors while in the maze during both segments, though the additional time taken was counted in the IMT and DMT.

Cognitive assessments

Research assistants administered an extensive neuropsychological battery to participants at baseline and annual follow-up visits under the supervision of a licensed neuropsychologist.[10–12] The Blessed Information-Memory-Concentration test[14] was used to characterize general mental status (lower scores better) as well as a covariate in our analyses.[10–12] To examine the effect of FMT on decline in specific cognitive domains as secondary outcomes, we focused on three cognitive tests from the EAS battery that assessed the 'attention and executive function' domain that was linked with FMT performance at cross-section[1]: Trail making test version A (visual attention and motor speed) and version B (visual attention and mental flexibility) as well as the Digit symbol substitution test (speed of processing, visual attention and executive function).[10, 11] We also examined free recall scores on the Free and cued selective reminding test (episodic memory) that was predictive of dementia in the EAS.

[9] The administration, reliability, validity and normative data for the EAS neuropsychological battery have been described.[10, 11] [12]

During the short follow-up period, there were only 6 incident dementia cases diagnosed at consensus case conferences attended by study clinicians and neuropsychologist using Diagnostic and Statistical Manual fourth edition criteria.[10, 13] Hence, we focused on studying the association of baseline FMT performance with risk of developing pre-dementia syndromes, MCI and Motoric Cognitive Risk syndrome (MCR), that were previously reported to be associated with high risk of converting to dementia in the EAS[11, 13] as well as in other cohorts.[16] We examined both MCI and MCR as our primary outcomes as we wanted to capture a wide pool of individuals at risk for dementia. There was only partial overlap (39%) in individuals who meet criteria for both MCI and MCR in a previous multi-country study involving over 26,000 older adults.[17] Furthermore, MCR predicted dementia even after accounting for overlap with MCI in over 5000 individuals from EAS and other cohorts.[13, 17] We defined ‘incident major cognitive impairment’ as developing any one of incident MCI or MCR over study follow-up.

MCI and MCR diagnostic procedures in EAS have been described.[11, 13, 18] In brief, non-demented participants with subjective cognitive complaints (assessed using the 15-item Consortium to Establish a Registry for Alzheimer's Disease questionnaire, a memory question on the Geriatric depression scale,[19] or self-report on clinician’s interview)[20] but without functional limitations (assessed by a scale developed for assessing function in community-residing older adults[21] and study clinicians’ interviews) were classified as amnestic MCI if the memory domain was impaired (1.5 standard deviation (SD) below age-adjusted mean on free recall scores) or non-amnestic MCI if there was impairment on non-memory domains (1.5 SD below age-adjusted means on non-memory tests as previously described in EAS).[11, 22] As many EAS participants lived alone,[20] informant reports were not solely used to define subjective cognitive complaints.[18] MCR builds on MCI operational definitions,[23, 24] substituting the cognitive impairment criterion with slow gait and retaining the remaining criterion. Slow gait defined as gait speed one SD or more below age and sex appropriate mean values established in EAS,[18, 25] and the slow gait cutscores were reported in our previous MCR incidence study in EAS.[18] Unlike MCI, diagnosis of MCR does not require cognitive tests.[13, 17, 18] Dementia diagnoses were assigned based on established criteria at consensus case conferences attended by the study clinicians and neuropsychologist after reviewing clinical and neurological assessments as well as neuropsychological test scores.[10, 12, 13] All cognitive diagnoses were assigned blinded to FMT performance.

Covariates

Data collected at each visit from subjects and caregivers included sociodemographic variables (age, sex, and education), medications, depressive symptoms,[19] and activities of daily living.[21] Presence of diabetes, heart failure, hypertension, angina, myocardial infarction, depression, stroke, chronic obstructive lung disease, and arthritis was used to calculate a summary comorbidity index. Additional sources consulted included medical records and primary care providers.

Data analysis

Baseline characteristics were compared with descriptive statistics, applying non-parametric tests as appropriate. Cox proportional-hazards models adjusted for age, sex, education, Blessed test score, Global Health Scale scores and number of errors on FMT were used to compute adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for developing MCR, MCI or major cognitive impairment (the first instance of either MCI or MCR) based on baseline FMT performance. IMT and DMT are reported in 10-second increments to derive clinically relevant estimates. Errors on FMT resulted in increased time to complete IMT and DMT segments. However, FMT errors on both of the segments were not predictive of the study outcomes in our analyses, and were not reported as predictors but were included as covariates in all analyses. We examined FMT measures in tertiles (highest vs. lowest) to account for dose response effects. The difference between IMT and DMT was also examined as a measure of learning and to control for the effect of gait speed on our outcomes. Time to event was from baseline to visit at which pre-dementia syndrome was diagnosed or to final study contact, whichever came first. The eligible sample did not include any individuals with dementia at baseline. In addition, prevalent cases of pre-dementia syndromes were also excluded; prevalent cases of MCI and MCR were excluded from analyses examining incident MCI and incident MCR as outcomes, respectively. Prevalent cases of both MCI and MCR were excluded from the analysis with incident major cognitive impairment as the outcome. For the major cognitive impairment analysis, time to event was censored at the first instance of MCI or MCR on follow-up.

While MCR predicted dementia even after accounting for overlap with MCI in EAS and other cohorts,[13, 17] we conducted a sensitivity analysis to account for the influence of MCI diagnosis on FMT associations with MCR. We excluded individuals from the incident MCR analysis with either prevalent or incident MCI (diagnosed before incident MCR). We considered the possibility of diagnostic misclassification by repeating the incident major cognitive impairment analysis excluding those who were diagnosed in the first year of follow-up. Finally, we assessed if navigation performance was an early marker of cognitive decline compared to other conventional cognitive tests. All models reported were adjusted for the Blessed test scores[14] to account for baseline general mental status in this nondemented sample. In order to examine whether spatial navigational deficits were an early feature in dementia compared to other conventional cognitive tests, we also adjusted the full model (including the Blessed scores) for performance on the executive function and memory tests, which are reported to predict dementia in EAS and other cohorts.[9] Proportional hazards assumptions of all models were examined analytically and graphically and were adequately met.

Linear mixed effects models controlled for age, sex, and education were used to determine whether spatial navigation assessed by FMT (IMT and DMT were independent variables) was related to decline on the selected cognitive domains (secondary outcome).[26] These secondary analyses were meant to examine decline in individual cognitive domains implicated in early stages of various dementia syndromes.[10–12] To allow the entry point to vary across individuals, a random intercept was included in the model. ‘Time’ represents average rate of change in cognitive test performance over time. An interaction between FMT

measures and 'time' was included to model the effect of FMT performance on rate of change in cognitive function on the individual tests. Model assumptions were examined graphically and analytically, and were adequately met.

RESULTS

Study population

Table 1 shows that the mean age of the participants was 79.9 years, majority were women (62%), and a mean of 2.1 medical illnesses. All eligible participants completed FMT with an improvement in time to complete task from IMT (31.3 seconds) to DMT segments (23.3 seconds). There was a very low error rate on IMT (0.25 errors/ person) and DMT segments (0.18 errors/person) in this non-demented sample. The mean interval between the IMT and DMT segments was 17 ± 6 minutes. There were no adverse events during FMT.

Pre-dementia syndromes

Over a mean follow-up of 16.5 ± 13.7 months, there were 41 incident MCI (19 amnestic and 22 non-amnestic) and 30 incident MCR cases. Table 2 shows that IMT predicted incidence of MCI (aHR per 10-seconds 1.25, 95% CI: 1.06–1.48) and MCR (aHR per 10-seconds 1.53, 95% CI: 1.23–1.90). The association of IMT with MCI was explained by its association with incident non-amnestic MCI (p=0.002) and not with incident amnestic MCI (p = 0.944) (Table 2). DMT did not predict MCI, though the association was significant for MCR (p = 0.028).

When examined in tertiles, participants with IMT scores in the highest tertile (worse performance) were at increased risk of developing MCI overall (aHR 2.84, 95% CI: 1.15–7.09, p = 0.024), non-amnestic MCI (aHR 7.00, 95% CI: 1.67–29.38, p = 0.008) and MCR syndromes (aHR 6.06., 95% CI: 2.19–16.79, p = 0.001) compared to those in the lowest tertile. DMT scores in the highest tertile also predicted MCI overall (aHR 2.38, 95% CI: 1.01–5.60, p = 0.047), non-amnestic MCI (aHR 5.26., 95% CI: 1.33–20.80, p = 0.018) and MCR syndromes (aHR 6.62., 95% CI: 2.17–20.15, p = 0.001) compared to those in the lowest tertile. Neither IMT nor DMT predicted amnestic MCI.

Table 2 shows that the difference between IMT and DMT was associated with a decreased risk of MCI overall (aHR per 10-seconds difference 0.76, 95% CI: 0.62–0.94), non-amnestic MCI (aHR per 10-seconds difference 0.81, 95% CI:0.69–0.94) and MCR syndromes (aHR per 10-seconds difference 0.76, 95% CI: 0.59–0.98,), but not amnestic MCI.

In sensitivity analysis, excluding cases of prevalent and incident MCI, DMT (aHR per 10-seconds 2.13, 95%CI: 1.30–3.51, p = 0.003) predicted incident MCR, and a borderline association for IMT was noted (aHR per 10-seconds 1.30, 95%CI: 0.98–1.73, p = 0.069). In the full models that were additionally adjusted for memory performance using free recall scores, IMT predicted both MCI (aHR per 10-seconds 1.28, 95%CI: 1.09–1.50, p = 0.003) and MCR (aHR per 10-seconds 1.53, 95%CI: 1.23–1.89, p<0.001). IMT remained significant predictor of both MCR and MCI when also adjusted for baseline performance on the three selected executive function tests . For instance, after adjusting for baseline Digit

symbol substitution test scores in our models, IMT still predicted MCI (aHR 1.23; 95% CI 1.05–1.46, p = 0.013) as well as MCR (1.45, 95% CI 1.16–1.81, p = 0.001).

Both IMT (p = 0.006) and DMT (p = 0.006) predicted incident major cognitive impairment (Table 2). While there were 6 incident dementia cases diagnosed over follow-up; four met criteria for incident MCI and the remaining two met criteria for incident MCR on earlier visits before the visit at which dementia was diagnosed. To account for any diagnostic misclassification, we repeated this analysis excluding the 14 incident major cognitive impairment cases that were diagnosed in the first year following the baseline FMT measurement. IMT (aHR 1.24, 95% CI 1.03–1.49, p = 0.026) but not DMT (aHR 1.28, 95% CI 0.92–1.79, p = 0.148) predicted major cognitive impairment occurring more than one year after the baseline.

Cognitive domains

Table 3 shows the relationship (two-way interaction term) of IMT and DMT segments on FMT with decline on the four selected cognitive tests. IMT predicted decline on Trail making Test version A but not on the remaining tests. DMT predicted decline on two out of the three selected executive function tests (Trail making test versions A and B) but not on the Digit symbol substitution test. Neither IMT nor DMT predicted memory decline.

Discussion

Our findings show that spatial navigation performance in a cohort of non-demented community-dwelling older adults predicts the development of pre-dementia syndromes associated with high risk of converting to dementia. The IMT segment of the FMT was a stronger predictor of pre-dementia syndromes than DMT. IMT predicted incidence of MCI and MCR; a ten second increase in IMT on the FMT was associated with a 25% increased risk of developing MCI and a 53% increased risk of developing MCR. DMT predicted risk of developing MCR and major cognitive impairment as well as decline in two out of the three tests chosen to examine the various cognitive processes classified under the rubric of attention and executive function. In particular, the FMT predicted decline in Trail making tests, which assesses visual attention, mental flexibility and motor speed processes that are essential for successful navigation.[1] Our findings also indicate a dose response effect; worst performers on both FMT measures (highest tertile) had an over two-fold increased risk of developing MCI and over six-fold increased risk of developing MCR compared to the best FMT performers (lowest tertile).

IMT on the FMT predicted incidence of pre-dementia syndromes even after accounting for performance on conventional memory and non-memory tests as well as other confounders including gait speed that have been previously reported to predict dementia in the EAS and other cohorts;[9, 26] supporting the occurrence of spatial navigational deficits as an early feature in dementia. The association of spatial navigation with pre-dementia syndromes is also supported by previous cross-sectional clinical, neuroimaging and biomarker studies.[3–5, 7, 8, 27] For instance, in a key series of studies, Czech researchers examined spatial navigation using a human version of the Morris water maze.[5] Participants were asked to mark an invisible target inside a small blue velvet covered circular arena.[5, 6] They learned

the location of the target spot on a map of this human maze earlier.[5, 6] Both egocentric (relative to starting position) and exocentric navigation (relying on markers on the chamber wall for guidance) were examined.[5, 6] Participants with MCI performed worse on tests involving exocentric navigation in this human variant of the maze task.[6] Spatial navigation performance in this human maze was associated with right hippocampal volume in participants with amnestic MCI.[2]

While it is tempting to consider FMT a marker of risk for non-Alzheimer dementia based on its predictive validity for non-amnestic MCI and decline in executive function, further study is warranted. FMT performance in this cohort also predicted MCR, which was reported to convert to vascular dementia in the EAS[13] and to AD in other cohorts.[17] FMT predicted decline in Trail making tests in our study. Trail making test B was reported to predict MCI conversion to dementia and AD[28, 29] as well as predicted cognitive decline in older adults with subjective cognitive complaints.[30] Specific gene variants such as APOE and TOMM40 genotypes that are associated with increased risk of developing AD were reported to influence exocentric but not egocentric navigation in older adults with amnestic MCI.[31, 32] Neuroimaging studies indicate that exocentric navigation relies on hippocampal and parietal regions,[3, 33, 34] which are known to be vulnerable to Alzheimer pathology. On the other hand, FMT did not predict incidence of amnestic MCI or memory decline in our sample. Right hippocampal structures are suggested to have a more prominent role in navigation,[2, 3, 33] whereas the left hippocampus is involved more in episodic memory process that are impaired in amnestic MCI,[22] which may in part explain FMT's differential prediction of MCI subtypes. However, much remains unexplained about these hippocampal laterality findings and the inter-relationship of spatial navigation and episodic memory.[33] While amnestic MCI is considered a precursor of AD,[22] epidemiological studies suggest that its etiology is heterogeneous including vascular pathology that could influence clinical presentations and progression.[35] Hence, further studies are needed to establish whether spatial navigation processes assessed by FMT portent progression in Alzheimer or non-Alzheimer pathology or both.

Strengths of the study include the well-characterized population, established assessment and diagnostic procedures, and systematic follow-up. Outcomes were diagnosed blinded to FMT performance. While the study design precluded examining dementia as an outcome, the short follow-up is a clinically relevant interval in the context of prognostication for clinicians and researchers. The pre-dementia and cognitive domain outcomes studied are clinically meaningful, and have been the focus of numerous studies that have been helpful in providing biological and clinical insights into dementia. Potential limitations are noted. The focus of our first longitudinal investigation was to establish the validity of FMT as a predictor of cognitive decline. Though simple to administer with limited technical requirements, FMT needs further validation before consideration as an assessment tool in clinical settings but it will be helpful at present in research settings to study the earliest stages of dementia and link with biological pathways. Follow-up studies are needed to establish underlying brain substrates and pathological processes that contribute to FMT performance. Longer follow-up will not only further elucidate FMT's association with risk of developing dementia but also with specific dementia subtypes. The FMT measures showed stronger associations with decline on Trails version A and not on version B, despite the latter being more challenging.

This finding may be due to the short follow-up, ceiling effects on Trails B performance, or weaker associations of FMT with higher order cognitive skills such as mental flexibility captured by Trails B. Also, a greater age effect has been reported on Trails B (average age 80 years), whereas there is a stronger education effect on Trails B, which may have been minimized in our relatively well-educated sample (mean 15 years schooling).[36, 37] While virtual reality environments or pen and paper mazes have been used to study navigation, their relationship to real time navigation is not clear and these tasks may recruit different brain regions than real time navigation.[38] Moreover, computer-based virtual reality tests may be difficult for older adults to perform, especially those with cognitive impairment.[8, 39] Logistical considerations limited the size of the maze and inclusion of walls in the design. However, it may not be practical in many clinical and research settings to erect large scale mazes with walls. Participants were able to visualize the whole maze in the FMT, and may utilize distal visual clues to plan their route though this hypothesis is not universally accepted.[40] Given the limited number of human studies, it is not clear whether visualizing the whole maze versus a portion (if there were walls) would engage different navigational systems for place learning in humans, though restricting view may be more cognitively demanding.[40, 41] It is possible that there may be an element of egocentric navigation involved while the subject is in the midst of negotiating the floor maze, and making direction changes. Whether exocentric and egocentric navigation processes are independent is not fully established and is an area of active research.[42–44] Mobility disabled patients may not be able to do the FMT, and alternate navigational tasks need to be developed for this subgroup.

Real world studies of human navigation with longitudinal follow-up are rare. Our findings suggest that spatial navigation deficits occur early in the course of dementia, and precede the occurrence of pre-dementia syndromes.

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HIGHLIGHTS

- Spatial navigational deficits are common in patients with dementia.
- Spatial navigation performance in non-demented older adults predicts development of pre-dementia syndromes.
- Spatial navigation performance predicts decline in executive function tests.
- Spatial navigation impairment is an early feature in dementia.

RESEARCH IN CONTEXT

Systematic review

We reviewed the literature using PubMed, book chapters, and presentations. Spatial navigational deficits were described in pre-dementia syndromes as well as dementia. These relevant citations are appropriately cited. However, the temporal relationship of spatial navigation performance to cognitive decline has not been established in the context of prospective studies.

Interpretation

Our findings suggest that spatial navigational deficits occur early in the course of dementia, and predict the development of pre-dementia syndromes.

Future directions

The manuscript proposes a novel spatial navigational task that can help study early clinical stages of dementing illnesses. Biological mechanisms and brain substrates for this spatial navigational task need to be further studied.

Table 1

Baseline characteristics of study population and maze descriptions (n = 442). Values are means ± standard deviation unless otherwise noted.

Age, years	79.92 ± 5.71
Sex, % (n) female	61.5 (272)
Education, years	14.71 ± 3.31
Global health scale score (0–9)	2.10 ± 1.26
Depression, % (n)	12.0 (53)
Diabetes, % (n)	19.2 (85)
Heart Failure, % (n)	3.2 (14)
Hypertension, % (n)	66.7 (295)
Myocardial Infarction, % (n)	8.8 (39)
Angina, % (n)	7.2 (32)
Stroke, % (n)	9.0 (40)
Chronic Obstructive Lung Disease, % (n)	8.8 (39)
Arthritis, % (n)	74.7 (330)
Cognitive test performance	
Blessed test (range 0–32)	1.76 ± 1.84
Trail-Making Test A (range 0–300 s)	52.33 ± 20.48
Trail-Making Test B (range 0–300 s)	130.12 ± 66.27
Digit Symbol-Substitution test (range 0–93)	46.83 ± 12.95
Free & cued selective reminding test – free recall (range 0–48)	32.34 ± 6.04
Floor Maze Test characteristics	
Immediate Maze Time, mean (sec)	31.35 ± 23.42
Immediate Maze Time, Errors	0.25 ± 0.62
Delayed Maze Time, mean (sec)	23.30 ± 14.75
Delayed Maze Time, Errors	0.18 ± 0.49
Maze time difference (sec)	−7.84 ± −19.19

*Maze time difference is the difference between Delayed Maze Time and Immediate Maze Time.

Table 2

Association of Floor Maze test performance (immediate maze time and delayed maze time) with incidence of mild cognitive impairment syndrome (MCI), motoric cognitive risk syndrome (MCR) and major cognitive impairment (either MCI or MCR). Hazard ratios are reported for each 10-second increase in IMT, DMT and Maze time difference.

	Incident cases, n	Adjusted Hazard Ratio (95% CI), p-value*
Immediate Maze Time		
MCI	41	1.254 (1.063–1.480), p = 0.007
Amnestic MCI	19	0.991 (0.769–1.277), p = 0.944
Non-amnestic MCI	22	1.198 (1.067–1.345), p = 0.002
MCR	30	1.530 (1.230–1.903), p < 0.001
Major Cognitive Impairment	55	1.264 (1.069–1.494), p = 0.006
Delayed Maze time		
MCI	41	1.187 (0.897–1.571), p = 0.230
Amnestic MCI	19	0.847 (0.460–1.559), p = 0.593
Non-amnestic MCI	22	1.137 (0.867–1.492), p = 0.354
MCR	30	1.321 (1.031–1.693), p = 0.028
Major Cognitive Impairment	55	1.493 (1.119–1.993), p = 0.006
Maze time difference (DMT-IMT) **		
MCI	41	0.760 (0.615–0.939), p = 0.011
Amnestic MCI	19	0.987 (0.705–1.381), p = 0.937
Non-amnestic MCI	22	0.805 (0.688–0.942), p = 0.007
MCR	30	0.763 (0.593–0.981), p = 0.035
Major Cognitive Impairment	55	0.864 (0.691–1.080), p = 0.199

* Adjusted for age, sex, education, Blessed test score, Global Health Scale score, and maze errors

** Maze time difference is the difference between DMT and IMT in each participant, and is a measure of learning.

Table 3

Linear mixed effects model of Immediate Maze Time (IMT) and Delayed Maze Time (DMT) performance on the Floor Maze Test with cognitive test scores.

	IMT Estimate (95% CI)	p-value*	DMT Estimate (95% CI)	p-value*
Trail-Making Test A	2.15 (1.41 – 2.90)	<0.001	4.64 (3.42 – 5.86)	<0.001
Time	−0.05 (−1.43 – 1.34)	0.947	−0.56 (−2.20 – 1.07)	0.498
Trail-Making Test A*Time	0.59 (0.23 – 0.95)	0.001	1.06 (0.43 – 1.68)	0.001
Trail-Making Test B	6.35 (4.02 – 8.68)	<0.001	12.30 (8.36 – 16.24)	<0.001
Time	4.17 (−0.66 – 9.00)	0.091	2.42 (−3.18 – 8.03)	0.396
Trail-Making Test B*Time	1.18 (−0.07 – 2.44)	0.064	2.32 (0.18 – 4.45)	0.034
DSST	−1.19 (−1.66 – −0.72)	<0.001	−2.86 (−3.64 – −2.09)	<0.001
Time	−0.88 (−1.54 – −0.21)	0.010	−0.63 (−1.41 – 0.15)	0.115
DSST*Time	−0.09 (−0.26 − 0.08)	0.306	−0.23 (−0.53 – 0.07)	0.129
Free Recall (FCSRT)	−0.20 (−0.43 – 0.03)	0.095	−0.76 (−1.14 – −0.37)	<0.001
Time	−0.04 (−0.49 – 0.41)	0.857	−0.28 (−0.82 – 0.26)	0.308
Free Recall *Time	−0.11 (−0.23 – 0.01)	0.063	−0.05 (−0.25 – 0.16)	0.662

*Adjusted for baseline age, sex, and education.

FCSRT = Free and Cued Selective Reminding Test, DSST: Digit symbol substitution test