Published in final edited form as:

Alzheimer Dis Assoc Disord. 2019 ; 33(1): 68–71. doi:10.1097/WAD.0000000000000266.

Functional Activity and Neuropsychiatric Symptoms in Normal Aging and Mild Cognitive Impairment: The Mayo Clinic Study of Aging

Janina Krell-Roesch, PhD¹, Leah P. Cerhan, BSc*, Mary M. Machulda, PhD², Rosebud O. Roberts, MB,ChB^{3,4}, Michelle M. Mielke, PhD^{3,4}, David S. Knopman, MD⁴, Jeremy A. Syrjanen, MSc³, Teresa J. Christianson, BSc³, Ronald C. Petersen, MD,PhD^{3,4}, and Yonas E. Geda, MD,MSc^{1,3,5,6}

¹Translational Neuroscience and Aging Program, Mayo Clinic, Scottsdale, Arizona

²Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota

³Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

⁴Department of Neurology, Mayo Clinic, Rochester, Minnesota

⁵Department of Psychiatry and Psychology, Mayo Clinic, Scottsdale, Arizona

⁶Department of Neurology, Mayo Clinic, Scottsdale, Arizona

INTRODUCTION

It is generally assumed that persons with mild cognitive impairment (MCI) have little or no functional impairment. Thus, one of the criteria of MCI is essentially normal activities of daily living. However, some have reported functional deficits among MCI patients as compared to cognitively normal (CN) persons^{e.g. 1–4}. Identifying potential factors that contribute to subtle or overt functional deficits in MCI may have prognostic value in understanding the progression of MCI to dementia. Furthermore, we and others have reported that neuropsychiatric symptoms (NPS) are common among elderly persons. In a sample derived from the Mayo Clinic Study of Aging, 51% of persons with MCI and 27% of CN participants had at least one NPS; and in general, the prevalence of NPS was significantly higher among MCI as compared to CN persons⁵. To date, little is known as to whether NPS are associated with functional activity in persons with MCI. We therefore investigated the functional status among persons with MCI as compared to cognitively normal study participants; and further examined as to whether findings were impacted by NPS.

Corresponding Author: Yonas E. Geda, MD, MSc. Professor of Neurology and Psychiatry. Mayo Clinic, 13400 E. Shea Blvd. Scottsdale, AZ 85259, USA, Phone: 480-301-6870, geda.yonas@mayo.edu.

*Ms. Cerhan was a summer undergraduate research student under the mentorship of Professor Geda at Mayo Clinic, Rochester, Minnesota.

METHODS

Design and Setting:

We conducted a case-control study derived from the Mayo Clinic Study of Aging (MCSA), a population-based study in Olmsted County, Minnesota. MCSA study protocols have been approved by the IRB of the Mayo Clinic and Olmsted Medical Center in Rochester, Minnesota. All participants provided written informed consent.

Participants:

Eligible participants were cases and controls aged ≥ 70 years (we defined MCI persons as cases and CN persons as controls) with valid data from Functional Activities Questionnaire (FAQ) and Neuropsychiatric Inventory Questionnaire (NPI-Q).

Measurement of Normal Cognition and MCI:

The cognitive assessment in the MCSA is described in detail elsewhere⁶. Briefly, all participants underwent a face-to-face evaluation including 1) neurological examination performed by a physician, 2) risk factors ascertainment conducted by a nurse or study coordinator, and 3) neuropsychological testing administered by a psychometrist to assess four cognitive domains (memory, language, visuospatial skills, executive functions). An expert consensus panel of physicians, nurses, and a neuropsychologist evaluated the results and classified the participants as being CN or having MCI. The diagnosis of MCI was made based on the published Mayo Clinic criteria.

Measurement of Functional Status:

Functional status was measured using the Functional Activities Questionnaire (FAQ)⁷, a 10-item questionnaire on instrumental activities of daily living (IADL) such as writing checks, paying bills, balancing checkbook; shopping alone for clothes, household necessities, or groceries; playing a game of skill, working on a hobby; preparing a balanced meal; or remembering appointments, family occasions, holidays, medications. Regardless of the cognitive status of the participant, an informant is asked to rate the participant's abilities according to a scoring system (ranging from 3, dependent to 0, normal/ never did the activity but could do now). By summing the scores for all 10 items, we calculated a FAQ total score for each participant (minimal score: 0, maximal score: 30). Higher FAQ scores indicate higher degrees of functional impairment. The FAQ was administered by a research nurse or study coordinator.

Measurement of Neuropsychiatric Symptoms:

NPS were measured using the Neuropsychiatric Inventory Questionnaire (NPI-Q)⁸ which assesses 12 emotional behaviors (agitation, delusion, hallucination, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep, and eating/appetite). For all study participants, the NPI-Q was administered as a structured interview to an informant by a research nurse or study coordinator.

Statistical Analysis:

We used two sets of multivariable logistic regression models to compute odds ratios (OR) and 95% confidence intervals (95% CI). In the first set of models, we used functional status as measured by FAQ to predict cognitive status [CN vs. MCI (event)]. Analyses were adjusted for age, sex, education, medical comorbidities (Charlson index), body mass index (BMI) and APOE $\epsilon 4$ carrier status. We also further adjusted for each NPS individually to evaluate the impact of NPS on functional status in predicting normal cognition vs. MCI. In the second set of regression models, we investigated the association between NPS (presumed dependent variables) and FAQ score (presumed independent variable) for both CN and MCI participants separately. These models were also adjusted for age, sex, education, medical comorbidities, BMI and APOE $\epsilon 4$. Finally, we ran both sets of regression models stratified by APOE $\epsilon 4$ carrier status. All statistical analyses were done using the two-tailed alpha level of 0.05 and performed with SAS® (SAS Institute, Cary, N.C.).

RESULTS

The sample consisted of 3003 persons (51.1% males); 2539 were CN and 464 had MCI (350 had amnesic MCI, and 114 had non-amnesic MCI). The median FAQ score (IQR) was 1.0 (0.0, 3.0) for MCI persons, and 0.0 (0.0, 0.0) for CN persons. Participants with MCI had higher prevalence of NPS than CN persons (Table 1).

FAQ total score predicting normal cognition vs. MCI:

The OR for total FAQ scores predicting cognitive status [CN vs. MCI (event)] was 1.39 (95% CI 1.32, 1.47; $p < .001$) after adjusting for age, sex, and education. Additional adjustment for NPS had a negligible impact on the OR; with point estimates ranging between 1.36 (1.29, 1.43; $p < .001$) for apathy and 1.39 (1.32, 1.46; $p < .001$) for eating/appetite (data not shown). Similarly, when we adjusted the model for age, sex, education, medical comorbidities, BMI and APOE $\epsilon 4$, the OR was 1.38 (95% CI 1.31, 1.46; $p < .001$). Additional adjustment for NPS had only minor impact on the OR; the point estimates ranged between 1.35 (1.28, 1.43; $p < .001$) for apathy and 1.38 (1.31, 1.46; $p < .001$) for eating/appetite (data not shown). When we stratified the analysis by APOE $\epsilon 4$ carrier status, the OR adjusted for age, sex, and education was 1.32 (1.22, 1.43; $p < .001$) for carriers and 1.43 (1.33, 1.53; $p < .001$) for non-carriers. Additional adjustment for NPS did not significantly change the OR. The point estimates ranged for APOE $\epsilon 4$ carriers between 1.29 (1.19, 1.40; $p < .001$) for depression and 1.32 (1.21, 1.43; $p < .001$) for agitation; and for APOE $\epsilon 4$ non-carriers between 1.39 (1.29, 1.49; $p < .001$) for apathy and 1.42 (1.31, 1.53; $p < .001$) for nighttime behavior.

Association between NPS and FAQ total score in CN and MCI:

Higher FAQ scores were associated with greater odds of having NPS in both MCI and CN persons (Tables 2 and 3). On average, point estimates were higher among CN as compared to MCI participants.

CONCLUSION

As expected, CN and MCI persons of this community-based study sample scored very low on the FAQ. This finding gives empirical credence to one of the criteria of MCI, i.e., MCI persons have little or no functional impairment. However, we observed that each one-unit increase in FAQ is associated with 39% greater odds of having MCI. This finding is in line with previous studies that have reported higher FAQ scores among MCI than CN persons^{e.g. 1,4}. Similarly, studies using other questionnaire-based assessments reported differences in functional status between MCI and CN persons^{e.g. 2}; whereas few reported only some differences between MCI and controls depending on the assessment^{e.g. 3}.

As NPS are common in elderly CN and MCI persons and are associated with increased risk of cognitive decline, we examined the effect of functional status on presence of NPS. We observed that higher FAQ scores were significantly associated with presence of NPS among both CN and MCI persons, except for euphoria among MCI participants. However, additional adjustment for NPS of the primary regression model, which used total FAQ scores to predict cognitive status, did not significantly alter the odds of having MCI. This suggests that NPS are associated with impaired functional status, but may not impact the relationship between functional activity and cognitive status (CN vs. MCI). To our knowledge, only few studies have investigated the association between NPS and functional status. For example, a study conducted at UCSF found that NPS, particularly apathy and nighttime behavior, predicted functional status in AD patients⁹. Similarly, Italian investigators reported that NPS were significantly associated with impairment of IADL in patients with AD and vascular dementia¹⁰.

The major strength of our study is the large, population-based sample of elderly persons aged 70 years. All study participants underwent numerous face-to-face evaluations and were classified as CN or having MCI based on an expert consensus panel. The main limitation of our study is its cross-sectional design. Thus, it is not possible to determine direction of causality between ‘exposure’ and outcome of interest. Another limitation pertains to the use of FAQ and NPI-Q, which are informant-report questionnaires and may be prone to recall bias. However, the NPI-Q is a validated and commonly used tool to assess NPS. Furthermore, it has been speculated that informant-report questionnaires to assess IADL may be more accurate than self-report questionnaires among MCI persons.

In conclusion, we observed that higher FAQ scores are associated with increased odds of having MCI among elderly community-dwelling persons. Additional adjustment for NPS did not significantly alter the relationship between functional activity and cognitive status. However, higher FAQ scores among both CN and MCI persons were associated with increased odds of presence of NPS. As in any case-control study, our results should be considered as preliminary until confirmed by a prospective cohort study.

ACKNOWLEDGMENTS

Support for this research was provided by NIH grants: National Institute of Mental Health (K01 MH068351), and National Institute on Aging (U01 AG006786, K01 AG028573, R01 AG034676, and R01 AG057708). This project was also supported by the Robert Wood Johnson Foundation, the Robert H. and Clarice Smith and Abigail Van

Buren Alzheimer's Disease Research Program, the GHR Foundation, Edli Foundation (The Hague, The Netherlands) and the Arizona Alzheimer's Consortium.

Conflicts of Interest and Source of Funding:

The authors declare no conflicts of interest. Support for this research was provided by NIH grants: National Institute of Mental Health (K01 MH068351), and National Institute on Aging (U01 AG006786, K01 AG028573, R01 AG034676, and R01 AG057708). This project was also supported by the Robert Wood Johnson Foundation, the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program, the GHR Foundation, Edli Foundation (The Hague, The Netherlands) and the Arizona Alzheimer's Consortium.

REFERENCES

1. Brown PJ, Devanand DP, Liu X, et al. Functional impairment in elderly patients with mild cognitive impairment and mild Alzheimer disease. *Arch Gen Psychiatry*. 2011;68(6):617–626. [PubMed: 21646578]
2. Hughes TF, Chang CC, Bilt JV, et al. Mild cognitive deficits and everyday functioning among older adults in the community: The Monongahela-Youghiogheny Healthy Aging Team Study. *Am J Geriatr Psychiatry*. 2012;20(10):836–44. [PubMed: 22337146]
3. Jefferson AL, Byerly LK, Vanderhill S, et al. Characterization of activities of daily living in individuals with mild cognitive impairment. *Am J Geriatr Psychiatry*. 2008;16(5):375–383. [PubMed: 18332397]
4. Tabert MH, Albert SM, Borukhova-Milov L, et al. Functional deficits in patients with mild cognitive impairment: prediction of AD. *Neurology*. 2002;58(5):758–764. [PubMed: 11889240]
5. Geda YE, Roberts RO, Knopman DS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. *Arch Gen Psychiatry*. 2008;65(10):1193–1198. [PubMed: 18838636]
6. Roberts RO, Geda YE, Knopman DS, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology*. 2008;30(1):58–69. [PubMed: 18259084]
7. Pfeffer RI, Kurosaki TT, Harrah CH, Jr, et al. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982;37(3):323–329. [PubMed: 7069156]
8. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12(2):233–239. [PubMed: 11001602]
9. You SC, Walsh CM, Chiodo LA, et al. Neuropsychiatric Symptoms Predict Functional Status in Alzheimer's Disease. *J Alzheimers Dis*. 2015;48(3):863–869. [PubMed: 26402074]
10. D'Onofrio G, Sancarlo D, Panza F, et al. Neuropsychiatric symptoms and functional status in Alzheimer's disease and vascular dementia patients. *Curr Alzheimer Res*. 2012;9(6):759–771. [PubMed: 22715983]

Table 1:

Demographic characteristics of study participants

Variable	CN (n = 2539)N (%)	MCI (n = 464)N (%)
Males	1272 (50.1)	264 (56.9)
Age, years^a	77.7 [73.8, 82.3]	81.3 [75.6, 84.3]
70–79	1538 (60.6)	195 (42.0)
80–91	1001 (39.4)	269 (58.0)
Education, years^a	13.0 [12.0, 16.0]	12.0 [12.0, 15.0]
> 12 years	1490 (58.7)	201 (43.3)
Charlson Index^a	3.0 [2.0, 5.0] ^b	4.0 [3.0, 7.0]
FAQ Total Score^a	0.0 [0.0, 0.0]	1.0 [0.0, 3.0]
BMI (kg/m²)^a	27.3 [24.6, 30.5] ^c	27.3 [24.3, 30.2] ^d
APOE ε4	636 (25.5) ^e	144 (31.7) ^f
NPS		
Depression	282 (11.1)	120 (25.9)
Apathy	119 (4.7)	80 (17.2)
Anxiety	128 (5.0)	69 (14.9)
Agitation	67 (2.6)	37 (8.0)
Irritability	188 (7.4)	86 (18.5)
Eating/ appetite	121 (4.8)	47 (10.1)
Aberrant motor behavior	16 (0.6)	9 (1.9)
Nighttime behavior	209 (9.9) ^g	69 (17.7) ^h
Disinhibition	39 (1.5)	20 (4.3)
Euphoria	14 (0.6)	5 (1.1)
Delusion	9 (0.4)	12 (2.6)
Hallucination	7 (0.3)	3 (0.6)

CN = cognitively normal; MCI = mild cognitive impairment; FAQ = Functional Activities Questionnaire; NPS = Neuropsychiatric symptoms as measured by Neuropsychiatric Inventory Questionnaire (NPI-Q).

^aMedian [interquartile range];

^b₁,

^c₄₁,

^d₁₆,

^e₄₆,

^f₁₀,

^g₄₂₃ and

^h₇₄ participants with no data.

Table 2:

Association between NPS and FAQ total score among CN and MCI participants

NPS	CN (n = 2539)				MCI (n = 464)			
	OR ¹ (95% CI)	p ¹	OR ² (95% CI)	p ²	OR ¹ (95% CI)	p ¹	OR ² (95% CI)	p ²
Depression	1.27 (1.18, 1.36)	<0.001	1.26 (1.17, 1.36)	<0.001	1.11 (1.06, 1.16)	<0.001	1.10 (1.05, 1.16)	<0.001
Apathy	1.44 (1.33, 1.57)	<0.001	1.46 (1.34, 1.60)	<0.001	1.23 (1.16, 1.30)	<0.001	1.21 (1.14, 1.29)	<0.001
Anxiety	1.32 (1.22, 1.43)	<0.001	1.30 (1.19, 1.41)	<0.001	1.06 (1.00, 1.12)	0.036	1.06 (1.00, 1.12)	0.064
Agitation	1.37 (1.24, 1.50)	<0.001	1.36 (1.23, 1.51)	<0.001	1.17 (1.10, 1.24)	<0.001	1.17 (1.09, 1.25)	<0.001
Irritability	1.41 (1.31, 1.53)	<0.001	1.41 (1.30, 1.53)	<0.001	1.13 (1.07, 1.19)	<0.001	1.13 (1.07, 1.20)	<0.001
Eating/appetite	1.29 (1.18, 1.40)	<0.001	1.27 (1.16, 1.38)	<0.001	1.16 (1.10, 1.23)	<0.001	1.17 (1.10, 1.24)	<0.001
Nighttime behavior	1.25 (1.15, 1.35)	<0.001	1.23 (1.14, 1.34)	<0.001	1.21 (1.14, 1.29)	<0.001	1.22 (1.14, 1.30)	<0.001

FAQ = Functional Activities Questionnaire; CN = cognitively normal; MCI = Mild Cognitive Impairment; NPS = Neuropsychiatric Inventory Questionnaire (NPI-Q); OR = odds ratio; CI = confidence interval.

¹ = adjusted for age, sex, and education;

² = adjusted for age, sex, education, medical comorbidities, body mass index and APOE ε4. Motor behavior, disinhibition, euphoria, delusion, and hallucinations were excluded from logistic regression analysis due to low counts.

Table 3:

Association between NPS and FAQ total score among CN and MCI participants: Stratified by APOE ε4 carrier status

	CN (n = 2539)		MCI (n = 464)	
NPS	OR (95% CI)	p	OR (95% CI)	p
Depression				
APOE ε4 +	1.28 (1.14, 1.44)	<0.001	1.08 (0.99, 1.17)	0.094
APOE ε4 -	1.26 (1.15, 1.38)	<0.001	1.12 (1.05, 1.19)	<0.001
Apathy				
APOE ε4 +	1.42 (1.24, 1.64)	<0.001	1.21 (1.09, 1.34)	<0.001
APOE ε4 -	1.48 (1.32, 1.65)	<0.001	1.26 (1.16, 1.36)	<0.001
Anxiety				
APOE ε4 +	1.34 (1.18, 1.52)	<0.001	1.04 (0.93, 1.15)	0.48
APOE ε4 -	1.28 (1.15, 1.42)	<0.001	1.06 (0.99, 1.13)	0.098
Agitation				
APOE ε4 +	1.30 (1.11, 1.53)	0.002	1.15 (1.02, 1.30)	0.021
APOE ε4 -	1.42 (1.25, 1.60)	<0.001	1.20 (1.10, 1.30)	<0.001
Irritability				
APOE ε4 +	1.29 (1.14, 1.47)	<0.001	1.16 (1.05, 1.28)	0.003
APOE ε4 -	1.49 (1.34, 1.65)	<0.001	1.12 (1.05, 1.19)	<0.001
Eating/ appetite				
APOE ε4 +	1.38 (1.19, 1.59)	<0.001	1.15 (1.04, 1.27)	0.005
APOE ε4 -	1.24 (1.11, 1.38)	<0.001	1.16 (1.08, 1.25)	<0.001
Nighttime behavior				
APOE ε4 +	1.32 (1.16, 1.51)	<0.001	1.15 (1.03, 1.29)	0.013
APOE ε4 -	1.19 (1.07, 1.32)	0.001	1.23 (1.14, 1.34)	<0.001

Analyses adjusted for age, sex, and education. FAQ = Functional Activities Questionnaire; CN = cognitively normal; MCI = Mild Cognitive Impairment; NPS = Neuropsychiatric symptoms as measured by Neuropsychiatric Inventory Questionnaire (NPI-Q); OR = odds ratio; CI = confidence interval. APOE ε4 + = APOE ε4 carrier; APOE ε4 - = APOE ε4 non-carrier. Motor behavior, disinhibition, euphoria, delusion, and hallucinations were excluded from logistic regression analysis due to low counts.