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The source of cognitive complaints differentially predicts diagnostic conversion in non-demented older adults

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Abstract

Objective—The objective of this study was to compare whether different sources of cognitive complaint (i.e., subjective and informant) predict diagnostic conversion in nondemented older adults.

Methods—Participants from the National Alzheimer's Coordinating Center had a baseline diagnosis of normal cognition (NC; n=4414, 73±8 years, 69% female) or mild cognitive impairment (MCI; n=1843, 74±8 years, 52% female). Multinomial logistic regression related baseline cognitive complaint (no-complaint, self only, informant only, or both self-and informant) to diagnostic outcome (reversion, stable or conversion).

Results—At follow-up, 14% of NC participants converted to MCI/dementia (3.5±1.8 years), and 41% of MCI participants converted to dementia (3.0±1.6 years). Among NC participants, self-complaint only (OR=2.1; 99%CI=1.5–2.9, p<0.001), informant-complaint only (OR=2.2; 99%CI=1.2–3.9, p<0.001), and both self-and informant-complaint (OR=4.2; 99%CI=2.9–6.0, p<0.001) were associated with diagnostic conversion, compared to no-complaint. Among participants with MCI—compared with no-complaint, informant-complaint only (OR, 2.2; 99% CI, 1.2–4.3, P = .002), and both self- and informant-complaint (OR, 2.9; 99% CI, 1.8–4.8; P < .001)—were associated with conversion.

Conclusions—Cognitive complaints are related to conversion among non-demented older adults. Complaint from both (i.e. mutual complaint) sources was most predictive of diagnostic outcome, followed by informant complaint, highlighting the need for obtaining informant

corroboration to enhance prognosis and distinguish underlying pathological processes from normal cognitive aging. Self-complaint was inconsistently related to diagnostic outcome.

Keywords

Mild cognitive impairment; Alzheimer's disease; cognitive complaints; prognosis; conversion

1. Introduction

Mild cognitive impairment (MCI) is widely regarded as a prodromal stage of dementia¹ because many individuals diagnosed with MCI convert to Alzheimer's disease (AD).² Current MCI diagnostic criteria require quantitative evidence of neuropsychological impairment, relative preservation of functional abilities, and a concern regarding a change in cognition, reported by the patient or someone close to the patient (i.e., an informant) or noted by a clinician.³ Prior research suggests that self-reported cognitive complaints predict cognitive decline⁴ and diagnostic outcome.⁵ However, self-reported cognitive complaints are highly prevalent among older adults⁶ and lack specificity (i.e., cognitively normal elders frequently endorse cognitive problems).⁷ Also, elders with an underlying neurodegenerative disease sometimes lack insight⁸ and may self-assess their cognition incorrectly. One solution to overcome limitations associated with self-reported cognitive complaint is use of an informant or an individual who knows the patient well. Emerging evidence suggests that informant complaint may be a better predictor of cognitive progression than self complaint.^{9,10}

There has been limited empirical consideration of how the combination of self and informant cognitive complaints relate to diagnostic outcomes. Such information would be helpful in refining the diagnostic profile of MCI. It is certainly plausible that pooling information from sources may be a more valuable clinical prognostic indicator than either information source alone. The current study aims to reconcile the prognostic properties of cognitive complaint in relation to longitudinal diagnostic outcomes of individuals with normal cognition (NC) and MCI by considering a combination of self and informant cognitive complaints. Leveraging the National Alzheimer's Coordinating Center (NACC) database, we hypothesized that individuals with both self and informant complaint (i.e. mutual complaint) have a greater risk of converting over a follow-up period (i.e., from NC to MCI or MCI to dementia) than elders with no cognitive complaint or only one type of complaint (i.e., self or informant complaint only). As therapeutic targets to slow or arrest the pathological process of AD are expected to emerge in the coming years,¹¹ it is essential to identify individuals at greatest risk for conversion to dementia. Early intervention could prevent or delay the onset of clinical dementia, preserve functional independence, and minimize cognitive decline for at risk elders.¹²

2. Methods

2.1 Setting and participants

As previously reported,¹³ NACC maintains a database of participant information collected from ~30 national Alzheimer's Disease Centers (ADCs) previously or currently funded through the National Institute on Aging. In 2005, NACC implemented the Uniform Data Set

(UDS), a standard evaluation protocol, including clinical demographic information, medical history, neurological examination, and neuropsychological evaluation.¹⁴ Participants 55 to 90 years of age, evaluated between 9/01/2005 and 12/01/2012, and diagnosed at first visit with NC or MCI were included in the current study. Participant selection and exclusion details are provided in Figure 1 and resulted in a sample of 6261 participants for the current study. The study was approved by local Institutional Review Boards prior to data access and analysis.

2.2 Cognitive complaint

Cognitive complaint was defined based on clinician-facilitated interviews with the participant and informant. From this interview, the clinician dichotomously reported the presence or absence of cognitive complaint for the participant (self) and the informant.

2.3 Cognitive diagnostic classification

The cognitive diagnosis for each participant is based upon clinician judgment or a multi-disciplinary consensus team using information from the comprehensive UDS work-up. Classifications relevant to the current study include:

1. NC is defined by (a) Clinical Dementia Rating (CDR)¹⁵=0 (no dementia), (b) no deficits in activities of daily living directly attributable to cognitive impairment, and (c) no evidence of objective cognitive impairment. Normal cognition is defined as standard scores falling 1.5 standard deviations within the age-adjusted normative mean¹⁶ on neuropsychological tests assessing language, attention, memory, and executive functioning.
2. MCI determinations are based upon Peterson et al. criteria¹⁷ and defined as (a) a CDR 0.5 (reflecting mild severity of impairment), (b) relatively spared activities of daily living, (c) objective cognitive impairment in at least one cognitive domain (i.e., performances falling greater than 1.5 standard deviations outside the age-adjusted normative mean in memory, language, attention, or executive functioning) or a significant decline over time on the neuropsychological evaluation, (d) Mini Mental State Examination (MMSE) score ≥ 23 ,^{18,19} (e) report of a cognitive change by the patient or informant or as observed by a clinician, and (f) absence of a dementing syndrome (defined below).
3. Dementia was defined as meeting criteria for AD,²⁰ or other dementias^{21,22,23,24–26} defined as (a) objective cognitive impairment (i.e., performances falling greater than 1.5 standard deviations outside the age-adjusted normative mean) in at least two cognitive systems (i.e., memory, language, attention or executive functioning), and (b) cognitive impairment contributes directly to impaired activities of daily living.²⁷

2.4 Cognitive diagnostic outcome classification

Diagnostic outcome was defined by comparing the participant's baseline (i.e., first UDS visit) diagnosis with their most recent UDS follow-up visit diagnosis. Among the NC participants, diagnostic outcome was defined as (1) stable (NC to NC) or (2) conversion (NC

to MCI or NC to dementia). Among the MCI participants, diagnostic outcome was defined as (1) reversion (MCI to NC), (2) stable (MCI to MCI), or (3) conversion (MCI to dementia).

2.5 Statistical analysis

For all participants, baseline cognitive complaint was defined using four mutually exclusive levels: (1) no cognitive complaint, (2) self cognitive complaint only, (3) informant cognitive complaint only, or (4) both self and informant cognitive complaint, i.e. mutual complaint. Baseline clinical characteristics, including age, sex, race, education, follow-up period (time from first to most recent UDS visit), and global cognitive functioning (as assessed by the MMSE¹⁸), were compared across the four complaint categories separately for each diagnostic group (i.e., NC, MCI) using chi-square and analysis of variance tests.

For hypothesis testing, multinomial logistic regression was used to relate complaint status (using no complaint as the referent) to diagnostic outcome adjusting for age, sex, race, education, follow-up period, and MMSE. Restricted cubic splines with 5 knots were used to model continuous variables (age, education, MMSE, and years of follow-up) to relax the linearity assumption of covariate effects. Nonlinear terms of continuous variables were removed if no significant trends were detected. Two-way interactions were considered (i.e., race*sex, race*complaint, sex*complaint) and only interactions with significant effects remained in the model. For the NC participants, the multinomial logistic regression was reduced to logistic regression for binary variables as there were only two diagnosis outcome levels. The model then analyzed the effect of complaint status on the odds of conversion versus remaining stable. For the MCI participants, the multinomial logistic regression compared the effect of complaint status across three categories of diagnosis outcome with stable as the referent. Significance was set a-priori at $p < 0.01$, and results are presented as odds ratios (OR) with 99% confidence intervals (CI). Analyses were conducted using R 2.12.1 (www.r-project.org).

3. Results

3.1 Participant characteristics

At baseline, participants included $n=4414$ NC participants and $n=1843$ individuals with MCI. Among NC participants, the four cognitive complaint subgroups did not differ with respect to age, race, or education, but differed on sex ($\chi^2=36$, $p < 0.001$), MMSE ($F(3,4410)=15.0$, $p < 0.001$), and length of follow-up ($F(3,4410)=7.8$, $p < 0.001$). Among MCI participants, the complaint subgroups did not differ with respect to age, education, or length of follow-up period but differed with respect to sex ($\chi^2=18$, $p < 0.001$), race ($\chi^2=77$, $p < 0.001$), and MMSE ($F(3,1839)=12.0$, $p < 0.001$). See Table 1 for details.

3.2 Cognitive complaint & NC diagnostic outcome

All the nonlinear effects of age, education, MMSE, and follow-up periods were not statistically significant (all p -values > 0.17). Similarly, all interactions were not statistically significant (all p -values > 0.27). Therefore, the final model included only main effects of the baseline characteristics with linear effects for continuous variables. Compared to NC

participants with no cognitive complaint, participants with self complaint only (OR=2.1; 99%CI=1.5–2.9, $p<0.001$), informant complaint only (OR=2.2; 99%CI=1.2–3.9, $p<0.001$), and both self and informant complaint (OR=4.2; 99%CI=2.9–6.0, $p<0.001$) were at increased risk of converting to MCI or dementia. Compared to NC participants with self complaint, both self and informant complaint were at increased risk of converting to MCI or dementia (OR=1.8; 99%CI=1.2–2.9, $p<0.001$). See Table 2. The probability of conversion against age by years of follow-up was plotted for each complaint category, and participants with both complaints have the highest probability of conversion, followed by participants with informant complaint only, self complaint only and no complaint. See Figure 2a.

Among the NC participants, we secondarily examined how type of complaint related to each of the two diagnostic conversion outcomes (i.e., MCI and dementia). Compared to NC complaints with no complaint, participants with self complaint only (OR=2.3; 99%CI=1.6–3.2, $p<0.001$) and both self and informant complaint (OR=3.7; 99%CI=2.5–5.7, $p<0.001$) were at increased risk of converting to MCI. Compared to NC participants with no complaint, participants with informant complaint only (OR=4.7; 99%CI=2.1–10.5, $p<0.001$) and both self and informant complaint (OR=5.7; 99%CI=3.1–10.6, $p<0.001$) were at increased risk of converting to dementia.

3.3 Cognitive complaint & MCI diagnostic outcome: reversion versus stable

Similar to the final model for NC participants, the model for MCI participants included main effects of baseline characteristics only with linear effects for age, education, MMSE, and years of follow-up. MCI participants with informant complaint (OR=0.3; 99%CI=0.1–0.6, $p<0.001$) and both self and informant complaint (OR=0.2; 99%CI=0.1–0.4, $p<0.001$) were less likely to revert to normal than remain stable as compared to MCI participants with no complaint. Furthermore, compared to participants with self complaint only, MCI participants with both self and informant complaint were less likely to revert to normal than remain stable (OR=0.3; 99%CI=0.2–0.6, $p<0.001$). See Table 2. The probability of reversion against age was plotted using the same participant profile as for NC participants. See Figure 2b.

3.4 Cognitive complaint & MCI diagnostic outcome: conversion versus stable

MCI participants with informant complaint only (OR=2.2; 99%CI=1.2–4.3, $p<0.001$) and both self and informant complaint (OR=2.9; 99%CI=1.8–4.8, $p<0.001$) were more likely to progress to dementia compared to MCI participants with no complaint. MCI individuals with both self and informant complaint were more likely to convert to dementia compared to participants with self complaint only (OR=2.7; 99%CI=1.6–4.6, $p<0.001$). See Table 2. The probability of conversion against age was plotted using the same participant profile as for NC participants. See Figure 2c.

4. Discussion

Leveraging a large, multicenter cohort, we found that among cognitively normal older adults, a combination of both self and informant cognitive complaint (i.e. mutual complaint) was associated with a four-fold risk of progression to MCI or dementia over the follow-up

period. An informant complaint alone or a self complaint alone conferred a two-fold increased risk of progression over the follow-up period (as compared to no complaint). A self complaint was less predictive of conversion than the presence of both self and informant complaint.

A similar pattern was observed in MCI participants with a combination of both self and informant complaint yielding a nearly three-fold greater risk of converting than remaining stable. The presence of just an informant complaint was related to diagnostic conversion, conferring over two times the risk for converting from MCI to dementia than remaining stable. MCI participants with both a self and informant complaint were nearly 80% less likely to revert than remain diagnostically stable over the follow-up period, and MCI individuals with only an informant complaint were 75% less likely to revert. The presence of only a participant (i.e., self) complaint was not statistically predictive of diagnostic conversion or reversion as compared to remaining stable among individuals with MCI.

Our findings are not only aligned with prior work relating self complaint in cognitively normal elders²⁸ and informant complaint⁹ in MCI to diagnostic outcome but extend this work in several ways. First, our methodology integrated self and informant sources of complaint alone and in combination to assess conversion risk. In doing so, we augment existing literature by suggesting the presence of both patient and informant cognitive complaint may have important prognostic value over either one alone. Many cognitively impaired older adults go undiagnosed in the primary care setting,²⁹ with prevalence estimates suggesting that 16% of individuals over age 70 years have MCI,³⁰ and one in eight individuals over age 65 has dementia.³¹ Although there is no current cure for AD, early identification is important for a couple of reasons. First, literature supports early identification, as patients benefit from dementia pharmacological treatments (i.e., cholinesterase inhibitors).³²

Second, early identification may promote lifestyle and behavioral interventions, such as increased physical activity, which have been shown to enhance cognition^{33,34} and decrease diagnostic conversion^{35,36} risk. Taken together with growing evidence supporting the benefit of early identification of dementia³⁷ and health care policy reform requiring annual cognitive screening for all Medicare beneficiaries, our findings emphasize that integrating a family member or reliable informant into the primary care evaluation of older patients can provide important information for cognitive prognosis. In the event that both a patient and their loved one complain about memory changes, more thorough cognitive screening or a memory diagnostic referral might be warranted.

Third, we examined the prognostic value of cognitive complaints not only for diagnostic conversion^{10,38} but also diagnostic reversion and stability in MCI. Fluctuations in MCI are common, as many people diagnosed with MCI fail to meet diagnostic criteria one year later.³⁹ Making accurate prognostic determinations for individuals with MCI poses a challenge for clinicians.⁴⁰ However, the current results offer some resolution, as a combination of self and informant complaint in MCI yields nearly three times the risk of converting to dementia as compared to reverting to normal cognition over nearly a three

year period. This finding implies a combination of complaints reflects the presence of an underlying neurodegenerative process that will progress.

Despite being a criterion for MCI diagnosis, quantification of cognitive complaints is poorly defined. Methods assessing cognitive complaint range from a single dichotomous (yes/no) question⁹ to a more extensive multi-item questionnaire,³⁸ and the individual reporting the complaint may be the patient, an informant, or the clinician. Questions vary in wording, such as “Do you have complaints about your memory?” or “Have you noticed a significant decline in your thinking?” Therefore, standardized methods assessing cognitive complaint are needed to refine MCI diagnostic profiling, further enhance prognostic implications, and decrease diagnostic fluctuations.

Cognitive complaints are quite common among older adults.⁷ Among our two participant groups, the presence of self complaint only was inconsistent in predicting diagnostic conversion (i.e., predictive in NC but not MCI). The observed discrepancy, consistent with prior studies,^{10,28} warrants some discussion. We found that among cognitively normal elders, self complaint only was related to an increased risk of converting to MCI or dementia rather than remaining stable over the follow-up period. This finding suggests an underlying biological basis for subjective cognitive complaints among cognitively normal elders, a concept supported by prior evidence linking self complaint with an in-vivo structural neuroimaging changes reflecting the earliest pathological signs of dementia (i.e., atrophy within the medial temporal lobe)^{41,42} and an increased presence of AD neuropathology post-mortem in non-demented individuals.⁴³ Coupled with prior findings, our observations suggest that older adults who are known to be cognitively normal but who are complaining of cognitive changes should not be dismissed as “worried well.”

In contrast, we observed that self complaint is not related to increased risk of diagnostic conversion among MCI individuals. The discrepancy between self and informant complaint in our MCI cohort is consistent with previous literature¹⁰ and may be attributable to compromised awareness of cognitive impairment (anosognosia) or memory loss (metamemory) observed in both MCI⁸ and early AD⁴⁴ populations. Areas associated with self-perception and awareness of deficits (i.e., right prefrontal cortex⁴⁵ and right hippocampus⁴⁶) are often affected by early AD pathology.^{47,48} Therefore, our observation that self complaint in MCI was not associated with increased risk of conversion may be due to inconsistencies in awareness across MCI participants.

A number of strengths are associated with this study. First, methodology incorporated a combination of complaint sources, as compared to previous research that has considered self or informant complaint alone. The current study considered multiple MCI diagnostic outcomes (i.e., reversion, stability, and conversion), which extends previous studies that have not differentiated MCI stability from reversion. The use of the NACC UDS represents a number of strengths and enhancements to the previous literature, including a large sample size, a comprehensive and standardized neuropsychological protocol, and standardized diagnostic criteria.

Despite numerous strengths, several key limitations must be considered. NACC participants, although representative of ~30 ADCs throughout the United States, are primarily White and well-educated and participants in ADCs are often from a memory clinic or self-referred for participation. These factors may lead to different baseline characteristics as compared to a population-based study and limit the generalizability of these results. Furthermore, given that estimates of conversion to MCI and dementia vary between clinic^{49–51} and community samples,^{49,51} the findings from this study may reflect sample characteristics specific to the NACC cohort. Population-based analyses aimed at understanding the prognostic value of cognitive complaint are necessary. Secondly, methods for determining cognitive complaints vary across sites. Furthermore, cognitive complaint is rated in a dichotomous nature, which does not allow for assessing complaint gradations or severity in relation to diagnostic outcome; however, the simplicity of the dichotomous rating may have more implications for active primary care settings, where an extensive cognitive complaint interview would not be feasible. Finally, the follow-up time was limited to three years on average, but this limitation is tempered by the large sample size providing ample power to detect diagnostic conversion in the limited time frame.

The current findings are an important step in understanding how cognitive complaint enhances prognostic implications for both cognitively normal and MCI individuals in primary care settings. Further research is needed to better understand best practices for assessing and quantifying cognitive complaint and the temporal nature of subjective and informant cognitive complaint onset in relation to cognitive decline or diagnostic conversion. Such research advances are necessary to refine the definition of cognitive complaint as a diagnostic entity in MCI, inform treatment decisions for those individuals at greatest risk for progression as more effective therapeutic targets become available, and provide practical information and assessment tools for primary care providers of older adults.

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Figure 1. Participant Enrollment & Exclusion Details

Note: The exclusion numbers provided are not mutually exclusive. Missing data include complaint status at baseline. Cognitively impaired patients without MCI were excluded because of nonstandardized classification criteria. NACC UDS, National Alzheimer's Coordinating Center Uniform Data Set; MCI, mild cognitive impairment, TIA, transient ischemic attack.

Figure 2. depicts the predicted probability of diagnostic outcome for each cognitive complaint group by age. Figure 2a reflects the likelihood of conversion in individuals with normal cognition. Figure 2b reflects the likelihood of conversion in individuals with MCI as compared to remaining diagnostically stable. Figure 2c reflects the likelihood of reversion in individuals with MCI as compared to remaining diagnostically stable.

Table 1

Clinical Characteristics by Cognitive Complaint Category

	Cognitively Normal Participants				
	No Complaint n=3300	Self Complaint n=656	Informant Complaint n=139	Self + Informant Complaint n=319	p value
Age, mean (SD), y	72.6 (8.2)	72.7 (8.4)	73.9 (8.4)	72.8 (7.4)	0.35
Sex (% Female)	70	70	57	56	<0.001\$,##,†,‡
Race (% White)	80	77	87	81	0.015
Education, mean (SD), y	15.8 (5.7)	16.0 (7.2)	15.1 (3.4)	15.9 (8.8)	0.09
Baseline MMSE score [†] , mean (SD)	29.0 (1.4)	28.9 (1.4)	28.6 (1.7)	28.5 (1.6)	<0.001\$,‡,‡,##,**,†
Follow-up Period [‡] , mean (SD), y	3.6 (1.8)	3.3 (1.7)	3.4 (1.7)	3.2 (1.7)	<0.001\$
Conversion Status Frequency					
Stable/Persistent (%)	91	83	80	71	---
Progressive/Converters (%)	9	17	20	29	---
Mild Cognitive Impairment Participants					
	No Complaint n=263	Self Complaint n=197	Informant Complaint n=151	Self + Informant Complaint n=1232	p value
Age, mean (SD), y	74.3 (7.2)	74.4 (7.9)	76.3 (7.1)	74.2 (7.5)	0.02
Sex (% Female)	57	64	45	50	<0.001**,†,‡
Race (% White)	68	67	80	85	<0.001‡,‡,‡,‡,‡,‡,‡,‡
Education, mean (SD), y	15.8 (9.6)	15.0 (3.4)	15.3 (3.2)	15.8 (5.7)	0.04
Baseline MMSE score [†] , mean (SD)	28.0 (1.8)	27.5 (1.8)	27.6 (1.9)	27.3 (1.9)	<0.001\$,‡,‡
Follow-up Period [‡] , mean (SD), y	3.1 (1.7)	3.0 (1.8)	3.2 (1.6)	2.9 (1.6)	0.21
Conversion Status Frequency					
Reverters (%)	32	25	8	6	---
Stable/Persistent (%)	51	55	50	45	---
Progressive/Converters (%)	17	20	42	49	---

Note: Complaint categories are mutually exclusive and defined based on clinician-facilitated interviews with the participant and informant. MMSE=Mini Mental State Examination.

[†]MMSE score range from 0–30 with lower score=worse performance;

[‡]Follow-up period is time from the first visit until time to the last visit; Post-hoc group comparisons with Bonferroni correction:

§ no complaint > both complaints;
 ¶ no complaint > self complaint;
 # no complaint > informant complaint;
 ** self complaint > informant complaint;
 †† self complaint > both complaints;
 ‡‡ no complaint < both complaints;
 §§ self complaint < both complaints

Table 2

Odds Ratios for Diagnostic Outcome

Normal Cognition					
	Self Complaint [‡]	p value	Informant Complaint [‡]	p value	Self + Informant Complaint [‡]
Convert vs. Stable ^{##}	2.1 [1.5–2.9] [*]	<0.001	2.2 [1.2–3.9] [*]	<0.001	4.2 [2.9–6.0] [*]
Mild Cognitive Impairment					
	Self Complaint [‡]	p value	Informant Complaint [‡]	p value	Self + Informant Complaint [‡]
Revert vs. Stable ^{##}	0.8 [0.4–1.5]	0.37	0.3 [0.1–0.6] [*]	<0.001	0.2 [0.1–0.4] [*]
Convert vs. Stable ^{##}	1.0 [0.5–1.9]	0.85	2.2 [1.2–4.3] [*]	0.002	2.9 [1.8–4.8] [*]

Note: Data presented as Odds Ratio [99% Confidence Interval];

* p<.01;

[‡] predictor referent=no complaint;

^{##} outcome referent=stable, Complaint categories are mutually exclusive and defined based on clinician-facilitated interviews with the participant and informant;