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Clinical research risk assessment among individuals with mild cognitive impairment

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Abstract

Objective—To determine whether individuals with mild cognitive impairment (MCI) differ from cognitively normal (NC) elders on a risk assessment task and whether participants and their study partners evaluate risk/benefit similarly.

Design—Cross-sectional.

Setting—University medical setting.

Participants—Seventy-nine participants (NC n=40; MCI n=39), 60–90 years (73±7 years; 53% female) and 64 study partners (NC n=36; MCI n=28), 38–84 years (68±10 years; 67% female).

Measurements—Participants and study partners completed a risk assessment task that involved ranking from least to most risk four hypothetical vignettes for memory loss research (brain autopsy, blood draw, oral medication, neurosurgery). Participants also completed decisional capacity for research and neuropsychological protocols.

Results—MCI participants' risk rankings differed from NC risk rankings ($p<0.001$) with MCI participants ranking brain autopsy higher and an oral medication trial lower. Demographic, decisional capacity, and neuropsychological variables could not explain MCI participant performances. Participants and their study partners had comparable risk assessment performance (p-values=1.0). MCI study partners performing similar to their MCI participant counterparts but different from NC study partners ($p=0.002$; i.e., ranking autopsy higher and oral medication lower).

Conclusion—Findings suggest individuals with MCI assess risk differently than NC peers by overestimating the risk (or underestimating the benefit) of brain autopsy and underestimating the risk (or overestimating the benefit) of oral medication. Study partners display a similar pattern. These observations may be secondary to MCI participants' (and their study partners') personal connection to the potential benefits of an experimental medication for memory loss.

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Keywords

mild cognitive impairment; research ethics; research participation; study partners; research proxy

Objective

Alzheimer's disease (AD) is a major public health issue that will worsen over the next decade,[1] increasing the need for clinical research advances in prevention and treatment. Such research is particularly important among elders with mild cognitive impairment (MCI) who manifest the earliest symptoms of AD.[2]

Individuals with AD[3] differ from their cognitively normal peers on measures of decisional capacity for research participation, particularly their abilities to understand, appreciate, and reason. However, people with mild or early AD typically retain their ability to express a choice about whether to participate in research,[4] though this willingness decreases with an increased perception of risk.[5] Thus, when persons with AD are considering research participation, even though they may have compromised decisional abilities, they may still preserve their ability to assess risk.

Less is known, however, about how individuals with MCI assess risk when considering research participation. According to diagnostic criteria,[6] individuals with MCI are functionally independent, though they may exhibit mild difficulties performing complex functional tasks. Indeed, individuals with MCI perform less well on research,[7] medical,[8] and financial[9] decisional capacity tools as compared to their cognitively normal (NC) peers. However, prior studies suggest patients with AD preserve the ability to assess risk for research participation,[5] so it is plausible that individuals with MCI would perform comparable to their NC peers on a risk assessment task in which they must consider the potential risk and benefit ratio of hypothetical research vignettes focused on the diagnosis and treatment of abnormal cognitive aging.[10]

There are several reasons why it is important to understand how individuals with MCI assess risk and benefit for research opportunities. First, cognitive aging research is increasingly focused on the identification of biomarkers to enhance in vivo detection of the AD pathophysiological process among individuals with MCI who may benefit from disease-modifying therapeutics, so individuals with MCI are becoming an increasingly preferred cohort for biomarker and therapeutic studies with varying risks and benefits.[11] Second, as many as 48% of individuals with MCI convert to AD over a 4 year period, and many biomarker and treatment studies have a longitudinal component in which a subset of participants with MCI will likely decline.[12] Third, cognitive aging studies often require a study partner to co-participate, and as a participant's cognitive symptoms progress, these study partners often contribute to research participation decisions,[4] particularly if participants are no longer able to make such decisions independently.[13] Research has suggested that individuals with AD and their study partners similarly assess risks associated with various research scenarios, meaning that as research risks increase both patients and their study partners are less willing to participate.[5] However, it is not yet known whether individuals with MCI and their study partners similarly view risks and benefits for different, ecologically valid research scenarios (i.e., diagnostic and treatment studies for memory loss). Such information will contribute to recruitment and enrollment efforts of elders with the earliest signs of cognitive impairment, particularly for longitudinal studies in which cognition may decline for some participants.

This study had two purposes. First, we aimed to characterize MCI participants' "risk assessment performance" measured by asking participants to rank from least to most risk

ecologically relevant, hypothetical research vignettes with varying risk and benefit.[10] Consistent with past research suggesting patients with mild to moderate AD preserve the ability to assess risk for research participation,[5] we hypothesized that participants with MCI would have similar risk assessment performance compared to age-, sex-, race-, and education-matched NC participants. Second, using the same vignettes, we compared participants' risk assessment performance with that of their respective study partner, hypothesizing that both NC and MCI participants would have similar risk assessment performance with their respective study partners.

Methods

Participants

As previously described,[7] participants included 80 individuals recruited from the Boston University Alzheimer's Disease Center (BU ADC) research registry and affiliated neurologists' offices. As part of the research registry, participants are seen annually for a memory diagnostic work-up, which includes a clinical interview with the participant and a reliable informant, neurological and physical examinations, and a neuropsychological assessment. Using this information, a multidisciplinary consensus conference (i.e., neurologists, neuropsychologists, nurse practitioner) reach clinical diagnoses using widely accepted criteria.[2,6,14] Participants for the current study were age 60 to 90 years, community dwelling, and English speakers. Exclusion criteria included a history of major psychiatric illness (e.g., schizophrenia, bipolar disorder), neurological illness (e.g., stroke, epilepsy, dementia, mental retardation), or head injury with significant loss of consciousness. One participant did not complete the risk assessment task (described below), so participants eligible for the current study included 39 individuals diagnosed with MCI[2,6,14] and 40 NC elders free of cognitive and functional impairment based on multidisciplinary consensus diagnosis (see Table 1 for participant characteristics).

At the time of recruitment, each MCI and NC participant was asked to identify a "study partner," defined as someone with whom they interacted frequently and could complete questionnaires on the participant's daily functioning.[15] For this particular manuscript, study partners were excluded if they were unable to attend the study visit in person to complete the risk assessment protocol, which resulted in 28 study partners for the MCI participants ("MCI study partners") and 36 study partners for the NC participants ("NC study partners"). The protocol was approved by local Institutional Review Boards. All participants were considered capable of providing informed consent, and participants and study partners provided written informed consent prior to the study visit.

Risk Assessment Task

Four previously published hypothetical research vignettes with varying risk/benefit ratios were used to evaluate risk assessment.[10] The ecologically relevant vignettes share the goal of advancing the field of abnormal cognitive aging, but each vignette contains a unique study implementing different procedures: brain autopsy, blood draw, oral medication, and neurosurgery. The vignettes were presented on individual cards and read aloud to each participant in a predetermined random order (i.e., blood draw, neurosurgery, oral medication, brain autopsy). Participants were asked to rank the vignettes from least to most risk based upon their perceived risk-benefit ratio. The investigative team *a priori* defined the order of ranking of the vignettes from least to most risk: brain autopsy, blood draw, oral medication, and neurosurgery. At the time of data collection, each participant's ranking was coded as the rank order of each vignette. For the purposes of the current study, these rankings were re-coded into a dichotomous variable (1=all vignettes ranked in the *a priori*

defined order; 0=if one or more vignettes ranked out of order). MCI and NC participants as well as their respective study partners completed the risk assessment protocol.

Decisional Capacity Assessment

The MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) evaluates decision-making capacity via a semi-structured interview.[16] The present study customized the MacCAT-CR with a hypothetical, but ecologically relevant, FDA Phase III clinical trial of a drug to treat memory decline.[7] The hypothetical protocol included a randomized, double-blind, placebo-controlled study with multiple visits, brain MRI, lumbar puncture, neuropsychological assessment, blood draw, and EKG. The interview assessed four decisional capacity abilities, including Understanding (13 items), Appreciation (3 items), Reasoning (4 items), and Expression of a Choice (1 item). Each item is scored 0–2, and higher scores indicate better performance. Only the NC and MCI participants completed the MacCAT-CR protocol. Decisional capacity performances were used in post-hoc analyses between the NC and MCI participants to better understand differences in risk assessment performance.

Neuropsychological Evaluation

MCI and NC participants completed a neuropsychological protocol in which measures were selected a priori to represent different cognitive systems of interest for the current study:[7] (1) *Global Cognition*: Mini-Mental State Examination (MMSE);[17] (2) *Episodic Memory*: California Verbal Learning Test-II (CVLT-II) Long Delay Free Recall;[18] (3) *Verbal Reasoning*: Wechsler Adult Intelligence Scale-III (WAIS-III) Similarities; (4) *Nonverbal Abstract Reasoning*: WAIS-III Matrix Reasoning;[19] (5) *Information Processing Speed*: Delis-Kaplan Executive Function System (D-KEFS) Number Sequencing; and (6) *Executive Functioning*: DKEFS Number-Letter Sequencing.[20] The Wide Range Achievement Test 3rd Edition (WRAT-3) Reading subtest[21] was used to assess literacy or education quality.[22] Only the NC and MCI participants completed the neuropsychological protocol, and these data were used in post-hoc analyses between the NC and MCI participants to better understand differences in risk assessment performance.

Data Analyses

Prior to hypothesis testing, clinical characteristics (age, education, sex, race, MMSE) were compared between the participant groups (NC versus MCI) and study partner groups (NC study partners versus MCI study partners). To test the hypothesis that NC and MCI participants would perceive risks similarly, we compared vignette accuracy (i.e., defined as a dichotomous variable) using chi-square tests. Mann-Whitney 2-sample tests were used to calculate between-group comparisons (NC versus MCI participants) of mean rankings, defined as the ranking position (1, 2, 3 or 4) of each vignette. Post-hoc analyses using independent-samples t-tests examined relations between risk assessment performance and a subset of the MacCAT-CR dimensions (Understanding, Appreciation, Reasoning) and neuropsychological performances (MMSE, WRAT-3 Reading, WAIS-III Similarities, WAIS-III Matrix Reasoning, DKEFS Number Sequencing, DKEFS Number-Letter Sequencing, CVLT-II Long-Delay Free Recall) to assess whether decisional capacity or neuropsychological performances accounted for between-group risk assessment differences.

Exact McNemar tests compared participants and their study partners on the risk assessment task (i.e., defined as a dichotomous variable), separately by diagnostic group (MCI participants versus MCI study partners; NC participants versus NC study partners). Secondary analyses compared the two study partner groups on the risk assessment task using chi-square tests, and Mann-Whitney 2-sample tests calculated between-group comparisons

(NC study partners versus MCI study partners) of mean rankings (i.e., defined as the ranking position of each vignette).

Significance was set *a priori* at α=0.05. Fisher's exact test was used instead of chi-square test when expected cell frequency assumptions were not met.

Results

Clinical Characteristics

There were no between-group differences for the MCI and NC participants for age ($t_{(77)}$= −1.4, p=0.17), education ($t_{(77)}$=1.4, p=0.18), sex (x^2=1.5, p=0.22), or race (x^2=0.1, p=0.73). As expected, the MCI participants had significantly lower MMSE ($t_{(77)}$=4.5, p<0.001) and WRAT-3 Reading scores ($t_{(77)}$=4.8, p<0.001) than the NC participants.

There were no between-group differences for the MCI and NC participants' study partners for age ($t_{(62)}$=1.7, p=0.10), sex (x^2=0.01, p=0.92), race (x^2=0.6, p=0.43), or MMSE ($t_{(62)}$=1.8, p=0.08). However, the MCI study partners did have lower education levels ($t_{(62)}$=3.3, p=0.001) and WRAT-3 Reading scores ($t_{(62)}$=3.1, p=0.003) than the NC study partners. See Table 1 for details.

Risk Assessment Comparison for MCI and NC Participants

Risk assessment performance differed between the two participant groups (x^2=14.6, p<0.001), such that the MCI participants performed less accurately than the NC participants. Mean ranking comparisons suggested that the MCI participants may have overestimated the risk (or underestimated the benefit) associated with the brain autopsy vignette (Mann-Whitney z=−2.8, p=0.005) and underestimated the risk (or overestimated the benefit) of the clinical trial (Mann-Whitney z=−2.9, p=0.004; see Table 2). A post-hoc between-group binary logistic regression was calculated to test if WRAT-3 Reading score attenuated the findings; however, the risk assessment performance difference between the two groups persisted (Wald chi-square=5.3, df=1, p=0.02).

In post-hoc models, MCI participants with accurate (n=23, 59%) versus inaccurate (n=16, 41%) risk assessment performances did not differ for age ($t_{(37)}$=0.3, p=0.79), education ($t_{(37)}$= −0.03, p=0.98), sex (x^2=0.2, p=0.69), or race (x^2=1.9, p=0.16). Similarly, no differences emerged for the MacCAT-CR dimensions, including Understanding ($t_{(37)}$=−1.4, p=0.18), Appreciation ($t_{(37)}$=−0.7, p=0.48), or Reasoning ($t_{(37)}$=−0.8, p=0.45). Finally, no between-group differences emerged for neuropsychological performances, including MMSE ($t_{(37)}$=−0.5, p=0.59), WRAT-3 Reading ($t_{(37)}$=−1.8, p=0.08), Similarities ($t_{(37)}$=−1.1, p=0.30), Matrix Reasoning ($t_{(37)}$=−0.6, p=0.58), DKEFS Number Sequencing ($t_{(37)}$=1.8, p=0.07), DKEFS Number-Letter Sequencing ($t_{(36)}$=1.3, p=0.22), or CVLT Long Delay Free Recall ($t_{(37)}$=−0.6, p=0.58).

To explore the MCI participants' preference to overestimate the risk of brain autopsy, post-hoc analyses examined BU ADC brain donation status focusing on participants who refused (n=9) or assented to donation (n=51), excluding individuals still considering donation (i.e., do MCI individuals who are unwilling to donate their brain to the BU ADC overestimate the risk of brain autopsy?). In post-hoc analyses, there was no difference between NC (n=32) and MCI participants (n=28) for brain donation status (x^2=1.7, p=0.28). When restricted to MCI participants, brain donation status did not differ between participants with accurate (n=16, 57%) versus inaccurate (n=12, 43%) risk assessment performances (x^2=0.3, p=0.67).

To better understand why MCI participants underestimated the risk of an oral medication trial, post-hoc analyses examined whether specific decisional capacity items about oral

medication risk and benefit were related to risk assessment performance. A difference was found on the MacCAT-CR item assessing understanding of specific procedural risks and benefits of participation in the hypothetical drug trial ($t_{(37)}$=−2.1, p=0.04), such that MCI participants with inaccurate risk assessment performances reported fewer procedural risks and benefits than MCI participants with accurate risk assessment performances. While there was a difference between the NC and MCI participant groups for their willingness to participate in the MacCAT-CR hypothetical trial (x^2=8.2, p=0.004), among the MCI participants, willingness to participate was not associated with risk assessment accuracy (x^2=0.1, p=0.77). Furthermore, there was no difference between MCI participants with accurate versus inaccurate risk assessment performances about the hypothetical trial and the MacCAT-CR measure of their appreciation of whether they were being asked to be in the trial for their own personal medical benefit (x^2=0.01, p=1.0).

Risk Assessment Comparison Between Participants & Study Partners

There was no between-group difference for risk assessment performance between the NC participants and their study partners (exact McNemar=0.2, df=1, p=0.7) or between the MCI participants and their study partners (exact McNemar=0.0, df=1, p=1.0).

In post-hoc analyses, the two study partner groups differed on the risk assessment task (x^2=10.5, df=1, p=0.001), such that the MCI study partners performed less accurately. Mean rankings (see Table 2) suggested the MCI study partners, like MCI participants, overestimated risk (or underestimated the benefit) associated with the brain autopsy vignette (Mann-Whitney z=−2.6, df=1, p=0.01) while underestimating risk (or overestimating the benefit) associated with the clinical trial vignette (Mann-Whitney z=−2.3, df=1, p=0.02).

In a post-hoc between-group binary logistic regression, the risk assessment performance difference between the two groups persisted despite inclusion of WRAT-3 Reading score (Wald chi-square=5.8, df=1, p=0.02), education (Wald chi-square=5.2, df=1, p=0.02), or MMSE (Wald chi-square=7.7, df=1, p=0.006) in the model.

Conclusions

The current study characterized how individuals with MCI assess risk and benefit for varied hypothetical but ecologically relevant research opportunities. Findings suggest that MCI participants assess the risk-benefit ratio of a blood draw and neurosurgical study similar to NC elders; however, a number of MCI participants overestimate the risk of a brain autopsy study and underestimate the risk of an oral medication trial relative to their NC peers. These differences could not be explained by demographics, reading ability, cognitive performances, decisional capacity abilities, or brain donation status.

There are several explanations for MCI participants' tendency to underestimate risk relative to the oral medication trial. First, because of their own personal memory loss, the MCI participants may overestimate the potential personal benefit of an experimental medication for minimizing memory loss, compared to other research without a possibility of direct personal benefit (e.g., brain autopsy). While the MCI participants with accurate and inaccurate vignette rankings did not differ in their willingness to join a hypothetical clinical trial testing an experimental medication for memory loss, we did find that MCI participants in general are more likely than their NC peers to express an interest in joining such a trial.

Alternatively, MCI participants may appreciate clinical trial design differently or they may not understand procedural risks and potential benefits of participating in a clinical drug trial in the same way as their NC peers. In post-hoc analyses, we found that MCI participants with inaccurate risk rankings had lower scores on a MacCAT-CR item assessing

understanding of risks and benefits of participating. It is important to note that when the MCI participants with accurate and inaccurate vignette rankings were compared, no differences were noted between the subgroups in their appreciation of whether the hypothetical clinical trial was for their own personal benefit. As an increasing number of clinical trials are targeting individuals with the earliest signs of memory loss,[23–26] more research is warranted to further understand how individuals with MCI weigh risks and potential personal benefits of such trials.

The MCI participants also overestimated the risk associated with brain autopsy as compared to NC peers, which may reflect an underestimation of benefit associated with donating one's brain. However, brain donation status within our ADC did not differ between the MCI and NC participants. Just as older adults "at risk" for clinical dementia are of significant interest to clinical trial research, they are also of interest for neuropathological research.[27,28] Neuropathological studies can contribute to the discovery and development of important therapeutic targets, and clinicopathological research enhances our understanding of the clinical expression of early AD neuropathology and improves in vivo diagnostic methods. While we did not find donation status to differ as a function of risk assessment, more research is needed to understand whether individuals with MCI or early AD truly view the risk and benefit of autopsy differently. This information could enhance educational procedures for brain donation programs in research settings.

A second aim of the study was to characterize the accuracy of risk assessment between participants and their study partners. We observed concordance between participant and study partner's risk assessment accuracy for both the MCI and the NC groups. The MCI study partners performed similarly to their loved ones in that they overestimated the risk of brain autopsy and underestimated the risk of an oral medication trial. The risk ranking difference between the two study partner groups could not be accounted for by cognitive status, education, or reading skills in post-hoc models. The observation of concordance between study partners and participants is consistent with prior work reporting that a willingness to participate in clinical research vignettes of varying risk (e.g., blood draw, brain surgery) was concordant between patients with mild to moderate AD and AD caregivers.[5] One explanation for the current observation is that, just like the MCI participants, the MCI study partners have a personal connection to memory loss. They live with or are close to someone affected by abnormal cognitive changes, so they may value the potential benefit of an experimental medication more than someone without any personal connection.

Among individuals with clinically significant cognitive impairment, study partners are integral in the decision making process for enrolling their loved ones in research.[29,30] While patients often select proxies who will make decisions that consider both the patient's personal preferences and the proxy's opinion of what is in the patient's best interest,[10] patients select proxies who are also flexible about research participation decisions.[31] Our findings enhance the literature by reporting that individuals in the prodromal phase of AD select study partners who perform similarly on a risk assessment task. This observation is particularly timely given that many cognitive aging studies with MCI cohorts are longitudinal, and participants are expected to decline over time,[32] requiring a proxy to make future research participation decisions on their behalf.

The current study is among the first to examine risk assessment in individuals with MCI and risk ranking concordance with their study partners and has many strengths. First, our ecologically valid risk assessment task included vignettes focused on memory loss interventions,[10] which were highly relevant to our participant and study partner cohorts. Second, in addition to the risk assessment tool, we implemented a neuropsychological

assessment of multiple cognitive systems and a well-validated decisional capacity assessment tool (i.e., MacCAT-CR), which allowed for statistical consideration of potential confounders to explain the risk assessment results. Third, recruitment of individuals from a local NIA-funded ADC provided us with NC and MCI participants who had undergone a comprehensive memory work-up (independent of this study's protocol).[7,15] Finally, recruitment of participants from our local Center simultaneously provided information on brain donation status, which allowed us to conduct secondary analyses to explore factors underlying risk assessment rankings.

Despite multiple strengths, there are several methodological limitations. First, the sample size was relatively small, so we consider our findings preliminary and in need of replication. Second, our analytical plan included many models, which may have yielded spurious results. Third, our sample was predominantly White and highly-educated, which limits generalizability to other ethnic and racial groups or individuals with lower levels of education. Fourth, despite inclusion of a neuropsychological and decisional capacity protocol, our methodology may not have sufficiently encompassed all potential confounders to explain the risk assessment results. Finally, and perhaps most importantly, our study design did not allow participants to rank the vignettes equally in terms of risk and benefit. Because the vignettes were ordered from least to most risk, an incorrect ranking of one vignette automatically resulted in at least one additional incorrect ranking. Thus, it is highly plausible that the MCI participants incorrectly ranked only one vignette (e.g., oral medication trial); however, our relative ranking methodology forced an incorrect ranking of a second vignette (i.e., brain autopsy). Therefore, the observation that MCI participants (and their study partners) both overestimated the risk for brain autopsy and underestimated the risk for a clinical trial may be an artifact due to our ranking methods. To circumvent this limitation, we used a dichotomous variable for quantifying risk assessment performance. However, we cannot rule out the potential that the ranking method contributed some error, and only one of these two risk assessment differences may be valid.

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Table 1

Demographic and clinical characteristics of participants and study partners

Characteristic, units	NC participants n=40	MCI participants n=39	NC study partners n=36	MCI study partners n=28
Age, years	72±5 (60–82)	74±8 (60–90)	70±7 (51–84)	66±13 (38–83)
Education, years	16±2 (12–21)	16±3 (12–21)	17±3[a] (12–21)	15±3[a] (12–21)
WRAT-III Reading, total score	55±2[b] (50–57)	50±6[b] (34–57)	54±3[c] (44–57)	51±4[c] (40–57)
MMSE, total score	29±1[d] (27–30)	28±2[d] (22–30)	29±1 (26–30)	28±2 (24–30)
Sex, % female	60	46	67	68
Race, % White	83	80	86	79
Study partner lives with participant, %	--		58	54
Study partner and participant are family[e], %	67	70	--	--
Study partners reporting daily contact with participant, %	--	--	61	64

Note: Data presented as mean ± standard deviation (range) or percentage (%); NC=cognitively normal control; MCI=mild cognitive impairment; WRAT=Wide Range Achievement Test; MMSE=Mini-Mental State Examination; For participants, independent sample t-tests were used to calculate between-group comparisons for age, education, WRAT-III, and MMSE (df=78). For study partners, independent sample t-tests were used to calculate between-group comparisons for age (df=75), education (df=73), WRAT-III (df=62), and MMSE (df=62). Chi-square test was used for sex and race.

[a] Significant difference between NC and MCI study partners (t=3.3, p=0.001)

[b] Significant difference between NC and MCI participants (t=4.8, p<0.001)

[c] Significant difference between NC and MCI study partners (t=3.1, p=0.003)

[d] Significant difference between NC and MCI participants (t=4.5, p<0.001)

[e] Defined as spouses, domestic partners, children, or siblings

Table 2

Risk assessment mean rankings

	NC participants	MCI participants	p-value	NC study partners	MCI study partners	p-value
Autopsy Vignette	1.0±0.2	1.4±0.8	0.005[a]	1.1±0.2	1.5±0.9	0.01[b]
Blood Draw Vignette	2.0±0.2	2.0±0.6	0.6	2.0±0.4	2.1±0.7	0.6
Oral Medical Vignette	3.0±0.2	2.7±0.6	0.004[c]	3.0±0.2	2.7±0.7	0.02[d]
Neurosurgery Vignette	4.0±0.2	3.9±0.5	0.3	4.0±0.2	3.8±0.7	0.09

Note: Data presented as mean ± standard deviation; Mann-Whitney tests were used to calculate between group comparisons for each vignette

[a] Significant difference between NC and MCI participants (z=−2.8, df=1,79, p=0.005)

[b] Significant difference between NC and MCI study partners (z=−2.6, df=1,64, p=0.01)

[c] Significant difference between NC and MCI participants (z=−2.9, df=1,79, p=0.004)

[d] Significant difference between NC and MCI study partners (z=−2.3, df=1,64, p=0.02)

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