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OLD WORRIES AND NEW ANXIETIES – BEHAVIORAL SYMPTOMS AND MILD COGNITIVE IMPAIRMENT IN A POPULATION STUDY

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Abstract

Objective—To disentangle the complex associations of depression and anxiety with mild cognitive impairment (MCI) at the population level. We examined subgroups of anxiety symptoms and depression symptom profiles in relation to MCI, which we defined using both cognitive and functional approaches.

Design—Epidemiologic, cross-sectional study.

Settings and Participants—Age-stratified random population-based sample of 1982 individuals aged 65 and over.

Measurements—Three definitions of MCI: 1) a purely cognitive classification into Amnesic and Non-Amnesic MCI; 2) a combined cognitive-functional definition by International Working Group (IWG) criteria; 3) a purely functional definition by the Clinical Dementia Rating (CDR)=0.5. Three Depression profiles were identified by factor analysis of the modified Center for Epidemiological Studies - Depression Scale: core mood, self-esteem/interpersonal, and apathy/neurovegetative profiles. Three Anxiety groups: chronic mild worry, chronic severe anxiety, and recent-onset anxiety, were based on screening questions.

Results—Recent-onset anxiety was associated with MCI by Non-Amnesic and IWG criteria, chronic severe anxiety was associated with MCI by all definitions, while chronic mild worry was associated with none. Of the depression profiles, the core mood profile was associated with CDR-

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defined MCI, the apathy/neurovegetative profile was associated with MCI by Amnesic, IWG, and CDR definitions, while the self-esteem/interpersonal profile was associated with none.

Conclusions—In this population-based sample, subgroups with different anxiety and depression profiles had different relationships with cognitive and functional definitions of MCI. Anxiety, depression, and MCI are all multidimensional entities, interacting in complex ways that may shed light on underlying neural mechanisms.

OBJECTIVE

Older adults constitute a growing proportion of those seeking mental health services in specialty as well as primary care sectors. Clinicians increasingly encounter patients with depression, anxiety, and other behavioral symptoms in the context of cognitive impairment. Mild cognitive impairment (MCI), a cognitive state intermediate between normal aging and dementia, often but not always progresses to dementia (1). Multiple studies have demonstrated associations of behavioral and psychological symptoms with dementia (2–4). In contrast, the literature describing associations of MCI with depression and anxiety presents a more patchy landscape, largely focused on the relationship between depression and prognostic risk in MCI (5, 6).

A particular challenge is posed by variations across studies, both in the definition of MCI, and in the measurement of behavioral and psychological symptoms. Results also vary because of inherent differences between clinic-based samples of patients seeking services, and population-based samples of randomly selected participants. Two large population-based studies used the Neuropsychiatric Inventory (7) to identify behavioral symptoms most often associated with MCI. In the multi-center Cardiovascular Health Study (8), MCI defined by cognitive assessment was frequently associated with depression, apathy and irritability. In the Mayo Clinic Study of Aging (9), apathy, agitation, anxiety, irritability, and depression were associated with MCI defined by the International Working Group criteria (also known as the “Winblad criteria.”) (10). A recent review described an overall prevalence of 35–85% of neuropsychiatric symptoms in MCI (11); depression, anxiety and irritability were the most common symptoms. The association between depression and MCI is consistently reported, but the association of MCI with anxiety symptoms remains controversial. While some studies have reported no differences in anxiety symptoms between cognitively intact individuals and MCI (12), others showed elevated proportions with anxiety in MCI both in community (8, 9) and in clinical samples (13, 14).

We sought to deconstruct anxiety and depression and explore their finer-grained relationships with MCI defined in three distinct ways, within a large, population-based study cohort of older adults.

METHODS

Study site and population

The study cohort named the Monongahela-Youghiogheny Healthy Aging Team (MYHAT) is an age-stratified random population sample drawn from the publicly available voter registration list for a small-town region of Pennsylvania (USA)(15). Community outreach, recruitment, and assessment protocols were approved by the University of Pittsburgh IRB for protection of human subjects. Recruitment criteria were (a) age 65 years or older, (b) living within the selected towns, (c) not already in long-term care institutions. Individuals were ineligible if they (d) were too ill to participate, (e) had severe vision or hearing impairments, (f) were decisionally incapacitated. We recruited 2036 individuals over a two-year period. Since the project was designed to study mild cognitive impairment, we excluded the most severely impaired individuals who scored <21/30 on the age-education-

adjusted Mini-Mental State Evaluation (MMSE)(16). The remaining 1982 individuals underwent the detailed in-home assessment including, but not limited to, the elements below.

Depression and anxiety symptoms

Depression symptoms—Participants were screened with the modified Center for Epidemiological Studies - Depression Scale (mCES-D) (17, 18). This previously reported modification includes all 20 original CES-D items but asks about their presence “most of the time” over the preceding week, in a yes/no format coded as 1/0, so that the maximum possible score is 20. When treating the score as a categorical variable, we use a threshold reflecting the 90th percentile score on the mCES-D: a score of 5, representing the presence of any five symptoms. Besides the total score, three weighted factors were derived based on exploratory factor analysis (see Results).

Anxiety symptoms—We used three questions to screen for anxiety symptoms: (1) “Would you describe yourself as a worrier?” (2) “Would you say that you easily become nervous or upset?” (3) “Would you say you had always been this way, or is this a recent change?” We asked Questions 2 and 3 if subjects responded positively to the first question. Questions # 1 and # 2 are Generalized Anxiety Disorder screening questions from the Penn State Worry Questionnaire (19); we introduced Question # 3 to further identify new-onset anxiety. These questions were selected for face validity and ease of reliable administration by trained non-clinician interviewers.

Cognitive assessments

We assessed cognitive functioning using a comprehensive test battery on which we have reported population-based norms (20). These tests tap the cognitive domains of attention/processing speed (Trail-Making test A, Digit Span Forward), executive function (Trail-Making Test B, Clock Drawing, Verbal Fluency for initial letters P & S), memory (WMS-R Logical Memory (immediate and delayed recall), WMS-R Visual Reproduction (immediate and delayed recall), Fuld Object Memory Evaluation with Semantic Interference), language (Boston Naming Test, Verbal Fluency for Animals, Indiana University Token Test), and visuospatial function (WAIS-III Block Design). We created a composite score for each domain as previously described (20).

Mild Cognitive Impairment definitions

We classified participants according to three sets of criteria for MCI: a purely cognitive classification (10, 21), the purely functional Clinical Dementia Rating [CDR] (22), and the current standard International Working Group (IWG) criteria (10) which include both cognitive and functional elements and thus more closely approximate clinical practice.

Under the purely cognitive classification (21), we classified individuals as cognitively normal if all of their cognitive domain scores fell within one standard deviation (SD) of the appropriate mean, based on our previously published norms; as severely cognitively impaired if two or more domain scores fell 2 or more SDs below the mean; and as MCI if one or more scores fell between 1 and 2 SDs below the mean. Those with MCI were further subclassified into Amnesic and Non-Amnesic MCI depending on the presence or absence of memory impairment.

On the Clinical Dementia Rating (CDR) (22), based solely on cognitively-driven functional decline, independent of neuropsychological test scores, we designated as MCI those participants who received a CDR rating of 0.5 (21).

We operationalized the standard IWG criteria based on (a) objective cognitive deficit as above, (b) two or more subjective complaints from a standardized list, (c) absence of dementia: CDR <1, (d) no impaired instrumental activities of daily living on the Older Americans Resources and Services (OARS) scale (23); (e) essentially normal mental status: MMSE ≥ 21 (20).

Statistical methods

We calculated descriptive statistics for the demographic characteristics of the entire sample and for the different MCI definitions and subgroups described above. We used participants' responses to the three anxiety questions to create three anxiety groups (see Results). Exploratory factor analysis with PROMAX rotation, performed on the twenty mCES-D items, revealed a three-factor structure (see Results) that we used to create three depression symptom profiles (23). To investigate the associations of MCI with anxiety and depression symptoms, we first fit univariable logistic regression models with each MCI definition as the dependent variable and the each anxiety group, each three depression profile, and mCES-D score ≥ 5 as independent variables. We then fit multivariable logistic regression models including all anxiety groups and depression profiles. We also fit univariable linear regression models to investigate the relationships between depression, anxiety, and the five cognitive domain composite scores treated as continuous measures. All models were adjusted for age, sex, and education.

We used variance inflation factor (VIF) to test collinearity among the mCES-D total score and the factors obtained from factor analysis. We observed no collinearity among the anxiety groups, the depression factors, or between the anxiety and depression variables. We observed collinearity between the mCES-D score and the 3 depression factors (VIF >5) and therefore excluded the mCES-D score from the multivariable analysis.

In *post-hoc* analyses, we explored the associations of the depression factors, the anxiety groups, and the MCI definitions with a panel of vascular factors, in order to discern potential confounding associations. We identified as potential confounders those vascular variables that were associated with at least one MCI definition and at least one anxiety or depression variable. We included potential confounders as covariates in the final multivariable models. In all analyses, 2-sided *P* values less than 0.05 considered statistically significant. All analyses were performed using SAS statistical software, version 9.2 (24).

RESULTS

Of the 1982 study participants with normal or mildly impaired cognition, 1879 had complete data on the variables of interest and comprise the sample for these analyses. These individuals had mean (SD) age 77.59 (7.40) years; 61.26% were women, and 95.21% were white. They had a median educational level of high school graduate; 41.25% had more than high school education. As regards medication use, 14.1 % reported taking antidepressant and/or antianxiety drugs. Proportions of the sample meeting criteria for the different MCI definitions, and for each MCI subgroup, its demographic characteristics, proportions with anxiety and depression symptoms, and medication use, are presented in Table 1.

Depression symptom profiles

In an exploratory factor analysis of the mCES-D in the cohort as a whole, a three-factor solution was retained, cumulatively accounting for 68.93% of the total variance. The first factor, which we designated as “*core mood*,” accounted for 56.9% of the variance and included the following items: feeling depressed, crying, feeling sad, being bothered, not being able to shake off the blues. The second factor, designated as “*self-esteem*/

interpersonal,” accounted for 6.34% of the variance and included: not feeling just as good as other people, not feeling hopeful, feeling that life had been a failure, feeling lonely, talking less, feelings that others were unfriendly, feelings that others dislike him/her, not enjoying life. The third factor, designated as “*apathy/neurovegetative*,” accounted for 5.69% of the variance and included: feeling that everything is an effort, feeling that one could not get going, decreased appetite, difficulty in focusing. The “restless sleep” item loaded equally on the second and the third factors. We repeated the mCES-D factor analysis in a subsample restricted to participants with MCI, and obtained the same three-factor solution, with similar factor loading and explaining a similar proportion of the variance (data not shown).

Anxiety symptom profiles

We created three groups based on responses to the anxiety questions. *Chronic mild worry* included individuals (N= 300) responding positively to Anxiety Question #1 (“Would you describe yourself as a worrier?”) but negatively to the subsequent two anxiety questions. *Chronic severe anxiety* included participants (N= 422) responding affirmatively to both Question #1 and Question #2 (“Would you say that you easily become nervous or upset?”), but negatively to Question #3 (“Would you say you had always been this way, or is this a recent change?”). The “mild” and “severe” designations describe the relative severity difference between the first and second groups. *Recent-onset anxiety* included individuals (N=110) who responded positively to Questions #1 and #3, regardless of their answers to Question # 2.

Anxiety symptoms, Depression symptoms, and MCI

Tables 2 and 3 show the results of univariable and multivariable models. After adjustment for demographics and for other anxiety and depression symptoms, the multivariable analyses (Table 3) showed that *mild chronic worry* was not significantly associated with any MCI definitions. In contrast, *chronic severe anxiety* had significant associations with all MCI definitions. *New onset anxiety* was associated with Non-Amnesic MCI and with MCI as defined by the standard IWG criteria. The *apathy/neurovegetative depression profile* was associated with Amnesic MCI, CDR=0.5, and with MCI by IWG criteria. The *core mood profile* was only associated with MCI as defined by CDR. Other associations significant in the univariable analysis (Table 2) lost their significance after adjustment for demographics and the other behavioral symptoms in the multivariable analysis (Table 3).

Reported use of antidepressant or anti-anxiety drugs was not associated with either MCI or total mCES-D, the anxiety groups, or the depression factors in the univariable analyses (data not shown), and was therefore excluded from the multivariable models.

In the *post-hoc* analyses to examine potential vascular confounders, the following variables were univariably associated with at least one of the MCI definitions as well as at least one of the anxiety or depression variables: self-reported history of stroke, high blood pressure, irregular heart rhythm, and congestive heart failure; measured diastolic blood pressure, and measured waist to hip ratio. In the final multivariable models, including these potential vascular confounders as confounders, the results remained unchanged (data not shown).

Anxiety and depression symptoms and cognitive domains

We found significant univariable associations between the five cognitive domains (attention, executive functions, language, memory, visuospatial abilities) and the anxiety and depression symptoms (Table 4). Here, each cognitive domain is measured as a continuous variable, unlike in the MCI analyses where it is categorized as impaired or unimpaired relative to demographic norms. Thus, a negative coefficient indicates that the behavioral item is associated with a lower cognitive domain score. Except for chronic mild worry, all

the anxiety and depression variables were significantly associated with poorer performance in the domains of attention and executive functioning. Chronic severe anxiety was also associated with worse performance in language, memory, and visuospatial domains, while recent onset anxiety was negatively associated with visuospatial performance. The number of depression symptoms (total mCES-D score = 5) was negatively associated with performance in all domains. Worse performance in all domains was associated with all three depression profiles except the core mood profile whose association with memory performance did not reach significance.

DISCUSSION

In this study of a population-based cohort of older adults, we applied a novel approach in exploring the relationship of mild cognitive impairment to anxiety and depression. By first deconstructing the broad cognitive and behavioral concepts, we were able to examine the finer-grained relationships among them. We defined mild cognitive impairment in three ways: purely cognitive, amnestic and non-amnestic; purely functional; and combined cognitive-functional. We categorized anxiety into three groups taking into account both severity and chronicity, and identified three different depression profiles based on the factor structure of the mCES-D.

Anxiety and MCI

Our approach revealed that chronic severe anxiety was associated with all definitions of MCI. These included MCI types that involve memory deficits: the purely cognitive Amnestic MCI as well as the functionally-based CDR, both of which are regarded as suggestive of underlying Alzheimer's disease(25, 26). Both severe chronic anxiety and recent-onset anxiety were associated with Non-Amnestic MCI, a less diagnostically suggestive subtype and less likely than the Amnestic form to progress to dementia(27, 28). Both chronic and recent-onset anxiety were also associated with MCI by the broad IWG definition which can be fulfilled with either amnestic or non-amnestic components. Chronic mild worry showed no association with MCI.

Notably, most older studies used just one MCI definition [the 1999 Mayo Criteria for Amnestic MCI (29) which predated the 2004 International Working Group criteria]. Most of them also used the single anxiety item from the Neuropsychiatric Inventory (7) to define anxiety symptoms (30). This item ("Does the patient become upset when separated from you? Does s/he have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?") primarily taps separation anxiety in patients with dementia, as reported by their caregivers. That question does not address milder symptoms that individuals in the community might self-report, or symptoms such as excessive worry (31, 32). Thus, the use of wide nets to capture intricate associations may partly explain inconsistencies across previous studies, as regards the association between anxiety and MCI. Instead, for this report, we defined three different anxiety profiles that capture symptom variations present in the population. In our sample, approximately a quarter older adults with MCI reported chronic anxiety, while recent onset anxiety was more rare. Moreover, our results suggest a complex association between anxiety and MCI, contingent on the onset and severity of anxiety symptoms as well as on the neuropsychological profile and functional consequences of the MCI.

Depression and MCI

We found the apathetic/neurovegetative depression profile was associated with Amnestic MCI and with the all-encompassing IWG definition; both core mood and apathy/neurodegenerative profiles were associated with the purely functional CDR =0.5, which

itself is weighted towards memory. The self-esteem interpersonal profile was not associated with any form of MCI.

The overall depression-MCI association has been already reported in the literature (5, 8, 33). We took this relationship a step further, using profiles based on a three-factor structure of the mCES-D to obtain a more detailed picture of depression. The association of the apathy/neurovegetative profile with the Amnesic MCI, is noteworthy in light of recent reports that apathy, rather than a diagnosis of depression, predicted progression from Amnesic MCI to dementia of Alzheimer's disease (3, 34). Viewed together, these findings suggest that, in the heterogeneous clinical presentations of late-life depression (35), apathy may represent the phenomenological manifestation of a cerebral degenerative process (dementia masked as depression). Alternatively, prominent neurovegetative symptoms may reflect a hyperactive hypothalamus-pituitary-adrenal axis, which has been frequently associated with accelerated cognitive decline (36, 37).

Effect Sizes

The strength of the associations we detected in these population-level data is potentially meaningful. For example, the elevated probability of having MCI as defined by CDR ranges from 35% (OR 1.35) for those with the core mood profile to 83% for those with the apathetic profile. For MCI as defined by the IWG criteria, we observed an over twofold elevation in probability for those with recent onset anxiety. The proportion of variance in the cognitive domains explained by the depression and anxiety variables ranged from about 20% for attention and visuospatial function to about 28% for language, memory, and executive functions.

Strengths and Limitations

Advantages of this study include (a) the large population-based cohort minimizing the selection bias inherent in clinical samples; (b) the extensive assessment of cognition; (c) the use of several operational definitions of MCI, that allowed us to disentangle the cognitive and functional components and generalize our results across various definitions; and (d) the deconstruction of unitary concepts of depression and anxiety, allowing their components to be isolated and examined separately in relation to cognition. However, although the screening questions for anxiety were extracted from validated questionnaires, our approach to classifying anxiety has not been independently validated. Moreover, since the severity and chronicity of the three anxiety groups have been defined relative to one another, future studies using structured measures of course and severity are needed to replicate our findings more definitively. Since the widely used and validated CES-D scale does not include an item explicitly addressing "apathy," we used as proxies the items "feeling that everything is an effort" and "feeling that one could not get going." Also, we could not explore the duration or longitudinal course of depressive symptoms (e.g. early versus late-onset). Given the primary aims and population-based design of the study, the participants did not undergo standard psychiatric evaluations that could diagnose depression and anxiety disorders.

Implications and future directions

Considering the cross-sectional nature of this report, the observed associations should be interpreted cautiously. The prognostic significance of behavioral symptoms in MCI can only be clarified through longitudinal studies, including continued follow-up of this cohort. However we offer some judicious speculation regarding the mechanisms underlying our findings, so as to yield testable hypotheses for further study.

Some authors have argued that increased anxiety represents not a risk factor but rather a consequence of the individual's self-awareness of cognitive impairment (38). The

association we found of new-onset anxiety symptoms with Non-Amnesic MCI may support this perspective, as Non-Amnesic MCI is correlated with poor performance in abilities related to health and safety (39). Possibly, this association captures individuals' anxious reactions to their perceived diminishing abilities in non-amnesic domains like attention, executive function, and visuospatial abilities. The associations among the different cognitive domains and anxiety/depression symptoms support this possibility. Other studies have suggested that the anxiety-cognitive impairment association lies in the opposite direction, i.e., that anxiety increases the risk of cognitive decline, due to a "cognitively toxic" effect mediated by elevated cortisol levels (40, 41). The positive association between chronic severe anxiety and MCI by all definitions supports this perspective. Thus, one must consider the potential for long-term impact on later-life cognition of anxiety (42) over a long period beginning in earlier life, a possibility that can be tested by long-term follow up of adults with midlife anxiety.

Another possible mechanism might involve cerebrovascular disease interfering with both cognition and regulation of emotions(43). In our data, the associations between MCI, anxiety, and depression persisted independently of the potentially confounding vascular risk factors, but we do not have neuroimaging data, such as white matter hyperintensity burden, to fully test this hypothesis.

We offer one further possible hypothesis for future study, admittedly going beyond the data presented here. The relationship between anxiety and cognitive impairment *may* be both "time-dependent" and "dose-dependent." Time-wise, late-onset anxiety might signal diminishing performance in various non-amnesic cognitive domains, while chronic pre-existing anxiety is associated with cognitive impairment in all domains, including memory. Dose-wise, mild worry seems to have little impact on cognitive functioning, while severe anxiety has a broad effect on all cognitive domains. The mechanisms underlying our findings will be fruitful areas for further investigation.

Meanwhile, older patients would be well-served by clinicians prepared not only to assess cognition and everyday functioning, but also to distinguish between old worries and new anxieties in individuals with mild cognitive impairment.

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Table 1a
Characteristics of participants with four different definitions of MCI (categorical variables).

MCI definition	Overall		Gender		Education level		Race		Anxiety symptom groups						Medication	
	N	%	N	% women	N	% greater than high school	N	% white	Mild chronic worry		Chronic severe anxiety		Recent onset anxiety		N	% take anti-depressant or anti-anxiety medication
									N	%	N	%	N	%		
Cognitive MCI	695	36.8	427	61.4	276	39.7	632	90.9	99	14.2	176	25.3	49	7.1	97	15.6
Amnesic MCI	240	16.8	144	60.0	99	41.2	224	93.3	36	15.0	66	27.5	14	5.8	36	16.5
Non-Amnesic MCI	455	27.7	283	62.2	177	38.9	408	89.6	63	13.8	110	24.2	35	7.7	61	15.1
CDR=0.5	542	27.8	302	55.7	208	38.4	500	92.2	78	14.4	144	26.6	39	7.2	83	16.0
IWG-MCI	349	17.9	206	59.0	136	38.9	321	91.9	48	13.7	100	28.6	30	8.6	49	15.1

Table 1b

Characteristics of participants with four different definitions of MCI (continuous variables).

MCI definition	Age				Depression profiles											
	mean	SD	min	max	Core mood profile				Self-esteem-interpersonal profile				Apathy/NV profile			
					mean	SD	min	max	mean	SD	min	max	mean	SD	min	max
Cognitive MCI	78.17	7.54	65	99	0.22	0.55	-0.23	3.29	0.30	0.73	-0.17	5.42	0.34	0.74	-0.17	4.83
Amnesic MCI	78.70	7.32	65	97	0.23	0.57	0.23	3.19	0.36	0.85	-0.17	5.42	0.40	0.83	-0.14	4.83
Non-Amnesic MCI	77.89	7.64	65	99	0.22	0.54	-0.23	3.29	0.27	0.66	-0.17	5.01	0.31	0.70	-0.17	4.53
CDR=0.5	79.66	7.35	65	99	0.29	0.65	-0.41	4.43	0.42	0.87	-0.17	6.08	0.48	0.89	-0.14	4.83
IWG -MCI	78.44	7.56	65	99	0.27	0.56	-0.23	2.90	0.37	0.83	-0.17	5.42	0.45	0.84	-0.10	4.83

CDR = Clinical Rating Scale; IWG= International Working Group 2004; MCI= Mild Cognitive Impairment; NV = neurovegetative; SD = standard deviation; min = minimum; max = maximum.

Table 2

Associations of anxiety and depression with four different MCI definitions: univariable models*

	Amnesic MCI			Non-Amnesic MCI			CDR=0.5			IWG-MCI		
	OR (95% CI)	Test statistic	P value	OR (95% CI)	Test statistic	P value	OR (95% CI)	Test statistic	P value	OR (95% CI)	Test statistic	P value
Chronic Mild Worry	1.18 (0.78, 1.78)	0.60	0.44	1.04 (0.75, 1.45)	0.06	0.8	1.25 (0.93, 1.70)	2.15	0.14	1.18 (0.83, 1.69)	0.85	0.36
Chronic Severe Anxiety	1.87 (1.32, 2.63)	12.51	<0.001	1.52 (1.16, 2.03)	9.13	0.003	1.77 (1.37, 2.28)	19.28	<0.001	1.93 (1.45, 2.57)	20.48	<0.001
Recent Onset Anxiety	1.49 (0.80, 2.77)	1.55	0.21	1.96 (1.24, 3.09)	8.42	0.004	1.99 (1.30, 3.05)	9.87	0.002	2.33 (1.48, 3.69)	13.18	0.003
Total mCES-D score 5	1.08 (1.02, 1.15)	6.15	0.01	1.04 (0.98, 1.10)	1.74	0.18	1.16 (1.11, 1.21)	38.33	<0.001	1.10 (1.04, 1.15)	12.80	<0.001
Core mood Depression profile	1.12 (0.88, 1.42)	0.88	0.34	1.09 (0.90, 1.32)	0.73	0.39	1.37 (1.16, 1.62)	14.06	<0.001	1.23 (1.02, 1.49)	4.84	0.03
Self-esteem/Interpersonal Depression profile	1.23 (1.04, 1.45)	5.66	0.01	1.06 (0.91, 1.25)	0.57	0.45	1.44 (1.26, 1.65)	29.06	<0.001	1.22 (1.06, 1.41)	7.66	0.006
Apathy/Neurovegetative Depression profile	1.36 (1.13, 1.63)	10.39	0.001	1.18 (1.00, 1.40)	3.89	0.04	1.68 (1.46, 1.94)	51.38	<0.001	1.41 (1.22, 1.63)	20.98	<0.001

CDR = Abbreviations: CDR= Clinical Rating Scale; CI= confidence interval; IWG= International Working Group 2004; mCES-D= modified Center for Epidemiological Studies–Depression Scale; MCI= mild cognitive impairment; OR= odds ratio; test statistic= Wald chi-squared test statistic with one degree of freedom.

* Results based on 28 multiple logistic regression models, each with one the following covariates: 3 anxiety groups, mCES-D score (<5 or 5), 3 depression profiles, with all variables adjusting for age, gender, education level, and race.

Table 3

Associations of anxiety and depression with four different MCI definitions: multivariable analyses*

	Amnesic MCI			Non-Amnesic MCI			CDR=0.5			IWG-MCI		
	OR (95% CI)	Test statistic	P value	OR (95% CI)	Test statistic	P value	OR (95% CI)	Test statistic	P value	OR (95% CI)	Test statistic	P value
Chronic Mild Worry	1.21 (0.74, 1.70)	0.29	0.59	1.03 (0.74, 1.43)	0.03	0.86	1.19 (0.88, 1.62)	1.24	0.26	1.14 (0.80, 1.63)	0.54	0.46
Chronic Severe Anxiety	1.73 (1.21, 2.46)	9.05	0.003	1.52 (1.14, 2.02)	8.24	0.004	1.54 (1.18, 2.01)	10.29	0.001	1.80 (1.34, 2.41)	15.45	<0.001
Recent Onset Anxiety	1.29 (0.67, 2.49)	0.58	0.45	1.94 (1.21, 3.11)	7.52	0.006	1.55 (0.98, 2.45)	3.54	0.06	2.11 (1.31, 3.42)	9.28	0.002
Core mood Depression profile	0.72 (0.49, 1.05)	2.99	0.08	0.94 (0.70, 1.27)	0.17	0.68	0.74 (0.57, 0.98)	4.48	0.03	0.84 (0.62, 1.31)	1.33	0.25
Self-esteem/Interpersonal Depression profile	1.06 (0.77, 1.46)	0.11	0.73	0.84 (0.63, 1.12)	1.36	0.24	1.03 (0.81, 1.31)	0.05	0.82	0.87 (0.66, 1.14)	1.08	0.3
Apathy/Neurovegetative Depression profile	1.46 (1.05, 2.03)	4.97	0.02	1.29 (0.98, 1.70)	3.28	0.07	1.83 (1.44, 2.33)	24.16	<0.001	1.59 (1.23, 2.06)	12.29	<0.001

CDR= Clinical Rating Scale, CI=confidence interval; IWG= International Working Group, mCES-D= modified Center for Epidemiological Studies-Depression Scale; MCI= mild cognitive impairment; OR= odds ratio; test statistic= Wald chi-squared test statistic with one degree of freedom.

* Results based on four multiple logistic regression models each including 3 anxiety groups and 3 depression profiles, with all models adjusting for age, gender, education level, and race.

Table 4
Association between each cognitive domain score and each risk factor, using five multiple linear regression models that adjust for demographic variables*

	Attention			Executive			Language			Memory			Visuo spatial		
	Coef	Test (95% CI)	Test statistic	P value	Coef	Test (95% CI)	Test statistic	P value	Coef	Test (95% CI)	Test statistic	P value	Coef	Test (95% CI)	P value
Chronic Mild Worry	0.02	(-0.07,0.11)	0.25	0.61	-0.01	(-0.10, 0.07)	0.07	0.79	0.01	(-0.08, 0.10)	0.09	0.76	-0.02	(-0.14, 0.10)	0.77
Chronic Severe Anxiety	-0.14	(-0.22, -0.06)	11.83	<0.001	-0.20	(-0.28, -0.13)	27.64	<0.001	-0.16	(-0.24, -0.08)	13.02	<0.001	-0.20	(-0.31, -0.10)	<0.001
Recent Onset Anxiety	-0.16	(-0.30, -0.02)	5.06	0.02	-0.19	(-0.32, -0.06)	7.83	0.005	-0.08	(-0.21, 0.06)	0.46	0.49	-0.30	(-0.48, -0.11)	0.002
Total mCES-D score ≥5	-0.02	(-0.04, -0.01)	8.15	0.004	-0.03	(-0.05, -0.02)	18.30	<0.001	-0.03	(-0.05, -0.02)	21.63	<0.001	-0.04	(-0.06, -0.02)	<0.001
Core mood Depression profile	-0.06	(-0.12, -0.01)	4.59	0.03	-0.08	(-0.13, -0.03)	9.17	0.002	-0.07	(-0.12, -0.01)	3.13	0.07	-0.09	(-0.17, -0.02)	0.01
Self-esteem/Interpersonal Depression profile	-0.05	(-0.09, 0.00)	4.07	0.04	-0.06	(-0.11, -0.02)	8.97	0.002	-0.08	(-0.12, -0.03)	21.68	<0.001	-0.10	(-0.16, -0.04)	<0.001
Apathy/Neurovegetative Depression profile	-0.08	(-0.13, -0.04)	12.02	<0.001	-0.12	(-0.16, -0.08)	28.99	<0.001	-0.10	(-0.15, -0.05)	30.55	<0.001	-0.14	(-0.21, -0.08)	<0.001

CI = confidence interval; Coef= coefficient estimate; mCES-D= modified Center for Epidemiological Studies– Depression Scale; test statistic= Wald chi-squared test statistic with one degree of freedom.

* Risk factors are Chronic Mild Worry, Chronic Severe Anxiety, Recent Onset Anxiety, dichotomized total mCES-D score (<5 or ≥5), Core mood depression profile, Self-esteem/Interpersonal Depression profile, Apathy/Neurovegetative Depression profile; demographic variables are age, gender, education level, and race; each change in cognitive domain score was obtained from the estimated slope of a mixed-effect model of cognitive domain value in which the predictor was time.