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Research Article

Apathy and the Risk of Predementia Syndromes in Community-Dwelling Older Adults

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Abstract

Objectives: Apathy is a potential predictor of dementia in older adults, but this investigation has been limited to older adults with a preexisting neurological illness like mild cognitive impairment (MCI), stroke or Parkinson's disease. The objective of this study was to investigate the association between apathy at baseline and incident predementia syndromes, including MCI and motoric cognitive risk syndrome (MCR), subjective cognitive complaints and slow gait, in community-dwelling older adults.

Method: We prospectively studied the association between apathy (using the 3-item subscale of the Geriatric Depression Scale [GDS3A]) and incident cognitive disorders in 542 community-dwelling older adults enrolled in the Central Control of Mobility in Aging study using Cox proportional hazard models. Associations were reported as hazard ratio (HR) with 95% confidence intervals (CIs), adjusting for age, education, baseline cognitive performance, and depressive symptoms.

Results: Apathy was associated with incident MCR (HR 2.39, 95% CI: 1.10–5.20), but not predementia syndromes overall nor MCI. In sensitivity analyses of MCI subtypes, apathy was associated with nonamnestic MCI (HR 2.44, 95% CI: 1.14–5.22), but not amnestic MCI. Our study was limited by a short follow-up time (median 13.6 months; interquartile range 29.8) and a brief subscale measurement of apathy, GDS3A.

Discussion: In our study, apathy predicted MCR but not MCI in community-dwelling older adults. These results and the current literature suggest that apathy is an early risk factor for dementia. Additionally, apathy may be a novel treatment target that could forestall the disability of dementia.

Keywords: Amotivation, Cognitive disorders, MCI, MCR

Emerging literature has shown a relationship between psychological symptoms like depression and risk of neurodegenerative disorders including dementia (Bennett & Thomas, 2014; Landes, Sperry, Strauss, & Geldmacher, 2001; Nagayama et al., 2016; Oguru, Tachibana, Toda, Okuda, & Oka, 2010). Recent investigations highlight apathy as a separate entity from depression (Marin, Fogel, Hawkins, Duffy, & Krupp, 1995; Starkstein, Petracca, Chemerinski, & Kremer, 2001), which has been uniquely associated with cognitive and functional decline in neurologic diseases (Camargo, Serpa, Jobbins, Berbetz, & Sabatini, 2018; Palmer et al., 2010; Vicini Chilovi et al.,

2009). Apathy predicts worse functional and cognitive outcomes after a stroke and in Parkinson's disease (PD) (Caeiro, Ferro, & Costa, 2013; Cohen, Aita, Mari, & Brandt, 2015; Hama et al., 2007). In a cohort of outpatients with PD, apathy was associated with executive dysfunction and reduced functional autonomy (D'Iorio et al., 2017). In a systematic review of apathy secondary to stroke, people with apathy after a stroke were almost 3 times as likely to have cognitive impairment (Caeiro et al., 2013). Several studies also suggest that apathy is a predictor of dementia in older adults, but this investigation has been limited to older adults with a preexisting neurological illness like mild cognitive impairment (MCI), stroke or PD (Mikami, Jorge, Moser, Jang, & Robinson, 2013; Robert et al., 2006). For instance, Vicini Chilovi and colleagues (2009) found that the rate of conversion from MCI to dementia was higher for people with the syndrome of apathy, as compared to those with apathy and depression or depression alone. These populations are already at an elevated risk of developing dementia based on the pathophysiology of the underlying disease; therefore, it is difficult to ascertain the independent role of apathy in the pathogenesis of dementia.

Prospective cohort studies have examined the association between apathy and cognitive decline in community-dwelling populations. The Baltimore Epidemiological Catchment Area (ECA) study found that apathy was associated with cognitive decline at 1-year follow-up and functional decline at 13 years follow-up in 1,100 community-dwelling older adults (Clarke, Ko, Lyketsos, Rebok, & Eaton, 2010). Recently, van Dalen and colleagues found that apathy was associated with a 26% increased risk of dementia in over 3,000 community-dwelling older adults (Jan Willem van Dalen, Van Wanrooij, Moll van Charante, Richard, & van Gool, 2018). Still, neither study investigated the association between apathy and incident predementia syndromes like MCI or motoric cognitive risk syndrome (MCR). Predementia syndromes are transitional states between normal aging and dementia, which can help to identify high-risk populations, inform potential disease pathways, and establish targets for intervention (Burns & Zaudig, 2002). The heterogeneity of these syndromes likely parallels the varied types of dementia that they predict (Panza et al., 2006). MCI has a prevalence ranging from 17% to 34% and has a reported annual conversion rate to dementia of 10%–5% (Burns & Zaudig, 2002). While MCI is a well-described syndrome of memory complaints with objective evidence of cognitive impairment on testing (Burns & Zaudig, 2002), MCR is a recently described predementia syndrome characterized by slow gait and subjective cognitive complaints (Verghese, Wang, Lipton, & Holtzer, 2013). MCR is a clinically accessible concept as it requires no neuropsychological testing and can easily be identified in a clinical setting (J. Verghese et al., 2014). Furthermore, while there is some overlap between MCR and MCI (35% of people with MCR met criteria for nonamnestic MCI and 19% had amnestic MCI in the Einstein Aging Study [Verghese et al., 2013] and 39% of individuals with MCR, also met MCI criteria in a multicountry cohort [Joe Verghese et al., 2014]); MCR captures an additional population at high risk for dementia. In a pooled analysis of 17 countries, the prevalence of MCR is 9.7% (Joe Verghese et al., 2014) and it is associated with a threefold increased risk of dementia, especially vascular dementia (Verghese et al., 2013).

The goal of our study was to examine the relationship between apathy and incident predementia syndromes in a cohort of community-dwelling older adults enrolled in the Central Control of Mobility in Aging (CCMA) study (Holtzer et al., 2015). We hypothesize that the presence of clinically significant apathy will predict predementia syndromes when compared with participants without apathy. Establishing apathy as a risk factor for predementia syndromes will highlight a noninvasive marker of dementia risk (J. W. van Dalen et al., 2018) and potentially early target for prevention of dementia progression (Ismail et al., 2016).

Method

Participants

A total of 542 community-residing adults (≥65 years old) without dementia enrolled in the CCMA study were included. The primary aims of this prospective cohort study are to determine the cognitive and neural predictors of mobility in late life. The CCMA study recruitment and procedures have been previously described (Holtzer et al., 2015). Participants were contacted by mail and telephone from population lists in Westchester County, NY. A structured telephone interview was administered to potential participants to obtain verbal assent, assess medical history, and mobility function (Baker, Bodner, Allman, 2003). In order to rule out dementia, we included the AD8 questionnaire in the telephone interview, which is a reliable and sensitive tool to distinguish individuals with and without dementia based on memory, orientation, judgment, and function (Galvin et al., 2005). Participants, who passed the telephone interview, received comprehensive neuropsychological, psychological, and mobility assessments as well as a structured neurological examination. CCMA participants were followed longitudinally at yearly intervals. Written informed consents were obtained at clinic visits according to study protocols and approved by the Albert Einstein College of Medicine Institutional Review Board.

Assessment of Apathy

Apathy is a psychological syndrome characterized by lack of motivation, interest, flattening of affect, and social withdrawal (Marin et al., 1995). While measures of apathy are varied, there is no gold standard (Clarke et al., 2011). In larger cohort studies like the Baltimore ECA study (Clarke

et al., 2010) and the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial (Jan Willem van Dalen et al., 2018) apathy was assessed using subscales of depression assessment tools. Participants in the CCMA study completed the Geriatric Depression Scale (GDS) Long Form (Yesavage et al., 1982), a 30-item questionnaire from which the 15-item GDS Short Form (GDS15) (Sheikh & Yesavage, 1986) is derived. Based on confirmatory factor analysis of the GDS15, the GDS3A (which consists of three items) has been used to measure apathy in community-dwelling populations (Adams, Matto, & Sanders, 2004). The GDS3A consists of the following three items on the GDS15 (Mitchell, Mathews, & Yesavage, 1993) (score range 0–3 points) (Bertens et al., 2016): (1) Have you dropped many of your activities and interests? Positive response: Yes; (2) Do you prefer to stay at home, rather than going out and doing new things? Positive response: Yes; and (3) Do you feel full of energy? Positive response: No. A score of two or more indicates presence of apathy. van der Mast and colleagues reported a sensitivity of 69% and a specificity of 85% for the GDS3A when compared to the Apathy Evaluation Scale (AES) (Clarke et al., 2011) in a cohort of community-dwelling older adults (van der Mast et al., 2008). Additionally, several large cohort studies employed the GDS3A, in order to examine the longitudinal associations between apathy and outcomes including frailty and dementia (Ayers et al., 2017; Jan Willem van Dalen et al., 2018). In addition, the GDS3A has been used both to examine the neural correlates of apathy (Grool et al., 2014) and the inflammatory correlates of apathy (Eurelings, Richard, Eikelenboom, van Gool, & Moll van Charante, 2015), independent of depression.

Predementia Syndromes

Diagnosis of MCI was assigned at consensus in diagnostic case conference (Albert et al., 2011) utilizing participant's report of cognitive complaints without functional limitations and 1.5 *SD* below the age-adjusted means on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, Tierney, Mohr, & Chase, 1998). MCI subtypes were classified as amnestic, if the memory domain was impaired, or nonamnestic, if nonmemory domains were impaired (Albert et al., 2011). Nonmemory domains assessed on the RBANS included visuospatial, language, and attention. Executive function was measured using the Trail Delta, which is the difference between the performance time on the Trail A and Trail B tasks in seconds (Drane, Yuspeh, Huthwaite, & Klingler, 2002). While MCI was defined using neuropsychological test performance, MCR is defined as the presence of subjective cognitive complaints (with or without objective complaints) and slow gait in participants without dementia or mobility disability (inability to ambulate even with assistance or walking aids) (Verghese et al., 2013). Gait was assessed using the GAITRite system (CIR Systems, Franklin, NJ), a computerized walkway (dimensions 180 × 35.5 × 0.25 inches) with embedded pressure sensors, in a quiet well-lit room, at each wave. Participants are asked to walk on the mat at their "normal pace" for two trials without any attached monitoring devices (Ayers et al., 2017). The GAITRite software automatically computes gait parameters based on footfall. Slow gait has been previously categorized in the CCMA cohort as 1 *SD* below age- and sex-adjusted means with a prevalence of 15.1% (Ayers et al., 2017).

Covariates

Covariates included in the analyses were chosen based on confounders that have been identified in the literature as well as bivariate analyses, and included demographic characteristics (gender, years of education, and age), general cognitive status assessed by the RBANS total score (Randolph et al., 1998), and self-reported comorbidities. Presence or absence of physician-diagnosed depression, diabetes, heart failure, hypertension, angina, myocardial infarction, strokes, PD, chronic obstructive lung disease, and arthritis were used to calculate a global health score (range 0–10) (Verghese, Holtzer, Lipton, & Wang, 2009). A score of ≥2 on the remaining nonoverlapping 12 items of the GDS15 (GDS12) was consistent with depression (Adams et al., 2004). In several cohort studies that have assessed apathy using the GDS3A (Ayers et al., 2017; Jan Willem van Dalen et al., 2018), the GDS12 was used to quantify nonapathy-related depressive symptoms. This approach is supported by principal component factor analysis of the GDS15, which identified three independent domains: general depressive affect, life satisfaction, and withdrawal/apathy (Mitchell et al., 1993). A similar factor structure has been identified in the GDS Long Form using confirmatory factor analysis (Adams et al., 2004).

Statistical Analysis

Bivariate analyses of the baseline characteristics of participants by apathy status were completed. The independent sample *t* test was used for normally distributed continuous variables. Mann–Whitney *U*-test was used for nonnormally distributed variables including the Trails Delta score. Categorical variables were assessed using a Pearson's chi-square test. The Fisher's exact test was used for race/ethnicity and self-report of PD as more than 20% of cells had less than an expected count of 5.

In order to assess the association between apathy (as measured by the GDS3A) and risk of predementia syndromes, Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) to predict any incident predementia syndromes (including MCI and MCR), as well as incident MCI and MCR in separate models. Prevalent cases of MCR or MCI were excluded from the analysis. Sensitivity analyses were conducted to assess the association between apathy and

Table 1. Baseline Characteristics of CCMA Participants by Apathy Status (*N* = 542)

Demographic characteristics	Study population Mean (±*SD*)	No apathy (*N* = 382) Mean (±*SD*)	Apathy (*N* = 160) Mean (±*SD*)	Statistics	*p* Value
Age, years	76.0 (±6.7)	75.6 (±6.31)	77.1 (±6.74)	$t = 2.59$	.01*
Female, % (*N*)	55.2 (299)	54.7 (209)	56.3 (90)	$X^2 = 0.11$	.77
Race/ethnicity, % (*N*)				Fisher's = 3.02	.376
White	79.7 (432)	81.4 (311)	75.6 (121)		
Black	16.4 (89)	14.7 (56)	20.6 (33)		
Hispanic	2.0 (11)	2.1 (8)	1.9 (3)		
Other	1.8 (10)	1.8 (7)	1.9 (3)		
Education, years	14.7 (±2.95)	14.7 (±2.95)	14.2 (±2.90)	$t = -1.92$	.06
Medical comorbidities					
Depression	10.9 (59)	9.2 (35)	15.0 (24)	$X^2 = 3.79$	.07
Diabetes	19.4 (105)	18.1 (69)	22.5 (36)	$X^2 = 1.36$	.28
Hypertension	61.1 (331)	57.6 (220)	69.4 (111)	$X^2 = 7.89$	.01*
Myocardial infarction	6.3 (34)	6.0 (23)	6.9 (11)	$X^2 = 0.13$	.85
CHF	1.5 (8)	1.6 (6)	1.3 (2)	$X^2 = 0.07$	1.00
Stroke	5.4 (29)	5.2 (20)	5.6 (9)	$X^2 = 0.03$	1.00
Parkinson's disease	0.4 (2)	0.3 (1)	0.6 (1)	Fisher's = 0.638	.50
GHS[a]				$X^2 = 13.34$	.001*
None	15.7 (85)	18.1 (69)	10.0 (16)		
1 or 2	63.7 (345)	64.9 (248)	60.6 (97)		
≥3	20.7 (112)	17.0 (65)	29.4 (47)		

Note. CCMA = Central Control of Mobility in Aging; CHF = congestive heart failure.
[a]Global health score: number of comorbidities.
*$p < .05$.

amnestic and nonamnestic subtypes of MCI; and to examine the association between depressive symptoms (as measured by the GDS12) and the construct of depression including apathy symptoms (as measured by the GDS15) and incident predementia syndromes. The time scale included in the Cox proportional hazard model was follow-up time (months) from baseline to the first instance of MCI or MCR or final contact visit, adjusted for age, education, baseline global cognition (RBANS), and depressive symptoms (GDS12). For instance, if a participant was diagnosed with MCI at one wave and MCR at a following wave, the time to incident cognitive disorder was calculated based on the earlier MCI diagnosis. Given a limited number of incident cases of cognitive disorders, covariates were added in a forward stepwise method, keeping in covariates that either were significantly associated with the dependent variable with a p value < .05 or have been previously identified as an important confounder. There was no significant interaction between apathy and depression. Models were checked for the proportional hazards assumption graphically and with statistical tests, and were adequately met. All analyses were conducted using SPSS version 24 (SPSS Inc., Chicago, IL).

Results

Study Population

A total of 542 nondemented participants from the CCMA cohort were included in the final analysis. The prevalence of apathy was 29.5%. There were 75 new cases of MCI (42 amnestic, 32 nonamnestic, one unknown), 30 cases of MCR, and one case of dementia. The median follow-up time was 13.6 months (interquartile range 29.8), and did not differ by apathy status. Table 1 compares participants in the CCMA cohort by apathy status. People with apathy were older than those without apathy. Ethnicity, gender, and years of education were not significantly different by apathy status. Participants with apathy were more likely to have hypertension and have more medical comorbidities in general. There was borderline significance between the groups in depression, which was expected based on the overlap in depression and apathy symptoms.

Baseline Cognitive Performance (Results Not Shown)

There was no difference in neuropsychological test performance in the RBANS nor the Trails Delta at baseline between those with apathy and those without apathy.

Incident Predementia Syndromes

About 40% of participants with incident MCR also met criteria for MCI. Table 2 shows unadjusted and adjusted models for incident predementia syndromes (MCI or MCR), and separate models for MCR and MCI. Baseline

Table 2. Cox Proportional Hazard Models of the Risk of Incident Predementia Syndromes, MCI, and MCR for Baseline Apathy (*N* = 537)

	Any predementia syndrome (MCI, MCR)		MCR		MCI	
Model	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Model 1	1.15 (0.73–1.82)	.55	1.86 (0.90–3.83)	.09	1.17 (0.72–1.88)	.53
Model 2	1.47 (0.92–2.35)	.10	2.49 (1.18–5.25)	.02*	1.57 (0.97–2.56)	07
Model 3	1.56 (0.96–2.53)	.07	2.39 (1.10–5.20)	.03*	1.64 (0.99–2.71)	.06

Note. Model 1: adjusted for age and years of education; Model 2: Model 1 and global cognition based on RBANS score; Model 3: Model 2 and adjusted for depression. CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment; MCR = motoric cognitive risk syndrome.
*$p < .05$.

Table 3 : Cox Proportional Hazard Models of the Risk of Incident Amnestic MCI and Nonamnestic MCI for Baseline Apathy (*N* = 537)

	Amnestic MCI		Nonamnestic MCI	
Model	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Model 1	0.85 (0.44–1.65)	.63	1.81 (0.89–3.66)	.10
Model 2	1.19 (0.61–2.34)	.61	2.38 (1.15–4.93)	.02*
Model 3	1.25 (0.62–2.50)	.54	2.44 (1.14–5.22)	.02*

Note. Model 1: adjusted for age and years of education; Model 2: Model 1 and global cognition based on RBANS score; Model 3: Model 2 and adjusted for depression. CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment.
*$p < .05$.

apathy was associated with incident MCR (HR 2.39, 95% CI: 1.10–5.20) after adjusting for age, education, global cognition, and depressive symptoms, but not MCI nor incident predementia syndromes overall. In sensitivity analyses of MCI subtypes (Table 3), apathy was associated with nonamnestic MCI (HR 2.44, 95% CI: 1.14–5.22), independent of age, education, global cognition, and depressive symptoms, but not amnestic MCI.

Depressive symptoms, as measured by the remaining 12 items of the GDS15 (excluding the three apathy items), were not associated with incident predementia syndromes overall or in separate models of MCI and MCR. The construct of depression, as measured by the GDS15 (Table 4) which includes the three apathy items, was associated with incident MCR (HR 1.17, 95% CI: 1.01–1.35), adjusted for age, education, global cognition. The GDS15 score was not significantly associated with MCI in general or MCI subtypes.

Discussion

In this study of community-dwelling older adults, we evaluated the association between baseline apathy and risk of incident predementia syndromes as well as MCI and MCR, separately. Presence of apathy at baseline was associated with a twofold increased risk of incident MCR, but not an increased risk of predementia syndromes overall, MCI, or amnestic MCI. Baseline apathy showed a suggestive trend with incident MCI, which in our sensitivity analyses was explained by the twofold increased risk of developing nonamnestic MCI. The overlap in apathy associations between the MCR and nonamnestic MCI outcomes is consistent with previous work from our group (Verghese et al., 2013) and a recent study from Sekhon and colleagues (Sekhon, Launay, Chabot, Allali, & Beauchet, 2018), which demonstrates frequent overlap in people who meet criteria for both MCR and nonamnestic MCI.

By focusing on risk of predementia syndromes, which are transitional states between normal cognition and dementia, our findings complement the existing literature on the association between apathy and risk of cognitive decline. Our findings also strengthen the larger body of literature, which suggests that behavioral symptoms in persons without dementia may be early markers for cognitive decline and progression to dementia (Ismail et al., 2017, 2018).

Our study had several limitations. Firstly, we used a brief subscale of the GDS15 to measure apathy, which has fair sensitivity and specificity (van der Mast et al., 2008). Consequently, there is a risk of misclassification bias. While a more detailed scale like the 18-item AES or formal psychiatric evaluations would be desirable, it is not feasible in the setting of large cohort studies nor is there an established gold standard for diagnosing apathy using questionnaires (Clarke et al., 2011). Additionally other large cohorts, like the Baltimore ECA, Leiden-85, and PreDIVA, have employed similar strategies to measure apathy (Clarke et al., 2010; Jan Willem van Dalen et al., 2018; van der Mast et al., 2008). The GDS3A has also been used to evaluate the association between apathy and structural changes on neuroimaging in persons without dementia (Grool et al., 2014) as well as apathy and inflammatory markers (Eurelings et al., 2015). Another limitation was the limited follow-up time (median 13.6 months). Longer follow-up time would allow for more incident cases of predementia syndromes, thus increasing power. However, our results are consistent with other studies that have found an association between apathy and cognitive outcomes longitudinally (Clarke et al.,

Table 4. Cox Proportional Hazard Models of the Risk of Incident Predementia Syndromes, MCR, MCI, and MCI Subtypes for Baseline GDS15 Score ($N = 537$)

	Any predementia syndrome (MCR, MCI)		MCR		MCI	
Model	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Model 1	1.05 (0.95–1.17)	.33	1.18 (1.02–1.35)	.02*	1.07 (0.96–1.19)	.25
Model 2	1.04 (0.93–1.15)	.53	1.19 (1.01–1.35)	.04*	1.05 (0.94–1.17)	.39
	MCI subtypes		Amnestic MCI		Nonamnestic MCI	
Model			HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Model 1			1.05 (0.90–1.23)	.52	1.09 (0.92–1.26)	.29
Model 2			1.04 (0.88–1.21)	.66	1.07 (0.92–1.26)	.38

Note. Model 1: adjusted for age and years of education; Model 2: Model 1 and global cognition based on RBANS score. CI = confidence interval; HR = hazard ratio; MCI = mild cognitive impairment; MCR = motoric cognitive risk syndrome.
*$p < .05$.

2010; Jan Willem van Dalen et al., 2018). Taken together, these findings provide preliminary data to inform future investigations in community-based cohorts with longer follow-up or pooled analyses of similar populations.

Our study is the first to identify an association between apathy and a cognitive and locomotor outcome, MCR. Our group has found that depressive symptomology was associated with impairment in gait parameters that are commonly seen in MCR such as velocity, stride, and swing time variability on a simple walking task (Brandler, Wang, Oh-Park, Holtzer, & Verghese, 2012), but the GDS15 was used to quantify depression, which includes the three apathy items of the GDS3A. Future investigations should investigate the differential impact of apathy and depression on gait performance. Moreover, clarifying the role of apathy as an early risk factor for dementia, which precedes predementia syndromes, highlights a potential noninvasive, inexpensive clinical marker (J. W. van Dalen et al., 2018) and presents an early target for prevention of dementia progression (Ismail et al., 2016). In addition, future clinical trials should investigate the effect of treating apathy in community-dwelling older adults on cognitive outcomes like predementia syndromes.

Conclusion

In our study, apathy predicted MCR but not MCI in community-dwelling older adults. These results and the current literature suggest that apathy is an early risk factor in the dementia pathway. Additionally, apathy may be a novel treatment target that could forestall the disability of dementia.

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Conflict of Interest

None reported.

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