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Appetite and weight loss symptoms in late life depression predict dementia outcomes

Sayoni Saha^{1,2}, Daniel Hatch, PhD^{2,3}, Kathleen M. Hayden, PhD⁵, David C. Steffens, MD⁶, and Guy G. Potter, PhD^{2,4}

¹Duke University, Durham, NC

²Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University, Durham, NC

³Center for the Study of Aging and Human Development, Duke University, Durham, NC

⁴Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC

⁵Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, NC

⁶Department of Psychiatry, University of Connecticut School of Medicine

Abstract

Objective: Identify depression symptoms during active late-life depression (LLD) that predict conversion to dementia.

Methods: We followed a cohort of 290 participants from the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study. All participants were actively depressed and cognitively normal at enrollment. Depression symptom factors were derived from prior factor analysis: 1) Anhedonia and Sadness; 2) Suicidality and Guilt; 3) Appetite and Weight Loss; 4) Sleep Disturbance; 5) Anxiety and Tension. Cox regression analysis modeled time to AD and non-AD dementia onset on depression symptom factors, along with age, education, sex, and race. Significant dementia predictors were tested for interaction with age of depression onset.

Results: Higher scores on the Appetite and Weight Loss symptom factor were associated with an increased hazard of both AD and non-AD dementia. This factor was moderated by age of first depression onset, such that higher scores were associated with higher risk of non-AD dementia when depression first occurred earlier in life. Other depression symptom factors and overall depression severity were not related to risk of AD or non-AD dementia.

Conclusions: Results suggest greater appetite/weight loss symptoms in active episodes of LLD are associated with increased likelihood of AD and non-AD dementia, but possibly via different pathways moderated by age of first depression onset. Results may help clinicians identify

Address correspondence to: Guy G. Potter, PhD, Psychiatry, Box 3903, Duke University Medical Center, Durham, NC, 27710-3903, fax: 919-681-7668, phone: 919-660-7581, guy.potter@duke.edu.

Conflicts of Interest

None declared by all authors

individuals with LLD at higher risk of developing AD and non-AD dementia, and help design interventions that reduce this risk.

Keywords

Alzheimer's disease; late-life depression; appetite loss; dementia

OBJECTIVE

Dementia is a debilitating condition in late life and a leading cause of death (1), with Alzheimer's disease (AD) as the most common type of dementia. Accordingly, researchers and clinicians have sought to identify sociodemographic, genetic, and lifestyle-related risk factors for AD and other age-related dementias. In recent decades, studies have found a link between major depressive disorder (MDD) occurring in late-life (late-life depression, or LLD) and the risk of AD and other dementias (2–4). However, LLD is a heterogeneous disorder that includes individuals with first onset of depression later in life, as well as those with first onset of depression earlier in life. As reviewed and analyzed in a study by Byers and Yaffe, findings consistently indicate that early onset depression is a risk factor for dementia, but there are questions about the nature of this association (5). With respect to depression as a prodrome of dementia, Ownby *et al.* found that a longer interval between depression diagnosis and AD diagnosis was associated with a higher risk of AD, in support of depression as a risk factor rather than a prodrome (6). In contrast, Steffens *et al.* conducted a twin study finding that risk ratios for AD decreased substantially with increasing intervals between the age of first depression onset and age of AD onset. Their results suggested that later age of first depression onset is most often a prodrome of AD (7). While other researchers also found that later onset of depression is a prodrome of AD or dementia (8, 9), some have argued that the evidence is inconclusive (5, 10). Though the mechanisms relating LLD to AD and other dementias remain unresolved, prediction of dementia risk is an important aspect of this resolution and an important goal of clinical care.

Although the specific mechanisms linking LLD and dementia remain to be discovered, dissecting underlying symptom constructs of LLD may be useful in better understanding their association. This may also indicate markers that help identify patients at potential risk. Potter *et al.* used factor analysis to identify depression symptom factors associated with neurocognitive performance in a cognitively normal sample with LLD, finding that higher scores loading on a factor reflecting Appetite and Weight Loss symptoms were associated with lower scores on episodic memory, executive functions, and verbal fluency (11). These results were consistent with those of Charlton *et al.* (12), who found a principal component of weight loss and gastrointestinal symptoms to be associated with lower episodic memory and executive function scores in another nondemented sample with LLD. Given that lower neuropsychological performances among nondemented individuals with LLD predict conversion to dementia (13), it is important to examine whether an appetite/weight loss symptom factor associated with lower neuropsychological performance is also associated with dementia. Although appetite loss and weight loss are mechanistically different, they often co-occur (14), and have been associated with cognitive decline among individuals without depression (15, 16).

The goal of the current study was to identify depression symptom factors during an active symptom period of LLD that differentiate individuals who convert to dementia from those who do not. To do this, we used data from the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study, in which cognitively normal individuals were assessed during an active episode of LLD and followed prospectively to assess neurocognitive outcomes (17). Depression symptoms were based on factor scores from a prior study of the NCODE sample (11), which yielded a factor structure of: 1) Sadness and Anhedonia, 2) Guilt and Suicidality, 3) Appetite and Weight Loss, 4) Sleep Disturbance, and 5) Anxiety and Tension. Based on our prior research on cognitively normal individuals with LLD, we hypothesized that higher scores on the Appetite and Weight Loss factor at baseline would be associated with increased risk of AD and non-AD dementia; however, because other features of depression may also be associated with dementia, including sleep disturbance (18) and anxiety (19), we included all depression symptom factors in our models. We additionally planned to test whether age of first depression onset moderated any association between depression symptom factors and risk of AD or non-AD dementia.

METHODS

Design

The current study is a secondary analysis of 290 individuals from an actively followed cohort of older adults assessed during an episode of LLD, who were followed prospectively for an average of 7.1 years to identify depression symptom factors associated with risk for AD and other dementias. At baseline, participants were assessed for MDD and screened to rule out any additional psychiatric and neurological conditions, including dementia. During follow up, they participated in a longitudinal treatment study and were assessed for AD and other dementias.

Participants

All individuals were above the age of 60 at study enrollment, and were diagnosed with MDD, as detailed below. Participants with 1) other psychiatric conditions, 2) alcohol or drug dependence, or 3) neurological conditions including dementia at baseline were excluded from the study. Although nondepressed control participants were enrolled in the NCODE study, the current study only included individuals enrolling with active LLD, due to the current focus on depression symptoms. Participants met the criteria for MDD outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and supplemented by criteria from the Duke Depression Evaluation Schedule (20), which includes self-reported age of first depression onset. Once participants were enrolled in the NCODE study, they were treated according to the STAGED treatment algorithm, which seeks to balance consistent approaches to medication selection across the study with optimizing individual patient response (21). Treatment was monitored and participants were clinically evaluated at least every three months during their participation in the study. The Duke University Institutional Review Board approved the study.

Measures

Dementia screening.—A geriatric psychiatrist screened participants for dementia during their initial clinical assessment based on examination, cognitive screening, existing medical records, and consultation with referring doctors (17). Only patients who were classified as nondemented at baseline were followed longitudinally. Participants were administered the Mini-Mental State Examination (MMSE) during the initial clinical assessment. Individuals with baseline MMSE scores under 25 were excluded from the analysis since they were potentially ambiguous for prodromal dementia (17).

Individuals who were followed longitudinally in the study completed annual visits including psychiatric assessment, review of medical conditions, psychosocial assessment, functional assessment, and neuropsychological testing. Individuals enrolled with depression were also seen for treatment visits as clinically indicated, but at least quarterly. A consensus diagnostic panel annually reviewed cases of suspected cognitive impairment. This panel included geriatric psychiatrists, a cognitive neuroscientist, neuropsychologists with specialization in memory disorders, and a neurologist specializing in memory disorders. Cases were presented individually, and included review of clinical history and neuropsychological test performance. After each case was presented, panel members selected a consensus diagnosis from a pre-established list. The panel followed published criteria for consensus diagnoses reflecting cognitive impairment (cognitive impairment, no dementia, or CIND), AD (22), and non-AD dementias, and applied clinical judgment where recognized criteria were not available (17). AD cases included patients with either probable or possible AD, the latter of which excluded diagnoses of amnesic mild cognitive impairment, or MCI. Forms of non-AD dementia included vascular dementia (23) and frontal lobe dementia (24). Non-AD dementia participants also included those who were characterized with dementia based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (25) if no clear cause for dementia was identified, or if the diagnosis was too complex to diagnose as possible AD. For dementia diagnoses, age of onset was specified by the consensus panel. For analyses of AD, we excluded individuals with non-AD dementia, and for analyses of non-AD dementia, we excluded individuals with AD. The resulting comparison group was composed of individuals with diagnoses of cognitively normal and CIND. For participants diagnosed with AD or non-AD dementia, age of dementia onset was used in conjunction with baseline age to compute survival time. To compute survival (censored) time for non-cases, the month and year of baseline date and date of last diagnosis visit were used.

Depression Measures.—The Montgomery-Asberg Depression Rating Scale (MADRS) (26) and the Hamilton Rating Scale for Depression (HRSD17) (27) were administered at enrollment by a geriatric psychiatrist to assess depression severity. As described in a previously published paper (11) we used all items from the MADRS and HRSD17 in a factor analysis, with a principal component extraction and varimax rotation. As described in that paper, the rationale for combining scales was to produce a broader range of depression symptom characterization than either measure provides alone (28). This produced five factors: 1) Anhedonia and Sadness; 2) Suicidality and Guilt; 3) Appetite and Weight Loss; 4) Sleep Disturbance; 5) Anxiety and Tension. All individuals in the present study were included in the original factor analysis (22), and their individual standardized factor scores

were applied to the current models. While our *a priori* models tested depression factor scores, we also tested whether dementia risk was associated with overall depression severity, based on total MADRS and HRSD17 scores.

Covariates.—Participants were interviewed at baseline to assess their demographic backgrounds based on age, years of education, gender, and race. In addition, participants were asked if a doctor had ever diagnosed health conditions associated with risk of AD, including hypertension, diabetes, heart trouble, stroke and chronic heart illness.

Analyses

To analyze differences in the three diagnostic groups, we used ANOVA testing and chi-square tests. For ANOVA analyses, Tukey's Honestly Significant Difference (HSD) Test tests were also used to report significant differences between groups.

Cox Proportional Hazards Models.—Cox regression models were used to prospectively estimate AD and non-AD dementia risk from baseline NCODE participant data. Cox regression models are advantageous as they account for individuals who left the study early or completed the study without developing dementia, but may eventually develop the condition. The model also accounts for participants who were observed over varying durations of follow-up, as occurred in the NCODE study. Cox regression models maintain that hazards should be proportional over the period of observation. To test this assumption, interaction terms between each predictor variable and time were computed. None of these interaction terms were statistically significant, indicating that this assumption was met for all predictors. We used AD and non-AD dementia as outcomes in separate models. Each of the five depression symptom factors were entered together in the model as predictor variables, along with covariates, which included age, years of education, sex, and race. To assess the effect of overall depression, AD and non-AD dementia were also regressed on MADRS total scores. To assess whether the effect of depression symptoms depended on the age at which depression first occurred, depression factors that significantly predicted risk of AD or non-AD dementia were interacted with age of first depression onset.

RESULTS

The depressed study sample included 243 nondemented individuals, 27 individuals with AD, and 20 individuals with non-AD dementia (Table 1). Age was significantly related to cognitive status [$F(2, 287) = 10.64, p < .001$]; Tukey's HSD tests revealed that non-demented individuals were younger at baseline than those with AD and non-AD dementia (see Table 1). Appetite/weight loss symptoms were also significantly associated with cognitive diagnosis [$F(2, 282) = 12.24, p < .001$], with Tukey's HSD tests revealing nondemented individuals to have lower scores on this symptom factor than participants with AD and non-AD dementia. There was no significant association between baseline MMSE score and cognitive status outcomes.

Table 2 reports Cox proportional hazards models regressing incidence of AD and non-AD dementia on depression symptom factors, controlling for age, education, sex, and race; $df=1$ for all Wald χ^2 tests reported in Table 2. Results indicated higher appetite/weight loss

symptoms to be associated with a 69% increased hazard of AD ($HR=1.69$, 95% CI : 1.18–2.42, Wald $\chi^2=8.13$, $p=.004$). No other symptom factors were related to AD risk, nor was overall depression severity based on the MADRS. A follow-up test using the HRSD17 was also nonsignificant. We then tested the interaction between the Appetite and Weight Loss symptom factor and age of first depression onset, which was significant ($HR=1.03$, 95% CI : 1.004–1.053, Wald $\chi^2=5.42$, $p=.02$). To interpret this, we stratified the association between appetite/weight loss symptoms and AD risk by age of depression onset, using age 60 as a cut point (less than 60 vs. 60+). This indicated that among individuals with first onset of depression in earlier in life, appetite/weight loss did not significantly predict AD onset ($HR=0.60$, 95% CI : 0.22–1.62, Wald $\chi^2=1.02$, $p=.31$, see Figure 1); however, among individuals with first onset of depression later in life, higher appetite/weight loss symptoms were associated with a trend for 71% increased hazard (Figure 1; $HR=1.71$, 95% CI : 0.93–3.16, Wald $\chi^2=2.96$, $p=.09$).

Results for Cox models regressing non-AD Dementia on depression symptom factors and covariates are also presented in Table 2. Appetite/weight loss symptoms were significantly associated with non-AD dementia risk ($HR=2.10$, 95% CI : 1.19–3.69, Wald $\chi^2=6.53$, $p=.01$). Risk of non-AD dementia was not related to the other depression symptom factors, nor was it related to overall depression severity. A follow-up test using the HRSD17 was also nonsignificant. When non-AD dementia was regressed on the interaction between appetite and age of depression onset, this interaction was significant ($HR=0.97$, 95% CI : 0.95–0.996, Wald $\chi^2=5.31$, $p=0.02$). To interpret this interaction, we stratified by age of depression onset, using age 60 as a cutpoint (less than 60 vs. 60+). This indicated that among individuals with first onset of depression earlier in life, higher appetite/weight loss symptoms were associated with a three-fold increased hazard of non-AD dementia ($HR=3.39$, 95% CI : 1.75–6.57, Wald $\chi^2=13.07$, $p<.001$, see Figure 2), whereas among individuals with first onset of depression later in life, there was a trend toward reduced hazard (Figure 2; $HR=0.33$, 95% CI : 0.09–1.19, Wald $\chi^2=2.88$, $p=.09$).

CONCLUSIONS

Our novel finding was that a factor reflecting greater Appetite and Weight Loss symptoms during an active period of LLD predicted risk of both AD and non-AD dementia, over an average of 7.1 years of follow-up. Other depression symptom factors were not associated with dementia risk in LLD. Overall depression severity was not a significant predictor of AD or non-AD dementia. Our results are consistent with existing reports that greater appetite/weight loss symptoms during an active episode of LLD are associated lower neurocognitive scores among dementia-free individuals (11, 12), and the current results extend these findings to predicting dementia risk in LLD.

Our results also suggest that age of depression onset may be important in disambiguating the associations among appetite/weight loss symptoms, LLD and dementia. We found that greater appetite/weight loss symptoms were related to increased hazard of non-AD dementia with first onset of depression *earlier in life*. There also seemed to be an effect of age of onset in development of AD, where appetite/weight loss symptoms showed a trend toward increased hazard of AD with first onset of depression *later in life*. The survival curves shown

in Figures 1 and 2 help illustrate the nature of the moderating relationships; however, the smaller number of AD cases in our stratified model may have limited our ability to identify a statistically significant association. These findings raise the possibility that individuals with LLD may arrive at dementia via different pathways and/or different mechanisms related to appetite loss versus weight loss. Our study was not designed to disentangle the mechanistic associations among age of first depression onset, dementia risk, and dementia type; however, our results do suggest that depression symptoms related to appetite loss and weight loss—whether independently or together—may be key contributors to neurocognitive decline in LLD. Disentangling these associations and their mechanisms is the goal for future studies.

One potential mechanism is that appetite loss is accompanied by nutritional deficiency. Researchers have noted that individuals diagnosed with mental illnesses often exhibit deficiency in essential vitamins, minerals, and omega-3 fatty acids that are essential to healthy brain function (29, 30), and nutritional deficiency may present an accelerated path to AD (31). Another potential mechanism is that food consumption is linked to hormone release in the brain that contributes to synaptic transmission, learning, memory, and mood. Appetitive peptides, such as insulin and leptin, have been associated with mood changes and AD risk (32, 33). Finally, the geriatric syndrome of physical frailty, which is characterized by weight loss, is often comorbid with LLD (34), is associated with executive dysfunction in LLD (35), and is more strongly associated with risk of non-AD dementia compared to AD (36, 37). With respect to mechanistic understanding, one limitation of the current study is the lack of objective or serial assessments relating to appetite loss, like weight or body mass index, as well as information pertaining to appetite, diet, and weight prior to the baseline episode of LLD. These measurements will be important for future research aimed at disambiguating the associations among appetite loss, weight loss, age of depression onset, and dementia risk in affected individuals.

The current study had a modest number AD and dementia cases, which may have limited our ability to detect statistically significant relationships for depression symptom factors other than Appetite and Weight Loss. For instance, anxiety has previously been reported to predict progression to AD (38). One distinction that might underlie this inconsistency is that previous studies examined generalized anxiety disorder, while this study examined a more limited range of anxiety symptoms in depression. Similarly, we did not find sleep problems associated with likelihood of AD onset, though they have been previously reported in AD (19). While sample sizes are often less than desired in case-control studies, the sample size of depressed individuals in the current study was larger than most prospective studies of dementia risk in LLD, and was sufficient to detect a significant association for the Appetite and Weight Loss factor in support of our hypothesis.

We note that participants were enrolled in a naturalistic treatment study designed to optimize individual treatment response, which means individuals varied in the type and number of depression medications they were prescribed. A single agent trial is preferred for many research designs; however, it is not realistic in a long-term prospective study, and our naturalistic approach is more reflective of how individuals with LLD are treated in the community. Despite individualized approaches to treatment, most individuals were taking an

SSRI, and in general, this class of drugs is found to improve rather than worsen appetite in depressed individuals (30).

While further research is needed to examine the potential biological mechanisms by which appetite and weight loss symptoms in LLD are associated with dementia risk, findings from the current study may help clinicians identify individuals at higher risk for developing dementia based on presenting depression symptoms of appetite and weight loss. Ultimately, focusing on mechanisms of appetite and weight loss symptoms in LLD could inform future prevention efforts.

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Figure 1.

Kaplan-Meier survival curves of time to incident Alzheimer's disease by quartile of Appetite and Weight Loss Factor, stratified by age of depression onset. [A] Depression onset before 60 Years of Age. [B] Depression onset at 60 years of age or older. Quartiles based on factor scores derived from factor analysis described in text.

Figure 2.

Kaplan-Meier survival curves of time to incident non-AD dementia by quartile of Appetite and Weight Loss Factor, stratified by age of depression onset. [A] Depression onset before 60 Years of Age. [B] Depression onset at 60 years of age or older. Quartiles based on factor scores derived from factor analysis described in text.

Table 1.

Demographic Characteristics of 290 NCODE Study Participants

	No dementia	AD	Non-AD dementia	Test Value
	(n = 243)	(n = 27)	(n = 20)	
Age Mean (SD)	67.52 (6.54) _a	72.26 (6.29) _b	72.25 (5.32) _b	$F(2,287) = 10.64^{***}$
Baseline MMSE Mean (SD)	28.53 (1.40)	27.89 (1.63)	28.40 (1.47)	$F(2,287) = 2.47$
Education Mean (SD)	14.35 (2.52)	14.0 (3.10)	13.90 (2.29)	$F(2,287) = 0.46$
Survival Years	6.93 (4.86)	7.19 (5.29)	6.75 (5.06)	$F(2,287) = 0.05$
Sex , n (%) male	88 (36.2%)	9 (33.3%)	7 (35.0%)	$\chi^2(2) = 0.10$
Race n (%) white	202 (83.1%)	21 (77.8%)	15 (75.0%)	$\chi^2(2) = 1.20$
Health Conditions , n (%)				
Hypertension	123 (51.3%)	15 (55.6%)	13 (65.0%)	$\chi^2(2) = 1.50$
High Sugar/Diabetes	38 (15.8%)	1 (3.7%)	2 (10.0%)	$\chi^2(2) = 3.24$
Stroke	15 (6.4%)	3 (15.0%)	1 (3.7%)	$\chi^2(2) = 2.63$
Depression Factors				
Appetite	-0.28 (0.80) _a	0.34 (1.04) _b	0.46 (1.02) _b	$F(2,282) = 12.24^{***}$
Sadness	-0.10 (.91)	0.20 (1.06)	0.17 (0.76)	$F(2,282) = 1.94$
Guilt	0.02 (0.98)	0.01 (0.93)	-0.04 (0.99)	$F(2,282) = 0.04$
Sleep	-0.05 (1.00)	-0.05 (1.14)	-0.13 (1.05)	$F(2,282) = 0.06$
Anxiety	-0.03 (0.92)	-0.10 (1.34)	0.09 (0.95)	$F(2,282) = 0.22$

Notes: SD = Standard Deviation. Tukey HSD test subscripts provided for significant results. Factor scores for depression factors derived from factor analyses as described in text.

*
p<.05

**
p<.01

p<.001.

Table 2.

Cox Regression Models Predicting AD and Non-AD Dementia Regressed on Depression Factors, with No Dementia Group as Reference

<i>Variable</i>	AD (n=265)		Non-AD Dementia (n=259)	
	<i>HR</i>	<i>CI</i>	<i>HR</i>	<i>CI</i>
<i>Depression Factor Score</i>				
Appetite	1.69	1.06–2.67	2.10	1.19–3.69
Sadness	1.41	0.91–2.17	1.53	0.87–2.69
Guilt	0.78	0.52–1.18	0.76	0.48–1.20
Sleep	0.80	0.52–1.23	0.77	0.46–1.27
Anxiety	0.84	0.55–1.27	0.95	0.59–1.53
<i>Covariates</i>				
Age	1.12	1.05–1.19	1.10	1.03–1.18
Education	0.95	0.81–1.11	0.98	0.83–1.17
Sex	0.84	0.31–2.26	0.67	0.23–1.89
Race	1.00	0.34–2.88	1.65	0.57–4.76

Notes: HR = Hazard Ratio. CI= Confidence Interval. Wald χ^2 tests were used to assess statistical significance. All df=1 for Wald χ^2 tests.