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Depressive Symptoms in Healthy Apolipoprotein E ε4 Carriers and Noncarriers: A Longitudinal Study

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ABSTRACT

Objective: To determine if symptoms of depression accelerate in cognitively normal apolipoprotein E (*APOE*) ε4 carriers as compared to noncarriers.

Method: Six hundred thirty-three cognitively and functionally normal members of the Arizona *APOE* Cohort aged 21–86 years underwent neuropsychological testing every 1 to 2 years that included the Hamilton Depression Rating Scale, the Beck Depression Inventory, the Geriatric Depression Scale, and the Personality Assessment Inventory. We estimated the longitudinal change on these measures using mixed models that simultaneously modeled cross-sectional and longitudinal effects of age on depression scores by *APOE* status and the interaction between the two. We also estimated incident depression on the basis of accepted clinical cut-scores on depression measures and use of depression medications.

Results: The mean length of follow-up was 7.7 years. Comparing *APOE* ε4 carriers with noncarriers revealed no significant longitudinal difference in the rate of change or slope of change on any depression scale or subscale. There was also no difference in incident depression or antidepressant drug use between the carrier and noncarrier groups.

Conclusions: These data fail to support a relationship between *APOE* genotype and longitudinal change in depression symptoms, suggesting that depression symptoms may not be intrinsic to the early preclinical phase of Alzheimer's disease.

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A variety of studies have suggested that depression in patients with mild cognitive impairment (MCI) increases the risk of progression to Alzheimer's disease dementia.[1–4] Studies evaluating the possible impact of depression on the risk of transitioning from normal cognitive aging to MCI have been mixed.[4–6] Geda and colleagues[5] have suggested 4 possible mechanisms for this possible link between depression and incident MCI. One of those 4 possibilities is that depressive symptoms may be an "early noncognitive manifestation of dementia"; that is, depressive symptoms could be a part of the preclinical course of Alzheimer's disease. Similarly, others have hypothesized that depressive symptoms may be an early manifestation of rather than a risk factor for dementia and Alzheimer's disease, suggesting that the underlying neuropathology that causes MCI or dementia may also cause depressive symptoms.[2] If depressive symptoms exhibit a similar gradual progression as do memory changes, then one would predict a gradual transition during the preclinical stage that reaches clinical proportions during MCI.

Apolipoprotein E (*APOE*) ε4 is the most prevalent known genetic risk factor for Alzheimer's disease. We have previously shown that age-related memory decline accelerates preclinically in *APOE* ε4 carriers who remain cognitively normal relative to noncarriers who remain cognitively normal.[7] Although there is not a 100% correlation between *APOE* status and development of Alzheimer's disease, this preclinical memory decline is consistent with the prominent memory impairment that eventually characterizes amnestic MCI and Alzheimer's disease dementia, supporting the hypothesis that divergence of memory performance may be an indicator of subclinical Alzheimer's disease pathology in this genetically at-risk group. If depression is intrinsic to the Alzheimer's disease syndrome, then a similar increase in depressive symptoms could be expected preclinically in those at genetic risk for Alzheimer's disease. The primary aim of this longitudinal investigation is to evaluate whether depressive symptomatology increases preclinically, analogous to accelerated memory decline.

METHOD

Participants

Six hundred thirty-three cognitively normal members of the Arizona *APOE* Cohort aged 21–86 years underwent neuropsychological testing every 1 to 2 years that included the Hamilton Depression Rating Scale (HDRS),[8] Beck Depression Inventory (BDI),[9] and Geriatric Depression Scale (GDS),[10] as well as the Personality Assessment Inventory (PAI)[11] containing clinical depression scales and subscales. Most were aged 50–69 years at entry into the study (median age = 58 years) and recruited through local newspaper advertisements that requested healthy individuals who had a first-degree relative with Alzheimer's disease. The first subjects were enrolled in 1992, and enrollment and follow-up continue to date. This sample has been well described in earlier studies.[7,12,13] Entry criteria for cognitively normal status included a score of at least 27 on the Mini-Mental State Examination[14] (with at least 1 of 3 on the recall subtest), a score of 10 or less on the HDRS, and perfect scores on the Functional Activities Questionnaire[15] and Instrumental Activities of Daily Living Questionnaire.[16] Current major depression was a

Clinical Points

- The *APOE* ε4 allele is known to increase risk of developing dementia and to increase the velocity of memory decline in cognitively normal carriers.
- Current evidence suggests that there is no correlation between *APOE* ε4 and increased symptoms of depression in carriers who remain cognitively normal.
- Depression symptoms do not appear to be prominent in the preclinical phase of Alzheimer's disease.

specific exclusion criterion, but a history of past depression or current treatment with an antidepressant medication was not. All participants included in this analysis remained cognitively and functionally normal at subsequent follow-up visits, as judged by a neurologist and neuropsychologist after review of comprehensive neurologic, functional, and neuropsychological data. This study was approved by the Mayo Clinic Institutional Review Board, and after complete description of the study to the subjects, written informed consent was obtained.

Statistical Analysis

Cross-sectional and longitudinal analysis. Demographics and other characteristics at study entry were compared among *APOE* groups using 2-sample *t* tests or analysis of variance (ANOVA) *F* tests for continuous variables and χ^2 tests for categorical variables. We estimated the longitudinal change in depression measures using mixed models that simultaneously modeled cross-sectional and longitudinal effects of age on depression scores by *APOE* status and the interaction between the two. This statistical modeling method is the same as we have employed previously in other papers.[7] Specifically, for each outcome, each observed data value was modeled using a mixed model that included a random intercept term allowing for each subject to have a different intercept, a fixed effect for *APOE* status, fixed effects capturing the cross-sectional components (centered age [ie, age minus 60] at first study visit for the given subject [ie, baseline age], the square of centered baseline age, and the interaction for each of these effects with *APOE* status), and fixed effects capturing the longitudinal components (centered age at the time of the given data value [ie, current age], the square of centered current age, and the interaction for each of these effects with *APOE* status). For details on the specifics of this analytic modeling approach, please see the supplemental material included with Caselli et al.[7] The model includes both linear and quadratic terms to allow for evaluation of *amount* of change over time as well as *slope* of change over time controlling for age and depression score at baseline. Subsequent models also adjusted for use of depression medications and other baseline characteristics at each epoch. Results remained consistent and thus are not reported herein. The specific outcome measures included the total raw score on the BDI, the total raw score on the GDS, and the T-score on the overall depression scale of the PAI (PAI-DEP), as well as its subscales related to affective, cognitive, and physiologic features of depression. We did not evaluate HDRS score as an outcome measure in the longitudinal analysis because this was a specific initial entry criterion statistically constraining scores on this measure. We did include the HDRS in the incident depression analysis described below.

Incident depression. In addition to the longitudinal modeling, we also estimated incident depression in a subsample. This analysis included those with at least 2 epochs of data who were normal on all depression measures in the battery at entry and were not taking any depression medications at entry (n = 348). Of note, our *APOE* cohort entry criteria included an HDRS total score below 10; however, we did not exclude participation in our study on the basis of any other depression measure (eg, PAI, BDI). Therefore, to estimate incident depression most conservatively, we also excluded those at or above the recommended clinical cutoffs of a PAI-DEP T-score of 70 or BDI raw score of 14 at baseline. A subject was declared an incident depression case if the subject had an HDRS score greater than 10, BDI score greater than or equal to 14, or PAI-DEP score greater than or equal to 70 after entry or if the subject began taking a depression medication after entry. Maximum poststudy entry scores on each depression measure were compared between groups using a 2-sample *t* test or ANOVA *F* test. Initiation of depression medications after entry and proportion of incident depression cases (for each depression measure and overall) were compared between groups using χ^2 tests. In supplemental analysis (not shown), time to incident depression was also estimated using Kaplan-Meier estimates and compared between groups using log-rank tests as well as Cox proportional hazards models adjusted for age at study entry. Results were consistent across methods, and thus results based on χ^2 tests are presented herein.

RESULTS

Table 1 shows demographic characteristics of the sample by *APOE* ε4 carrier versus noncarrier status as well as the ε4 heterozygote and homozygote groups separately. The groups were well balanced for most baseline characteristics. The carrier and noncarrier groups did not differ regarding age, sex distribution, education, prior history of depression, use of depression medications, or duration of follow-up. There were more Hispanic/Latino participants in the noncarrier group than in the carrier group (15.2% vs 8.3%; $P = .009$), and there was a higher percentage of reported family history of dementia in the carriers compared to the noncarriers (76.9% vs 56.2%; $P < .0001$). The increased family history of dementia was expected given the methods of recruitment and our intentional enrichment for the *APOE* ε4 genotype. Adjusting the statistical models for ethnicity and family history variables did not change the results.

Longitudinal Analysis

Longitudinal analyses of the BDI, GDS, and PAI identified no statistically significant differences (all $P > .05$)

Table 1. Demographic Characteristics by Apolipoprotein E (*APOE*) ε4 Status

	Noncarriers (n = 368)	Carriers (n = 265)	Total (n = 633)	*P*[a]	Heterozygotes Only (n = 194)	Homozygotes Only (n = 71)	*P*[b]
Age, y				.17[c]			.38[e]
Mean (SD)	57.4 (11.4)	56.2 (11.8)	56.9 (11.6)		56.1 (12.5)	56.5 (9.7)	
Median	58.5	57.5	57.5		57.5	57.5	
Range	20.5–85.5	22.5–82.5	20.5–85.5		31.5–81.5	20.5–85.5	
Age deciles, n							
20–29 y	11	5	16		5	0	
30–39 y	21	23	44		17	6	
40–49 y	27	36	63		32	4	
50–59 y	150	102	252		65	37	
60–69 y	120	68	188		50	18	
70–79 y	35	25	60		20	5	
80–89 y	4	6	10		5	1	
Sex, n (%)				.39[d]			.68[d]
Female	252 (68.5)	190 (71.7)	442 (69.8)		139 (71.6)	51 (71.8)	
Male	116 (31.5)	75 (28.3)	191 (30.2)		55 (28.4)	20 (28.2)	
Race, n (%)				.90[d]			.97[d]
White	353 (95.9)	254 (95.8)	607 (65.9)		186 (95.9)	68 (95.8)	
Black	6 (1.6)	6 (2.3)	12 (1.9)		4 (2.1)	2 (2.8)	
Native American	5 (1.4)	3 (1.1)	8 (1.3)		2 (1.0)	1 (1.4)	
Asian	4 (1.1)	2 (0.8)	6 (0.9)		2 (1.0)	0 (0.0)	
Ethnicity, n (%)				.009[d]			.02[d]
Hispanic/Latino	56 (15.2)	22 (8.3)	78 (12.3)		19 (9.8)	3 (4.2)	
Non-Hispanic	312 (84.8)	243 (91.7)	555 (87.7)		175 (90.2)	68 (95.8)	
Education, y				.95[c]			.92[e]
Mean (SD)	15.7 (2.4)	15.7 (2.5)	15.7 (2.4)		15.7 (2.5)	15.6 (2.6)	
Median	16	16	16		16	16	
Range	11–24	8–24	8–24		8–24	8–20	
Self-reported prior history of depression, n (%)				.64[d]			.73[d]
No	270 (73.4)	190 (71.7)	460 (72.7)		137 (70.6)	53 (74.6)	
Yes	98 (26.6)	75 (28.3)	173 (27.3)		57 (29.4)	18 (25.4)	
Depression medication use at entry, n (%)				.78[d]			.12[d]
No	321 (87.9)	225 (87.2)	502 (79.6)		173 (89.6)	52 (80.0)	
Yes	44 (12.1)	33 (12.8)	129 (20.4)		20 (10.4)	13 (20.0)	
Duration of follow-up, y				.68[c]			.92[e]
Mean (SD)	7.6 (3.9)	7.7 (3.6)	7.7 (3.4)		7.7 (3.6)	7.8 (3.9)	
Median	7.3	7.9	7.7		7.8	8.0	
Range	1.1–16.7	1.5–16.3	1.1–16.7		1.8–15.2	1.5–16.3	
First-degree relative with dementia				< .001[d]			< .001[d]
Data missing, n	3	1	4		1	0	
No, n (%)	160 (43.8)	61 (23.1)	221 (35.1)		51 (26.4)	10 (14.1)	
Yes, n (%)	205 (56.2)	203 (76.9)	408 (64.9)		142 (73.6)	61 (85.9)	
APOE genotype, n				NA			NA
ε2/2	1	0	1		0	0	
ε2/3	41	0	41		0	0	
ε3/3	326	0	326		0	0	
ε3/4	0	194	194		194	0	
ε4/4	0	71	71		0	71	

[a]*P* value for comparison between noncarriers and carriers.
[b]*P* value for comparison between noncarriers, heterozygotes, and homozygotes.
[c]Two-sample *t* test.
[d]χ^2 test.
[e]Analysis of variance *F* test.
Abbreviation: NA = not applicable.

in longitudinal change of depression symptoms between *APOE* ε4 carriers and noncarriers (Table 2). There was some linear change over time in the model terms related only to age (not shown). This change reflected a slight increase in depression symptom endorsement with age regardless of genotype. However, there was no added or independent impact of ε4 carrier status. For example, PAI-DEP scores increased slightly with age ($P < .001$, Figure 1). However, there was no difference in longitudinal change related to carrier status (quadratic effect $P = .12$; linear effect $P = .40$).

As shown in Table 2, there were some trends approaching significance, uncorrected for multiple comparisons. For example, a trend toward accelerated change on the PAI was seen in the heterozygotes compared to noncarriers ($P = .06$ and $P = .04$), and a trend toward a greater amount of change on the BDI was seen in homozygotes compared to noncarriers ($P = .06$). Table 3 shows the annual rate of change on each measure by age decile and carrier status. Even for those few statistically significant measures such as the BDI in homozygotes compared to noncarriers, the

Table 2. Results of Longitudinal Analysis: Linear and Quadratic Terms

	BDI	GDS	PAI-DEP (overall)	PAI-DEP Affective	PAI-DEP Cognitive	PAI-DEP Physiological
Noncarrier vs carrier						
Quadratic *P* value	.77	.92	.12	.11	.78	.07
Linear *P* value	.37	.51	.40	.24	.39	.98
Noncarrier vs heterozygote						
Quadratic *P* value	.77	.97	.06	.04	.32	.12
Linear *P* value	.94	.26	.69	.33	.83	.71
Noncarrier vs homozygote						
Quadratic *P* value	.95	.80	.91	.77	.20	.16
Linear *P* value	.06	.52	.33	.50	.22	.54

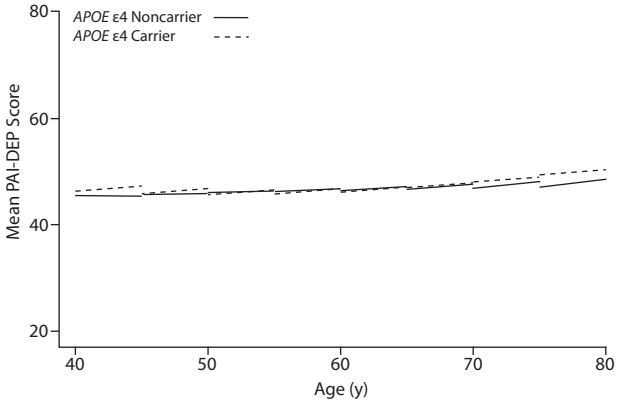
Abbreviations: BDI = Beck Depression Inventory, GDS = Geriatric Depression Scale, PAI-DEP = Personality Assessment Inventory depression scale.

actual rate of change was very small (0–0.10 points per year in the noncarriers compared to 0.10–0.20 points per year in the homozygotes) and clinically insignificant.

Incident Depression

Table 4 provides estimates of incident depression by noncarrier, heterozygote, and homozygote status on the HDRS, BDI, or PAI-DEP or by initiation of depression medication use after entry. If the subject was positive on any 1 of these measures after the baseline normal epoch or began using depression medication after the baseline epoch, the subject was considered a possible case of incident depression. There was no significant difference between noncarriers, the heterozygote group, and the homozygote group in the proportion of possible incident depression (16.1%, 15.9%, and 16.7%, respectively; $P = .99$).

Figure 1. Longitudinal Analysis of Change in Personality Assessment Inventory Depression Scale (PAI-DEP) T-Score by Apolipoprotein E (*APOE*) ε4 Status



CONCLUSIONS

Memory loss is a hallmark feature of Alzheimer's disease and required for clinical diagnosis, while depression is neither.[17] Nonetheless, some studies have found a higher rate of incident MCI and dementia among depressed patients, leading to the suggestion that depression may be an intrinsic part of the clinical course of Alzheimer's disease.[5] If depression is intrinsic to the clinical course of Alzheimer's disease as is memory loss, then one would expect depressive symptoms to escalate preclinically, whether or not they reached the threshold of clinical depression. *APOE* ε4 genotype is a known genetic risk factor for late-onset Alzheimer's disease, and, as expected, longitudinal memory testing disclosed more rapid decline with age in ε4 carriers than noncarriers.[7] In contrast, we found no such effect for measures of depression despite observing a modest age-associated gradual increase in depressive symptoms more generally. While this does not exclude the possibility that a subset of patients with clinical depression may be at higher risk for incident MCI and Alzheimer's disease, or a very weak correlation that this study was not powered to detect, our results suggest that if subclinical change in depression is present in those at increased genetic risk for Alzheimer's disease, it is either much less easily detectable than memory decline or not present in this early preclinical phase of the pathologic process.

A longitudinal study[1] found that those with MCI and depression were at more than twice the risk of developing dementia over a 3-year period than those with MCI without depression. However, a recent review[2] suggests that the overall research is mixed. For example, data from the Alzheimer's Disease Neuroimaging Initiative did not find a predictive relationship between the endorsement of symptoms of depression (even at a subsyndromal level) and progression from MCI to dementia.[3] Using data from the National Alzheimer's Coordinating Center (NACC), researchers found only a very small increase in risk of progression from MCI to Alzheimer's disease in those MCI subjects who remained depressed during the observation period (relative risk [RR] = 1.22).[4] In a prospective cohort study with a median follow-up period of 3.5 years, Mayo Clinic investigators found a 2-fold increase in risk of transition from normal cognition to incident MCI in those with depression.[5] They also found a synergistic interaction between APOE ε4 genotype and depression on MCI risk such that the joint effect of depression and APOE genotype was greater than the independent effects of these factors. However, the Italian Longitudinal Study on Aging,[6] a similar cohort study that also had a 3.5-year follow-up period, did not find an association between depressive symptoms and rate of incident MCI. Most recently, again using the large NACC cohort, another

Table 3. Estimated Score Change per Year on Depression Measures by Carrier Status and Age Decile

	Noncarrier			Heterozygote			Homozygote		
	Age 50–59	Age 60–69	Age 70–79	Age 50–59	Age 60–69	Age 70–79	Age 50–59	Age 60–69	Age 70–79
BDI	−0.01	0.03	0.08	−0.02	0.04	0.09	0.11	0.16	0.21
GDS	0.12	0.08	0.04	0.28	0.24	0.19	−0.07	−0.06	−0.05
PAI-DEP (overall)	0.05	0.14	0.23	0.20	0.17	0.14	0.15	0.23	0.31
PAI-DEP affective	−0.04	0.07	0.17	0.18	0.14	0.10	0.00	0.14	0.28
PAI-DEP cognitive	−0.04	0.06	0.15	0.14	0.07	0.11	−0.05	0.17	0.38
PAI-DEP physiological	0.15	0.21	0.26	0.25	0.18	0.10	0.41	0.28	0.15

Abbreviations: BDI = Beck Depression Inventory, GDS = Geriatric Depression Scale, PAI-DEP = Personality Assessment Inventory depression scale.

Table 4. Incident Depression Estimates by Apolipoprotein E ε4 Carrier Status[a]

	Noncarrier (n = 205)	Heterozygote (n = 107)	Homozygote (n = 36)	*P* Value
HDRS				
Mean (SD)	3.4 (2.6)	3.5 (2.9)	3.9 (3.3)	.60[b]
Median	3.0	3.0	3.0	
Range	0–12	0–12	0–14	
Score > 10, n (%)	3 (1.5)	1 (0.9)	2 (5.6)	.17[c]
BDI				
Mean (SD)	6.2 (5.0)	6.7 (4.3)	6.6 (5.4)	.64[b]
Median	5.0	6.0	5.0	
Range	0–30	0–20	0–25	
Score ≥ 14, n (%)	10 (4.9)	7 (6.5)	2 (5.6)	.83
PAI-DEP T-score				
Mean (SD)	48.9 (6.8)	50.2 (8.6)	51.0 (9.1)	.19[b]
Median	49.0	49.0	48.5	
Range	36–72	36–86	40–78	
Score ≥ 70, n (%)	1 (0.5)	3 (2.8)	2 (5.6)	.06[c]
Depression medication added after entry, n (%)	25 (12.2)	14 (13.1)	5 (13.9)	.95[c]
Incident depression, any measure or addition of depression medications, n (%)				.99[c]
No	172 (83.9)	90 (84.1)	30 (83.3)	
Yes	33 (16.1)	17 (15.9)	6 (16.7)	

[a]Among 348 subjects with no depressive symptoms on any measure and taking no depression medications at first epoch. All subjects have measurements taken at more than 1 epoch.
[b]Analysis of variance *F* test.
[c]χ^2 test.
Abbreviations: BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale, PAI-DEP = Personality Assessment Inventory depression scale.

group[4] found an increased risk of progression from normal cognition to MCI in those who were always depressed throughout the study period (RR = 2.35) compared to those who were never depressed during the study period. Of note is that risk was significantly lower for those who were depressed in the initial visit but not depressed throughout the rest of the follow-up period (RR = 1.41). There was no increased risk for progression from normal to MCI in those with a history of depression in remission prior to the study period.

Finally, a recent analysis[18] found that depression was associated with an increased risk of incident dementia, and those with MCI and depression had a higher risk for progression to dementia. However, depression was not associated with increased risk of incident MCI. The authors concluded that depression may accompany the stage of disease when cognitive impairment is present (MCI/dementia) but does not precede clinical change in cognition. This is consistent with our hypothesis, and the lack of association between depression and *APOE* genotype further supports the assertion that depression is not associated with the preclinical stage of disease.

Although we were unable to demonstrate a difference in depressive symptomatology or incident depression between *APOE* subgroups, we did not address the possibility that depression, when present, might be more disabling in *APOE* ε4 carriers or those with preclinical Alzheimer's disease. We have previously found that ε4 homozygotes in particular suffer greater setbacks from fatigue[19] and anxiety[20] than noncarriers, and we found that ε4 heterozygotes suffered greater cognitive effects of a pharmacologic challenge with lorazepam than ε4 noncarriers.[21] Thus, it is possible that previous associations between depression and incident dementia could reflect a similar phenomenon in that a similar level of depressive symptoms may be more disabling for ε4 carriers than noncarriers. This would also be consistent with previous findings[5] that *APOE* genotype and depression seemed to have additive effects with regard to conversion from MCI to dementia in that functional status is the defining difference between MCI (in which patients are not yet disabled by their cognitive impairment) and mild dementia (in which they are functionally impaired).

The main limitation of this study is that only a few participants have progressed to incident MCI. We cannot therefore exclude the possibility that depressive symptomatology might accelerate later during the preclinical course more proximate to the time of symptomatic memory decline (eg, a late preclinical phase of developing neuropathology). We continue to follow this cohort to address this possibility. Another possible limitation of our study could be sensitivity of our methods for detecting depression. However, our cohort members were not depressed at the time of enrollment (on the basis of the HDRS and *DSM* criteria), and depression was assessed throughout follow-up with multiple instruments in order to maximize sensitivity. Inclusion of the PAI specifically allows for separate evaluation of subtypes of depressive symptoms including affective (ie, sadness), cognitive (ie, hopelessness), and physiologic (ie, appetite change). Thus, we believe it is unlikely that our negative findings could be explained by insensitivity of the test battery. Further, we found no evidence for a difference in incident depression or antidepressant use rates between *APOE* ε4 carriers and noncarriers.

We have found that memory declines early in the preclinical course of Alzheimer's disease,[7] but that, closer to the symptomatic conversion to MCI, executive skills may decline as well in some patients.[22] The cognitive profile of depression resembles a dysexecutive syndrome, and, in both depression and prodromal MCI, patients can have reduced initiation, are less able to multitask, and may have trouble with concentration. Possibly, resemblance of this late preclinical stage cognitive profile with the cognitive profile in depression may lend some credence to the theory that depression in the older adult is a near-term harbinger of MCI. However, the lack of relationship between *APOE* genotype and depressive symptoms suggests that escalation in depression symptoms may not be a characteristic feature of the preclinical phase of Alzheimer's disease.

Drug names: lorazepam (Ativan and others).
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