Depressive Symptoms, Sex, and Risk for Alzheimer's Disease

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Depression associates with increased risk for dementia and Alzheimer's disease (AD), although it is unclear whether it represents an actual risk factor or a prodrome. To determine the relative hazard of premorbid depressive symptomatology for development of dementia and AD, we studied risk for incident dementia and AD over a 14-year period in 1,357 community-dwelling men and women participating in the 40-year prospective Baltimore Longitudinal Study of Aging. Screening for depressive symptoms, comprehensive medical and neuropsychological evaluations were prospectively collected every 2 years. Time-dependent proportional hazards of development of AD or dementia were calculated separately for men and women, with symptoms of depression detected at 2-, 4-, and 6-year intervals before onset of dementia symptoms. Vascular risk factors were analyzed as covariates. Premorbid depressive symptoms significantly increased risk for dementia, particularly AD in men but not in women. Hazard ratios were approximately two times greater than for individuals without history of depressive symptoms, an effect independent of vascular disease. We conclude that the impact of depressive symptoms on risk for dementia and AD may vary with sex. Further studies assessing separately the role of depression as a risk factor in men and women are necessary.

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The relation of depression and risk for dementia and Alzheimer's disease (AD) is controversial.[1–11] It is unclear how often mild cognitive impairment seen in nondemented depressed elderly individuals develops into subsequent cognitive decline and dementia.[12,13] Conversely, depressive symptoms are described in 35 to 50% of dementia or AD cases, particularly in early stages.[3,14,15] A meta-analysis on history of depression and risk for dementia,[16] however, could not determine if depression is an early prodrome or a risk factor, despite evidence supporting an association between depression and dementia in both case–control and prospective studies. Furthermore, a history of medically treated depression has been associated with increased risk for dementia,[10] particularly for late-onset depression, although depression may be a risk factor even for episodes occurring up to 25 years before dementia onset.[1,9]

A series of prospective studies suggest that baseline depressive symptoms are associated with increased risk for AD in older people,[4–8,17–19] although the finding is not universal.[7,20,21]

The discrepancy between epidemiological studies that show increased risk for dementia with depression[4,8] and those that do not underlines the elusiveness of the prognostic significance of depression, symptoms of depression, or both. In this study, we examined the 14-year prospective relationship between premorbid symptoms of depression and clinical diagnoses of dementia and AD in the Baltimore Longitudinal Study of Aging (BLSA), a longitudinal study of community-dwelling adults.[22]

Subjects and Methods

Subjects are volunteer participants in the BLSA, a study performed by the National Institute on Aging.[22] Participants are community-dwelling volunteers who return every 2 years to the Gerontology Research Center of the National Institute on Aging for comprehensive evaluations.

The work was done at the Department of Neurology, Johns Hopkins University School of Medicine (Baltimore, MD) and at the BLSA of the Intramural Research Program of the National Institute on Aging.

We analyzed 1,357 participants (576 women, 781 men) who had at least one follow-up after age 55 years between January 1985 and December 1999. The mean number of follow-ups was 4.4 (range, 2–10), with a mean interval of

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6.1 (range, 1–30). The cohort comprises predominantly upper-middle-class white professionals with above-average education. Since 1985, we studied participants specifically for incidence of dementia and AD; methods have been described in detail elsewhere.[23] Participants were examined at regular intervals with a battery of neuropsychological tests and neurological, laboratory, and radiological examinations. Subjects showing changes indicative of incident dementia were systematically studied. Diagnosis of dementia and dementia type was formulated during multidisciplinary evaluations based on prospectively collected evidence. All participants provided written informed consent.

Diagnosis of Alzheimer's Disease and Other Dementias

Diagnoses of dementia and AD were based on Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised criteria[24] and National Institute of Neurological and Communication Disorders-Alzheimer's Disease and Related Disorders Association criteria,[25] respectively. Subjects with cognitive changes not meeting diagnostic criteria were labeled as "suspects" and followed longitudinally.

Measures

Participants were administered the Center for Epidemiologic Study–Depression (CES-D) Scale,[26] a 20-item inventory of the National Institute of Mental Health Center for Epidemiological Studies, to assess frequency and severity of depressive symptoms. The inventory has been extensively validated[27] and is widely accepted in epidemiological studies of depression in general populations. The CES-D Scale correlates strongly with other self-reported depression inventories and with variables related closely to clinical diagnoses of depression. Scores for clinically depressed patients are greater than for nondepressed subjects.[28] A standard cutoff score of 16 or greater has been validated as indicating clinically significant depressive symptoms, identifying a large proportion of individuals with major depressive disorders.[29]

Analyses

We used time-dependent, proportional hazards to examine risk for AD associated with depressive symptoms. The dependent measure was age at diagnosis or the last observed (censored) age of nondiagnosed subjects. Because depressive symptoms and dementia have differential sex prevalences and we had a large sample of either sex, we performed a number of primary analyses on the whole sample, as well as separately for women and men. To assess individuals with truly normal cognitive function and to exclude those who might have depressive symptoms as prodromes of dementia, we performed all analyses both including and excluding subjects labeled as "suspects" at any of the diagnostic conferences.

First, we predicted AD onset from time-dependent values of CES-D scores as a continuous measure, as well as dichotomized at 16 and 20, a widely accepted cutoff indicating greater severity of depressive symptoms.[27,30] Because melancholic depressive complaints may be specific for true depression[31] and to minimize the effect of physical illness and other factors on depressive symptoms, we also performed the analyses according to a subscale based on a "cluster" of negative affective symptoms.[30]

Because of the potential interplay of vascular disease with both AD and depression,[32,33] in a second set of analyses, clinical diagnoses of heart disease, hypercholesterolemia, hypertension, cerebrovascular disease, diabetes, and obesity were included as fixed covariates to determine their contribution to risk for AD and dementia. Because of the potential protective effect of education,[34,35] number of years of education was included as a fixed covariate. Moreover, because depressive symptoms could be a consequence of the onset of AD, we performed these analyses with various lags between last CES-D assessment and age of diagnosis or censoring. There was no lag in the first series of analyses, a 2-year lag in the second series of analyses, and a 4-year lag in the third series of analyses. We checked the specificity of our results for risk of AD by repeating all analyses with "any dementia" as the outcome.

Results

Table 1 shows baseline and follow-up cohort characteristics. In the study period, for women, a total of 49 incident cases of dementia were diagnosed, 40 of which represented AD; for men, diagnosis of incident dementia was made for 76 participants, 67 of which represented AD. The rate of diagnosis in this cohort was comparable with that of similar studies. Power analysis showed that the number of cases diagnosed was sufficient for 80% power for a $p < 0.05$. Table 2 shows the distribution of the incident cases of AD and dementia according to CES-D scores, dichotomized at the cutoffs of 16 and 20. Despite the presence of a greater number of male participants in the BLSA, sex distribution differences were not significant for either AD or any dementia diagnoses ($\chi^2 = 0.59$; $p = 0.44$). Table 3 shows time-dependent hazard ratios (HRs) of development of AD and any dementia, with presence of depressive symptoms on the CES-D at any time before diagnosis (no lag) and 2 and 4 or more years before diagnosis. For women, there were no significant risks at any time lag, for any dementia or AD associated with CES-D scores, either as a continuous variable or at the cutoffs of 16 and 20. For men, risk was significantly greater with CES-D scores indicating depressive symptoms at any time lag. Even applying the most conservative CES-D cutoff of 20 and time lag of 4 or more years before diagnosis, to minimize chances of including individuals with either prodromal symptoms of dementia or nonspecific depressive complaints, HRs remained significant only for men (AD: HR = 2.63, confidence interval [CI] = 1.28–5.40; any dementia: HR = 1.78, CI = 0.92–3.47; $p < 0.05$). When the analyses were repeated excluding subjects labeled as "suspects" at any diagnostic conference, risk for AD and any dementia remained significantly increased for men with depressive symptoms at any time but not for women (data not shown). Moreover, when these anal-

Table 1. Descriptive Statistics at Baseline and Last Follow-up for the Whole Sample and Separately for 576 Women and 781 Men

	Baseline			Last Follow-up		
Characteristic	Mean	SD	Range	Mean	SD	Range
Age (yr)	65.5	12.0	38–98	70.8	12.1	50–96
CES-D	7.1	6.8	0–46	7.5	7.0	0–45
Education	16.8	2.7	4–25	—	—	—

	Women			Men			Women			Men		
Characteristic	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age (yr)	64.0	12.4	40–94	66.8	11.5	38–95	69.5	13.5	50–102	73.2	11.9	50–99
CES-D	7.2	7.1	0–42	7.1	6.6	0–46	7.7	7.2	0–35	7.4	6.9	0–45
Education	16.3	2.6	9–24	17.1	2.8	4–25	—	—	—	—	—	—

SD = Standard deviation; CES-D = Center for Epidemiologic Study–Depression.

yses were repeated adding cerebrovascular risk factors and years of education as covariates, HRs of developing AD and dementia at any time lag remained significantly increased in men but not in women (data not shown). When the analyses were done excluding "suspects" from the risk set, the results were equivalent. Presence of obesity conferred a significantly greater risk for development of AD in all analyses, particularly for men (HR = 3.83, CI = 1.55–9.48, $p < 0.01$, with CES-D > 20 and the exclusion of suspects). An opposite effect was noted for education (HR = 0.89, CI = 0.82–0.96, $p < 0.01$). Table 4 shows the results referred to the most conservative analyses (CES-D > 20, exclusion of suspects, 4-year lag). Finally, all results remained equivalent performing the analyses with the negative affective symptoms CES-D subscale (data not shown).[30]

Discussion

The results of this study, based on a 14-year prospective follow-up of a cohort of 1,357 initially nondemented subjects, indicate that history of depressive symptomatology represents a significant risk factor for development of dementia, especially AD, for men but not women. This risk remained two times greater than risk for men without depression when the lag between detection of symptoms and diagnosis of dementia was increased, suggesting that prodromal dementia was not the cause of the affective symptomatology. The use of more restrictive criteria for detection of depression, with the cutoff score of 20 on the CES-D, showed an even greater risk for development of AD in men endorsing more severe depressive symptoms. The findings were unchanged when individuals clinically suspected of having mild cognitive impairment were excluded from the risk set, again suggesting that the depressive symptoms were not caused by impending dementia. The risk for men was not substantially modified when we used the affective subscale of the CES-D,[30] which is believed to be more specific for true depression.

To our knowledge, this is the first study reporting a difference between men and women in risk for dementia as determined by depressive symptoms. Large sex differences exist in rates of depression and clinical manifestations of affective distress,[36,37] with men usually being less willing to admit to experiencing symptoms.[37–39] It is possible that depressive symptoms are more extreme among men having such symptoms.

Table 2. Baseline Distribution for Cases of Alzheimer's Disease and Any Dementia by CES-D Cutoff Separately by Sex

	Alzheimer's Disease		Any Dementia	
CES-D	Women	Men	Women	Men
<16	31/507 (6%)	36/701 (5%)	36/507 (7%)	54/701 (8%)
≥16	9/69 (13%)[a]	13/80 (21%)[b]	13/69 (18%)[a]	22/80 (28%)[b]
<20	34/536 (6%)	42/746 (6%)	42/536 (8%)	67/746 (9%)
≥20	6/40 (15%)[a]	7/35 (20%)[b]	7/40 (15%)	9/35 (26%)

Cross-sectional prediction of Alzheimer's disease and any dementia for men and women separately from baseline CES-D scores dichotomized at the cutoffs of 16 and 20.

[a]$p < 0.05$; [b]$p < 0.01$.

CES-D = Center for Epidemiologic Study–Depression.

Table 3. Time-Dependent Hazard Ratios for Risk of Alzheimer's Disease and Any Dementia according to CES-D Scores

		Outcome			
		Alzheimer's disease		Any dementia	
Lag	Covariate	Women	Men	Women	Men
None	CES-D	0.99 (0.95–1.02)	1.06 (1.04–1.09)[a]	1.02 (0.99–1.04)	1.06 (1.04–1.08)[a]
	CES-D ≥16	0.69 (0.34–1.38)	2.10 (1.32–3.33)[a]	1.22 (0.74–1.99)	2.26 (1.58–3.22)[a]
	CES-D ≥20	0.84 (0.34–2.09)	2.45 (1.38–4.35)[a]	1.51 (0.82–2.78)	2.20 (1.38–3.51)[a]
2 years	CES-D	0.99 (0.95–1.02)	1.07 (1.04–1.10)[a]	1.02 (0.99–1.05)	1.06 (1.03–1.08)[a]
	CES-D ≥16	0.70 (0.34–1.48)	2.05 (1.26–3.35)[a]	1.37 (0.82–2.28)	2.11 (1.44–3.10)[a]
	CES-D ≥20	0.95 (0.38–2.39)	2.37 (1.28–4.39)[a]	1.77 (0.96–3.28)	2.03 (1.22–3.40)[a]
4 years	CES-D	0.98 (0.94–1.02)	1.06 (1.03–1.10)[a]	1.02 (0.98–1.05)	1.05 (1.02–1.08)[a]
	CES-D ≥16	0.69 (0.29–1.64)	1.99 (1.10–3.60)[a]	1.34 (0.74–2.43)	1.95 (1.21–3.14)[a]
	CES-D ≥20	1.01 (0.36–2.83)	2.63 (1.28–5.40)[a]	1.63 (0.77–3.44)	1.78 (0.92–3.47)[a]

Hazard ratios obtained from time-dependent Analyses of CES-D scores as Risk factor to develop Alzheimer's disease and any dementia, calculated with no lag, 2-year lag, and 4-year lags between time of CES-D score acquisition and time of diagnosis.

*$p < 0.05$.

CES-D = Center for Epidemiologic Study–Depression.

Therefore, depression might be underestimated in men but overestimated in women, leading to an increased number of false-positives among women and diluting the risk in this group.

However, the greater prevalence of depression and AD in women,[36,37,40–42] effects of estrogens on AD risk,[43–45] and effects of gonadal hormones on neuronal physiology[46–48] suggest that sex-related biological factors modulate the risk for these diseases.

This study has several methodological strengths supporting the validity of our findings. The data on all variables were collected prospectively, with continuity of study population and data acquisition methods. Longitudinal use of the CES-D allowed determining incident depressive symptoms at time of assessment. The CES-D has advantages over other scales[26] by relying heavily on mood-related items and less on apathy and vegetative symptoms, which can overlap with, or be secondary to, a dementing illness.[31] In this study, specificity was further improved by using the affective symptoms subscale.[30] Although high scores on a diagnostic instrument do not translate automatically into a clinical diagnosis of depression, the use of both cutoffs, 16 and 20, on the CES-D are considered reliable indicators of an affective illness.[27]

Our length of follow-up, which was considerably

Table 4. Time-Dependent Hazard Ratios for Risk of Alzheimer's Disease and Any Dementia according to CES-D Scores >20, Covaried for Cerebrovascular Factors and Education, after the Exclusion of "Suspects"

		Outcome			
		Alzheimer's Disease		Any Dementia	
Lag	Covariate	Women	Men	Women	Men
4 or more years	CES-D >20	1.85 (0.62–5.52)	2.38 (1.15–4.94)[a]	2.36 (1.05–5.32)[a]	1.58 (0.79–5.31)
	Education (yr)	1.07 (0.96–1.19)	0.89 (0.82–0.96)[b]	1.02 (0.93–1.11)	0.95 (0.88–1.01)
	Cardiac disease	0.59 (0.23–1.52)	0.60 (0.33–1.08)	0.59 (0.26–1.33)	0.68 (0.43–1.08)
	Hypercholesterolemia	0.59 (0.23–1.53)	0.35 (0.14–0.89)[a]	0.53 (0.24–1.18)	0.45 (0.24–0.86)[a]
	CVD	0.41 (0.12–1.41)	1.56 (0.85–2.87)	1.63 (0.81–3.30)	1.45 (0.89–2.37)
	Hypertension	0.87 (0.46–1.64)	0.58 (0.32–1.04)	0.92 (0.53–1.60)	0.80 (0.52–1.23)
	Diabetes	0.00 (0.00–0.00)	0.26 (0.08–0.90)[a]	0.00 (0.00–0.00)	0.93 (0.49–1.79)
	Obesity	1.96 (0.43–8.93)	3.83 (1.55–9.48)[b]	1.21 (0.26–5.54)	1.94 (0.91–4.13)

Time-dependent hazard ratios for risk of Alzheimer's disease and any dementia obtained using the CES-D cutoff score of 20 or greater, covariates of cerebrovascular risk factors, and years of education as risk for Alzheimer's disease and any dementia, calculated with a 4-year lag, between time of CES-D score acquisition and time of diagnosis, after the exclusion of "suspects" (individuals suspected of having minimal cognitive impairment) from the risk set.

[a]$p < 0.05$; [b]$p < 0.01$.

CES-D = Center for Epidemiologic Study–Depression;
CVD = cerebrovascular disease.

longer than most other prospective longitudinal studies,[4–8,17] increased the opportunity to distinguish affective symptoms secondary to early dementia from true depressive symptomatology.

The large sample size of both men and women also provided power to detect sex-specific differences in risk. Stratification of the sample by sex permitted study of the effects of the variables in each group, without diluting the effects in a single sample.

This study has a number of limitations. The subjects are self-selected volunteers in a life-long project. Although this suggests sensitivity to health-related issues, we do not believe this influences our results, because the research question does not relate to public awareness of either depression or dementia. Our sample comprises highly educated individuals who are not representative of the general population, and we cannot exclude that men in this cohort endorse more depressive symptoms than men with lower education or socioeconomic status. However, in subjects with higher education, depressive symptoms have been reported to be more important as prodromes than as risk factors for AD.[19] Sex differences in response to the CES-D might contribute to the differences in risk noted in our cohort.[26,49–52] The lack of an effect on risk for AD by depressive symptoms in women could be secondary to a dilution effect because of overestimation of depression in this group. Alternatively, the strong effect seen in men might indicate that risk is related only to depressions severe enough that even more reluctant subjects would be willing to admit to symptoms.

Our data on stability of the CES-D scores over time and use of medications unfortunately did not allow us to assess whether risk was greater in the more severely affected individuals, if treatment modified risk, or if treatment-resistant depression was the true risk factor. Because of the data characteristics, the role of cerebrovascular risk factors could be studied only by using presence of clinical diagnoses as dichotomous variables. The large sample size, however, allowed sufficient power for the analyses, even if changes on risk because of different degrees of severity of the comorbidities could not be evaluated.

There are plausible biological reasons for the development of prodromal depressive symptoms in AD, given the widespread disruption of mood-regulating systems found in the brain of AD patients.[53–57] The increased risk in individuals with history of depression could result from shared environmental or genetic susceptibility.[58–60] Depression, however, could have direct causal or facilitatory effects on development of dementia. Changes in hippocampal morphology and volume are seen in long-standing depressive disorders,[61–63] possibly through mechanisms involving the hypothalamus–pituitary axis and adrenal corticosteroids,[64–66] leading to a decrease in neuronal anatomical reserve.[67] Notably, in animal models, the negative effects of stress-induced corticosteroid increases have been demonstrated only in male animals,[68] and important sex differences do exist in the neuroanatomy of the hippocampus.[69] Furthermore, in humans, striking sex differences about neurofibrillary changes are found in the mediobasal hypothalamus, a region involved in mood regulation.[70–72]

Although the biological mechanisms explaining our findings are yet to be understood, the sex-related neurochemistry and neuroanatomy underlying cognition and mood regulation strongly suggest a differential vulnerability in risk for AD conferred by depression in men and women. Future studies are needed to verify whether the effect of depression on risk for AD truly varies with sex in the general population.

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