ORIGINAL ARTICLE

Midlife vs Late-Life Depressive Symptoms and Risk of Dementia

Differential Effects for Alzheimer Disease and Vascular Dementia

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Context: Depression and dementia are common in older adults and often co-occur, but it is unclear whether depression is an etiologic risk factor for dementia.

Objective: To clarify the timing and nature of the association between depression and dementia.

Design: We examined depressive symptoms assessed in midlife (1964-1973) and late life (1994-2000) and the risks of dementia, Alzheimer disease (AD), and vascular dementia (VaD) (2003-2009) in a retrospective cohort study. Depressive symptoms were categorized as none, midlife only, late life only, or both. Cox proportional hazards models (age as timescale) adjusted for demographics and medical comorbidities were used to examine depressive symptom category and risk of dementia, AD, or VaD.

Setting: Kaiser Permanente Medical Care Program of Northern California.

Participants: Thirteen thousand five hundred thirty-five long-term Kaiser Permanente members.

Main Outcome Measure: Any medical record diagnosis of dementia or neurology clinic diagnosis of AD or VaD.

Results: Subjects had a mean (SD) age of 81.1 (4.5) years in 2003, 57.9% were women, and 24.2% were nonwhite. Depressive symptoms were present in 14.1% of subjects in midlife only, 9.2% in late life only, and 4.2% in both. During 6 years of follow-up, 22.5% were diagnosed with dementia (5.5% with AD and 2.3% with VaD). The adjusted hazard of dementia was increased by approximately 20% for midlife depressive symptoms only (hazard ratio, 1.19 [95% CI, 1.07-1.32]), 70% for late-life symptoms only (1.72 [1.54-1.92]), and 80% for both (1.77 [1.52-2.06]). When we examined AD and VaD separately, subjects with late-life depressive symptoms only had a 2-fold increase in AD risk (hazard ratio, 2.06 [95% CI, 1.67-2.55]), whereas subjects with midlife and late-life symptoms had more than a 3-fold increase in VaD risk (3.51 [2.44-5.05]).

Conclusions: Depressive symptoms in midlife or in late life are associated with an increased risk of developing dementia. Depression that begins in late life may be part of the AD prodrome, while recurrent depression may be etiologically associated with increased risk of VaD.

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At present, 5.3 million individuals in the United States have Alzheimer disease (AD), and the associated health care costs in 2010 were $172 billion.[1] Prevalence and costs of AD and other dementias are projected to rise dramatically during the next 40 years unless a prevention or a cure can be found.[2] Therefore, it is critical to gain a greater understanding of the key risk factors and etiologic underpinnings of dementia from a population-based perspective.

Depression commonly occurs in individuals with cognitive impairment and dementia.[3] Although some studies have found that depression coincides with[4-6] or follows[7,8] the onset of dementia in older adults, most studies and several meta-analyses have concluded that depression precedes dementia and is associated with approximately a 2-fold increase in the risk of developing cognitive impairment or dementia.[9-16] It remains controversial, however, whether depression reflects an etiologic risk factor, is part of the dementia prodrome, or shares genetic or other neuropathologic features with dementia.[10,17]

Vascular disease has been hypothesized as one of the potential mechanisms underlying the association between depression and dementia.[18] Evidence suggests a reciprocal relationship between vascular disease and depression, in which each condition is associated with an increased risk of developing the other.[19-21] Growing evidence also suggests that vas-

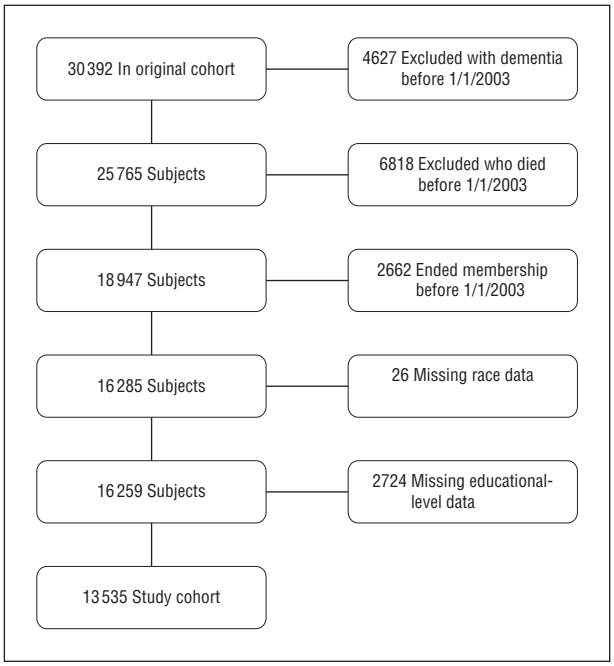

Figure 1. Flowchart of study participants.

cular disease contributes to the clinical manifestation of dementia symptoms.[22-24] Several cross-sectional studies have found that depressive symptoms are more common in vascular dementia (VaD) than AD,[25-28] which provides some support for the vascular disease–depression-dementia hypothesis. However, to our knowledge, prior studies have not determined whether depression is more likely to lead to VaD longitudinally, which would provide greater support for an etiologic association attributable to vascular disease.

Another limitation of most prior studies in this area is they have had relatively short follow-up periods. Given that dementia has a long preclinical period, these studies cannot clearly differentiate between etiologic risk factors and symptoms of preclinical disease. Thus, life-course studies with extended follow-up periods are critical for clarifying the timing and nature of the association between depression and dementia.

We examined the association between depressive symptoms and dementia during 45 years in a longitudinal study of more than 13 000 long-term members of the Kaiser Permanente Medical Care Program of Northern California. The primary goals of our study were to (1) clarify the timing of the association by examining the effects of depressive symptoms in midlife and late life and (2) clarify the role of vascular disease by examining associations with AD and VaD separately.

METHODS

STUDY POPULATION

The study population consisted of members of the Kaiser Permanente Medical Care Program of Northern California (hereinafter referred to as Kaiser) who participated in a voluntary health examination called the Multiphasic Health Checkup (MHC) in San Francisco and Oakland from 1964 through 1973 when they were 40 to 55 years of age. Kaiser is a nonprofit, integrated health maintenance organization that provides comprehensive inpatient and outpatient care to more than one-fourth of the population in the geographic areas served. The MHC was administered at the San Francisco and Oakland medical clinics to collect data on health habits and medical conditions of Kaiser members. The original MHC cohort included 30 392 individuals. Our analyses excluded individuals who had a dementia diagnosis (n=4627), died (n=6818), or ended their Kaiser membership (n=2662) before January 1, 2003, and those with missing data on race (n=26) or education (n=2724) for a final analytic cohort of 13 535 individuals (**Figure 1**).

Study procedures were approved by the Kaiser Division of Research Internal Ethics Committee, the Committee on Human Research at the University of California, San Francisco, and the Research and Development Committee at the San Francisco Veterans Affairs Medical Center. Analyses were performed by experienced Kaiser data analysts. To maximize patient confidentiality, non-Kaiser investigators were provided with data summaries only.

MIDLIFE DEPRESSIVE SYMPTOMS

As part of the midlife health survey, Kaiser members were asked: "Do you often feel unhappy or depressed?" Study participants who answered yes to this question were classified as having depressive symptoms in midlife. We also searched hospitalization records and classified individuals who were hospitalized for depression from 1971 through 1979 as having midlife depressive symptoms. Depression was determined using the following diagnostic codes from the *International Classification of Diseases, Ninth Revision* (*ICD-9*): 296.2 (major depressive disorder), 296.3 (recurrent major depressive disorder), 298.0 (depressive-type psychosis), 300.4 (dysthymic disorder), and 311.0 (depressive disorder not elsewhere classified). Of those classified as having midlife depressive symptoms, 8.7% had been hospitalized for their depression; of these, 57.6% also answered yes to the survey question on depressive symptoms.

LATE-LIFE DEPRESSIVE SYMPTOMS

Late-life depression was determined by searching Kaiser's comprehensive electronic medical record database system, which includes diagnoses from all inpatient and outpatient encounters at Kaiser medical centers and clinics, for depression diagnoses from January 1, 1994, through December 31, 2000, using the same *ICD-9* codes described. Additional episodes of late-life depression were identified by searching hospitalization records from January 1, 1990, through December 31, 1999.

DEMENTIA DIAGNOSES

Dementia diagnoses were determined from Kaiser's electronic medical record system from January 1, 2003, through July 31, 2009. We used a 3-year lag between depression diagnoses and dementia ascertainment to better ensure that our dementia cases reflected incident diagnoses. Specific *ICD-9* diagnoses included AD (331.0), VaD (290.40), presenile/senile dementia (290.0 and 290.10), dementia with depressive features (290.13, 290.21, and 290.43), and dementia with behavioral disturbances (294.10 and 294.11).

All diagnoses were used for analyses of all-cause dementia. Analyses of AD and VaD were restricted to diagnoses made in neurology clinics to maximize diagnostic specificity. In these analyses, individuals who developed other types of dementia were excluded. We have previously used similar procedures to identify cases of dementia, AD, and VaD among Kaiser members.[29-32]

Table 1. Baseline Characteristics of 13 535 Study Participants by Depressive Symptom Category[a]

Characteristic	Symptom Category				*P* Value[b]
	None (n = 9808)	Midlife Only (n = 1913)	Late Life Only (n = 1239)	Midlife and Late Life (n = 575)	
Age in 2003, mean (SD), y	81.1 (4.5)	80.8 (4.3)	81.5 (4.6)	80.9 (4.6)	<.001
Age at event or censored, mean (SD), y	85.9 (4.4)	85.5 (4.3)	85.8 (4.6)	85.2 (4.7)	<.001
Female sex	5192 (52.9)	1358 (71.0)	844 (68.1)	439 (76.3)	<.001
Race/ethnicity					
Asian	662 (6.7)	68 (3.6)	48 (3.9)	17 (3.0)	<.001
Black	1338 (13.6)	323 (16.9)	127 (10.3)	84 (14.6)	<.001
White	7379 (75.2)	1411 (73.8)	1023 (82.6)	440 (76.5)	<.001
Other	429 (4.4)	111 (5.8)	41 (3.3)	34 (5.9)	<.001
Educational level					
Grade school	1304 (13.3)	364 (19.0)	169 (13.6)	107 (18.6)	<.001
High school	3319 (33.8)	755 (39.5)	429 (34.6)	231 (40.2)	<.001
College	5185 (52.9)	794 (41.5)	641 (51.7)	237 (41.2)	<.001
Medical conditions					
Stroke	2689 (27.4)	537 (28.1)	449 (36.2)	197 (34.3)	<.001
Midlife diabetes mellitus	1876 (19.1)	416 (21.7)	274 (22.1)	140 (24.3)	<.001
Hypertension	8231 (83.9)	1653 (86.4)	1078 (87.0)	506 (88.0)	<.001
Hyperlipidemia	5892 (60.1)	1172 (61.3)	759 (61.3)	356 (61.9)	.58
Cardiovascular disease	5148 (52.5)	1001 (52.3)	754 (60.9)	354 (61.6)	<.001
Midlife BMI, mean (SD)	24.9 (3.6)	25.0 (4.1)	24.9 (3.8)	25.0 (4.0)	.79

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Unless otherwise specified, data are expressed as number (percentage) of subjects. Percentages have been rounded and might not total 100.
[b] Based on χ^2 test for category variables and analysis of variance for continuous variables.

OTHER MEASURES

The MHC questionnaire included a detailed interview on demographics, health behaviors, health status, medical conditions, and family history. Race/ethnicity was self-reported as Asian, black, white, or other and was included in analyses as a potential confounder. In addition to the MHC questionnaire, several clinical measurements were also collected at the midlife examination, including height, weight, and systolic and diastolic blood pressure. Height and weight were combined to calculate body mass index. Participants were considered to have midlife hypertension if they had 1 of the following: a self-report of physician-diagnosed hypertension, use of antihypertensive medication, systolic blood pressure of at least 140 mm Hg, or diastolic blood pressure of at least 90 mm Hg. Midlife diabetes status was defined by a self-report of physician-diagnosed diabetes mellitus, use of insulin or oral hypoglycemic agents, a fasting (last food eaten in ≥8 hours) glucose level of at least 140 mg/dL or a nonfasting (last food eaten in ≤4 hours) glucose level of at least 200 mg/dL (to convert glucose levels to millimoles per liter, multiply by 0.0555).

Diagnoses of stroke, hypertension, and cardiovascular disease also were recorded from outpatient records and hospital discharge diagnoses from 1978 through the end of the study using the following *ICD-9* codes: ischemic stroke (433-438), hemorrhagic stroke (430-432), and cardiovascular disease (410, 411, 413, 414, 428, 440, 443, and V717).

ANALYSES

Subjects were classified into one of the following 4 depression groups according to depressive symptoms: none, midlife only, late life only, or midlife and late life. Those with no depressive symptoms were used as the comparison group in all analyses. The unadjusted percentage of individuals who developed dementia, AD, and VaD was compared across the depression groups using χ^2 tests. Survival analysis and Cox proportional hazards models using age as the timescale were used to compare the time to dementia, AD, and VaD in each of the 4 depression groups. Person-years were calculated from the onset of follow-up (January 1, 2003) to the date of dementia diagnosis, with individuals censored at death, the end of Kaiser membership, or the end of the study period (July 31, 2009). Information on mortality was obtained through the California Automated Mortality Linkage System. Final multivariable models were adjusted for demographic factors (sex, race, and education) and number of medical comorbidities.

Table 2. Depressive Symptoms and Risk of All-Cause Dementia

Depressive Symptoms	All-Cause Dementia		
	No. (%) of Subjects	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
None	2026 (20.7)	1.00 [Reference]	1.00 [Reference]
Midlife only	450 (23.5)	1.22 (1.10-1.35)	1.19 (1.07-1.32)
Late life only	389 (31.4)	1.69 (1.51-1.88)	1.72 (1.54-1.92)
Midlife and late life	181 (31.5)	1.80 (1.54-2.09)	1.77 (1.52-2.06)

Abbreviation: HR, hazard ratio.
[a] Adjusted for education, sex, race, and number of comorbidities.

RESULTS

Our final sample included 13 535 long-term Kaiser members without any type of dementia at the onset of follow-up (January 1, 2003). The mean (SD) age of study participants at the beginning of follow-up was 81.1 (4.5) years and at dementia diagnosis or censoring, 85.6 (4.5) years; 57.9% were women and 24.2% were nonwhite (**Table 1**). Overall, 72.5% of subjects had no depressive symptoms at midlife or late life; 14.1%, midlife symptoms only; 9.2%, late-life

Table 3. Depressive Symptoms and Risk of AD and VaD

Depressive Symptoms	AD			VaD		
	No. (%) of Subjects	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	No. (%) of Subjects	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
None	500 (5.1)	1.00 [Reference]	1.00 [Reference]	201 (2.0)	1.00 [Reference]	1.00 [Reference]
Midlife only	97 (5.1)	1.08 (0.87-1.35)	1.06 (0.85-1.33)	46 (2.4)	1.26 (0.92-1.74)	1.24 (0.90-1.72)
Late life only	105 (8.5)	1.94 (1.57-2.39)	2.06 (1.67-2.55)	32 (2.6)	1.52 (1.05-2.21)	1.47 (1.01-2.14)
Midlife and late life	47 (8.2)	1.98 (1.46-2.66)	1.99 (1.47-2.69)	35 (6.1)	3.70 (2.58-5.29)	3.51 (2.44-5.05)

Abbreviations: AD, Alzheimer disease; HR, hazard ratio; VaD, vascular dementia.
[a]Adjusted for education, sex, race, and number of comorbidities.

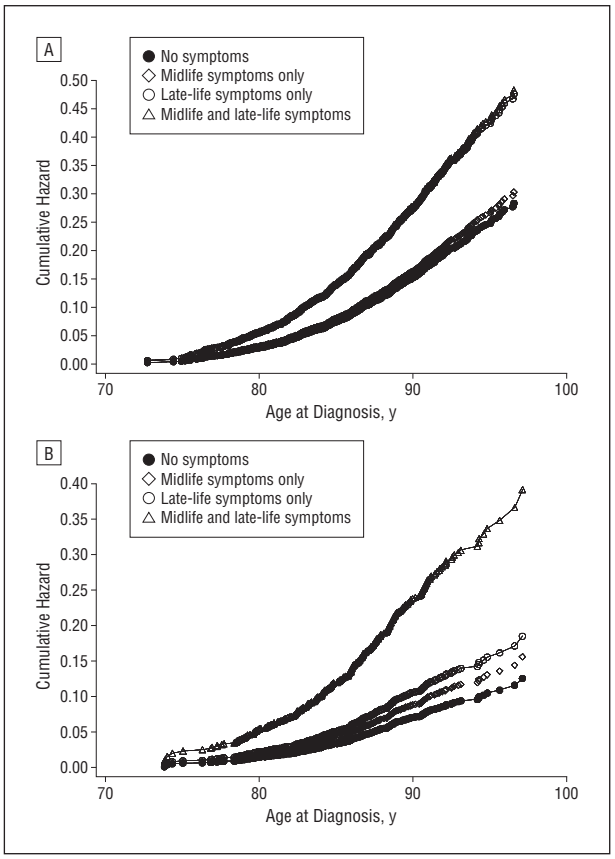

Figure 2. The unadjusted cumulative hazard of Alzheimer disease (AD) and vascular dementia (VaD). A, Cumulative hazard of AD by depressive symptom category. Compared with those with no depressive symptoms, the unadjusted cumulative hazard of AD was approximately doubled in those with late-life depressive symptoms only or midlife and late-life symptoms but was not significantly different in those with midlife symptoms only. B, The cumulative hazard of VaD by depressive symptom category. Compared with those with no depressive symptoms, the unadjusted cumulative hazard of VaD was increased by 50% in those with late-life depressive symptoms only and was more than tripled in those with midlife and late-life depressive symptoms but was not significantly different in those with midlife symptoms only.

symptoms only; and 4.2%, both. Subjects with depressive symptoms at any point during the life course were more likely to be women and to have a history of diabetes or hypertension. Asian subjects were more likely to have no depressive symptoms, whereas black subjects were more likely to have depressive symptoms in midlife only and white subjects were more likely to have depressive symptoms in late life only. In addition, individuals with depressive symptoms in midlife only or in midlife and late life were less likely to have a college education, and individuals with symptoms in late life only or in midlife and late life were more likely to have a history of stroke or heart disease. Hyperlipidemia and body mass index did not differ between the depression groups.

During the 6-year follow-up period, 20.7% of subjects with no depressive symptoms developed dementia compared with 23.5% of those with midlife symptoms only, 31.4% of those with late-life symptoms only, and 31.5% of those with midlife and late-life symptoms (**Table 2**). After adjustment for demographics and the number of medical comorbidities, the hazard of dementia was significantly increased by approximately 20% for those with depressive symptoms in midlife only (hazard ratio [HR], 1.19 [95% CI, 1.07-1.32]), approximately 70% for those with late-life symptoms only (1.72 [1.54-1.92]), and approximately 80% for those with both (1.77 [1.52-2.06]).

When we repeated analyses looking at diagnoses of AD and VaD from neurology clinics, 5.5% had received a diagnosis of AD and 2.3% had received a diagnosis of VaD (**Table 3**). In analyses adjusted for demographics and the number of medical comorbidities, subjects with midlife depressive symptoms only did not have a significantly increased risk of AD (HR, 1.06 [95% CI, 0.85-1.33]) or VaD (1.24 [0.90-1.72]). In contrast, subjects with late-life depressive symptoms only had not only a 2-fold increase in the risk of AD (HR, 2.06 [95% CI, 1.67-2.55]) but also a nearly 50% increase in the risk of VaD (1.47 [1.01-2.14]). Subjects with midlife and late-life depressive symptoms also had a 2-fold increase in the risk of AD (HR, 1.99 [95% CI, 1.47-2.69]) and more than a 3-fold increase in the risk of VaD (3.51 [2.44-5.05]). The cumulative hazard of AD and VaD by depressive symptom category is shown in **Figure 2**.

COMMENT

In this study of more than 13 000 long-term Kaiser members, depressive symptoms in midlife or in late life were associated with an increased risk of developing dementia. In addition, the risk of AD was approximately doubled in individuals with depressive symptoms in late life (alone or in combination with midlife symptoms), whereas the risk of VaD was more than tripled in those with midlife and late-life depressive symptoms. These findings have important public health implications because they raise hope that adequate treatment of depression in midlife may reduce dementia risk in late life.

Our findings are consistent with a large body of literature suggesting that depression in late life is associated with an increased risk of developing cognitive impairment, dementia, and AD.[9-16] They also are consistent with a small number of prior studies suggesting that depression earlier in life also is associated with an increased risk of dementia. An early case-control study found that depression was associated with increased dementia risk even if the first episode occurred 25 years before onset,[33] and a more recent study found an association between the number of depressive episodes and risk of dementia during 25 years.[15] However, these studies did not differentiate between single vs recurrent depressive episodes and, therefore, did not explicitly examine dementia risk in the subset of subjects who only had depressive symptoms in midlife.

There has been an ongoing debate in the field as to whether the association between depression and dementia reflects an etiologic relationship or whether depression is a prodromal symptom of dementia.[10,17] Our results suggest that the answer may differ depending on the dementia subtype. Depression that presents for the first time in late life may reflect the earliest symptoms of dementia, particularly AD, in some individuals. Future studies should examine whether it may be helpful clinically to monitor these individuals for symptoms of cognitive deterioration suggestive of dementia. It is possible that earlier recognition of dementia could facilitate better management of health care through earlier treatment with memory-enhancing agents, when they are most likely to be effective, as well as greater involvement of caregivers, simplification of medication regimens, and earlier discussions regarding goals of care.

On the other hand, recurrence of depression in late life may reflect a long-term process of subclinical cerebrovascular changes that may predispose toward development of VaD. This hypothesis is consistent with the vascular disease–depression-dementia hypothesis[18] and is supported by prior studies in which white matter hyperintensities on cerebral magnetic resonance images—which are considered to be markers of underlying cerebrovascular disease—are associated with greater risk of depression and dementia in late life.[34-37] Although our study provides support for the vascular disease–depression-dementia hypothesis, it remains possible that other hypothesized mechanisms also play a role in the association between depression and dementia. In particular, the hypothalamic-pituitary-adrenal axis has been proposed as an alternative mechanism in which chronic or recurrent depression leads to hypercortisolemia that in turn results in hippocampal damage and increased vulnerability to dementia.[9,10]

Strengths of this study include the large sample size, which enabled us to study VaD as well as AD; the integrated health care delivery setting, which minimizes the impact of access to health care and enabled us to adjust for other medical comorbidities during the lifespan; and the availability of data from midlife and late life, which enabled us to examine depression during the life course. Limitations of the study include the midlife depressive symptom measure, which was based primarily on a single self-reported question and likely resulted in lack of specificity. In addition, use of electronic medical record data for diagnoses of late-life depression and dementia likely resulted in low sensitivity and underrecognition of these conditions. We also were not able to confirm diagnoses of AD and VaD using operational criteria or through postmortem or neuroimaging studies. Given that vascular disease is an independent risk factor for AD, that pure VaD is relatively rare, and that most individuals with dementia at the population level have mixed AD/VaD pathology, some VaD diagnoses in this study may have reflected a more mixed etiology. To the extent that these misclassifications were nondifferential (ie, misclassification of depressive symptom status was similar in those with and without dementia diagnoses, and misclassification of dementia status was similar in those with and without depressive symptoms), our findings would be biased toward the null; thus, the true magnitude of these associations may be stronger than observed in this study. We also were unable to analyze data related to use of antidepressants or other psychotropic medications, which should be examined in future studies. In addition, our measures of vascular risk factors were relatively limited, so we were unable to directly examine the role of vascular disease as the etiologic mediator of the association between depression and VaD. Finally, because we excluded dementia cases diagnosed before January 1, 2003, our findings are restricted to late-life dementia.

CONCLUSIONS

Our findings suggest that chronic depression during the life course may be etiologically associated with an increased risk of dementia, particularly VaD, whereas depression that occurs for the first time in late life is likely to reflect a prodromal stage of dementia, in particular AD. Future studies are needed to determine whether adequate treatment of depression in midlife or in late life may help to maintain cognitive function and delay dementia onset. Given the anticipated increase in dementia prevalence during the next 40 years, even a small reduction in dementia risk would have a tremendous public health impact.[38]

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Additional Contributions: Jufen Zhou, MS, performed all the data analyses.

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