

Twenty-Year Depressive Trajectories Among Older Women

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Context: Despite the frequent occurrence of depressive symptoms among older adults, especially women, little is known about the long-term course of late-life depressive symptoms.

Objective: To characterize the natural course of depressive symptoms among older women (from the young old to the oldest old) followed up for almost 20 years.

Design: Using latent-class growth-curve analysis, we analyzed women enrolled in an ongoing prospective cohort study (1988 through 2009).

Setting: Clinic sites in Baltimore, Maryland; Minneapolis, Minnesota; the Monongahela Valley near Pittsburgh, Pennsylvania; and Portland, Oregon.

Participants: We studied 7240 community-dwelling women 65 years or older.

Main Outcome Measure: The Geriatric Depression Scale short form (score range, 0-15) was used to routinely assess depressive symptoms during the follow-up period.

Results: Among older women, we identified 4 latent classes during 20 years, with the predicted probabilities

of group membership totaling 27.8% with minimal depressive symptoms, 54.0% with persistently low depressive symptoms, 14.8% with increasing depressive symptoms, and 3.4% with persistently high depressive symptoms. In an adjusted model for latent class membership, odds ratios (ORs) for belonging in the increasing depressive symptoms and persistently high depressive symptoms classes, respectively, compared with a group having minimal depressive symptoms were substantially and significantly ($P < .05$) elevated for the following variables: baseline smoking (ORs, 4.69 and 7.97), physical inactivity (ORs, 2.11 and 2.78), small social network (ORs, 3.24 and 6.75), physical impairment (ORs, 8.11 and 16.43), myocardial infarction (ORs, 2.09 and 2.41), diabetes mellitus (ORs, 2.98 and 3.03), and obesity (ORs, 1.86 and 2.90).

Conclusions: During 20 years, almost 20% of older women experienced persistently high depressive symptoms or increasing depressive symptoms. In addition, these women had more comorbidities, physical impairment, and negative lifestyle factors at baseline. These associations support the need for intervention and prevention strategies to reduce depressive symptoms into the oldest-old years.

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WHILE EVIDENCE SUGGESTS that as many as 27% of community-dwelling older adults (≥ 65 years) experience depressive symptoms,¹ little is known about the long-term course and heterogeneity of late-life depression. Given the projected expansion of the older populations and the health and economic costs of depression,^{2,3} greater understanding of the long-term course of depressive symptoms into the oldest-old years and the typologies that describe this long-term course will inform intervention and prevention strategies.

Most prior investigations have assessed depressive symptoms at only one time point.⁴ However, while depression

peaks in young adulthood, it also tends to occur at high and varying rates in late life.⁵ Because of the associations of depression with morbidity, poor health outcomes, and mortality,⁶⁻¹⁰ a persistent increase in depressive symptoms over time may have major health implications. Few studies¹¹⁻¹⁶ have assessed trajectories of depressive symptoms in older participants, and these have been limited by short follow-up periods. In addition, because the oldest old (≥ 80 years) are the fastest growing age group in the United States and because a high incidence of depressive symptoms has been found among the oldest old,¹⁷ long-term investigation of depressive symptoms is needed in this age group.

The primary objective of our study was to characterize the natural course of de-

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pressive symptoms among older women followed up for almost 20 years into their ninth and tenth decades of life. A secondary objective was to examine if lifestyle factors, functional impairment, and comorbidities known to be associated with late-life depression differentially predict more severe depressive symptom trajectories.

METHODS

PARTICIPANTS

We analyzed 7240 older community-dwelling women from the Study of Osteoporotic Fractures, a prospective cohort investigation of 9704 women 65 years or older, originally recruited between 1986 and 1988, from population-based listings in the following 4 areas of the United States: Baltimore, Maryland; Minneapolis, Minnesota; the Monongahela Valley near Pittsburgh, Pennsylvania; and Portland, Oregon. Women were excluded from the study if they were unable to walk without help or had undergone bilateral hip replacement. At years 2 (1988-1990), 6 (1992-1994), 10 (1996-1998), 16 (2002-2004), and 20 (2007-2009), the participants were administered the Geriatric Depression Scale short form (GDS). Our study included 7240 women who had at least 2 GDS measurements during almost 20 study years. The sample was of 99.7% white race/ethnicity, with a mean (SD) age of 72.8 (4.7) years. During the study, 3654 women died, and 622 women ended the study early. The mean number of GDS measurements was 3.4, and the median follow-up duration was 12.2 years. All the women provided written informed consent, and the study was approved by the committees on human research at each site. In addition, the study analyses were approved by the institutional review board of the University of California, San Francisco.

MEASURES

Information on participants' age, education, marital status, and living arrangements was collected at baseline. The GDS, a 15-item questionnaire with scores ranging from 0 to 15 assessing the number of depressive symptoms based on binary item responses (ie, yes or no), was used to determine the trajectories of depressive symptoms during the follow-up period. A final GDS score was determined for women with no more than 5 missing items. This score was calculated by first taking the mean of the nonmissing items and then multiplying the mean by 15. The GDS was initially administered during year 2 (defined as the baseline examination in this study) and was routinely administered at follow-up years 6, 10, 16, and 20. The instrument is a validated and reliable self-report scale used to detect depressive symptoms in older participants¹⁸ because it is structured to minimize the measurement of common but nonspecific factors in older adults (eg, fatigue, sleep disturbance, and poor concentration).¹⁹ A GDS cutoff score of 6 indicates depression.

Lifestyle factors were measured at baseline and included baseline smoking, number of alcoholic drinks per week, physical activity, and social networks. Alcohol use was assessed as the current number of drinks consumed per week, with 7 or more drinks per week defined as frequent consumption.²⁰ Physical inactivity was defined as no, low-intensity, moderate-intensity, or high-intensity physical activity as measured with a modified scale by Paffenbarger et al.^{21,22} The Lubben Social Network Scale,²³ a validated 10-item self-report inventory assessing the type of relationships and the size and frequency of contact, was used to determine a mean social network score for each participant (score range, 0-5, with higher scores representing larger networks). We defined participants as having

a small social network if they fell below the median of the averaged Lubben Social Network Scale (<3.3). A similar cutoff defining small networks has been used in other Study of Osteoporotic Fractures²⁴ investigations.

Physical function was assessed at baseline for each of 5 activities (shopping, preparing meals, walking 2-3 blocks, performing heavy housework, and climbing 10 steps without resting). Global cognitive function was assessed using the modified version of the Mini-Mental State Examination,²⁵ with a maximum score of 26. Scores of less than 23 (equivalent to ≥ 1.5 SDs below the mean) indicated cognitive impairment.²² At baseline, a medical history was obtained, including stroke, breast cancer, diabetes mellitus, myocardial infarction, and clinical measures of hypertension and obesity, defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or higher. Finally, participants were asked about current use (within the past 30 days) of medications, including antidepressants; reports of current use were checked by examining the labels of drugs.

STATISTICAL ANALYSIS

Latent-class growth-curve analysis, implemented with statistical software (Proc Traj procedure, SAS, version 9.1.3; SAS Institute, Inc),²⁶ was used to estimate the mean trajectories of the GDS scores as a function of current age at each visit. In contrast to standard growth curve analysis, latent-class growth-curve analysis estimates the mean trajectories for 2 or more unobserved or latent classes, in combination with the probability of membership in each latent class for every observation in the sample. Using Proc Traj, the successive GDS scores were modeled as censored normal. In addition to demographic variables, included for face validity, the multivariable Proc Traj submodel used to estimate probabilities of latent class membership included covariates that were statistically significant ($P < .05$) in bivariate analyses. To describe bivariate associations, we estimated the prevalence of baseline characteristics within latent classes and assessed differences in characteristics across latent classes using weighted repeated-measures analyses. In these analyses, each participant contributed to each latent class in proportion to her predicted probability of class membership based on the Proc Traj results. Robust SEs were used to account for a lack of independence of the weighted data across the 4 groups.

We hypothesized a priori that there would be 5 latent classes, 4 closely resembling the classes estimated by Proc Traj in the 4-class model we selected and an additional class with declining GDS scores. However, a 5-class model did not include a declining trajectory, instead splitting 1 of the 4 other hypothesized classes into 2 similar subgroups. Moreover, the Bayesian information criteria, conventionally used to determine the number of latent classes, pointed to a large number of barely distinguishable classes. Therefore, we selected the 4-class model as a parsimonious description of the sample in best accord with our prior hypothesis. Statistical tests for models were 2-tailed, with $P < .05$ defining statistical significance.

RESULTS

Figure 1 shows the 4 latent class GDS mean trajectories estimated by the selected latent-class growth-curve analysis model, plotted by current age at each visit. The predicted probabilities of group membership totaled 27.8% with minimal depressive symptoms, 54.0% with persistently low depressive symptoms, 14.8% with increasing depressive symptoms, and 3.4% with persistently high depressive symptoms.

BIVARIATE ANALYSES

Table 1 and **Figure 2** summarize the results of our weighted bivariate analyses characterizing the 4 latent classes. Women with the highest vs lowest depression trajectories over time were slightly younger at baseline (71.9 vs 73.1 years) and had fewer years of education (11.8 vs 13.1 years) ($P < .001$ for trend) (Table 1). Current use of antidepressants was particularly low for all groups but increased from women with minimal to persistently high symptoms (ie, 0.6% with minimal depressive symptoms, 1.5% with persistently low depressive symptoms, 3.5% with increasing depressive symptoms, and 7.1% with persistently high depressive symptoms); women with ever use of antidepressants during the entire study period included 12.0% with minimal depressive symptoms, 20.6% with persistently low depressive symptoms, 31.0% with increasing depressive symptoms, and 41.1% with persistently high depressive symptoms.

We found that the highest disease burden was in the group with persistently high depressive symptoms (13.6% for myocardial infarction, 6.5% for stroke, 14.2% for diabetes, 43.2% for hypertension, and 32.5% for obesity) and that the lowest disease burden was in the group with minimal depressive symptoms (3.8% for myocardial infarction, 1.5% for stroke, 3.4% for diabetes, 32.0% for hypertension, and 13.6% for obesity) (all $P < .001$ for trend) (Figure 2A). We also examined the prevalence of breast cancer, and in going from minimal depressive symptoms to persistently high depressive symptoms, the trend was statistically significant but less remarkable (ie, 4.0%-7.0%; $P = .01$ for trend). For negative lifestyle factors, the prevalences of baseline smoking, physical inactivity, and small social network increased with the severity of the trajectory ($P < .001$ for trend), with physical inactivity and small social network having the largest differences in persistently high depressive symptoms vs minimal depressive symptoms (34.5% vs 12.0% and 70.5% vs 41.3%, respectively) (Figure 2B). Frequent alcohol consumption (≥ 7 drinks per week) seemed to have an inverse relationship, in which the group with persistently high depressive symptoms had the lowest prevalence (8.1%) compared with the prevalences among the other groups (range, 10.2%-12.7%) ($P = .02$ for trend). In addition, physical impairment and cognitive impairment increased from the group with minimal depressive symptoms to the group with persistently high depressive symptoms ($P < .001$ for trend) (Figure 2C).

MULTIVARIABLE MODEL

For the multivariable model, the strongest association was seen with physical impairment, for which the odds of increasing depressive symptoms and persistently high depressive symptoms during 20 years were 8 times higher (odds ratio [OR], 8.11; 95% CI, 5.98-11.02) and 16 times higher (OR, 16.43; 95% CI, 10.29-26.23) for those having any physical impairment compared with those having no physical impairment (**Table 2**). In addition, negative lifestyle factors were strong predictors of the trajectories of increasing depressive symptoms and persistently high depressive symptoms. Those who smoked

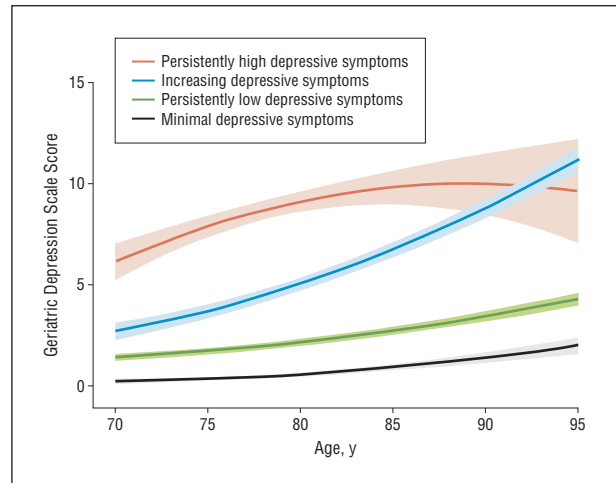


Figure 1. Mean trajectories of depressive symptoms by increasing age among older women.

were 5-fold more likely (OR, 4.69; 95% CI, 2.96-7.43) and 8-fold more likely (OR, 7.97; 95% CI, 4.37-14.54) to have increasing depressive symptoms and persistently high depressive symptoms, respectively. Compared with women who were active, women who were physically inactive were more than 2 times as likely (OR, 2.11; 95% CI, 1.52-2.93) to have increasing depressive symptoms and almost 3 times more likely (OR, 2.78; 95% CI, 1.77-4.36) to have persistently high depressive symptoms. Women who had a small social network had an almost 7-fold increased odds (OR, 6.75; 95% CI, 4.33-10.53) of persistently high depressive symptoms.

We found a 2-fold to 5-fold increased odds of a trajectory of persistently high depressive symptoms for those women who had a medical history of myocardial infarction, stroke, diabetes, obesity, or breast cancer (Table 2). Myocardial infarction, diabetes, and obesity were also significantly ($P < .05$) and independently associated with increasing depressive symptoms. However, stroke and breast cancer were associated only with persistently high depressive symptoms, while hypertension was significantly associated only with increasing depressive symptoms, independent of other covariates.

COMMENT

We identified 4 trajectories of depressive symptoms (minimal depressive symptoms, persistently low depressive symptoms, increasing depressive symptoms, and persistently high depressive symptoms) among older women who were followed up for almost 20 years. The prominent characteristics describing the trajectories of increasing depressive symptoms and persistently high depressive symptoms compared with minimal depressive symptoms were physical impairment, comorbidities (ie, diabetes, obesity, and myocardial infarction), and negative lifestyle factors (ie, baseline smoking, physical inactivity, and small social network). This study confirms that persistently high depressive symptoms and increasing depressive symptoms occur with concerning frequency during the course of aging, with survival to the oldest old being associated with increased symptom burden.

Table 1. Baseline Demographic Characteristics of 7240 Older Women According to Trajectories of Depressive Symptoms

Characteristic	Weighted				P Value ^a
	Minimal Depressive Symptoms (n = 1928)	Persistently Low Depressive Symptoms (n = 4137)	Increasing Depressive Symptoms (n = 939)	Persistently High Depressive Symptoms (n = 236)	
Age, mean (SE), y	73.1 (0.1)	72.9 (0.1)	72.3 (0.1)	71.9 (0.2)	<.001
Education, mean (SE), y	13.1 (0.1)	12.7 (0.0)	12.3 (0.1)	11.8 (0.2)	<.001
Married, % (SE)	48.0 (1.0)	49.3 (0.8)	48.8 (1.3)	42.4 (3.0)	.08
Living alone, % (SE)	43.9 (1.0)	42.6 (0.7)	42.8 (1.3)	45.3 (3.0)	.64

^aFor trend based on orthogonal contrasts in weighted generalized estimating equation models.

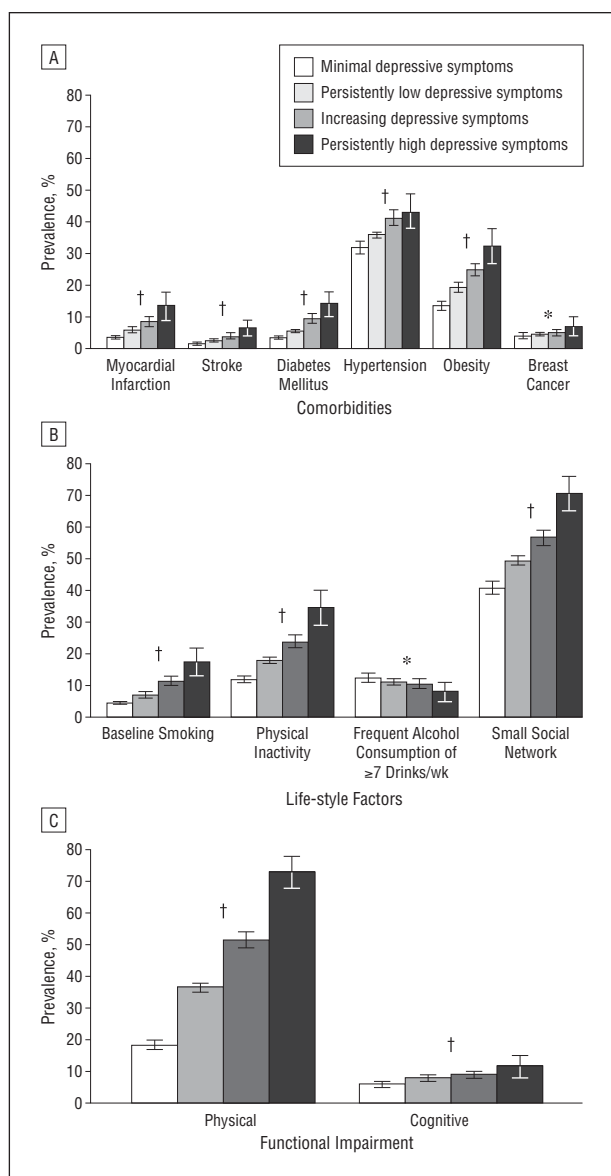


Figure 2. Prevalences across trajectory groups of depressive symptoms. A, Comorbidities. B, Lifestyle factors. C, Functional impairment. The bars indicate 95% CIs. * $P < .05$; † $P < .001$ (test for trend based on orthogonal contrasts in weighted generalized estimating equation models).

Few prior studies have considered the heterogeneity and natural course of depressive symptoms in older adults. Our findings are supported by a 6-year investigation from

the Longitudinal Aging Study Amsterdam,²⁷ in which 4 depression trajectory patterns were identified, namely, chronic, remission, chronic intermittent, and remission plus recurrence. Using a latent-class growth-curve analysis, we were able to characterize individuals by subtypes, identifying trajectories that may more realistically reflect the long-term course of late-life depression. Most previous latent class analyses describing heterogeneity in depressive symptoms have examined one point in time,²⁸⁻³³ while the few studies that have investigated trajectories during multiple years have included 1 or 2 years of data,^{14,15} used a one-item question to assess depression,¹² or had limited sample size to accurately assess follow-up data.¹⁶

Two studies that assessed 10 years and 12 years of depressive symptoms had inconsistent results. Our findings provide evidence supporting the 10-year study¹³ of 3922 older community-dwelling adults 60 years or older in which 4 distinct trajectories (ie, late peak, high chronic, persistent low, and persistent mild) were identified. In contrast, the 12-year study¹¹ identified 6 latent trajectories among 1260 community-dwelling adults 65 years or older. Unlike our results, this study found that 2 of the trajectories started high and declined with time. Finally, unlike this previous research, we had a large sample size (>7000 women) that provided information on a substantial number of oldest-old women, despite attrition due to dropouts and death.

Given our large sample size, we were able to study a comprehensive list of covariates known to be associated with late-life depression as potential predictors of the trajectories of persistently high depressive symptoms and increasing depressive symptoms. Studies^{4,6,34-37} have consistently found that various medical conditions, lifestyle factors, and functional impairment are associated with late-life depression or increased depressive symptoms; however, most of these studies were cross-sectional or describe factors related to a single mean trajectory of depression or depressive symptoms over time. In contrast, we identified multiple trajectories and generated a set of characteristics, in combination, that best predict probabilities of group membership in more severe depressive trajectories during the long term. To this end, we determined that the following variables differentially predicted trajectories of persistently high depressive symptoms and increasing depressive symptoms during 2 decades among older women (from the young old to the oldest old): obesity, diabetes, baseline smoking, physical inactivity, small social network, physi-

Table 2. Multivariable Model of Factors Independently Associated With Trajectories of Depressive Symptoms During 20 Years Compared With Minimal Depressive Symptoms^a

Variable	Minimal Depressive Symptoms	Odds Ratio (95% CI)		
		Persistently Low Depressive Symptoms	Increasing Depressive Symptoms	Persistently High Depressive Symptoms
Lifestyle Factors				
Baseline smoking	1.00 [Reference]	2.09 (1.34-3.26)	4.69 (2.96-7.43)	7.97 (4.37-14.54)
Frequent alcohol consumption of ≥ 7 drinks/wk	1.00 [Reference]	1.02 (0.77-1.35)	0.99 (0.69-1.43)	0.85 (0.44-1.63)
Physical inactivity	1.00 [Reference]	1.69 (1.25-2.27)	2.11 (1.52-2.93)	2.78 (1.77-4.36)
Small social network	1.00 [Reference]	2.14 (1.72-2.67)	3.24 (2.45-4.30)	6.75 (4.33-10.53)
Functional Impairment				
Physical	1.00 [Reference]	4.79 (3.66-6.28)	8.11 (5.98-11.02)	16.43 (10.29-26.23)
Cognitive	1.00 [Reference]	1.47 (0.99-2.20)	1.39 (0.88-2.20)	1.43 (0.74-2.79)
Comorbidities				
Myocardial infarction	1.00 [Reference]	1.60 (0.92-2.76)	2.09 (1.19-3.66)	2.41 (1.18-4.90)
Stroke	1.00 [Reference]	2.18 (0.80-5.94)	2.58 (0.93-7.16)	5.12 (1.63-16.08)
Diabetes mellitus	1.00 [Reference]	1.33 (0.76-2.34)	2.98 (1.75-5.10)	3.03 (1.49-6.14)
Hypertension	1.00 [Reference]	1.13 (0.93-1.38)	1.63 (1.29-2.07)	1.08 (0.73-1.60)
Obesity	1.00 [Reference]	1.51 (1.15-1.99)	1.86 (1.37-2.53)	2.90 (1.88-4.48)
Breast cancer	1.00 [Reference]	1.25 (0.79-1.99)	1.10 (0.62-1.94)	2.51 (1.24-5.09)

^aModel also adjusted for demographic variables (education, married, and living alone). Results that also adjusted for antidepressant use were similar.

cal impairment, and myocardial infarction. Although some previous latent trajectory studies^{11,12,14,16} have examined the association between depressive trajectories and related factors, the results have been mixed, with most investigators not considering these and other important covariates in combination.

The identification of 4 distinct trajectories of depressive symptoms during the course of 20 years has important implications. First, these trajectories provide new information concerning the heterogeneity of late-life depression.

Second, the findings suggest that if left unresolved the natural course of depressive symptoms in older women will become more burdensome, with almost 20% of women expected to have persistently high depressive symptoms or increasing depressive symptoms during the long term. Because the trajectories were determined using the latent class model, no specific cutoffs were assigned to the groups. However, the upper 2 trajectory groups (increasing depressive symptoms and persistently high depressive symptoms) suggest a trend toward clinically significant depression (ie, a GDS cutoff score of 6).

Third, by identifying important predictors of these trajectories, we are able to determine risk factors that may be targets for intervention and prevention. In particular, our study results suggest that modifiable risk factors (such as a reduction in obesity, increased physical activity or exercise, and more social engagement or connectedness) may help to reduce the progression of symptom burden. Although an association between chronic conditions (such as myocardial infarction and diabetes) and risk for depression has been supported by prior research,^{34,38,39} few investigators have considered the importance of lifestyle factors as predictors of depression above and beyond morbidity. In our study, lifestyle factors (ie, baseline smoking, physical inactivity, and small social network) had an impressive influence on increasing depressive symptoms and per-

sistently high depressive symptoms. Future studies on the effect of alterations in lifestyle factors associated with changes in depressive symptoms are needed to target lifestyle factors for intervention and prevention of late-life depression. In general, research investigating positive lifestyle factors as a modality for combating depression or depressive symptoms in older adults has been modest.⁴⁰ Furthermore, current antidepressant use was low in our study and ever use was less than 50% for those in the highest trajectory group. Although the literature has shown that the use of antidepressants has increased since our 1988 study baseline,⁴¹ the results herein suggest a greater need for early recognition and treatment of depression symptoms in late life. Moreover, our results have implications for increasing the use of maintenance regimens of antidepressant pharmacotherapy in older adults to reduce depressive symptoms during the long term. Such maintenance treatment is also strongly supported by the maintenance trials from Pittsburgh and elsewhere.^{42,43} In summary, investigation of combating symptom burden by improving physical function, managing cardiovascular conditions, and promoting positive lifestyle factors alone or in combination with antidepressant use is suggested by our findings.

Our results support evidence linked to the vascular depression hypothesis⁴⁴ that vascular disorders and vascular risk factors may precipitate and perpetuate the severity and chronicity of depression into late life. Because the risk for vascular disease increases in postmenopausal women,⁴⁵ our findings may suggest an increased risk for late-onset depression or change in the course of premenopausal depression after the onset of vascular disease. This implicates medications in lieu of or in addition to antidepressants (eg, drugs used for prevention and treatment of cerebrovascular disease), as well as lifestyle changes, to prevent and intervene against vascular depression in older women.

The strengths of this study include carefully measured potential predictors, a large sample of community-dwelling older women, and information on depressive symptoms during almost 2 decades. To our knowledge, this study is the first to characterize the natural course of depressive symptoms during 2 decades in older women, the group at greatest risk for living with high rates of late-life depression and related illness and disability.^{46,47}

Our study has some limitations. The sample was restricted to women. Although women are at much higher risk for developing depressive disorders and comprise a larger proportion of the oldest old, sex differences in the trajectories of depressive symptoms may be important, especially considering the potentially different targets of intervention and prevention. One prior study¹⁶ found that depressive trajectories in men were affected by perceived health and disability, while trajectories in women were influenced by disability and social support. In addition, the results of our study are not generalizable to nonwhite older adults or less healthy women. Moreover, we did not have a complete set of covariates available to investigate other potentially important baseline predictors of high and emerging depressive symptoms. This included incomplete information on medical history of cancer, socioeconomic status (eg, income), and sleep disturbance or sleep disorders. Although the Study of Osteoporotic Fractures collected data on breast cancer at baseline, information specific to other cancers that have been found to be associated with geriatric depression (such as colon cancer⁴⁸) was unavailable. Also, we had limited data on depression treatment and were unable to investigate the effect of treatment on changing trajectories. For example, we did not have information available on when the participants initiated antidepressant treatment (only that they were taking antidepressants in the prior 30 days from the interview date), nor did we have data available on their use of nonpharmacological treatment for depression. Furthermore, we did not have information on the history of depression and could not determine whether the baseline covariates were consequences of previous depression. Finally, because GDS data were collected at visits that were approximately 4 years apart, variation of depressive symptoms during these gaps is unknown.

Understanding the long-term course of depressive symptoms among those who live into their ninth and tenth decades of life is imperative. The results of this study help to describe these patterns by identifying 4 trajectories of depressive symptoms, highlighting the persistence of symptoms in the oldest old. Although we determined key predictors of more severe depressive trajectories (ie, comorbidities, physical impairment, and negative lifestyle factors at baseline), further investigation into combating increased burden during the long term is needed. In addition, these associations may be bidirectional, which suggests the need for further investigation in longitudinal analyses. Future research should test the bidirectionality of associations, such as physical or cognitive impairment and depressive symptoms, elucidating what is the causal relationship and where to intervene. Furthermore, future research needs to examine which other important covariates are not accounted for in the present study (eg, socioeconomic gradient) and to investigate

whether associations differ by sex and racial/ethnic diversity. Finally, because the number of trajectory classes selected was driven by prior hypothesis, our findings need to be carefully interpreted and confirmed by future work.

Given the increased life expectancy, the health and economic costs of depression, and the projected expansion of the older populations, the potential public health burdens of late-life depressive disorders implicated by our study results are concerning. These findings emphasize the importance of improving the recognition, monitoring, and treatment of depressive symptoms during the long term and of developing better interventions to forestall their development.

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Author Contributions: Dr Byers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Vittinghoff and Ms Lui performed the statistical analyses for the study.

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