

# Outcomes of Minor and Subsyndromal Depression among Elderly Patients in Primary Care Settings

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**Background:** Although depressive conditions in later life are a major public health problem, the outcomes of minor and subsyndromal depression are largely unknown.

**Objective:** To compare outcomes among patients with minor and subsyndromal depression, major depression, and no depression, and to examine putative outcome predictors.

**Design:** Cohort study.

**Setting:** Patients from primary care practices in greater New York City, and Philadelphia and Pittsburgh, Pennsylvania.

**Patients:** 622 patients who were at least 60 years of age and presented for treatment in primary care practices that provided usual care in a randomized, controlled trial of suicide prevention. Of the 441 (70.9%) patients who completed 1 year of follow-up, 122 had major depression, 205 had minor or subsyndromal depression, and 114 did not have depression at baseline.

**Measurements:** One year after a baseline evaluation, data were collected by using the following tools: Hamilton Depression Rating Scale, the depressive disorders section of the Structured Clinical Interview for DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition), Charlson Comorbidity Index, Multilevel Assessment Instrument for measuring instrumental activities of daily living, Physical Component Summary of the Medical Outcomes Study Short Form-36, and Duke Social Support Index.

**Results:** Patients with minor or subsyndromal depression had intermediate depressive and functional outcomes. Mean adjusted

1-year Hamilton depression score was 10.9 (95% CI, 9.6 to 12.2) for those with initial major depression, 7.0 (CI, 5.9 to 8.1) for those with minor or subsyndromal depression, and 2.9 (CI, 1.6 to 4.2) for those without depression ( $P < 0.001$  for each paired comparison). Compared with patients who were not depressed, those who had minor or subsyndromal depression had a 5.5-fold risk (CI, 3.1-fold to 10.0-fold) for major depression at 1 year after controlling for demographic characteristics ( $P < 0.001$ ). Cerebrovascular risk factors were not associated with a diagnosis of depression at 1 year after controlling for overall medical burden. Initial medical burden, self-rated health, and subjective social support were significant independent predictors of depression outcome.

**Limitations:** Participants received care at practices that had personnel who had been given enhanced education about depression treatment; 29.1% of participants withdrew from the study before completing 1 year of follow-up.

**Conclusions:** The intermediate outcomes of minor and subsyndromal depression demonstrate the clinical significance of these conditions and suggest that they are part of a spectrum of depressive illness. Greater medical burden, poor subjective health status, and poorer subjective social support confer a higher risk for poor outcome.

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\*Additional information regarding the authors' roles as study coordinators is available in the Appendix.

Depressive conditions in later life are a major public health problem because they are common and associated with considerable morbidity (1–10). However, most elderly persons who have clinically significant depressive symptoms do not meet diagnostic criteria for major depression or dysthymic disorder (4, 7, 11). Terms such as *minor*, *subsyndromal*, or *subthreshold* depression have been used to describe such “sub-major” depressive conditions. In younger adults, minor and subsyndromal depression are associated with greater cumulative functional disability than major depression (12); they probably exist along a dimensional spectrum of symptomatic severity (11, 13, 14), sometimes (but not always) representing a prodromal or residual phase of a major mood disorder.

In older persons, minor and subsyndromal depression are seen in various settings more commonly than major depression (1, 4, 11, 15–17) and are associated with similar functional morbidity. Most elderly persons with depressive symptoms never see mental health specialists but do see their primary care physicians (18). Because there is limited evidence to support specific treatments for minor and sub-

syndromal depression (19, 20), it is important for primary care physicians to initiate treatment primarily for patients at highest risk for poor outcomes. However, there are few published longitudinal data from primary care settings to guide identification of such patients. Previous observational studies did not include patients with minor or subsyndromal depression (21, 22) or distinguish them from those with major depression (23, 24). One previous study (25) found that patients with minor depression had out-

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comes that were poorer than those of persons who were not depressed. Outcomes were not universally poor, however, and were better than those of patients with major depression. The researchers noted that these findings required replication in a larger and more diverse sample.

Furthermore, little is known about predictors of geriatric depression outcomes in patients in primary care settings. Studies that reported a predictive role for medical illness burden (26) rarely focused on primary care, and many used self-reports of medical illness that were subject to confounding by depression (27). Small-vessel brain disease may contribute to the pathogenesis of some forms of depression seen later in life (28–31); cerebrovascular risk factors are associated with depression outcomes in other settings (32–35), but their role remains unclear in primary care (35, 36). Psychosocial factors, such as functional disability, social support, and stressful life events, contribute to depression in younger adults and to more severe depression in senior citizens, but their role in elderly patients in primary care settings is generally unknown (2, 37).

We hypothesized that 1) patients with minor or subsyndromal depression have an intermediate outcome in severity and diagnosis of depression, medical burden, and functional status compared with patients who have major depression and those who are not depressed and 2) initial overall medical burden, particularly cerebrovascular risk factors, are independently associated with outcomes of depression in elderly patients. We tested these 2 hypotheses in a large, multisite sample of elderly primary care patients who were followed for 1 year. We also explored functional status, social support, and stressful life events as outcome predictors.

## METHODS

### Patient Sample and Randomization Protocol

The Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) was a randomized trial of a collaborative care intervention for geriatric depression (38) in patients of primary care practices in greater New York City, and Philadelphia and Pittsburgh, Pennsylvania. Within matched pairs, practices were randomly assigned to an intervention group or a usual care (control) group. This study used only data from patients in 10 usual care practices; these sites comprised 2 academic practices and 8 community-based practices, 1 of which served primarily African-American patients. All patients received usual care from their primary care physicians; the physicians were initially educated about published treatment guidelines (39) and, for ethical reasons, were notified when a patient met research criteria for a depression diagnosis (40). The institutional review board of each of the 3 participating universities approved the research protocol and its formal written consent procedures.

### Context

The spectrum of depressive illness includes milder forms, about which we know relatively little.

### Content

Older patients selected from 10 primary care practices for depressive symptoms had major depression, minor or subsyndromal depression, or were not depressed. After 1 year, depression symptom severity was closely associated with the initial depression diagnosis. Patients with minor or subsyndromal depression had a much higher incidence of major depression than nondepressed patients, but most were no longer depressed or still had minor or subsyndromal depression.

### Cautions

Approximately 29% of patients withdrew before the end of the study.

### Implications

Minor or subsyndromal depression causes substantial morbidity and is a risk factor for major depression.

—The Editors

### Recruitment Procedures

As described elsewhere (38), the patients who participated in PROSPECT were recruited to generate a demographically representative sample. Depressive conditions were oversampled to increase the power to examine depression outcomes without precluding the ability to examine specific predictors because the relationships between variables over time were not affected by the enriched sample. Protocol eligibility requirements included age of 60 years or older, ability to give informed consent in English, and a score of 18 or higher on the Mini-Mental State Examination (41). We oversampled for depressive symptoms by using the Center for Epidemiologic Studies Depression Scale (42); all patients with scores of greater than 20 (43) and a random sample of 5% of patients with scores of 20 or less were approached for study participation. In addition, patients with scores of 20 or less who were not included in the latter random sample were recruited if they responded positively to supplemental questions about previous depressive episodes or treatment. Research personnel at the practice interviewed consenting patients in person. Patients received telephone assessments at 4 and 8 months and an in-person interview 1 year after the baseline evaluation. Of the 622 usual care patients completing intake measures, 441 (70.9%) completed 1-year follow-up visits. The withdrawal rate probably reflected the lack of direct benefits offered to patients in this observational study. The group of patients who completed 1-year evaluations contained fewer cigarette smokers at baseline than the group that did not complete follow-up (13.3% vs. 19.7%; chi-square = 3.9;  $P = 0.047$ ); other demographic and baseline

clinical characteristics of the groups were not significantly different.

**Study Measures**

All study measures were obtained from patient interviews that were conducted by trained research associates; study psychiatrists reviewed patient responses. We measured the primary outcome of depressive symptom severity by using the 24-item examiner-rated Hamilton Rating Scale for Depression (Ham-D) (44). We used the Structured Clinical Interview for DSM-IV (*Diagnostic and Statistical Manual for Mental Disorders*, fourth edition) (SCID) to make depression diagnoses (45, 46). The intra-class correlation coefficient of research associates across the 3 study sites was 0.97 for the Ham-D and 0.92 for the SCID, and reliability was monitored throughout the study to prevent drift.

Patients were classified into 1 of 3 diagnostic groups: major depression (*n* = 122), minor or subsyndromal depression (*n* = 205), or nondepressed (*n* = 114). Patients were assigned to the major depression group if they met SCID criteria for current major depression. To receive a

diagnosis of minor or subsyndromal depression, a patient needed to have at least 2 SCID-defined depressive symptoms, of which 1 symptom had to be depressed mood or anhedonia. The symptoms had to be present at threshold (that is, meeting DSM-IV criteria for severity and 2-week duration) or subthreshold (that is, present but not meeting the threshold criterion) levels. The nondepressed category comprised all other patients. The minor or subsyndromal depression group included patients who 1) met DSM-IV criteria for dysthymic disorder; 2) did not meet the criteria for dysthymic disorder or minor depression (“non-DSM-IV subsyndromal depression”); and 3) had minor depression as defined by PROSPECT criteria. Modified from the DSM-IV appendix criteria, the PROSPECT criteria require 4 threshold depressive symptoms, a Ham-D score of 10 or higher, and a symptom duration of 4 weeks or more. Secondary analyses compared outcomes between the patients with PROSPECT-defined minor depression and those with non-DSM-IV subsyndromal depression; separate analysis of the patients with dysthymic disorder was precluded by the subgroup’s small size.

**Table 1. Patient Demographic and Clinical Characteristics at Baseline\***

Variable	Patients with Major Depression ( <i>n</i> = 122)		Patients with Minor or Subsyndromal Depression ( <i>n</i> = 205)		Patients without Depression ( <i>n</i> = 114)	
	Patients with Data, <i>n</i>	Value	Patients with Data, <i>n</i>	Value	Patients with Data, <i>n</i>	Value
<b>Demographic characteristic</b>						
Age (60 to 95 y)	120	69.4 y (SD, 7.2)	203	73.1 y (SD, 8.1)	113	73.0 y (SD, 7.4)
Women	122	88 (72.1%)	205	154 (75.1%)	114	75 (65.8%)
Education completed (2 to 24 y)	121	12.7 y (SD, 3.4)	202	13.3 y (SD, 3.5)	114	13.2 y (SD, 3.5)
<b>Clinical characteristic</b>						
Hamilton Depression Rating Scale (19 to 30)	122	19.8 (SD, 6.3)	205	9.4 (SD, 5.3)	114	2.9 (SD, 2.5)
History of major depression (yes/no)	118	115 (97.5%)	205	37 (18.1%)	114	20 (17.5%)
Mini-Mental State Examination score (19 to 30)	122	27.1 (SD, 2.8)	204	27.7 (SD, 2.3)	114	27.6 (SD, 2.1)
Cerebrovascular risk factors score (2 to 21)	116	8.3 (SD, 3.4)	198	9.3 (SD, 4.0)	110	9.3 (SD, 3.6)
Charlson Comorbidity Index (0 to 12)	122	2.9 (SD, 2.3)	205	2.5 (SD, 2.2)	114	2.1 (SD, 2.0)
Instrumental activities of daily living (8 to 18)	104	15.2 (SD, 2.5)	192	15.4 (SD, 2.3)	108	15.9 (SD, 1.9)
Physical Component Summary (10 to 70)	93	39.7 (SD, 13.8)	170	41.1 (SD, 13.1)	93	43.7 (SD, 10.8)
<b>Social support</b>						
Social interaction (0 to 13)	103	5.5 (SD, 2.2)	189	6.4 (SD, 2.3)	105	7.0 (SD, 2.5)
Subjective support (7 to 21)	105	11.8 (SD, 2.6)	189	11.1 (SD, 2.4)	108	10.6 (SD, 2.1)
Instrumental support (0 to 12)	105	8.3 (SD, 3.1)	188	8.4 (SD, 2.8)	106	8.3 (SD, 2.6)
<b>Stressful life event</b>						
Presence of event (yes/no)	103	51 (49.5%)	190	100 (52.6%)	106	36 (34.0%)
How much of a change (1 to 7)	49	2.0 (SD, 1.2)	101	2.1 (SD, 1.3)	38	2.2 (SD, 1.3)
What kind of a change (1 to 7)	49	1.9 (SD, 1.0)	101	2.1 (SD, 1.3)	38	2.1 (SD, 1.2)
How much on mind (1 to 7)	49	1.8 (SD, 0.9)	101	1.9 (SD, 1.2)	38	2.3 (SD, 1.0)
Antidepressant use (yes/no)	105	52 (49.5%)	197	57 (28.9%)	107	18 (16.8%)

\* Data reported only for patients who completed 1 year of follow-up. Values reported with SDs are means.

Table 2. Outcomes at 1 Year by Baseline Depression Diagnosis\*

Initial Depression Diagnosis	Depression Diagnosis at 1 Year, n†				Total	
	Major Depression	Minor or Subsyndromal Depression				Nondepressed
		Minor Depression	Non-DSM-IV Subsyndromal Depression	Dysthymic Disorder		
Major depression	36	31	30	2	22	121
Minor or subsyndromal depression						
Minor depression	10	19	31	3	23	86
Non-DSM-IV subsyndromal depression	7	17	33	0	44	101
Dysthymic disorder	4	1	3	6	1	15
Nondepressed	1	8	19	2	83	113
Total	58	76	116	13	173	436‡

\* For overall group comparison, chi-square = 193 ( $P < 0.001$ ). In analyses of depression diagnosis subgroups, compared with patients who had a baseline diagnosis of non-DSM-IV subsyndromal depression (covarying age, sex, and educational level), the odds ratio for depression outcome in patients who had a baseline diagnosis of minor depression is 2.0 (95% CI, 1.01 to 4.0;  $P = 0.048$ ). DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.

† Adjusted for demographic characteristics.

‡ One-year depression diagnosis was not available for 5 participants: 1 with initial major depression, 3 with initial minor or subsyndromal depression, and 1 initially nondepressed.

We rated the cumulative severity of specified cerebrovascular risk factors (presence of antihypertensive therapy, cardiovascular disease, diabetes mellitus, cigarette smoking, atrial fibrillation, and left ventricular hypertrophy) by the weighted sum of points that were obtained from the American Heart Association's chart for predicting stroke risk, which is derived from the Framingham Heart Study (47). According to this measure, women's scores for antihypertensive therapy are based on a patient's systolic blood pressure (range, 0 to 6); because blood pressure measurements were not available, we assigned a score of 3 if the patient used antihypertensive therapy and a score of 0 if they did not. The Charlson Comorbidity Index was used as a validated measure of overall medical burden (48). We assessed cognition by using the Mini-Mental State Examination (41). Functional status was measured by the Multilevel Assessment Instrument's (49) Instrumental Activities of Daily Living scale and by the self-reported Physical Component Summary of the Medical Outcomes Study Short Form-36 (50). We used a modified version of the Louisville Older Persons Events Scale (51) to ascertain whether patients had experienced stressful life events during the past 6 months. Validated subscales of the Duke Social Support Index (52) were used to measure 3 aspects of social support: social interaction, subjective support, and instrumental support.

### Statistical Analysis

We tested our hypotheses by applying linear mixed-effects models for continuous outcomes and mixed-effects, proportional-odds regression models (53) for the trichotomous ordinal outcome of depression diagnosis (for example, major depression vs. minor or subsyndromal depression vs. nondepressed). All analyses were performed with SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, North Carolina). For trichotomous depression diag-

nosis outcomes, odds ratios indicate the relative risk for worsened depression diagnosis by cumulative categories (that is, from nondepressed to minor/subsyndromal depression and major depression, or from nondepressed and minor/subsyndromal depression to major depression). We used a chi-square score statistic for testing the proportionality assumption. Practice units were taken as a random effect to adjust for practice-level variability of outcome; the random effects were small and not significant at the 5% level. All of these primary analyses were controlled for age, sex, and educational level.

To examine a range of potentially relevant predictors of depression outcomes, we used clinical considerations to inform a hypothesis-driven series of regression analyses. As new variables were added to each successive regression, significant predictors from each preceding model were retained. Specifically, our first model included demographic variables and measures related to psychopathology (for example, initial depression diagnosis, history of major depression, use of antidepressant therapy at baseline, and Mini-Mental State Examination score). The second model added our measure of overall medical burden (Charlson Comorbidity Index). The third model added measures of functional status (Instrumental Activities of Daily Living and the Physical Component Summary of the Medical Outcomes Study Short Form-36). The fourth model added psychosocial measures (Duke Social Support Index and history of a stressful life event from the Louisville Older Persons Events Scale). The final models based on this hypothesis-driven elimination procedure were compared with backward elimination results for further confirmation. To conduct the latter, we first performed univariate analyses for the potential outcome predictors described above; variables with a univariate  $P$  value less than 0.15 were included in a full multivariate model to take potential suppressor effects into consideration (54). Variables that had nonsig-

nificant ( $P$  values  $\geq 0.05$ ) associations with the 1-year outcomes were removed through backward elimination to yield a parsimonious multivariate model.

Because of the potential for bias related to patient withdrawal and our elimination procedures, we conducted several additional sensitivity analyses by repeating the final multivariate models. We used general linear or ordinal proportional-odds models with practices as fixed effects; a hot-deck random imputation method (55) for missing data for a diagnosis at 1 year; and random imputation based on regression models for missing values for Ham-D score at 1 year, baseline Duke Social Support Index, and baseline Physical Component Score. Separate regression analyses were performed on each of these variables by using baseline Ham-D score as the independent variable. From each regression line, we generated random imputed values for the missing values from normal distributions. The estimated regression line denoted the mean, and the root-mean-square of the regression line denoted the SD. We also examined the effects of baseline depression diagnosis on depressive symptom severity and diagnosis at 1 year; all baseline predictor variables were included in a single multivariate model.

For all analyses, we defined statistical significance as a 2-tailed  $P$  value of 0.05 or less. When applicable, 95% CIs are reported.

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The funding source had no role in the design, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

## RESULTS

### Characteristics of Study Patients

Descriptive data for intake variables are presented in Table 1. Of 205 patients who were initially classified in the minor and subsyndromal depression group, 86 (42%) had minor depression, 15 (7%) had dysthymic disorder, and 104 (51%) did not have a DSM-IV diagnosis.

### Risk for Depression at 1 Year according to Initial Depression Status

After adjusting for demographic characteristics, we found a significant association between initial depression diagnosis and 1-year depressive symptom severity as measured by the Ham-D score ( $F = 52.9$ ;  $P < 0.001$ ). The mean adjusted Ham-D score at 1 year was 10.9 (CI, 9.6 to 12.2) for the baseline major depression group, 7.0 (CI, 5.9 to 8.1) for the baseline minor and subsyndromal depression group, and 2.9 (CI, 1.6 to 4.2) for the baseline non-depressed group; these scores were significantly different among the 3 groups ( $P < 0.001$  for each paired comparison). Comparing subgroups of the minor or subsyndromal depression group, the mean adjusted 1-year Ham-D scores between the patients with initial minor depression (7.2 [CI, 5.8 to 8.6]) and those with non-DSM-IV subsyndromal depression (6.3 [CI, 5.0 to 7.6]) were not significantly different (difference, 0.9 [CI, -0.8 to 2.6];  $P = 0.29$ ).

The association of initial depression diagnosis with depression diagnosis at 1 year was also significant after controlling for demographic characteristics (Table 2). The group of patients who had major depression at baseline had an odds ratio of 18.0 (CI, 8.8 to 37.1) for major depression

Table 3. Univariate Associations with Depression Outcomes at 1 Year\*

Baseline Variable	Hamilton Depression Score at 1 Year				Depression Diagnosis at 1 Year				
	$\beta$ (95% CI)	$P$ Value	Patients, $n$	Odds Ratio (95% CI)	$P$ Value	Patients, $n$	Patients with Major Depression	Patients with Minor and or Subsyndromal Depression	Patients without Depression
Age	-0.0006 (-0.08 to 0.08)	0.988	436	1.00 (0.97 to 1.02)	0.839	430	71.1 y (SD, 8.6)	72.3 y (SD, 7.9)	71.9 y (SD, 7.6)
Sex	0.96 (-0.41 to 2.33)	0.170	441	1.33 (0.84 to 2.11)	0.199	435	42/57 (73.7%)	153/205 (74.6%)	117/173 (67.6%)
Education	-0.18 (-0.35 to 0.00)	0.052	437	0.95 (0.90 to 1.01)	0.101	431	12.4 y (SD, 2.9)	13.1 y (SD, 3.6)	13.4 y (SD, 3.4)
History of major depression	4.14 (2.93 to 5.35)	<0.001	437	2.71 (1.84 to 4.01)	<0.001	431	39/56 (69.6%)	83/203 (40.9%)	48/172 (27.9%)
Mini-Mental State Examination	-0.20 (-0.46 to 0.05)	0.116	440	0.99 (0.92 to 1.07)	0.376	434	27.0 (SD, 2.9)	27.6 (SD, 2.4)	27.6 (SD, 2.2)
Charlson Comorbidity Index	0.60 (0.33 to 0.88)	<0.001	441	1.20 (1.09 to 1.32)	<0.001	435	3.4 (SD, 2.1)	2.7 (SD, 2.3)	2.0 (SD, 1.8)
Instrumental activities of daily living	-0.47 (-0.76 to -0.19)	0.001	404	0.92 (0.84 to 1.01)	0.077	399	15.2 (SD, 2.3)	15.3 (SD, 2.4)	15.8 (SD, 2.1)
Physical Component Summary	-0.14 (-0.19 to -0.08)	<0.001	356	0.97 (0.96 to 0.99)	0.010	352	35.6 (SD, 12.2)	41.3 (SD, 12.2)	43.4 (SD, 13.0)
Social support									
Social interaction	-0.56 (-0.83 to -0.30)	<0.001	402	0.83 (0.76 to 0.92)	0.002	392	5.3 (SD, 2.7)	6.2 (SD, 2.2)	6.9 (SD, 2.3)
Subjective support	0.74 (0.48 to 1.00)	<0.001	402	1.22 (1.11 to 1.33)	<0.001	397	12.2 (SD, 3.0)	11.4 (SD, 2.6)	10.5 (SD, 1.8)
Instrumental support	-0.17 (-0.40 to 0.07)	0.159	399	0.95 (0.88 to 1.02)	0.151	394	8.0 (SD, 3.2)	8.2 (SD, 2.9)	8.6 (SD, 2.6)
Stressful life event									
Event presence	1.06 (-0.25 to 2.37)	0.111	399	1.43 (0.92 to 2.21)	0.097	394	27/53 (50.9%)	94/184 (51.1%)	64/157 (40.8%)
How much change	0.05 (-0.69 to 0.80)	0.890	188	1.11 (0.87 to 1.42)	0.338	186	2.2 (SD, 1.2)	2.2 (SD, 1.4)	2.0 (SD, 1.1)
What kind of change	-0.32 (-1.11 to 0.47)	0.427	188	1.02 (0.78 to 1.32)	0.885	186	2.1 (SD, 1.1)	2.0 (SD, 1.3)	2.0 (SD, 1.1)
How much on mind	0.03 (-0.84 to 0.91)	0.939	188	1.13 (0.84 to 1.51)	0.380	186	2.2 (SD, 2.1)	1.9 (SD, 1.1)	1.9 (SD, 1.0)

\* Values presented with SDs are means.

**Table 4. Final Multivariate Model Predicting 1-Year Depression Symptom Severity (Hamilton Depression Rating Scale)**

Baseline Variable	$\beta$ (95% CI)	P Value
Diagnosis		
Major depression versus nondepressed	7.5 (5.8 to 9.2)	<0.001
Minor or subsyndromal depression versus nondepressed	3.6 (2.4 to 5.3)	<0.001
Physical Component Summary (possible score: 10 to 70)	-0.11 (-0.15 to -0.06)	<0.001
Subjective social support (possible score: 7 to 21)	0.55 (0.30 to 0.80)	<0.001

at 1 year ( $P < 0.001$ ) compared with those without depression at baseline; those with minor or subsyndromal depression at baseline had an odds ratio of 5.5 (CI, 3.1 to 10.0;  $P < 0.001$ ). The proportionality assumption underlying the mixed-effects proportional odds model was met ( $P = 0.41$ ) from a score test. Outcomes in the subgroup with minor depression were poorer than in the subgroup with non-DSM-IV subsyndromal depression (Table 2), but statistical significance was only marginal.

#### Association of Medical Illness and Other Predictors with Depression Outcomes

The severity of cerebrovascular risk factors at baseline was not significantly associated with Ham-D scores at 1 year after baseline diagnosis and demographic variables were controlled for. After omitting values associated with the vascular items from the Charlson Comorbidity Index, we determined that the absence or presence of covarying comorbid conditions had no effect on this association (when present,  $\beta = 0.13$ ;  $P = 0.173$ ). Initial cerebrovascular risk factor severity score was independently associated with depression diagnosis at 1 year (odds ratio, 1.08 [CI, 1.00 to 1.17];  $P = 0.050$ ), but the significance was decreased after controlling for the presence of comorbid conditions (odds ratio, 1.07 [CI, 0.99 to 1.16];  $P = 0.073$ ).

Table 3 shows the univariate associations of other baseline predictors with Ham-D scores and depression diagnosis at 1 year. The results depicted include the values for baseline variables on the basis of 1-year depression diagnosis. Tables 4 and 5 show the final multivariate models after we completed the aforementioned procedures; both the hypothesis-driven and backward eliminations resulted in the same final models. Of note, history of a major depressive episode was a powerful predictor in the univariate analyses but was not significantly associated with outcome after controlling for the other predictors and therefore does not appear in the final models. Furthermore, separate analyses (not shown) in which we used a multiplicative interaction term demonstrated that history of major depression did not moderate the relationship between initial depression diagnosis and Ham-D score or depression diagnosis at 1 year.

Of note, all sensitivity analyses that imputed missing data yielded results that were very similar to the final multivariate models shown in Tables 4 and 5, suggesting that the withdrawal of patients from the study had little effect on the significance of predictors. Furthermore, initial depression diagnosis was significantly associated with both depression diagnosis and Ham-D score at 1 year; estimated effects were similar even when all baseline variables were included in a single multivariate model.

#### Other Outcomes

Baseline depression diagnosis was independently associated with poorer 1-year scores for instrumental activities of daily living ( $F = 3.33$ ) after controlling for demographic variables ( $P = 0.037$ ). Of note, the group with major depression at baseline had a mean adjusted score of 15.2 (CI, 14.7 to 15.6) for this component at 1 year, which was significantly different from the score of 16.0 (CI, 15.6 to 16.4) for the group that did not have depression ( $P < 0.001$ ). The group with minor and subsyndromal depression had an intermediate adjusted 1-year score of 15.6 (CI, 15.3 to 16.0), which was not significantly different from the other 2 groups. Initial depression diagnosis was significantly associated with poorer scores on the Physical Component Summary of the Medical Outcomes Study Short Form-36 at 1 year ( $F = 4.48$ ;  $P = 0.012$ ). Of note, the group that had major depression at baseline had a mean adjusted score of 39.4 (CI, 36.5 to 42.4) for this component at 1 year, which was significantly different from the mean adjusted score of 45.5 (CI, 42.7 to 48.3) for the group that did not have depression ( $P = 0.003$ ). The group with minor and subsyndromal depression had an intermediate estimated 1-year score of 42.3 (CI, 40.1 to 44.5), which was not significantly different from the other 2 groups. Initial depression diagnosis was not significantly associated with Charlson Comorbidity Index for medical illness burden at 1 year ( $F = 1.71$ ;  $P = 0.182$ ) or with Mini-Mental State Examination scores for cognitive function ( $F = 0.53$ ;  $P = 0.59$ ).

**Table 5. Final Multivariate Model Predicting 1-Year Depression Diagnosis**

Baseline Variables	Odds Ratio (95% CI)	P Value
Diagnosis		
Major depression versus nondepressed	17.3 (8.1-36.8)	<0.001
Minor or subsyndromal depression versus nondepressed	5.1 (2.8-9.5)	0.002
Charlson Comorbidity Index (possible score: 0-12)	1.20 (1.07-1.35)	0.005
Subjective social support (possible score: 7-21)	1.2 (1.1-1.4)	0.004

## DISCUSSION

We confirmed some but not all of our study hypotheses. Elderly patients with minor or subsyndromal depression had better outcomes than patients with major depression and poorer outcomes than persons who were not depressed. This group had a risk for a diagnosis of major depression at 1 year that was more than 5 times greater than that of nondepressed elderly individuals, which is similar to the 1-year risk in younger adults with subsyndromal depression (56). Furthermore, the group with minor and subsyndromal depression had greater functional disability at 1 year; however, these patients were not as disabled as those in the major depression group. Of interest, the minor depression and non-DSM-IV subsyndromal depression subgroups did not differ substantially in their outcomes. These data support the clinical importance of both minor and subsyndromal depression and suggest that, as in younger persons, they represent part of a spectrum of depression severity rather than a discrete entity.

The results regarding cerebrovascular risk factors were similar to those of some but not all previous studies (34, 35). Our assessment omitted systolic blood pressure measurements, which may have limited our ability to detect an association. The Charlson Comorbidity Index cannot be fully disentangled from cerebrovascular risk factors or their effects on various end organs (even when modified by the removal of the vascular items); however, overall medical burden seems to contribute more than cerebrovascular risk factors to depression outcome in a broad primary care group. Other independent predictors of 1-year depression outcome included self-rated physical health status and subjective social support.

These findings must be considered in the context of the study's limitations. These data reflect the history of depressive conditions in enhanced primary care treatment as opposed to untreated natural history. Because this limitation would presumably reduce our ability to detect a difference in outcome between the participants with minor and subsyndromal depression and those who were not depressed, our positive findings are even more remarkable. A total of 29.1% of participants withdrew from the study before completing 1 year of follow-up; however, sensitivity analyses and comparisons of baseline statistics suggest that these withdrawals had little effect on the study findings. We also note that our definition of minor and subsyndromal depression included patients who had major depression that was in remission. It might be argued that our findings represent the poor outcomes of major depressive illness (captured in a less severely symptomatic state) and not those of "pure" minor or subsyndromal depression. However, history of major depression was not independently associated with outcome after accounting for other predictors in the final multivariate models.

Our results suggest that patients with minor or subsyndromal depression should receive intervention to reduce

the risk for enduring or worsening distress and disability. The appropriate intervention is unclear, however. Several randomized, controlled studies have found only a very limited treatment effect (or even no effect) for antidepressant medications in less severely symptomatic patients with "sub-major depression" (19, 20, 57). One recent large follow-up study that was conducted over 57 months (58) evaluated primary care practices that had instituted quality improvement programs for depression care. These programs, which focused on medication management or evidence-based brief psychotherapy, produced modestly better outcomes in younger adults with subthreshold depression than those seen in patients who had received usual care. The participants in this study were probably similar to the most symptomatic patients with minor or subsyndromal depression in our study. Several recent randomized, controlled studies (including PROSPECT) have analyzed collaborative care interventions that require on-site mental health expertise to guide the use of clinical algorithms (for medication or brief, focused psychotherapy) in elderly patients with highly symptomatic forms of minor depression (for example, depression with suicidal ideation) or with dysthymic disorder (38, 59–61). In the primary care setting, such interventions have been found to offer modest efficacy. A recent meta-analysis of published studies of treatments for depression in later life found modest effect sizes overall; although there were too few studies to allow meta-analysis of only patients with sub-major depression, a greater treatment effect was observed with psychotherapy than with medication in studies that included a mixture of patients who had major and sub-major depression (62). Consistent with these findings, a recent study demonstrated the effectiveness of an innovative community-based psychosocial intervention for minor depression (63).

In conclusion, the intermediate outcomes of minor and subsyndromal depression demonstrate their clinical significance and suggest that they are part of a spectrum of depressive illness. Greater medical burden, poorer self-rated health, and poorer subjective social support confer a higher risk for poor outcome. Future work is needed to identify subgroups of these highly heterogeneous conditions that might preferentially respond to specific psychosocial or pharmacologic interventions.

## APPENDIX

The 3 collaborative PROSPECT sites include the Advanced Centers for Intervention and Services Research of Cornell University (PROSPECT Coordinating Center: primary investigator, George S. Alexopoulos, MD; co-primary investigators, Martha L. Bruce, PhD, MPH, and Herbert C. Schulberg, PhD), the University of Pennsylvania (primary investigator, Ira Katz, MD, PhD; co-primary investigators, Thomas Ten Have, PhD, and Gregory K. Brown, PhD), and the University of Pittsburgh (primary investigator, Charles F. Reynolds, MD; co-primary investigator, Benoit H. Mulsant, MD).

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