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The Association of Depression, Cognitive Impairment without Dementia and Dementia with Risk of Ischemic Stroke: A Cohort Study

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Abstract

Objective—To determine if depression, cognitive impairment without dementia (CIND), and/or dementia are each independently associated with risk of ischemic stroke and to identify characteristics that could modify these associations.

Methods—This retrospective-cohort study examined a population-based sample of 7,031 Americans > 50 years old participating in the Health and Retirement Study (HRS) (1998-2008) who consented to have their interviews linked to their Medicare claims. The 8-item Center for Epidemiologic Studies Depression Scale and/or International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) depression diagnoses were used to identify baseline depression. The Modified Telephone Interview for Cognitive Status and/or ICD-9-CM dementia diagnoses were used to identify baseline CIND or dementia. Hospitalizations for ischemic stroke were identified via ICD-9-CM diagnoses.

Results—After adjusting for demographics, medical comorbidities, and health-risk behaviors, CIND alone (Odds Ratio [OR]: 1.37, 95%CI: 1.11, 1.69) and co-occurring depression and CIND (OR: 1.65, 95%CI: 1.24, 2.18) were independently associated with increased odds of ischemic stroke. Depression alone was not associated with odds of ischemic stroke (OR: 1.11, 95%CI: 0.88, 1.40) in unadjusted analyses. Neither dementia alone (OR: 1.09, 95%CI: 0.82, 1.45) nor co-occurring depression and dementia (OR: 1.25, 95%CI: 0.89, 1.76) were associated with odds of ischemic stroke after adjusting for demographics.

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Conclusions—CIND as well as co-occurring depression and CIND are independently associated with increased risk of ischemic stroke. Individuals with co-occurring depression and CIND represent a high-risk group that may benefit from targeted interventions to prevent stroke.

Keywords

depression; cognitive impairment; dementia; ischemic stroke

INTRODUCTION

Each year, nearly 800,000 Americans experience a stroke (1). In 2008, strokes accounted for nearly \$19 billion in healthcare costs (1). They are a leading cause of mortality among older adults with one in six strokes being fatal (1). Furthermore, a substantial proportion of stroke survivors face functional disability and cognitive impairment (2, 3), and nearly one-third develop depression (4). In light of the enormous public health burden imposed by strokes, increasing understanding of potentially modifiable risk factors is important.

Depression, cognitive impairment without dementia (CIND) and dementia are prevalent among older adults (5-7). Prior studies have examined depression or dementia as potential risk factors for stroke and have found that both are individually associated with increased risk of stroke (8-18). One of these studies suggested that the association of depression with risk of stroke may be modified by female sex (14). However, while depression is frequently co-occurring with mild cognitive impairment and dementia (19), no study to date has considered the impact of co-occurring depression and mild cognitive impairment or dementia on the risk of stroke. Further, some prior studies have been limited by reliance on administrative data alone (13, 15, 16), or on self-report data alone (9). Finally, if depression, CIND and dementia are indeed risk factors for strokes, then identifying sub-groups of older adults with depression, CIND or dementia at heightened risk is important for intervention targeting.

The present study uses data from an ongoing longitudinal investigation of health outcomes in adults over age 50 to examine if depression, CIND, and dementia are independently associated with risk of ischemic stroke. We hypothesized that depression, CIND, and dementia would each be independently associated with increased risk of a future ischemic stroke, and that co-occurring depression and CIND or dementia would be associated with greater risk of ischemic stroke than that conveyed by any one disorder alone. We also sought to determine if any associations found between baseline depression, CIND or dementia and subsequent ischemic stroke risk were modified by sex, lower socioeconomic status, or relevant medical comorbidities.

METHODS

Population

This study uses nationally representative data from Americans over age 50 participating in the Health and Retirement Study (HRS). Beginning in 1992, the HRS has enrolled over 31,000 individuals. Subjects are interviewed every two years with a follow-up rate

exceeding 90-95% (including proxies) (20). In addition to both high initial and re-interview response rates, non-response adjusted participant-level sample weights for each biennial interview are used to maintain representativeness over time as well as minimize the risk of healthy survivor bias (5). In addition, over 80% of eligible respondents have consented to linkage of their Medicare claims records with study data (20).

Our sample consisted of the 7,031 HRS respondents interviewed in 1998 or 2000 who consented to linkage of their Medicare claims records. We followed them through death ($n = 3,546$) or the 2008 interview.

Standard Protocol Approvals, Registrations, and Patient Consents

The HRS protocol was approved by the University of Michigan Institutional Review Board. Participants provided informed consent upon enrollment and again for linkage to Medicare claims.

Primary Independent Variable

The primary independent variable in our analyses was depression, CIND or dementia status at baseline defined categorically as no disorder, depression alone, CIND alone, dementia alone, co-occurring depression and CIND, or co-occurring depression and dementia.

We defined depression as either a score of ≥ 4 on the 8-item Center for Epidemiologic Studies Depression Scale (CES-D-8) (21) at the baseline HRS interview or a depression diagnosis in the Medicare claims in the previous two years based on International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes 296.2, 296.3, 298.0, 300.4, or 311.0. The CES-D-8 cutoff score of ≥ 4 was shown to be comparable to the cutoff score of ≥ 16 on the full CES-D (21), and has been used in other relevant studies (5, 22).

Cognitive impairment was assessed in the HRS using the modified Telephone Interview for Cognitive Status (TICS_m), a composite measure with items testing immediate and delayed recall, working memory with serial sevens subtraction, and backwards counting testing attention and processing speed (23). The version of the TICS_m used in the HRS was validated against neuropsychiatric interview in the Aging, Demographics and Memory Study, and found to have a weighted accuracy of 69.2% in correct classification of individuals as either having normal cognition, CIND, or dementia (23). We defined CIND as a TICS_m score of 7 to 11 at the baseline HRS interview (23). Dementia was defined as either a TICS_m score of ≤ 6 (23) or dementia diagnosis (ICD-9-CM codes 290.0-290.42, 291.2, 294.1, 294.8, 331.0, 331.1, 331.11, 331.19, or 331.82) in the Medicare claims in the two years before baseline.

Demographics, Medical Comorbidities and Health-Risk Behaviors

Demographic information (e.g., age, sex, race, education, marital/partnered status, and dual Medicare-Medicaid eligibility [individuals with Medicare whose income is low enough to qualify for additional health insurance coverage through Medicaid]) was obtained from the HRS interviews. Elixhauser (24) and Charlson comorbidity diagnoses (25) from the two

years before baseline found to be associated with depression, cognitive impairment and stroke risk (26-28) were obtained from Medicare claims. Information on alcohol use and smoking came from the HRS interviews.

Outcome of Interest

Our outcome of interest was ischemic stroke. We used ICD-9-CM codes 433, 434 and 436 to identify hospitalizations for which the principal discharge diagnosis was for ischemic stroke (29).

Statistical Analysis

We present descriptive data as means and standard deviations (SDs) or proportions. Since we did not have data on time from our exposures of interest to ischemic stroke, we used logistic regression models with robust error variances to estimate odds ratios (ORs) and 95% Confidence Intervals (95% CIs) for the association of baseline depression, CIND or dementia with ischemic stroke. First, we tested this association without adjustment. We then sequentially adjusted for potential confounders chosen *a priori* based on prior research identifying their associations with depression, CIND or dementia and stroke risk (8-18). Non-normally distributed covariates were categorized. The sequence of adjustments was: 1) demographic characteristics (e.g., age categorized by deciles, sex, race categorized as white versus non-white, education categorized as < high school graduate versus high school graduate, marital/partnered status categorized as married/partnered versus single/separated/widowed, dual Medicare-Medicaid eligibility); 2) comorbid conditions (myocardial infarction, cerebrovascular disease, congestive heart failure, valvular disease, pulmonary circulation disease, peripheral vascular disease, other neurological disorders, diabetes mellitus, and hypertension); and 3) health-risk behaviors (e.g., alcohol use categorized by the number of drinks per day, smoking status).

To determine if any associations found between baseline depression, CIND or dementia status and ischemic stroke risk were modified by sex, dual Medicare-Medicaid status, or important medical comorbidities (e.g., baseline cerebrovascular disease, diabetes, hypertension), we entered interaction terms (e.g., depression, CIND or dementia status x sex) one at a time into our adjusted regression models.

We conducted four sensitivity analyses. First, we repeated our regression analyses excluding individuals with a baseline history of cerebrovascular disease. Second, we estimated the association of baseline depression, CIND or dementia status with odds of ischemic stroke using only the CES-D-8 and TICSm thresholds to define cases of depression or dementia. Since the CES-D-8 was only administered to self-respondents (21), this sensitivity analysis only included the 6,256 eligible self-respondents. Third, we examined if our results were affected by using a CES-D-8 cut-off score of 3 in our depression definition since a prior study examining depression as a risk factor for stroke utilizing HRS data used this threshold for the CES-D-8 (9). Finally, we repeated our final regression model with propensity score adjustment to examine whether our results were biased by attrition due to death during follow-up (30). In this analysis, we initially ascertained bivariate associations between all covariates (e.g., demographics, comorbid conditions and health-risk behaviors) and death

during follow-up (30). Then, we fit a logistic regression model that predicted whether a participant would die during follow-up as a function of all significant covariates from bivariate analyses (30). Since all of the covariates had significant bivariate associations with death during follow-up, they were all included in this model. The predicted probabilities from this model were then used as a propensity score adjustment to our final logistic regression model for ischemic stroke (30).

We used two-sided significance tests for all analyses with statistical significance set at $P < 0.05$. Analyses were performed with appropriate components of the STATA 12 (Stata Corporation, College Station, TX) statistical software program.

RESULTS

Table 1 presents the baseline demographic characteristics, medical comorbidities, and health-risk behaviors of the entire sample and grouped by depression, CIND or dementia status. At baseline, 12.0% were depressed (188 [22.3%] by an ICD-9-CM depressive disorder diagnosis alone, 482 [57.2%] by CES-D-8 alone, and 172 [20.4%] by both) without clinically notable cognitive impairment, 13.4% had CIND without co-occurring depression, 7.6% had dementia (188 [35.2%] by an ICD-9-CM dementia diagnosis alone, 325 [60.9%] by TICSM alone, and 21 [3.9%] by both) without co-occurring depression, 5.5% had co-occurring depression (72 [18.5%] by an ICD-9-CM depressive disorder diagnosis alone, 262 [67.2%] by CES-D-8 alone, and 56 [14.3%] by both) and CIND, and another 4.3% had co-occurring depression (43 [14.1%] by an ICD-9-CM depressive disorder diagnosis alone, 154 [50.5%] by CES-D-8 alone, and 108 [35.4%] by both) and dementia (97 [31.8%] by an ICD-9-CM dementia diagnosis alone, 187 [61.3%] by TICSM alone, and 21 [6.9%] by both).

During the follow-up period (mean: 6.8 years, SD: 3.1 years), 875 (12.4%) participants were hospitalized at least once for an ischemic stroke. Of these individuals, 99 (11.3%) were depressed alone, 149 (17.0%) had CIND alone, 75 (8.6%) had dementia alone, 74 (8.5%) had co-occurring depression and CIND, and 47 (5.4%) had co-occurring depression and dementia.

Associations of Baseline Depression, CIND or Dementia with Odds of Stroke

In unadjusted analyses, CIND alone (OR: 1.55, 95%CI: 1.27, 1.90), dementia alone (OR: 1.36, 95%CI: 1.04, 1.77), co-occurring depression and CIND (OR: 1.95, 95%CI: 1.48, 2.56) and co-occurring depression and dementia (OR: 1.51, 95%CI: 1.09, 2.10) were all associated with greater odds of having an ischemic stroke during the follow-up period. Depression alone was not associated with odds of ischemic stroke (OR: 1.11, 95%CI: 0.88, 1.40).

After adjusting for participant demographic characteristics, CIND alone (OR: 1.39, 95%CI: 1.13, 1.71) and co-occurring depression and CIND (OR: 1.76, 95%CI: 1.33, 2.32) remained associated with increased odds of ischemic stroke (Table 2), while dementia alone and co-occurring depression and dementia were no longer significantly associated with odds of ischemic stroke. These associations persisted after adjusting for medical comorbidities (CIND alone: OR: 1.39, 95%CI: 1.13, 1.72; co-occurring depression and CIND: OR: 1.68,

95%CI: 1.27, 2.23) and health-risk behaviors (CIND alone: OR: 1.37, 95%CI: 1.11, 1.69; co-occurring depression and CIND: OR: 1.65, 95%CI: 1.24, 2.18).

The prevalence rates of ischemic stroke for all baseline characteristics found to be significantly associated with odds of stroke in the fully adjusted logistic regression model are available in Table S1 (Supplemental Digital Content 1).

Analyses of Effect Modification

There were significant interactions between baseline depression, CIND or dementia status with female sex and dual Medicare-Medicaid status (Table 3). In our cohort, the odds of ischemic stroke were significantly greater among women with CIND alone at baseline (OR: 1.63, 95%CI: 1.08, 2.48). Dual Medicare-Medicaid status among participants with CIND alone (OR: 1.75, 95%CI: 1.04, 2.94) or co-occurring depression and dementia (OR: 2.19, 95%CI: 1.06, 4.54) was associated with significantly greater odds of ischemic stroke.

In our cohort, cerebrovascular disease at baseline modified the association of dementia alone and odds of ischemic stroke (OR: 2.43, 95%CI: 1.08, 5.45). There appeared to be an interaction between CIND alone and baseline cerebrovascular disease which neared statistical significance (OR: 2.13, 95%CI: 0.91, 5.01). There was no evidence of effect modification by diabetes or hypertension.

Sensitivity Analyses

When we excluded individuals with cerebrovascular disease at baseline, CIND alone (OR: 1.29, 95%CI: 1.03, 1.60) and co-occurring depression and CIND (OR: 1.59, 95%CI: 1.18, 2.14) remained independently associated with increased odds of having an ischemic stroke.

Limiting the definitions of baseline depression and baseline dementia to a CES-D-8 score 4 alone and a TICSm score 6 alone, respectively, resulted in somewhat attenuated associations between CIND alone (OR: 1.24, 95%CI: 1.00, 1.52) and co-occurring depression and CIND (OR: 1.34, 95%CI: 0.98, 1.83) with odds of ischemic stroke.

When we used a CES-D-8 cutoff score of 3 in our depression definition, co-occurring depression and CIND continued to be independently associated with increased odds of ischemic stroke (OR: 1.51, 95%CI: 1.13, 2.02), while the association of CIND alone with odds of ischemic stroke was attenuated slightly (OR: 1.23, 95%CI: 0.95, 1.61). Depression alone (unadjusted OR: 1.03, 95%CI: 0.85, 1.26), dementia alone (OR adjusted for demographics: 1.11, 95%CI: 0.84, 1.46) and co-occurring depression and dementia (unadjusted OR: 1.21, 95%CI: 0.95, 1.54) continued to not have significant associations with odds of ischemic stroke.

Finally, CIND alone (OR: 1.35, 95%CI: 1.10, 1.67) as well as co-occurring depression and CIND (OR: 1.63, 95%CI: 1.22, 2.17) remained independently associated with increased odds of ischemic stroke after propensity score adjustment to account for death during follow-up.

DISCUSSION

In this nationally representative cohort of Americans over age 50, we identified a complex relationship between depression, CIND and dementia with subsequent risk of stroke. We found that CIND alone was independently associated with 37% greater odds of ischemic stroke, and co-occurring depression and CIND was independently associated with 65% greater odds of ischemic stroke. However, contrary to our original hypothesis, as well as the findings of prior studies (8-18), depression and dementia were not individually associated with increased odds of ischemic stroke in our entire cohort. The discordance between our findings and those of previous studies could be due to methodological differences such as our use of both self-report and administrative data versus either one alone, different measures used to ascertain depression and cognitive impairment across studies, or that many studies (8, 10, 13-16, 18) did not account for pre-existing cognitive impairment in examining depression as a risk factor and vice versa. Nevertheless, our results regarding the association of co-occurring depression and CIND with ischemic stroke risk add to existing research identifying individuals with co-occurring depression and cognitive impairment as a uniquely at-risk population for a wide-range of adverse outcomes including cognitive decline, institutionalization, and mortality (31, 32).

Although dementia alone and co-occurring depression and dementia were not independently associated with risk of ischemic stroke in our entire cohort, we did identify significant associations among relevant sub-groups. We found that dual Medicare-Medicaid status modified the association between CIND alone as well as co-occurring depression and dementia with risk of ischemic stroke. To the extent that dual Medicare-Medicaid status is an indication of lower socioeconomic status, particularly among the 45% of dual Medicare-Medicaid eligible individuals with co-occurring depression and dementia in our cohort, a possible explanation could be reduced adherence to preventive therapies due to financial concerns (33). Furthermore, prior work has identified that lower socioeconomic status may modify the impact of psychological distress on risk of stroke-related mortality (34). In addition, female sex modified the association of CIND alone with ischemic stroke risk. Building upon prior work that identified women at increased stroke risk compared to men (35), our data suggest that cognitively impaired women may be a sub-group at elevated risk. Overall, our results reinforce the findings of prior studies highlighting demographic factors that may identify important sub-groups of patients at risk for stroke that warrant prevention efforts including risk factor modification (14, 36).

Co-occurring depression and cognitive impairment may be associated with increased risk of ischemic stroke through several mechanisms. A biologically plausible mediator could be endothelial dysfunction and impaired regulation of coagulation pathways. Mild cognitive impairment and depression have been associated with fibrinogen dysregulation and exaggerated platelet reactivity (37, 38), both of which could predispose to vascular pathology such as ischemic stroke (39). A further mediator of the associations presented here could be functional disability due to major depression and/or cognitive dysfunction (40, 41). Our study suggests that additional research is warranted to elucidate the pathophysiological mechanisms that may link co-occurring depression and cognitive impairment with risk of stroke.

An important implication of identifying that co-occurring depression in older adults with CIND is independently associated with increased risk of ischemic stroke is that depression in cognitively impaired patients is treatable. Evidence-based treatments exist for older adults with co-occurring depression and cognitive impairment (42), and collaborative care interventions have been shown to increase access to these treatments, reduce depressive symptoms, and improve chronic medical illness management (43, 44). Further research is needed to examine if these interventions could aid in the prevention of incident strokes.

Our study has several limitations. Our baseline assessments cannot exclude the possibility that CIND in some participants may have been indicative of a transient process such as delirium. Also, depression status may have changed over the course of follow-up, raising the possibility that other more proximate factors may have played a greater role in conveying risk for ischemic stroke than co-occurring depression and CIND. However, it is important to note that prior work has established that depression in older adults with medical illnesses is frequently chronic (45), and rates of depression among HRS participants have been found to be fairly stable over time (5). Furthermore, the probable effect of dementia as a risk factor for ischemic stroke is likely greater than presented here since 10-20% of older adults with CIND progress to dementia annually (6). An additional limitation is that we lacked information on other possible risk factors for ischemic stroke such as atrial fibrillation, as well as data on treatment for depression in our cohort to be able to infer whether appropriate therapies could modify the association of co-occurring depression and CIND with risk of ischemic stroke presented here. A further limitation of our study is that we did not have data on time from our exposures of interest to ischemic stroke occurrence and therefore could not use Cox proportional hazards regression models to estimate hazard ratios for ischemic stroke.

Furthermore, we acknowledge that our assessments of baseline depression, CIND or dementia could be subject to misclassification bias since diagnosing depression in older adults with cognitive impairment is difficult, and cognitive impairment can be a sign of depression itself. Our baseline assessments also preclude consideration of depressive symptom severity as a potential mediator. Although the CES-D-8 has not been specifically validated in cognitively impaired patients nor has the TICSm been specifically validated in depressed individuals, both have been used previously in other relevant studies with high rates of these disorders (22, 46). While the version of the TICSm used in the HRS has modest discriminatory capabilities to identify dementia, our dementia definition was based on the TICSm threshold and also supplemented with ICD-9-CM dementia diagnoses. Finally, residual confounding remains a possibility, as in any observational study.

In conclusion, using a nationally representative sample of Americans over age 50, we have found that CIND as well as co-occurring depression and CIND are independently associated with increased odds of ischemic stroke. We also identified that demographic and socioeconomic characteristics such as sex and dual Medicare-Medicaid status may modify the association of depression, CIND and dementia with risk of ischemic stroke. Further research that elucidates the pathophysiology underlying the bi-directional relationship between depression, CIND and dementia with stroke, as well as develops cost-effective interventions preventing stroke that take into account depression and cognitive impairment,

is needed in light of the adverse consequences of strokes for patients, their loved ones and society.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CES-D-8	8-item Center for Epidemiologic Studies Depression Scale
CIND	cognitive impairment without dementia
HRS	Health and Retirement Study
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
OR	odds ratio
SD	standard deviations
TICSm	modified Telephone Interview for Cognitive Status
95%CI	95% Confidence Interval

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Table 1

Sample demographic, comorbid conditions and health-risk behavioral characteristics

	Entire cohort (n = 7,031)	No depression, CIND, or dementia (n = 4,015)	Depression alone (n = 842)	CIND alone (n = 945)	Dementia alone (n = 534)	Depression and CIND (n = 390)	Depression and dementia (n = 305)
Demographics							
Age							
<65	390 (6%)	187 (5%)	117 (14%)	34 (4%)	9 (1%)	33 (8%)	10 (3%)
65-74	3,127 (44%)	2,132 (53%)	376 (44%)	321 (34%)	100 (19%)	140 (36%)	58 (19%)
75-84	2,527 (36%)	1,362 (34%)	267 (32%)	396 (42%)	213 (40%)	148 (38%)	141 (46%)
85	987 (14%)	334 (8%)	82 (10%)	194 (20%)	212 (40%)	69 (18%)	96 (32%)
Sex							
Male	2,959 (42%)	1,853 (46%)	247 (29%)	422 (45%)	204 (38%)	128 (33%)	105 (34%)
Female	4,072 (58%)	2,162 (54%)	595 (71%)	523 (55%)	330 (62%)	262 (67%)	200 (66%)
Race							
White	6,064 (86%)	3,649 (91%)	750 (89%)	778 (82%)	375 (70%)	283 (73%)	229 (75%)
Non-white	966 (14%)	365 (9%)	92 (11%)	167 (18%)	159 (30%)	107 (27%)	76 (25%)
Education							
High school graduate	4,280 (61%)	2,839 (71%)	531 (63%)	459 (49%)	190 (36%)	160 (41%)	101 (33%)
< High school graduate	2,746 (39%)	1,171 (29%)	311 (37%)	486 (51%)	344 (64%)	230 (59%)	204 (67%)
Marital status							
Married/partnered	3,996 (57%)	2,617 (65%)	406 (48%)	492 (52%)	208 (39%)	149 (38%)	124 (41%)
Single/separated/widowed	3,030 (43%)	1,397 (35%)	435 (52%)	453 (48%)	325 (61%)	240 (62%)	180 (59%)
Dual Medicare-Medicaid							
No	5,635 (80%)	3,558 (89%)	638 (76%)	719 (76%)	333 (62%)	220 (56%)	167 (55%)
Yes	1,396 (20%)	457 (11%)	204 (24%)	226 (24%)	201 (38%)	170 (44%)	138 (45%)
Comorbid Conditions							
Myocardial infarction	260 (4%)	118 (3%)	43 (5%)	39 (4%)	22 (4%)	22 (6%)	16 (5%)
Cerebrovascular disease	359 (5%)	153 (4%)	39 (5%)	37 (4%)	56 (10%)	30 (8%)	44 (14%)
Congestive heart failure	490 (7%)	165 (4%)	78 (9%)	66 (7%)	69 (13%)	51 (13%)	61 (20%)
Valvular disease	272 (4%)	117 (3%)	44 (5%)	40 (4%)	24 (4%)	21 (5%)	26 (8%)
Pulmonary circulation disease	87 (1%)	40 (1%)	17 (2%)	9 (1%)	7 (1%)	6 (1%)	8 (3%)
Peripheral vascular disease	251 (4%)	106 (3%)	37 (4%)	28 (3%)	28 (5%)	24 (6%)	28 (9%)
Other neurological disorders	203 (3%)	69 (2%)	15 (2%)	13 (1%)	51 (10%)	13 (3%)	42 (14%)
Diabetes without chronic complications	465 (7%)	185 (5%)	76 (9%)	58 (6%)	54 (10%)	46 (12%)	46 (15%)
Diabetes with chronic complications	119 (2%)	49 (1%)	16 (2%)	14 (1%)	13 (2%)	14 (6%)	13 (4%)
Coagulopathy	72 (1%)	29 (1%)	1 (1%)	9 (1%)	7 (1%)	3 (1%)	5 (2%)
Hypertension	1,240 (18%)	529 (13%)	188 (22%)	160 (17%)	134 (25%)	103 (26%)	126 (41%)
Health-risk behaviors							
Alcohol use							

	Entire cohort (n = 7,031)	No depression, CIND, or dementia (n = 4,015)	Depression alone (n = 842)	CIND alone (n = 945)	Dementia alone (n = 534)	Depression and CIND (n = 390)	Depression and dementia (n = 305)
Daily drinker	1,664 (24%)	1,182 (29%)	147 (17%)	199 (21%)	58 (11%)	57 (15%)	21 (7%)
# of drinks per day among daily drinkers	1.8 (1.4)	1.7 (1.3)	1.8 (1.2)	1.8 (1.7)	1.9 (1.6)	1.8 (1.3)	2.4 (2.9)
Smoking status							
Never smoked	3,015 (43%)	1,664 (42%)	339 (40%)	440 (47%)	251 (48%)	172 (44%)	149 (49%)
Former smoker	3,197 (46%)	1,887 (47%)	386 (46%)	403 (43%)	242 (46%)	157 (41%)	122 (40%)
Current smoker	766 (11%)	434 (11%)	113 (14%)	96 (10%)	33 (6%)	59 (15%)	31 (10%)

All values are N(%) or mean (SD).

Abbreviation: CIND = cognitive impairment without dementia.

Table 2Adjusted associations of depression, CIND and dementia^a at baseline with odds of ischemic stroke

	Adjusted for demographics (n = 7,021)	Adjusted for demographics and comorbid conditions (n = 7,021)	Adjusted for demographics, comorbid conditions and health-risk behaviors (n = 6,969)
Odds Ratio (95% Confidence Interval)			
Depression alone	1.13 (0.89, 1.43)	1.08 (0.85, 1.38)	1.09 (0.85, 1.38)
CIND alone	1.39 (1.13, 1.71)[†]	1.39 (1.13, 1.72)[†]	1.37 (1.11, 1.69)[†]
Dementia alone	1.09 (0.82, 1.45)	1.08 (0.81, 1.43)	1.08 (0.81, 1.44)
Co-occurring depression and CIND	1.76 (1.33, 2.32)[‡]	1.69 (1.27, 2.23)[‡]	1.65 (1.24, 2.18)[‡]
Co-occurring depression and dementia	1.25 (0.89, 1.76)	1.16 (0.82, 1.65)	1.16 (0.82, 1.65)
Age			
65-74	1.45 (0.99, 2.12)	1.46 (0.99, 2.14)	1.53 (1.03, 2.26) [*]
75-84	1.91 (1.30, 2.80) [†]	1.88 (1.28, 2.77) [†]	1.99 (1.34, 2.97) [†]
85	2.15 (1.42, 3.25) [‡]	2.15 (1.41, 3.26) [‡]	2.28 (1.48, 3.51) [‡]
Female	0.83 (0.71, 0.97) [*]	0.83 (0.71, 0.97) [*]	0.84 (0.71, 0.99) [*]
Non-white	1.13 (0.92, 1.39)	1.12 (0.91, 1.38)	1.11 (0.90, 1.37)
< High school graduate	0.99 (0.84, 1.16)	0.96 (0.82, 1.13)	0.96 (0.81, 1.13)
Single/separated/widowed	1.17 (1.00, 1.38)	1.18 (1.00, 1.39)	1.17 (0.99, 1.38)
Dual Medicare-Medicaid	1.12 (0.92, 1.36)	1.08 (0.89, 1.32)	1.08 (0.89, 1.32)
Myocardial infarction		0.84 (0.57, 1.25)	0.86 (0.58, 1.28)
Cerebrovascular disease		1.57 (1.17, 2.11) [†]	1.57 (1.17, 2.11) [†]
Congestive heart failure		0.87 (0.65, 1.18)	0.89 (0.66, 1.20)
Valvular disease		1.18 (0.83, 1.69)	1.18 (0.82, 1.69)
Pulmonary circulation disease		0.77 (0.39, 1.52)	0.79 (0.40, 1.56)
Peripheral vascular disease		1.42 (1.01, 2.00) [*]	1.42 (1.01, 2.00) [*]
Other neurological disorders		0.55 (0.34, 0.87) [*]	0.56 (0.35, 0.89) [*]
Diabetes without chronic complications		1.34 (1.00, 1.78)	1.35 (1.01, 1.80) [*]
Diabetes with chronic complications		1.08 (0.63, 1.82)	1.08 (0.63, 1.83)
Coagulopathy		1.57 (0.89, 2.76)	1.59 (0.91, 2.80)
Hypertension		1.22 (0.99, 1.50)	1.23 (1.00, 1.52)
Alcohol consumption			
1 drink/day			1.04 (0.83, 1.31)
2 drinks/day			1.06 (0.78, 1.44)
3 drinks/day			0.73 (0.39, 1.34)
4 drinks/day			1.60 (0.98, 2.62)

	Adjusted for demographics (n = 7,021)	Adjusted for demographics and comorbid conditions (n = 7,021)	Adjusted for demographics, comorbid conditions and health-risk behaviors (n = 6,969)
Smoking			
Former smoker			0.93 (0.79, 1.10)
Current smoker			1.15 (0.89, 1.48)

Abbreviation: CIND = cognitive impairment without dementia.

* $P < 0.05$

† $P < 0.01$

‡ $P < 0.001$

^aThe comparison group for analyses of the association of depression, CIND or dementia with odds of ischemic stroke is those subjects with no disorder

Table 3

Analyses of effect modification of the association of depression, CIND and dementia with odds of ischemic stroke

	Odds Ratio (95% Confidence Interval)
Depression/CIND/Dementia × Sex (n = 6,969)	
Depression alone × Female	1.34 (0.80, 2.24)
CIND alone × Female	1.63 (1.08, 2.48)*
Dementia alone × Female	1.60 (0.91, 2.80)
Depression + CIND × Female	1.27 (0.71, 2.26)
Depression + Dementia × Female	1.83 (0.89, 3.74)
Depression/CIND/Dementia × Dual Medicare-Medicaid status (n = 6,969)	
Depression alone × Dual Medicare-Medicaid	1.43 (0.79, 2.58)
CIND alone × Dual Medicare-Medicaid	1.75 (1.04, 2.94)*
Dementia alone × Dual Medicare-Medicaid	1.43 (0.78, 2.62)
Depression + CIND × Dual Medicare-Medicaid	1.24 (0.67, 2.30)
Depression + Dementia × Dual Medicare-Medicaid	2.19 (1.06, 4.54)*
Depression/CIND/Dementia × Baseline cerebrovascular disease (n = 6,969)	
Depression alone × Prior cerebrovascular disease	0.97 (0.35, 2.67)
CIND alone × Prior cerebrovascular disease	2.13 (0.91, 5.01)
Dementia alone × Prior cerebrovascular disease	2.43 (1.08, 5.45)*
Depression + CIND × Prior cerebrovascular disease	1.13 (0.42, 3.04)
Depression + Dementia × Prior cerebrovascular disease	1.09 (0.43, 2.79)
Depression/CIND/Dementia × Baseline diabetes (n = 6,969)	
Depression alone × Baseline diabetes	0.73 (0.30, 1.75)
CIND alone × Baseline diabetes	1.02 (0.47, 2.22)
Dementia alone × Baseline diabetes	1.50 (0.65, 3.44)
Depression + CIND × Baseline diabetes	1.79 (0.81, 3.96)
Depression + Dementia × Baseline diabetes	0.77 (0.30, 2.01)
Depression/CIND/Dementia × Baseline hypertension (n = 6,969)	
Depression alone × Baseline hypertension	0.76 (0.43, 1.37)
CIND alone × Baseline hypertension	1.27 (0.76, 2.13)
Dementia alone × Baseline hypertension	1.56 (0.85, 2.84)
Depression + CIND × Baseline hypertension	0.91 (0.49, 1.68)
Depression + Dementia × Baseline hypertension	1.46 (0.72, 2.96)

Abbreviation: CIND = cognitive impairment without dementia

* $P < 0.05$