Joint Modeling of Multivariate Longitudinal Depressive Symptoms and Survival with Application to an Aging Study

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ABSTRACT

Background: The primary aim of this study was to use a joint analysis approach in order to examine the association between longitudinal depressive symptoms and survival in Mexican Americans.
Methods: The separate Cox regression and joint modeling were applied to data from the Hispanic Established Population for Epidemiological Study of the Elderly (HEPESE). Depressive symptoms were measured by the Center of Epidemiological Studies Depression Scale (CES-D). The trajectories of CES-D, modeled by random effect, were used as independent variables to fit the mortality curve adjusted by other variables including demographics and physical functioning.
Results: The separate Cox regression couldn't identify association between depressive symptoms and survival. The joint analysis indicated that the slope of CES-D score was not associated with mortality in older Mexican-Americans, however the intercept had negative effects on mortality.
Conclusion: There is significant association between baseline depression symptoms and mortality, whereas there is no association with slope in older Mexican Americans

Key words: Depression, mortality, longitudinal analysis, joint modeling, Mexican Americans

INTRODUCTION

The prevalence of depression measured by the Center of Epidemiological Studies Depression Scale (CES-D) [1] in older Mexican-Americans is 25.4%, which is much higher than Non-Hispanic Caucasians and African-Americans, whose prevalence ranges from 9 to 16.9% [2]. Older adults in ethnic minorities, including Mexican-Americans, are exposed to higher level of depression risk factors and several studies have found higher levels of depressive symptoms in this group compared to Non-Hispanic Whites [2, 8].

The literature on associations between depression and mortality is inconsistent. Depression negatively affects health and increases mortality through complicated mechanisms [3], but the association between depression and mortality among the elderly population remains a controversy. A longitudinal community based study confirms an association between depression and mortality in Australia [4] and a cohort study finds that depression is a significant predictor

for death in elderly people in Japan [5]. Blazer et al. reveal that there is an association between depression and mortality, with odds ratios of 1.74, 1.69, 1.29 and 1.21 for association between mortality and depression after adjusting to chronic disease and health habits, cognitive impairment, functional impairment and social support, respectively [6]. Schulz et al. examine a group of older adults, aged 65 years and older, from four US communities. They find that mortality within six year follow-up is associated with high baseline depressive symptoms after adjusting to socio-demographic factors, clinical disease, subclinical indicators and health risk factors [7]. Black et al. investigate the association between depressive symptoms and mortality in older Mexican-Americans in the Hispanic Established Population for the Epidemiological Study of the Elderly (HEPESE) and report that high levels of depressive symptoms concomitant with major chronic medical conditions increase the risk of death [8]. Ganguli and colleagues follow a community based population aged ≥ 67 for 10 years and find that depression alone predicts mortality in the short term rather than in the long term, but if in combination with poor self-rating of health, it strongly predicts mortality at all end points [9].

On the other hand, there are also some reports showing that there is no association between depression and mortality. Fredman et al. investigate an elderly community population with two years of follow-up and find no association between depression and mortality [10]. A 12-year longitudinal study among the elderly of a rural community in Taiwan reports for the association between depressive symptoms and mortality a hazard ratio of 1.55 (95% confidence interval (CI), 0.99 to 2.44) [11]. Anstey et al. examine older subjects within six waves and find that change in depressive status was not associated with mortality in older women, whereas it is associated in men [12]. Zhang and colleagues find that the baseline CES-D is not predictive for mortality using subjects from the Florida Retirement Study [13] but they find that the increase in depression over time is significantly associated with higher mortality. The association between depressive symptoms and mortality risk is affected by baseline physical health, length of follow-up and measurement of depression [10]. Unutzer et al. report results from a 7-year prospective study of depression and mortality in older adults and find that mild-to-moderate depression at baseline does not increase risk of mortality compared to those without significant depression [14]. The systematic review done by Schulz [15] indicates that, among 22 community studies, nine show a positive relationship, seven negative and six have mixed results. Adamson et al. study 13.097 people aged 75 and older participating in the community in the United Kingdom and report that depression confers a small risk of mortality in older people not explained solely by poor health [16].

There are several reasons for these conflicting results. First, there is a design issue with some studies. Although some studies have more than four waves of follow up or are longer than 5 years [11, 9, 27] some are not. The short follow-up cannot adequately capture the temporal relationship between depression and mortality in older populations. Second, different control variables are used in the analyses of the various studies. The evidences indicate control variables including age, gender, other demographic factors and socioeconomic variables, health indicators, such as chronic diseases, cognitive and functional impairment, potentially influence the association between depression and mortality [27].

Many methods have been proposed for jointly analysing longitudinal and survival data [17,18]. With joint modeling, the longitudinal trajectory (intercept and slope) of the variable with repeated measures can be predictor for the time to event, such as for the time to death. The joint model links two-sub functions, with one modeling repeated measures in order to capture changes and the other survival function modeling time to death. Ghisletta et al. conduct a joint analysis of longitudinal cognition and survival in an elderly population [19]. Zhang et al. use joint modeling of longitudinal change in depression symptoms to predict mortality in a community dwelling elderly population from Florida. They find that the change (slope) of depression increases mortality with a hazard ratio of 1.57 (CI, 1.18 to 2.08) [13].

It's very important to understand the progression and change trajectory of depressive symptoms and its effect on mortality risks in older Mexican-Americans. To our knowledge, it has not been addressed in previous studies. We examine the association between depression symptoms and mortality over seven years among older community dwelling Mexican Americans, from the Hispanic Established Population for the Epidemiological Study of the Elderly (HEPESE) [20]. We hypothesise that (i) depression measured by the Center of Epidemiological Studies Depression Scale (CES-D) at baseline is associated with seven-year mortality in older Mexican Americans; (ii) the longitudinal course (change) of depression affects mortality. We propose to jointly model longitudinal repeated measures of depression and time to death.

METHODS

Data and Sample

We employ data from the HEPESE. This dataset comprises four waves of follow-up: 1993-1994, 1995-1996, 1998-1999 and 2000-2001. The sample consists of 3050 Mexican-Americans at baseline, aged 65 years and older, residing in five of the southwestern states: Arizona, California, Colorado, New Mexico and Texas. Beginning with the second wave, some of the original subjects died or were lost to follow up and only 1683 subjects were interviewed at wave four [21].

Measures

Demographic Variables

The demographic variables include age, sex, years of education, annual household income (three categories), marital status and body mass index (BMI). Marital status was dichotomised as unmarried (consisting of separated, divorced widowed and never married people) and currently married, with married people as the reference group.

CES-D

Depression is measured with the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D score consists of the sum of 20 individual items measured on a four-point frequency scale, with score ranging from 0 to 60. Sample items include "I felt depressed", "I felt fearful", "I felt lonely" and "I felt sad" among others. Possible responses for each item on this 4-point Likert scale were: 0= never/none; 1= some/little; 2= occasionally/moderate; 3= most or all of time. Higher scores indicate greater level of depressive symptoms.

Mortality

The time to death was calculated by the date of death minus the date of the first interview, measured by month. A total of 933 (30.59%) subjects died by the fourth wave.

Number of Chronic Diseases

The number of chronic diseases was determined from seven items (cardiovascular disease, stroke, hypertension, diabetes, cancer, fractures and arthritis). The presence of disease was coded as "1" for "yes" or "0" for "no". Possible scores for chronic diseases ranges from 0 to 7.

Physical Functioning

The total number of limitations in activities of daily living (ADL) [22, 23], which included walking across a small room, bathing, personal grooming, dressing, eating, getting from a bed to a chair and using a toilet, was also an important physical functioning measurement at baseline. The range of this ADL scale is from 0 to 7, with higher scores indicating a greater number of ADL problems.

Health Behavior

Current smoking status and prescription drug use (yes or no) at baseline was also used in this analysis.

Cognitive status was assessed using Mini-Mental State Examination (MMSE) score.

Statistical Analysis

First, descriptive statistics of dependent and independent variables at baseline were summarised. Then Cox proportional hazard regression [24] was conducted to test whether the baseline CES-D score is predictive for mortality, with and without adjustment for baseline covariates. Kaplan-Meier Survival curve is plotted based on the dichotomised baseline CES-D score (≥16 indicating depression with indicator 1, otherwise no depression with 0).

Finally, we conducted joint modeling of both longitudinal observations of depression and death intensity by shared random effect. The trajectory of change in CES-D scores is modeled by a linear function. The intercept and slope of change in CES-D score are used as covariates in a Cox regression model to check the association between the trajectory of CES-D score over time and mortality, in adjusted and unadjusted models [13].

Using the model of repeated measure, CES-D score is

$$Y_{ij}=\alpha_{0j}+\alpha_{1J}t_{ij}+e_{ij},$$

Where Y_{ij} is the CES-D score of subject j at year i; α_{0j} and α_{1j} are the subject-specific random intercept and slope of changes in the CES-D score of subject j; Assume α_{0j} is from a normal distribution with mean α_0 and variance δ_0^2. Also assume α_{1j} is from a normal distribution with mean α_{1j} and variance δ_1^2. e_{ij} is the residual, following a normal distribution. Then the parameters of a linear mixed model are shared as covariates to predict mortality.

The hazard intensity function of the survival model for mortality is

$$\lambda_j(t)=\lambda_0(t)exp(\beta_0+\alpha_{0j}y_0+\alpha_{1j}y_1+\beta_1 chronic+\beta_2 age+\beta_3 sex+\beta_4 education+\beta_5 marital+\beta_6 income+\beta_7 ADL+\beta_8 MMSE+\beta_9 BMI+\beta_{10} smoking+\beta_{11} during),$$

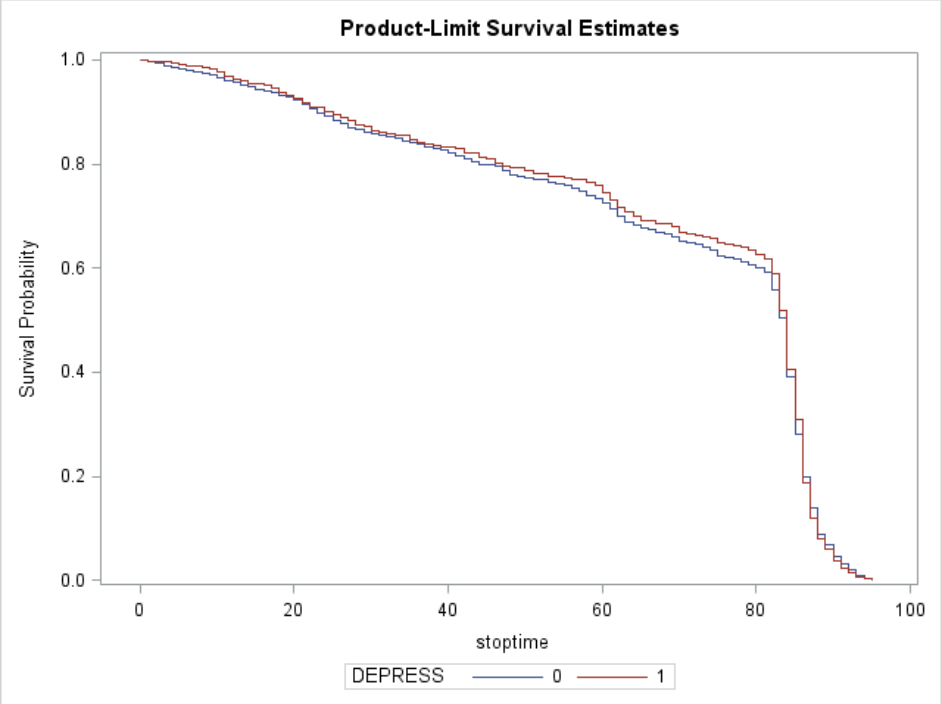
Where $\lambda_0(t)$ is the baseline hazard; control variables include chronic diseases, age, sex, education, marital status, income, ADL, smoking, cognitive status, drug and BMI. β are corresponding parameters; the parameters y_0 and y_1 are the subject-specific effects of the CES-D trajectory on mortality.

The joint likelihood is maximized by quasi-Newton methods and Gaussian quadrature estimates with five quadrature points; the nuisance parameter, baseline hazard is approximated by a piecewise constant baseline hazard [18]. The analysis is done by the procedure NLMIXED in SAS 9.2 [29].

TABLE 1. Summary of data.

WAVE	N	DEATH	% (CES-D≥16)	MEAN(SD) OF CES-D
I	3050	0	36.71	14.91 (7.58)
II	2439	239	24.92	14.30 (5.85)
III	1981	661	33.92	15.46 (6.64)
IV	1683	933	13.73	6.68 (7.33)

FIGURE 1. Kaplan-Meier Survival curve of two groups.



RESULTS

Table 1 illustrates the mean of CES-D score and the number of subjects who were followed, died or dropped out at each wave. The mean CES-D score were 14.91, 14.30, 15.46 and 6.68 in the first, second, third and fourth waves. The CES-D score from wave four is not used since the value is not consistent with the first three waves. The mortality rates were 7.84%, 21.67%, 30.59%, in the second, third and fourth waves, respectively.

Table 2 presents the descriptive statistics of the study subjects at baseline. The average age at baseline was 73.07 years (SD=6.78). The population consisted largely of subjects of low socioeconomic status (low income and few years of education). Of the total, 55.5% were married and 30% were current smokers. The average number of chronic diseases was 1.94 (SD=0.94). At baseline, females accounted for 57.6% of the sample.

Kaplan-Meier Survival curve (Figure 1) indicates there is no significant difference between group of depression with indicator 1 and group of no depression with 0 at baseline.

Table 3 presents the hazard ratio (HR) of mortality with and without adjustment for covariates. First, Cox proportional regression is conducted to predict mortality using the baseline CES-D score. Without adjustment, baseline CES-D score was not significantly associated with mortality (HR=0.998, p<0.69). After adjusting for age, sex, years of education, marital status, income, ADL scores, BMI, cognitive status, drug, smoke and number of chronic diseases, through multivariate analysis, the baseline CES-D score was not a significant predictor for mortality (HR=0.998, p<0.68). At baseline, the results indicate that ADL is a very significant predictor for death. ADL score has a negative effect on mortality (HR=0.88, p<0.01). Age, sex, years of education, marital status, income, BMI, cognitive status, drug, smoke, and number of chronic diseases at baseline were not significantly associated with mortality (Table 3).

TABLE 2. Descriptive characteristics of Subjects at Baseline in HEPESE study 1993-2001.

CHARACTERISTIC	MEAN ± SD OR PROPORTION
CES-D score	14.91 ± 7.58
Age	73.07 ± 6.78
Chronic disease	1.93 ± 0.93
ADL	0.52 ± 1.56
Years of education	4.84 ± 3.89
Cognitive status	24.69 ± 4.70
BMI	27.84 ± 5.29
Sex: male	42.4%
female	57.6%
Smoking	30.0%
Income	
$0-$4,999	14.24%
$5,000-$9,999	37.22%
$10,000-$14,999	21.40%
$15,000-$19,999	9.86%
>$20,000	17.28%
Marital Status	55.5%
Drug	66.73%

Joint modeling of dynamic depression and time to death

Table 4 presents the controlled hazard ratio of mortality for the trajectory of CES-D score. A multivariate joint model was fitted to estimate the effect. The estimated intercept (α_{0j}) of CES-D score from the sub-model of the longitudinal part, which indicated the estimated mean baseline CES-D score, is 14.67 (SD=0.12, p<0.001). The linear slope (α_{1j}) of the trajectory of CES-D score, which was the estimated mean annual change in CES-D score, is 0.14 (SD=0.03, p<0.001). The results from multivariate analysis show that the mean baseline of CES-D was significant in predicting mortality (HR=0.97, P<0.02), which means 1 point of increase in the CES-D score at baseline, predicting 3% lower mortality. The linear slope of CES-D was not a significant predictor (HR=0.93, P<0.17).

The effects of baseline covariates are also presented in table 4. At baseline, the results indicate that ADL is a very significant predictor for death. ADL score has a negative effect on mortality (HR=0.90, p<0.02). Age, sex, years of education, marital status, income, BMI, cognitive status, drug, smoke and number of chronic diseases at baseline were not significantly associated with mortality.

DISCUSSION

In this paper, we presented a joint random-effects model used to analyse longitudinal depression symptom observations and death, in order to investigate the trajectory (intercept and slope) in depression symptom over time and the association with mortality in a seven-year longitudinal study of older Mexican-Americans compared with the results from [13]. The results from Cox regression analysis using baseline covariates indicated that baseline depression was not significantly associated with mortality (HR=0.99, CI from 0.99 to 1.01, p<0.67). This result is consistent with dichotomised CES-D by Kaplan-Meier survival analysis.

Also, the results from joint longitudinal repeated measures and survival analysis revealed that dynamic change of CES-D score was not a significant risk factor for mortality after having controlled all covariates in older Mexican-Americans.

Results from joint longitudinal repeated measures and survival analysis showed that the intercept (i.e. estimated baseline CES-D) became significant in predicting mortality (HR=0.97, CI=0.94-0.99, P<0.02), which is contradictory to what was found in the traditional Cox regression and Kaplan-Meier survival analysis.

There is a possible explanation for the lack of longitudinal associations between depressive symptoms and mortality. First, the estimated mean and slope of change in depressive symptomatology scores of older Mexican Americans in this study are much lower compared with a previous study with Non-Hispanic White populations [13]. The intercept and slope of the CES-D score for older Mexican-Americans are 14.67 and 0.14, but were 18.27 and 0.56 points from the previous study [13]. So low mean depressive symptoms at baseline and slow increase levels did not contribute to death for older Mexican-Americans. Kim et al. [30] found that there is response bias to depressive symptom items in racially and ethnically diverse older adults. Mexican Americans were more likely than whites and blacks to endorse the large number of depressive symptom items. So CES-D score for older Mexican-Americans overestimated true depression level.

There are three primary limitations in the current study. First, the high proportion of drop-outs and non-responses could have caused some degree of selection bias in this analysis. Analysis of time to drop-out indicated that the baseline and following wave depression scores increased the risk of drop-out, suggesting that we could have underestimated depression

TABLE 3. Results of Cox regression using baseline variables.

PREDICTOR	ESTIMATE	SE	HR	95% CI	P-VALUE
CES-D	-0.002	0.004	0.99	0.99-1.01	<0.67
Sex					
Female					
Male	0.08	0.08	0.92	0.79-1.08	<0.09
Marriage					
Yes	-0.12	0.08	0.89	0.76-1.04	<0.15
No					
Drug					
Yes	0.02	0.09	1.02	0.86-1.20	<0.85
No					
Smoke					
Yes	-0.11	0.11	0.90	0.72-1.11	<0.33
No					
Income	0.01	0.03	1.01	0.96-1.08	0.63
Age	-0.01	0.01	0.99	0.97-1.01	<0.11
Education	-0.01	0.06	0.99	0.88-1.12	0.92
Chronic	0.05	0.04	1.06	0.80-0.97	<0.01
ADL	-0.12	0.05	0.88	1.04-1.16	0.01
BMI	0.01	0.04	1.01	0.92-1.11	0.85
MMSE	-0.01	0.01	0.99	0.97-0.1.01	0.66

scores. This may explain why the hypothesis of depression change associated with mortality was not supported. Second, the CES-D score is not a form diagnosis of clinical depression, but actually it is a scale designed to measure depressive symptomatology. Thus, there is response bias to depressive symptom items compared with racially and ethnically diverse older people. The third limitation is that data for CES-D, ADL and other covariates were self-reported measures. This may have resulted in under or over estimates of the prevalence of depressive symptomatology and influenced the association with mortality.

Despite these limitations, the results of the current analysis are strengthened by the use of a large sample and a long follow-up period to investigate the temporal association between depression and mortality. Furthermore, the sub-link of joint model, linear mixed model can capture the heterogeneity with random effects for individual subjects. The joint modeling can utilise the trajectory (intercept and slope) of depression to predict mortality in older Mexican Americans.

In summary, the results presented from the joint analysis of longitudinal depression and mortality indicated that the trajectory of change in CES-D score did not predict mortality in older Mexican Americans. The intercept (baseline CES-score) is different from different analysis methods.

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TABLE 4. Results of joint analysis of CES-D and mortality adjusted by baseline variables to predict mortality at 7-year follow-up.

Predictor	Estimate	SE	HR	95% CI	p-value
CES-D intercept	-0.03	0.01	0.97	0.95-1.00	0.02
CES-D slope	-0.07	0.04	0.93	0.85-1.03	0.17
Age	-0.01	0.01	0.99	0.98-1.00	0.05
Sex					
Male	-0.11	0.08	1.11	0.77-1.04	0.15
Female					
Smoking					
No	-0.10	0.11	0.90	0.73-1.11	0.32
Yes					
Drug					
No	0.01	0.08	1.01	0.87-1.18	0.85
Yes					
Marriage					
Married (Yes)	-0.08	0.07	1.08	0.79-1.07	0.28
No					
Education	-0.005	0.05	0.99	0.90-1.12	0.93
Income	0.02	0.03	1.02	0.97-1.07	0.47
ADL	-0.11	0.05	0.90	0.81-0.98	0.02
MMSE	-0.01	0.01	0.99	0.97-1.01	0.35
BMI	-0.01	0.04	0.99	0.90-1.07	0.77
Chronic	0.06	0.03	1.06	0.99-1.13	0.07

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