

1-1-2013

Vascular Depression: An Early Warning Sign of Frailty

Daniel Paulson

Wayne State University, daniel.paulson2@ucf.edu

Peter A. Lichtenberg

Wayne State University, p.lichtenberg@wayne.edu

Recommended Citation

Paulson, D. and Lichtenberg, P.A. (2013). Vascular depression: an early warning sign of frailty. *Aging & Mental Health* 17(1): 85-93.

DOI: [10.1080/13607863.2012.692767](https://doi.org/10.1080/13607863.2012.692767)

Available at: <http://digitalcommons.wayne.edu/psychfrp/19>

This Article is brought to you for free and open access by the Psychology at DigitalCommons@WayneState. It has been accepted for inclusion in Psychology Faculty Research Publications by an authorized administrator of DigitalCommons@WayneState.

NOTICE IN COMPLIANCE WITH PUBLISHER POLICY: This is an Author's Accepted Manuscript, formatted for archiving, of an article subsequently published as Paulson, D. and Lichtenberg, P.A. (2013). Vascular depression: an early warning sign of frailty. *Aging & Mental Health* 7(1): 85-93. [© Taylor & Francis], available online at: <http://www.tandfonline.com/10.1080/13607863.2012.692767>.

Vascular Depression: An Early Warning Sign of Frailty

DANIEL PAULSON and PETER A. LICHTENBERG

Department of Psychology / Institute of Gerontology, Wayne State University, 87 E. Ferry St., Detroit, MI 48202

Corresponding author DANIEL PAULSON email:paulson@wayne.edu tel:540-746-3806 fax:313-664-2667

Abstract Objectives: Frailty is a common geriatric disorder associated with ADL impairment, hospitalization, and death. Phenomenological evidence suggests that late-life depression (Katz, 2004), particularly vascular depression, may be a risk factor for frailty. This study tests that hypothesis.

Methods: We identified a sample of stroke-free women over the age of 80 from the Health and Retirement Survey. The sample included 984 respondents in 2000 (incidence sample). Of these, 459 were non-frail at baseline and still alive in 2004 (prevalence sample). Frail respondents experienced at least three of the following: wasting, exhaustion, weakness, slowness, and falls. Vascular depression was represented using two dummy variables. The first represented respondents with either high CVB (at least two cerebrovascular risk factors) or probable depression (score ≥ 3 on the 8-item CES-D), and the second represented respondents with both high CVB and probable depression.

Results: At baseline, the prevalence of frailty was 31.5%. Over 4 years the incidence of frailty was 31.8%. After controlling for age, education, ADL and IADL disability, arthritis, pulmonary disorders, cancer, and self-rated health, respondents with either high CVB or probable depression were more likely to be frail at baseline, and those with both were at even higher risk. Of those who were not frail at the 2000 wave, respondents who reported both high CVB and probable depression were more likely to become frail by 2004.

Discussion: These findings suggest that vascular depression is a prodrome for frailty.

Keywords Frailty, Vascular Depression, Older Women

INTRODUCTION

Research on frailty among older adults has increased over the past decade, both to define phenotypes and identify markers for future frailty (Fried et al., 2001; Varadhan et al., 2009). Frailty is clearly related to advanced age, heart dysfunction (Varadhan et al., 2009), subclinical vascular biomarkers (Newman et al., 2011), and being female (Fried et al., 2001). The clinical pathways that lead to frailty are poorly understood; our study attempts to increase knowledge of the underlying mechanisms of this common late-life syndrome by examining a specific pattern of medical comorbidity—vascular depression—and incorporating it into a model of other medical conditions and functional abilities to predict new-onset frailty cases in women over the age of 80.

The co-occurrence of vascular diseases and depression may signal that if elders are treated by standard means, they will decline into frailty (Rosso et al., 2011), a syndrome that imposes a significant burden on the health-care system (Fassbender, Fainsinger, Carson, & Finegan, 2009). While frailty, comorbidity, and disability are distinct concepts (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004), this study aims to increase our understanding of how vascular depression—which is a combination of particular medical comorbidities—and reported disability, based on Fried's (2001) conceptualization as requiring assistance with one or more activities of daily living (ADL) task, affect the incidence of frailty in older-old women. Older women have longer life expectancies than men, but face higher rates of frailty (Fried et al., 2001) and depression and more years of disability. Women over the age of 80 are a rapidly growing demo-

graphic group (National Center for Health Statistics, 2010) and are increasingly the subject of behavioral and medical interventions to enhance longevity, preserve independence and reduce morbidity. Research elucidating pathways to frailty among older women may inform interventions designed to preserve independence and quality of life and reduce health care costs for this vulnerable demographic group.

Frailty

Frailty is conceptualized as the combined effects of life stress that result in multisystemic dysregulation of homeostatic systems (Clegg, 2011; Fried et al., 2004). Although there are multiple models of frailty, Fried's (Fried et al., 2001) continues to be among the foremost (Clegg, 2011). In this model, frail individuals are described as having at least three of the following conditions: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity. Fried et al. (2001) reported that frailty is more common among women, Black elders, and those with lower education and income, relatively poor health, and greater medical comorbidity and disability. Frailty becomes more common with increasing age; base rates range from 3% to 7% of individuals between ages 65 and 75 (Fried, 2003) and more than 30% for individuals in their 90s (Walston et al., 2002). Frailty is also associated with comparably poor subjective health evaluations, vascular disease (Barzilay et al., 2007; Fried et al., 2001), arthritis (Fried et al., 2001), greater heart rate variability (Varadhan et al., 2009), and insulin resistance (Barzilay et al., 2007). Frail individuals experience decreased mobility and higher rates of impairment in performing ADLs, hospitalization, and death (Fried et al., 2001; Lupon et al., 2008), making this syndrome a significant public health concern. Self-rated health, arthritis, and ADL disability, in particular, are associated with both depression and frailty. Including such important control variables may protect against overrepresenting the relationship between vascular depression and frailty in epidemiological research.

Depression

Vascular depression is defined as the increased prevalence of depression symptoms in late life resulting from high cerebrovascular burden (CVB; Alexopoulos et al., 1997a). The vascular depression hypothesis has generated two complementary lines of research, both of which inform this discussion of vascular depression and frailty. One uses neuroradiological data to describe the relationship between prefrontal subcortical white matter hyperintensities, which are typically attributed to CVB, and late-life depression symptoms (Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008). Other studies, however, have reported no significant relationship between cerebral vascular change and depression (Rainer et al., 2006). The second line of research approaches the relationship from a clinical perspective, relating the presence of multiple cerebrovascular risk factors (diabetes, hypertension, etc.) to development of depression symptoms in late life (Mast et al., 2008). Recent work by our lab (Paulson, Bowen, & Lichtenberg, under review) based on the same sample used in this study found that respondents with high CVB have significantly more depression symptoms at baseline. We also identified a trend ($p=.07$) for individuals with high CVB developing more symptoms over 6 years. Overall, this finding supports a causal relationship between CVB and depressive symptoms in this sample. This conceptualization of vascular depression is not universally supported (Lyness et al., 1999). Nonetheless, both areas of vascular depression research generally support Alexopoulos et al.'s (1997a) hypothesis that affective functioning involves an elaborate network of fronto-striatal projections (Drevets, Price, & Furey, 2008) and appears to be highly sensitive to microvascular insult (Sneed et al., 2008).

Katz (2004) discussed the numerous theoretical and phenomenological connections between depression and varying models of frailty. He noted that white matter disease characterizes both late-onset depression and psychomotor deficits, which can be symptomatic of frailty. Katz did not, however, speculate as to whether vascu-

lar depression, as opposed to late-life depression, is related to frailty. Andrew and Rockwood (2007) reported that psychiatric disease is four times more common among frail elders than among the most robust elders. Interpretation of these results is limited, however, by the use of cross-sectional data and the identification of psychiatric illness based on retrospective self-report. Additionally, this study included CVB markers (hypertension, cardiac disease, and diabetes) as indicators of frailty, precluding analysis of these variables as risk factors *for* frailty. Other work has related depression to various correlates and indicators of frailty, including fall risk (Thomas et al., 2009), malnutrition (Thomas et al., 2009)—which can lead to wasting, steep decline in strength (Rantanen et al., 2000)—and deficits in ADL functioning and mobility (Penninx, Leveille, Ferrucci, van Eijk, & Guralnik, 1999).

Vascular Depression and Disability as an Early Indicator of Frailty

In this study, vascular depression was conceptualized as a prodrome for frailty. As described above, vascular depression has a neurological basis. Katz (2004) theorizes that cerebrovascular disease that causes prefrontal white-matter hyperintensities and vascular depression may also lead to posterior white matter hyperintensities, resulting in characteristics of frailty such as falls, slowness, and weakness. Recent findings of higher rates of cardiovascular disease and cerebral infarcts among frail elders support this hypothesis (Newman et al., 2011). Accordingly, vascular depression may be a highly sensitive, clinically relevant indicator of global cerebral disease process and, in turn, a harbinger of subsequent frailty and mortality. However, this hypothesis has not been explicitly tested; neither Katz nor Newman et al. (2011) examined whether vascular depression was a better predictor of frailty onset than either vascular disease without depression or depression without vascular disease.

The objectives of this study were to (1) describe the prevalence of frailty in a sample of stroke-free women over the age of 80 and the

incidence of new cases of frailty over 4 years, and (2) to test the hypothesis that vascular depression and disability predict both prevalent and incident (new onset) frailty among older-old women. To examine the specificity of vascular depression, we included as control variables other medical conditions (arthritis, pulmonary disease, and cancer) that are often related to disability.

METHODS

Sample

The Health and Retirement Survey (HRS) is an ongoing prospective multistage probability cohort study of U.S. households conducted by the University of Michigan with support from the National Institute on Aging (Heeringa & Conner, 1995). The first wave of the HRS occurred in 1992, with a 51- to 61-year-old cohort, and in 1998 was merged with the 70-and-older cohort of the Asset and Health Dynamics of the Oldest Old Study. Also in 1998, two additional cohorts were added to fill the gap between the two groups.

Our study included HRS data drawn from the 1998 wave, when many participants were added to the study. This sample included female respondents without history of stroke in 1998. Respondents were excluded if they were unable to independently complete survey materials (e.g., the CES-D, a measure of depressive symptoms) at the 2000 wave. This data set was otherwise demographically representative of the female U.S. population over age 80 and included 1,139 respondents. Complete frailty data was available at 2000 and 2004, so we included data drawn from these waves (waves 5 and 7) exclusively. Based on past work with this sample, it is known that attrition rates are around 20% per wave (2-year period) and primarily reflect mortality. Of the 984 respondents in at the 2000 wave (prevalence sample), 2004-wave frailty data were available for 621 respondents. Of the 356 respondents (36.2%) who attrited over this 4-year period, 314 died, 39 did not respond to data collection efforts, and 3 respondents elected to be

removed from the study. Key variables from this study were entered into a logistic regression predicting attrition. Attrition was significantly predicted by older age ($\beta=.117$, $Wald=36.93$, $p<.001$), IADL disability ($\beta=.33$, $Wald=5.00$, $p=.03$), pulmonary disease ($\beta=.59$, $Wald=5.16$, $p=.02$), worse self-rated health ($\beta=.19$, $Wald=4.08$, $p=.04$), and high CVB ($\beta=.53$, $Wald=13.63$, $p<.001$). More information about mortality-related attrition in this sample has been published elsewhere (Paulson, Bowen, & Lichtenberg, 2011).

Measures

Frailty We measured frailty based on a frailty phenotype identified using HRS data (Paulson & Lichtenberg, 2011). This phenotype was largely based on Fried's (2001) conceptualization of frailty. Due to differences between the HRS data and Fried's model of frailty, we adapted the frailty index to include the following: wasting, weakness, slowness, fatigue or exhaustion, and falls. The wasting criterion was met if a respondent reported loss of at least 10% of body weight over a 2-year period. The weakness criterion was met if they endorsed the question, "Because of health problems, do you have any difficulty with lifting or carrying weights over 10 pounds, like a heavy bag of groceries?" The slowness criterion was met if respondents answered in the affirmative to the question, "Because of a health problem, do you have any difficulty with getting up from a chair after sitting for long periods?" The fatigue or exhaustion criterion was met if the respondent answered in the affirmative to the question, "Since we last talked with you in [the last wave], have you had any of the following persistent or troublesome problems: . . . severe fatigue or exhaustion?" The falls criterion was met if the respondent answered in the affirmative to the question, "Have you fallen down in the past 2 years?" While Fried's criteria include low energy expenditure, this variable was not available in the HRS data. Instead, the frailty phenotype was modified to include falls, which have been found to be an indirect measure of energy expenditure (Montero-Odasso et al., 2011). This

phenotype was found to identify frailty at rates similar to those based on Fried's frailty phenotype. Like Fried's phenotype, frailty was more common among women, African American elders, those with poor self-rated health, ADL disability, and multiple medical comorbidities. Frailty was also inversely associated with education and income (Paulson & Lichtenberg, 2012). None of these frailty items were drawn from the Center for Epidemiological Studies Depression Scale (CES-D). Individuals who met at least three of the criteria were identified as frail.

Self-Reported Medical Conditions (Comorbidities) and CVB Medical data (hypertension, diabetes, history of heart disease, arthritis, pulmonary disorders, cancer) and lifetime history of smoking were collected by self-report. CVB was conceptualized in this study as the cumulative burden associated with cerebrovascular risk factors. Past work (Mast, Neufeld, MacNeill, & Lichtenberg, 2004; Mast, Yochim, MacNeil, & Lichtenberg, 2004; Yochim, Mast, & Lichtenberg, 2003) has supported the concept of a threshold effect whereby older adults with two or more risk factors, such as clinically-defined hypertension or cardiac disease, are at higher risk for probable depression. This approach is easily adaptable to large, publically-available databases such as the HRS. Consistent with these studies, respondents with high CVB were those with two or more cerebrovascular risk factors (hypertension, diabetes, cardiac disease, and history of smoking). Hypercholesterolemia was not included because it was not reported in the data at every wave.

Disability ADL disability was measured based on how many of the following activities the respondent reported requiring assistance with: bathing, eating, dressing, walking across a room, and getting in or out of bed. Scores ranged from 0 to 5. Disability related to instrumental activities of daily living (IADLs) was measured by identifying which of the following the respondent required assistance with: using a telephone, taking medication, and handling money. Scores ranged from 0 to 3.

Self-Rated Health Change in self-rated health was assessed with the question, “Compared to your health when we talked with you in [last wave], would you say that your health is better now, about the same, or worse?” Response options were “much better,” “somewhat better,” “same,” “somewhat worse,” and “much worse,” comprising a 5-point scale.

Depressive Symptoms A shortened, 8-item form of the original CES-D was used to evaluate depression (Radloff, 1977). Six of the eight items are negatively worded and two are positively worded. Participants are asked to respond “yes” or “no” to each item (“was depressed,” “everything was an effort,” “sleep was restless,” “was happy,” “felt lonely,” “enjoyed life,” “felt sad,” “could not get going”), based on whether or not they had experienced it during the preceding week. Scores ranged from 0 to 8, with higher scores indicating greater depressive symptoms. Using HRS data, the reliability of the 8-item CES-D measure was adequate, with high Cronbach’s alpha (.81-.83; (Steffick, 2000). The 8-item CES-D is a valid measure of mood (Steffick, 2000) and is broadly used in epidemiological studies of late-life depression (Beekman et al., 1997). Citing the recommended interpretation of this measure (Steffick, 2000), CES-D scores ≥ 3 were interpreted to indicate probable depression.

Vascular Depression Vascular depression is a combination of high vascular burden and probable depression. While past work, as described above, has identified a causal effect of high vascular burden on the subsequent development of depressive symptoms, structure of the available data and theoretical considerations (Alexopoulos et al., 1997b) informed our identification of vascular depression based on the co-occurrence of high CVB and probable depression. Following this rationale, three groups were identified. Participants were identified as having neither high CVB nor probable depression (group 1), either high CVB or probable depression (group 2), or as having vascular depression indicated by both probable depression and high CVB (group 3).

Statistical Methodology

Two chi-square tests of independence were completed to examine and describe the simple bivariate relationship between baseline vascular depression and A) the prevalence of frailty at 2000 and B) the incidence of new frailty in 2004. Our principle analyses use stepwise logistic regression to identify correlates of frailty prevalence at baseline and predictors of frailty incidence (*i.e.*: new cases of frailty) over 4 years. Vascular depression was characterized by the combination of high CVB and probable depression. To test how well vascular depression predicts frailty, this 3-group variable was dummy coded using 2 dummy variables. The first represents respondents with either high CVB or probable depression. The second represents respondents with both high CVB and probable depression. As show in Tables 3 and 4, both groups are contrasted against those respondents with neither high CVB nor probable depression. Complete frailty data were reported in the 2000 and 2004 waves. Data in the 2000 wave were used to identify significant covariates of frailty prevalence at baseline among all available respondents. How these variables predicted the incidence of new frailty in 2004 was assessed by excluding respondents who were frail at the 2000 wave. Complete frailty data were reported in the 2000 and 2004 waves. Data in the 2000 wave were used to assess how variables of interest predicted the prevalence of frailty at baseline among all available respondents. How these variables predicted the incidence of new frailty in 2004 was assessed by excluding respondents who were frail at the 2000 wave.

Results

Of 1,139 respondents living at the 2000 data collection, 992 respondents completed baseline survey materials at the 2000 baseline, and complete data were available for 984 of these respondents. These 984 respondents were included in the logistic regression identifying significant correlates of frailty prevalence described below. Of these, 310 were frail in 2000 (prevalence=31.5%) and were excluded from the second logistic regres-

sion model that predicted incidence of frailty. Of the remaining 674 respondents, 491 were still living in 2004 and complete data were available for 459 respondents. The second logistic regression included these 459 respondents. As shown in Table 1, the sample had a mean age at baseline (Year 2000) of 84.53 years ($SD=3.03$) and 11.24 mean years of education ($SD=3.13$).

Table 1 Description of baseline (2000 wave) characteristics and percentages of frail participants at 2000 and 2004 waves for both the prevalence ($n=984$) and incidence ($n=459$) samples

Variable	Prevalence (N=984)	Incidence (N=459)
	Mean (SD)	Mean (SD)
Age	85.62 (3.82)	84.53 (3.03)
Education	11.02 (3.44)	11.24 (3.13)
ADLs	.64 (1.12)	0.24 (0.69)
IADLs	.21 (.55)	0.10 (0.38)
2000 CES-D	2.07 (1.98)	1.55 (1.70)
	% of Sample	% of Sample
Ethnicity		
White	79.6	80.2
Black	14.3	12.4
Latina	5.3	6.1
Other	1	1.5
CV Risk Factors		
Hypertension	57.6	52.9
Diabetes	11.5	7
Cardiac	34.8	25.1
Smoking	34.9	34.9
Number of CV Risk Factors		
0	16.7	21.8
1	41.2	44.9
2	30.3	25.5
3	10.6	7.4
4	1.3	0.4
Non-CV Health		
Arthritis	69.6	59.3
Pulmonary	7.2	4.8
Cancer	14.8	14.6
2000 CVB (% High)	42.2	33.3
2000 CES-D (%High)	32.8	22
2000 % Frail	31.5	0.0
2004 % Frail	N/A	31.8

The sample was predominantly White, and most respondents remained independent at baseline, as suggested by the relatively low levels of ADL and IALD impairment. Of the 984 respondents included in the 2000 prevalence analysis, 32.8% had CES-D scores of at least 3—suggesting

probable depression—and the mean CES-D score was 2.07 ($SD=1.98$). Of the 459 respondents included in the 2004 incidence analysis, 22% had CES-D scores at the 2000 data collection that suggested probable depression; the mean 2000 CES-D score was 1.55 ($SD=1.70$).

Over the 4-year course of the study, the incidence of frailty was 31.8% ($n = 146$). Table 2 displays prevalence rates in 2000 (all available respondents who met inclusion criteria) and frailty incidence rates in 2004 (excluding any respondents who were frail in 2000) among respondents at each level of the vascular depression variable. As can be seen in Table 2, frailty was most common among those with vascular depression. Indeed, when compared to those with either depression alone or vascular burden alone, those with vascular depression were significantly more likely to be frail, both at baseline ($X^2=13.59$, $p<.001$) and four years later ($X^2=5.77$, $p=.02$). Interestingly, those with either depression or vascular burden were more likely than those without either to be frail both at baseline ($X^2=22.49$, $p<.001$) and four years later ($X^2=5.55$, $p=.02$).

Table 2 Number of prevalence-sample and incidence-sample respondents and frequencies of frailty by vascular depression group: Participants without high CVB or probable depression (CES-D score ≥ 3), with high CVB or probable depression, and with both high CVB and probable depression.

	2000 Prevalence		
	<i>n</i>	# Frail	% Frail
Low CVB, Low CES-D	413	83	20.1%
High CVB or High CES-D	404	141	34.9%
High CVB, High CES-D	167	86	51.5%
	2004 Incidence		
	<i>n</i>	# Frail	% Frail
Low CVB, Low CES-D	248	62	25.0%
High CVB or High CES-D	168	60	35.7%
High CVB, High CES-D	43	24	55.8%

Results of the first step-wise logistic regression describing frailty prevalence in 2000 are displayed in Table 3. At the 2000 wave, 31.5% of the sample was identified as frail. Age, education, ADLs, IADLs, arthritis, pulmonary disorders, cancer, and self-reported health change in 2000 were included in the first step of the model. In this first step, significant correlates of frailty prevalence included age ($\beta=.06$, $Wald=9.11$, $p=.003$), ADLs ($\beta=.641$, $Wald=57.89$, $p<.001$), arthritis ($\beta=1.09$, $Wald=30.47$, $p<.001$), and change in self-rated health ($\beta=.46$, $Wald=20.91$, $p<.001$). The addition of the vascular depression variable substantially improved the model ($X^2=13.40$, $p<.001$). In the final prevalence

model, significant correlates of prevalent frailty included age ($\beta=.06$, $Wald=9.42$, $p=.002$), ADL disability ($\beta=.60$, $Wald=49.70$, $p<.001$), arthritis ($\beta=1.05$, $Wald=27.86$, $p<.001$), self-rated health change ($\beta=.39$, $Wald=14.63$, $p=.001$), and vascular depression dummy variables representing both participants with either high CVB or probable depression ($\beta=.46$, $Wald=6.48$, $p=.01$) and participants with both high CVB and probable depression ($\beta=.80$, $Wald=12.16$, $p<.001$). This model had a sensitivity of .451 and specificity of .914. Positive predictive value (PPV) was .707 and negative predictive value (NPV) was .784. The incremental validity using the PPV was .392 and .099 using the NPV.

Table 3 Results of logistic regression predicting frailty in 2000 ($N=984$).

	Step 1				Step 2			
	β	SE	Wald	95% CI	β	SE	Wald	95% CI
Age	.06	.02	9.11**	1.02-1.11	.06	.02	9.42**	1.02-1.11
Education	.02	.02	.97	.98-1.07	.03	.02	2.11	.99-1.08
ADLs	.64	.08	57.89***	1.61-2.24	.60	.09	49.69***	1.54-2.16
IADLs	-.02	.16	.02	.72-1.33	-.02	.16	.02	.72-1.33
Arthritis	1.09	.20	30.47***	2.02-4.40	1.05	.20	27.85***	1.93-4.22
Pulmonary	.41	.28	2.16	.87-2.62	.40	.28	2.05	.86-2.60
Cancer	.34	.21	2.62	.93-2.14	.33	.22	2.37	.91-2.12
S-R Health Δ	.46	.10	20.91***	1.30-1.93	.39	.10	14.63***	1.21-1.80
Vasc Dep D1					.45	.18	6.48*	1.11-2.24
Vasc Dep D2					.80	.23	12.16***	1.42-3.50
Constant	-9.26	1.84	25.25		-9.52	1.85	26.62	

* $p\leq.05$; ** $p\leq.01$; *** $p\leq.001$; S-R Hlth Δ =Self-rated health change; ADLs=Activities of Daily Living; IADLs=Instrumental Activities of Daily Living; Vasc Dep D1: Respondents with either high CVB or CES-D scores ≥ 3 ; Vasc Dep D2: Respondents with high CVB or CES-D scores ≥ 3 scored 1, respondents with both high CVB and CES-D scores ≥ 3 scored 2.

Results of the second step-wise logistic regression describing frailty incidence in 2004 are displayed in Table 4. Variables were entered in the same manner as the first logistic regression. In the first step of the logistic regression, only ADLs ($\beta=.50$, $Wald=7.85$, $p\leq.01$) and self-reported health change ($\beta=.69$, $Wald=15.89$, $p\leq.001$) significantly predicted incidence of frailty in 2004. In the second step, the addition of the vascular depression variable significantly

improved the overall model ($X^2=9.28$, $p=.01$). In this final model, frailty incidence was predicted by ADLs ($\beta=.49$, $Wald=7.22$, $p\leq.01$) and self-rated health change ($\beta=.65$, $Wald=13.41$, $p\leq.001$). The first vascular depression dummy variable, representing participants with either high CVB or probable depression, showed a trend toward significance ($\beta=.43$, $Wald=3.48$, $p=.06$). The second vascular depression dummy variable, representing respondents with both high CVB and

probable depression, significantly predicted frailty incidence in 2004 ($\beta=1.04$, $Wald=8.07$, $p=.004$). Participants who were non-frail in 2000 but had both high CVB and probable depression were 2.84 times as likely to develop frailty in comparison to those with neither vascu-

lar depression symptom. This second model had low sensitivity (.27) but high specificity (.95), and both good PPV (.70) and NPV (.73). This model had incremental validity of .378 using the PPV and .053 using the NPV.

Table 4 Results of logistic regression predicting frailty in 2004 ($N=459$).

	Step 1				Step 2			
	β	SE	Wald	95% CI	β	SE	Wald	95% CI
Age	.05	.03	1.96	.98-1.12	.05	.03	2.04	.98-1.12
Education	-.03	.03	.75	.91-1.04	-.02	.03	.43	.91-1.05
ADLs	.50	.18	7.85*	1.16-2.36	.49	.18	7.22*	1.14-2.32
IADLs	.45	.32	1.95	.83-2.93	.43	.32	1.82	.82-2.85
Arthritis	.38	.22	2.99	.95-2.25	.33	.22	2.20	.90-2.16
Pulmonary	-.74	.55	1.76	.16-1.42	-.56	.56	1.03	.19-1.70
Cancer	.23	.29	.63	.71-2.23	.18	.30	.38	.67-2.15
S-R Health Δ	.69	.17	15.89***	1.42-2.81	.65	.18	13.41***	1.35-2.70
Vasc Dep D1					.43	.23	3.48*	.98-2.40
Vasc Dep D2					1.04	.37	8.07**	1.38-5.84
Constant	-7.08	2.99	5.62		-7.35	3.01	5.95	

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$; + $p = .06$ S-R Hlth Δ =Self-rated health change; ADLs=Activities of Daily Living; IADLs=Instrumental Activities of Daily Living; Vasc Dep D1: Respondents with either high CVB or CES-D scores ≥ 3 ; Vasc Dep D2: Respondents with high CVB or CES-D scores ≥ 3 scored 1, respondents with both high CVB and CES-D scores ≥ 3 scored 2.

A follow-up analysis was run in which the first dummy variable, formerly representing respondents with either high CVB or probable depression, was separated into two dummy variables, one reflecting probable depression only, and the other reflecting high CVB only. With regards to significant correlates of prevalent frailty, there was a trend for high CVB only ($\beta=.34$, $Wald=2.87$, $p=.09$). Probable depression alone was a significant correlate of prevalent frailty ($\beta=.62$, $Wald=7.35$, $p=.007$). Nevertheless, the dummy variable representing respondents with both high CVB and probable depression remained a robust correlate of frailty ($\beta=.81$, $Wald=12.53$, $p<.001$). A second follow-up logistic regression identified significant predictors of incident frailty using this same analytic strategy. It was found that neither high CVB alone ($\beta=.33$, $Wald=1.58$, $p=.21$) nor probable depres-

sion alone significantly predicted incident frailty, although there was a trend for probable depression alone ($\beta=.60$, $Wald=3.50$, $p=.06$). As in the primary analysis, incident frailty was again predicted by the dummy variable representing individuals with both high CVB and probable depression ($\beta=1.04$, $Wald=8.06$, $p=.005$).

DISCUSSION

Our first finding is that the prevalence of frailty in this demographically representative sample of stroke-free women over the age of 80 was 31.5%. Of the respondents who were not frail at baseline, the incidence of frailty after 4 years was 31.8%. The second finding was that vascular depression—characterized as the co-occurrence of high CVB and clinically significant depression symp-

toms— was a significant correlate of prevalent frailty and a significant predictor of incident frailty in a sample of women over 80. Importantly, those with vascular depression had significantly higher rates of frailty than either those with depression alone or vascular burden alone. The prevalence and incidence estimates are generally consistent with other estimates of frailty frequency in this demographic. For instance, Fried (2001) reported frailty rates of 16.3% for respondents aged between 80 and 84 years, and 25.7% for those between 85 and 89 years. Walston et al. (2002) reported that 32% of participants age 90 and older were frail. Katz (2004) predicted that depression precedes frailty in late life. Our findings support this hypothesis and build on Katz's work by demonstrating that a specific subtype of depression (i.e., vascular depression) is a better predictor of new-onset frailty.

In addition to vascular depression, ADL disability, based on Fried's conceptualization, was a significant predictor of frailty onset. Fried et al. (2004) distinguished the concepts of comorbidity, disability, and frailty, while noting that in aging populations, these syndromes often overlap. The present findings support this conceptualization and extend the model by suggesting that certain combinations of comorbidity and disability have a temporal ordering with frailty. For instance, frailty was extremely uncommon among those without ADL disability and vascular depression.

One possible interpretation of these results is that frailty may be better predicted by chronicity of depression. Post-hoc analyses were conducted to examine the relationship of chronic depression symptoms with frailty across a 4-year period. It was found that of the 44 respondents who were non-frail at 2000 and had probable depression at both the 2000 and 2004 waves, 41% developed frailty. This chronic depression group had a similar incidence of frailty to the group with probable depression, but not high vascular burden (also 41%), and less frailty than the vascular depression group (55%). Thus, the data do not support this alternative interpretation.

The primary limitation of the study is the use of self-reported health data and lack of clinical evaluations for depression. However, this prac-

tice is common in population-based samples, and adequate agreement between self-reports of disease and medical chart reviews has been reported (Bush, Miller, Golden, & Hale, 1989; Psaty et al., 1995). Use of clinically-defined cerebrovascular risk factors precludes analysis of how severity of a disorder such as diabetes may predict depression symptoms. Future research using continuous measures of blood pressure or blood sugars may further elucidate these relationships. A second limitation of this analysis is that the high rate of mortality in this sample resulted in listwise deletion of the most medically vulnerable elders. Consequently, it is probable that these findings underestimate the strength of the relationship between disability, vascular depression, and frailty. Our approach to measuring vascular depression could be viewed as both a strength and a weakness—yet it facilitates analysis of how concomitant vascular burden and probable depression predict the development of frailty. Because we know of no other studies using this strategy, integration of these findings with other work is not possible at this time. Future research may explore how vascular depression and frailty relate to longevity among the older-old. Another limitation of this study is that performance on measures of executive functioning is likely predictive of frailty, but cognition is not represented in these analyses. Unfortunately, the HRS data does not include robust measures of executive functioning, and this analysis was not possible. Future research should further explore relationships between cognitive functioning and frailty.

The CES-D cutoff used in this study was recommended by Steffick (2000) as indicative of probable depression. The 8-item CES-D cutoff score of 3 yielded a higher rate of probable depression (32.8% in the incidence sample and 22% in the prevalence sample) than is found in most other samples. A more conservative cutoff score of 5 can be used, which yields a probable depression rate of 14%. Neither cutoff score, however, is a clinically determined diagnosis of depression. More important is the sensitivity of vascular depression to incident frailty. For instance, Haynie, Berg, Johansson, Gatz and Zarit (2001) reported a rate of 18.9% using a longer form of the CES-

D in a sample of similar age to that in this study, and a survey of community-dwelling Dutch adults over the age of 75 of 31.1% had scores exceeding the clinical cutoff using the CES-D (van't Veer-Tazelaar et al., 2008).

The findings of this study significantly extend our understanding of the impact of vascular depression as a pathway to frailty. As medical practice with older patients trends toward collaborative care, depression is emerging as a critical clinical indicator of decline in medical functioning. While vascular depression is conceptualized as having a neurological basis, some have described empirically supported interventions for this syndrome (Alexopoulos et al., 2011; Mackin & Arean, 2005), suggesting that vascular depression may be a modifiable risk factor for frailty, even in late life. Other interventions suggested by these findings include addressing CVB much earlier, thereby reducing the deleterious effects of hypertension, diabetes, and cardiac disease.

ACKNOWLEDGEMENTS

This work was generously supported by the Blue Cross Blue Shield of Michigan Foundation and by the T32 grant-supported NIH Pre-Doctoral Training Program in Aging and Urban Health at the Institute of Gerontology (T-32 AG00275-06).

REFERENCES

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997a). Clinically defined vascular depression. *American Journal of Psychiatry*, 54(4), 562-565.

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997b). 'Vascular depression' hypothesis. *Archives of General Psychiatry*, 54(10), 915-922.

Alexopoulos, G. S., Raue, P. J., Kiosses, D. N., Mackin, R. S., Kanellopoulos, D., McCulloch, C., & Arean, P. A. (2011). Problem-solving therapy and supportive therapy in older adults with major depres-

sion and executive dysfunction: Effect on disability. *Archives of General Psychiatry*, 68(1), 33-41.

Andrew, M. K., & Rockwood, K. (2007). Psychiatric illness in relation to frailty in community-dwelling elderly people without dementia: A report from the canadian study of health and aging. *Canadian Journal on Aging*, 26(1), 33-38. doi: 8774758W702Q2531 [pii]

Barzilay, J. I., Blaum, C., Moore, T., Xue, Q. L., Hirsch, C. H., Walston, J. D., & Fried, L. P. (2007). Insulin resistance and inflammation as precursors of frailty. *Archives of Internal Medicine*, 167, 635-641.

Beekman, A. T. F., Deeg, D. J. H., Van Limbeek, J., Braam, A. W., De Vries, M. Z., & Van Tilburg, W. (1997). Criterion validity of the center for epidemiologic studies depression scale (ces-d): Results from a community-based sample of older subjects in the netherlands. *Psychological Medicine*, 27(1), 231-235.

Bush, T. L., Miller, S. R., Golden, A. L., & Hale, W. E. (1989). Self-report and medical record report agreement of selected medical conditions in the elderly. *American Journal of Public Health*, 79, 1554-1556.

Clegg, A. (2011). The frailty syndrome. *Clinical Medicine*, 11(1), 72-75.

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure and Function*, 213, 93-118.

Fassbender, K., Fainsinger, R. L., Carson, M., & Finegan, B. A. (2009). Cost trajectories at the end of life: The canadian experience. *Journal of Pain and Symptom Management*, 38(1), 75-80.

Fried, L. P. (2003). Frailty. In C. Cassel, R. Leipzig, H. J. Cohen, E. B. Larson & D. Meier (Eds.), *Geriatric medicine: An evidence-based approach* (4th ed., pp. 1067-1074). New York: Springer-Verlag.

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *Journals of Gerontology*.

Series A, Biological Sciences and Medical Sciences, 59(3), 255-263.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., ... McBurnie, M. A. (2001). Frailty in older adults: Evidence for a phenotype. *Journal of Gerontology: Medical Sciences*, 56A(3), M146-M156.

Haynie, D. A., Berg, S., Johansson, B., Gatz, M., & Zarit, S. H. (2001). Symptoms of depression in the oldest old: A longitudinal study. *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, 56B(2), P111-P118.

Heeringa, S. G., & Conner, J. (1995). *Technical description of the health and retirement study sample design: Hrs/ahead documentation report dr-002*. Ann Arbor: University of Michigan.

Katz, I. R. (2004). Depression and frailty: The need for multidisciplinary research. *American Journal of Geriatric Psychiatry*, 12(1), 1-6.

Lupon, J., Gonzalez, B., Santa Eugenia, S., Altimir, S., Urrutia, A., Mas, D., ... Valle, V. (2008). Prognostic implication of frailty and depressive symptoms in an outpatient population with heart failure. *Revista Espanola Cardiologia*, 61(8), 835-842. doi: 13124994 [pii]

Lyness, J. M., Caine, E. D., King, D. A., Conwell, Y., Cox, C., & Duberstein, P. R. (1999). Cerebrovascular risk factors and depression in older primary care patients: Testing a vascular brain disease model of depression. *American Journal of Geriatric Psychiatry*, 7(3), 252-258.

Mackin, R. S., & Arean, P. A. (2005). Evidence-based psychotherapeutic interventions for geriatric depression. *Psychiatric Clinics of North America*, 28, 805-820.

Mast, B. T., Miles, T., Penninx, B. W., Yaffe, K., Rosano, C., Satterfield, S., ... Simonsick, E. M. (2008). Vascular disease and future risk of depressive symptomatology in older adults: Findings from the health, aging, and body composition study. *Biological Psychiatry*, 64(4), 320-326. doi: S0006-3223(08)00169-8 [pii] 10.1016/j.biopsych.2008.01.025

Mast, B. T., Neufeld, S., MacNeill, S. E., & Lichtenberg, P. A. (2004). Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *American Journal of Geriatric Psychiatry*, 12(1), 93-101.

Mast, B. T., Yochim, B., MacNeil, S. E., & Lichtenberg, P. A. (2004). Risk factors for geriatric depression: The importance of executive functioning within the vascular depression hypothesis. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 59A(12), 1290-1294.

Montero-Odasso, M., Muir, S. W., Hall, M., Doherty, T. J., Kloosek, M., Beauchet, O., & Speechley, M. (2011). Gait variability is associated with frailty in community-dwelling older adults. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 66A(5), 568-576.

National Center for Health Statistics. (2010). *Health, united states, 2010: With special feature on death and dying*. Hyattsville, MD.

Newman, A. B., Gottdiener, J. S., McBurnie, M. A., Hirsch, C. H., Kop, W. J., Tracy, R., ... Fried, L. P. (2011). Associations of subcortical cardiovascular disease with frailty. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 56A(3), M158-M166.

Paulson, D., Bowen, M. E., & Lichtenberg, P. A. (2011). Successful aging and longevity in older old women: The role of depression and cognition. *Journal of Aging Research*, 2011(2011). doi: 10.4061/2011/912680

Paulson, D., Bowen, M. E., & Lichtenberg, P. A. (under review). Does brain reserve protect older women from vascular depression?

Paulson, D., & Lichtenberg, P. A. (2011). *Late-life depression is a prodrome for frailty*. Paper presented at the 64th Annual Meeting of the Gerontological Society of America, Boston, MA.

Paulson, D., & Lichtenberg, P. A. (2012). *The paulson-lichtenberg frailty index: Construct validity for a self-report measure of frailty*. Wayne State University, Detroit, MI.

Paulson, D., & Lichtenberg, P. A. (Under Review). Vascular depression and frailty: A compound threat to longevity.

Penninx, B. W., Leveille, S., Ferrucci, L., van Eijk, J. T. M., & Guralnik, J. M. (1999). Exploring the effect of depression on physical disability: Longitudinal evidence from the established populations for epidemiologic studies of the elderly. *American Journal of Public Health*, 89, 1346-1352.

Psaty, B. M., Kuller, L. H., Bild, D., Burke, G. L., Kittner, S. J., Mittelmark, M., ... Robbins, J. (1995). Methods of assessing prevalent cardiovascular disease in the cardiovascular health study. *Annals of Epidemiology*, 5(4), 255-335.

Radloff, L. (1977). The ces-d scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, 1, 385-401.

Rainer, M. K., Mucke, H., Zehetmayer, S., Krampla, W., Kuselbauer, T., Weissgram, S., ... Fischer, P. (2006). Data from the vita study do not support the concept of vascular depression. *American Journal of Geriatric Psychiatry*, 14(6), 531-537.

Rantanen, T., Penninx, B. W., Masaki, K., Lintunen, T., Foley, D., & Guralnik, J. M. (2000). Depressed mood and body mass index as predictors of muscle strength decline in old men. *J Am Geriatr Soc*, 48(6), 613-617.

Rosso, A. L., Eaton, C. B., Wallace, R., Gold, R., Curb, J. D., Stefanick, M. L., ... Michael, Y. L. (2011). Combined impact of geriatric syndromes and cardiometabolic diseases on measures of functional impairment. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 66A(3), 349-354.

Sneed, J. R., Rindskopf, D., Steffens, D. C., Krishnan, K. R., & Roose, S. P. (2008). The vascular depression subtype: Evidence of internal validity. *Biological Psychiatry*, 64(6), 491-497. doi: S0006-3223(08)00403-4 [pii]
10.1016/j.biopsych.2008.03.032

Steffick, D. E. (2000). *Documentation of affective functioning measures in the health and retirement*

study. Hrs documentation report dr-005. Ann Arbor: Survey Research Center at the Institute for Social Research.

Thomas, P., Hazif-Thomas, C., Billon, R., Peix, R., Faugeron, P., & Clement, J. P. (2009). Depression and frontal dysfunction: Risks for the elderly? *L'Encephale*, 35(4), 361-369.

van't Veer-Tazelaar, P., van Marwijk, H. W. J., Jansen, A. P. D., Rijmen, F., Kostense, P. J., van Oppen, P., ... Beekman, A. T. F. (2008). Depression in old age (75+), the piko study. *Journal of Affective Disorders*, 106(3), 295-299.

Varadhan, R., Chaves, P. H. M., Lipsitz, L. A., Stein, P. K., Tian, J., Windham, B. G., ... Fried, L. P. (2009). Frailty and impaired cardiac autonomic control: New insights from principal components aggregation of traditional heart rate variability indices. *Journal of Gerontology: Medical Sciences*, 64A(6), 682-687.

Walston, J., McBurnie, M. A., Newman, A., Tracy, R. P., Kop, W. J., Hirsch, C. H., ... Fried, L. P. (2002). Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities. *Archives of Internal Medicine*, 162(20), 2333-2341.

Yochim, B., Mast, B. T., & Lichtenberg, P. A. (2003). Cerebrovascular risk factors and depressed mood in inner city older adults. *Clinical Psychologist*, 7(1), 11-20.