1.a. Full Title:
Association of Depression with Neuroimaging Markers of Brain Vascular Disease: The Atherosclerosis Risk in Communities Study

1.b. Abbreviated Title (Length 26 characters):
Depression and Brain Imaging

2. Writing Group: Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. EAF [please confirm with your initials electronically or in writing]

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3. Timeline:
The visit 5 brain MRI data, and DTI data are now available along with depression scores; we plan to use for a Capstone MPH project with submission in April 2015, with subsequent plans to
submit as an abstract to a national conference (American Neurological Association), with publication within 3-6 months after that.

4. Rationale:

Depression affects approximately 7 million U.S. adults over 65, and is associated with increased risk of morbidity, suicide, physical, social, and cognitive decline, self-neglect, and mortality with 16% of all suicides occurring in this population (8). Patients with depression and chronic illness incur significantly more healthcare costs than those with chronic illness alone (1). There is a well-established link between depression, stroke, diabetes, and cardiovascular atherosclerotic disease (2, 24, 26). Depression is associated with increased risk for re-hospitalization and slower recovery in medically ill patients and increased morbidity and disability in patients with cardiovascular disease (25). Though most analyses of the societal burden of depression do not consider depression based on age of onset, there is growing scientific consensus around the separate clinical identities of early- and late-onset depression as unique conditions with different underlying risk factors, neuroimaging findings, genetic factors, and demographics. Thus, it may be more appropriate to consider the public health and cost burdens of depression in separate groups based on age of onset in future studies (8). Early onset depression (EOD) and late onset depression (LOD) are generally defined as depression diagnosed before and after age 65, respectively (17). EOD has been shown to be more strongly tied to familial inheritance, while late onset depression (LOD) is recognized to have additional major causal factors outside of genetic susceptibility, including subcortical cerebral ischemia (6,9). The pathogenesis of LOD is thought to be multifactorial, but vascular factors likely play an important role in etiology and prognosis of geriatric depression (7). The terms, “vascular depression” and “subcortical ischemic depression” have been specifically defined as: (1) LOD or change in course of EOD after age 65; (2) persistent symptoms; and (3) association of depression with cardiovascular disease, risk factors, or clinical and/or neuroimaging signs of cerebrovascular disease including subcortical hyperintensities or white matter lesions (WML) (17). WMLs are a neuropathological classification for multiple histologic changes, including demyelination, lacunar infarcts, pallor, astrogliosis, amyloid angiopathy, while subcortical hyperintensities or leukoaraiosis refers to the neuroimaging correlate for ischemic vascular changes (4). In prior studies, subcortical hyperintensities have been associated with psychomotor slowing, negative family history of depression, function impairment, and other forms of cognitive impairment (27). It is estimated that 54% of patients with LOD meet criteria for vascular depression (3). This study will primarily focus on LOD in the ARIC study.

Brain imaging studies have the potential to elucidate the pathogenesis of vascular depression, while providing insight into potential treatment options, as initial studies have shown vascular depression is more refractory to treatment than EOD (4). Furthermore, lower fractional anisotropy on DTI in key neural white matter circuits thought to be implicated in LOD has been associated with poor antidepressant response (15). Age and hypertension have been shown to be positively correlated with subcortical hyperintensities (SH), though additional research is needed to establish the relationship between SH and other cardiovascular risk factors in community dwelling geriatric individuals with and without depression (7). Several theories exist for explaining the link between depression and vascular disease including, but not limited to: i.) increased platelet aggregation, ii.) that both depression and ischemia are linked to atherosclerosis, iii.) recurrent depression over the lifetime may increase the risk for
cerebrovascular disease, and iv.) damage to end arteries in the subcortical striato-pallido-thalamo-cortical pathways may disrupt existing neurotransmitter circuits involved in regulation of mood, which may either cause or predispose to depression (6). Multiple studies of neuroanatomic correlations of WMLs on brain imaging have attempted to define areas that may be implicated in vascular depression. White matter lesions in key frontal and prefrontal cortical pathways including the medial orbitofrontal cortex (mood lability and inhibition), the anterior cingulate circuit (apathy), and the dorsolateral prefrontal cortex (executive dysfunction) have shown significant correlation with depression in the elderly (7, 10). Lesions in the thalamus and basal ganglia have also been implicated in geriatric depression, and it is thought that silent cerebral infarction may play a role in late onset depression (9,11). It is important to note that late onset depression is recognized as a distinct entity from post-stroke depression (PSD), whereby PSD is less likely to present with dysphoria and more often includes vegetative symptoms, though the two may be related through the role of chronic vascular changes in the form of WMLs and lacunae in the basal and thalamic ganglions (4, 7, 16, 17, 19). Patients with subcortical lacunae and WMLs were more likely to be depressed, both before and after stroke, in comparison with patients with other types of stroke and are more likely to develop major executive dysfunction (12).

Based on current research, the presence of subcortical hyperintensities and cardiovascular risk factors do not predict response to treatment (9, 13). There is need for further research in this area, especially given the high disease burden, and current lack of consensus over the location and size of lesions most strongly correlated with LOD, the underlying causes of LOD as a unique entity, and the need for improved treatment options (5). A recently published meta-analysis of voxel-based DTI studies in patients with depression identified four areas consistently associated with decreased fractional anisotropy: right frontal lobe white matter, right fusiform gyrus, left frontal lobe and right occipital lobe. The right inferior longitudinal fasciculus, right inferior fronto-occipital fasciculus, right posterior thalamic radiation, and the interhemispheric fibres of the genu and body of the corpus callosum were the major fiber fascicles with potential implication in depression, providing compelling evidence for the role of these white matter tracts connecting the prefrontal cortex with key cortical and subcortical areas in depression (14). Additionally, Boccia, et. al recently published a coordinate-based meta-analysis to compare gray matter changes in Alzheimer's disease (AD) and late-life depression (LLD) and found reduced bilateral hippocampal volume in both, but AD was more strongly correlated with atrophy in the left anterior hippocampus and bilateral posterior cingulate cortex, while LOD was correlated with greater atrophy in the precuneus, superior frontal gyrus, and ventromedial frontal gyrus (27). Increased risk for development of LOD was found to be associated with degree of severity of WMHs among APOE-ɛ4 carriers in comparison with APOE-ɛ4 non-carriers (18). There is overall lack of agreement in the literature about the association of hippocampal atrophy with LOD and how this relationship relates to presence of Alzheimer’s disease and APOE- ɛ4 status (6). To our knowledge, researchers have not yet looked at the burden of depression specifically associated with microhemorrhages or cerebral amyloid angiopathy in the key brain regions, which may provide additional support for neuroanatomical correlation of these regions with LOD.

Late-life depression is also associated with an increased risk for all-cause dementia, vascular dementia, and Alzheimer’s disease. Specifically, one study found patients with LOD had a two-
fold increase in risk for Alzheimer’s disease and a three-fold risk for developing vascular dementia, suggesting that LOD may be an important predictor of increased risk for development of dementia (20), although the potential mechanism of this association is not well understood; it is possible that differences in brain volume and structure might mediate these associations. However, there is also high co-morbid incidence of LOD among patients with diagnosis of dementia, thus depression is thought to be both on the prodromal pathway to development of dementia as well as a co-morbid burden associated with existing dementia (26). Additional research is needed to investigate the effect of late-life depression prevention on risk of dementia, in particular vascular dementia and Alzheimer’s disease and to clarify the relationship between depression and dementia (21). This is one major limitation when analyzing the current body of literature in LOD and cerebrovascular disease and/or neuroimaging findings in brain regions implicated in LOD, as some researchers have not considered the co-morbid presence of MCI and dementia, though dementia has been implicated both as a risk factor and cause of depression (8). Cognitive status may therefore both be a confounder of a depression/brain imaging association, but also potentially may be a consequence of depression and any resultant brain imaging changes. The need to consider cognitive status both ways, and to include control for this and other potential confounding variables should be an important consideration in studies moving forward to more accurately assess the direct link between cerebrovascular disease, neuroimaging correlates, and LOD.

Of note, a prior Atherosclerosis Risk in Communities Study examined the cross-sectional relationship between cognitive function and depression in over 14,000 middle-aged adults in 1990-1992. The battery included the Delayed Word Recall test, the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised, and the Controlled Oral Word Association (Word Fluency) test. After controlling for race and community factors, depression was found to be associated with worse scores on the Delayed Word Recall and the Digit Symbol Subtest across both sexes. However, in this study, cognitive function testing was conducted in middle-age, while our study is most interested in dementia, depression, and neuroimaging changes among older individuals (23).

Another important limitation is the different tools and clinical measures used to diagnose depression and inconsistent definitions and nomenclature for WMHs across studies (15). The 2013 STRIVE study recently attempted to standardized reporting of vascular changes on neuroimaging (STRIVE) to improve cross-study comparison (15). Based on the STRIVE recommendations, WMHs are defined as cortical hyperintensities on T2-weighted images without cavitation, separate from recent small subcortical infarcts, which are defined as neuroimaging evidence of recent infarction in the territory of one arteriole with imaging or clinical characteristics of a lesion in the past few weeks. Lacunar infarcts are defined in STRIVE as fluid-filled, round/ovoid, subcortical lesions between 3 mm and 15 mm in diameter. Notably, lacunar infarcts are defined as falling between 3 and 20 mm in diameter for the ARIC study, and for consistency, we plan to use this definition. Microbleeds are defined as small (generally 2-5 mm) areas of signal void on T2*-weighted images (15). Although brain volumes and atrophy are not considered pathognomonic for vascular disease of the brain, and are likely multifactorial, the STRIVE guidelines also include atrophy as a marker of brain vascular disease not related to specific macrovascular injury such as trauma or infarction, supporting the importance of
evaluating its association with vascular disease.

In order to comprehensively characterize the relationship of depression status with brain MRI findings, and particularly microvascular MRI findings, as well as neurodegenerative findings as are typically seen with Alzheimer’s (measured by brain MRI (brain volumes)), we propose to examine the association between depression status (defined by score of >8 on the CES-D assessment during the 2011-2013 time period (ARIC-NCS)), and late-life brain MRI findings (2011-2013; ARIC-NCS) including measures of brain volume (total as well as regional volumes) as well as vascular lesions (WMH volume, number of infarcts, number of microbleeds, and DTI findings) in the Atherosclerosis Risk in Communities (ARIC) Study. We further hypothesize that injury (whether vascular or neurodegenerative (i.e. volume loss/atrophy)) to certain regions of the brain on MRI imaging will be more positively associated with depression. In secondary analyses, we will consider the subset of participants with an earlier measure of depression, from the Brain MRI or Carotid MRI ancillary study, to look at approximate age of onset of depression (to compare EOD to LOD), and will also evaluate earlier proxies to depression, including vital exhaustion, from visit 2.

5. Hypothesis/Study Questions:
Main Hypothesis: Depression status defined over the years of 2011 to 2013 will be positively associated with increased small vessel ischemic disease on MRI, including DTI and microbleeds, and smaller brain volumes, measured on brain MRIs obtained from 2011 to 2013.

Study Hypotheses/Questions:
1. More small vessel ischemic disease will be observed on MRI (including WMH, infarcts, reduced white matter integrity indicated by abnormal DTI measures, and microbleeds) in participants with depression compared to non-depressed subjects (where CES-D will be considered as a continuous predictor in addition to a dichotomized variable with 8 or greater considered “positive.”)
2. Depression will be associated with smaller overall brain volumes among participants in the ARIC study.
3. Depression will be associated with more brain atrophy or vascular disease burden, in the following regions, on brain MRI:
   - Medial orbitofrontal cortex
   - Subcallosal cingulate gyrus
   - Insula
4. The above proposed associations (#1-3) will still be significant among participants without mild cognitive impairment or dementia.
5. Among the subset of participants with CES-D measurement at the Brain MRI visit (2004-2006) or the Carotid MRI visit (2004-2006), time of onset of depression (time 1: positive at both time points (2004-2006 and 2011-2013); versus time 2: negative CES-D at time 1 followed by positive CES-D at time 2) will modify the relationship between depression and MRI changes described above. We hypothesize that participants with earlier onset will have more brain MRI changes than participants with a late onset.
6. We hypothesize that the above relationships will persist after adjustment for demographic characteristics (age, sex, educational level, APOE status, race/center) and vascular risk factors, including hypertension, myocardial infarction, diabetes, smoking status, LDL cholesterol, and
prior history of stroke (defined at ARIC-NCS, although we will explore status at V1 as possible confounders as well).
7. Finally, in a secondary analysis, we hypothesize that vital exhaustion (defined at visit 2/questionnaire) is associated with the same brain volume decreases and vascular lesions as identified in the above stated hypotheses.

Study Design
Cross-sectional analysis of depression status defined over the years of 2011 to 2013 with brain MRI data obtained from 2011 to 2013, with a sub-hypothesis evaluating depression status at a non-concurrent earlier visit (2004-2006) relative to MRI data from 2011 to 2013, and another sub-hypothesis evaluating “vital exhaustion” status in the larger cohort at visit 2 (1990-1992) in relation to MRI data from 2011 to 2013.

Study Population (Inclusion/Exclusion Criteria)
Participants who attended ARIC visit 5 (2011-2013), who were selected for a brain MRI scan, who completed a brain MRI scan of adequate quality, and who completed the depression screening will be eligible for this analysis. A subgroup analysis will be conducted among participants who were also evaluated with CES-D at the 2004-2006 Brain MRI ancillary study. A detailed description of the selection criteria for brain MRI at visit 5 is available in the ARIC Neurocognitive Exam (Stages 2 and 3) Manual 17. Briefly, selection criteria for a brain MRI scan at visit 5 included:
1. Absence of any contraindications to MRI: cardiac pacemaker, defibrillator or valvular prosthesis, histories of meningioma, arachnoid cyst, craniotomy, with resection or radiation therapy involving the skull or brain, or normal pressure hydrocephalus, metal fragments in the eyes, brain or spinal cord, cochlear implant, spinal cord stimulator, or other internal electrical device, permanent eyeliner, or weight >350 pounds.
2. All 2004-2006 ARIC brain MRI or Carotid MRI participants (regardless of their visit 5 cognitive status).
3. All “atypical” participants (goal recruitment n~1,200), defined as either low Mini-Mental State Exam score (visit 5 MMSE <21 for whites and <19 for blacks) or (low visit 5 domain z-scores on 2 or more cognitive domains [domain z-score < -1.5 SD] and definite cognitive decline on the Delayed Word Recall Test, Digit Symbol Substitution Test, Word Fluency Test [defined as current score minus highest prior score <20th percentile on 1 or more tests or <10th percentile on 2 or more tests]).
4. A random sample of “typical” participants (those who did not meet above criteria for “atypical”) (goal recruitment n~800). Sampling fractions were set for participants <80 years and ≥80 years (10% for MN, MD, and MS and 5% in NC to compensate for recruitment of brain MRI study participants).

Brain MRI’s from 2009 were completed as part of ARIC-NCS stage 3. Of those who completed a brain MRI at visit 5, we will additionally exclude any individuals missing covariates included in our statistical models (see below) or with too much motion artifact for reliable measurements of the described brain volumes and lesions.

Exposure: Depression
Our primary exposure will be depression status defined over the years of 2011 to 2013 (and 2004-2006 through 2011-2013 for the secondary analysis including Brain MRI data). Depression
status will be defined by CES-D score; we will evaluate CES-D as a continuous predictor in addition to a dichotomized variable with 8 or greater considered “positive”. In sensitivity analyses, we will consider expanding our definition of depression to include individuals on an antidepressant at the time of ARIC-NCS; this is not part of our primary definition since many people are placed on antidepressants for reasons other than depression. We will also consider mild cognitive impairment and dementia, which was determined by computer algorithm and expert committee using ARIC-NCS data, for the secondary analysis evaluating relationships among persons with normal cognition.

Outcome: Visit 5 Brain MRI Data
A detailed description of the visit 5 brain MRI protocol is available in the ARIC NCS MRI Manual 13. Briefly, visit 5 brain MRI scans (2011-2013) were performed using 3 Tesla scanners (MN: Siemens Trio [vb17 software]; MD: Siemens Verio [vb17 software]; MS: Siemens Skyra [D13 software]; NC: Siemens Skyra [D11 software]. The following sequences were obtained: Localizer, MP-RAGE (1.2 mm slices), Axial T2*GRE (4 mm slices), Axial T2 FLAIR (5 mm slices), Field Mapping (3 mm slices), Axial DTI (2.7 mm slices for Skyra and Verio scanners and 3 mm slices for Trio scanners).

We will investigate the association of depression with the following brain MRI variables:
1. Brain volume (from MP-RAGE)
   - Total brain volume (adjusted for total intracranial volume)
   - Regional brain volumes thought to be associated with LOD (7,9,10,14): (all evaluated in the MRS visit 5 dataset; total volumes to include right + left summed volumes)
     - Medial orbitofrontal cortex
     - Subcallosal cingulate gyrus
     - Insula
2. WMH Volume (from T2 FLAIR)
   - Total WMH volume (adjusted for total intracranial volume)
3. Region WMH volume in areas thought to be associated with LOD
   - Number of Infarcts (from T2 FLAIR)
   - Lacunar
   - Non-lacunar
4. Number and presence of microbleeds (from T2*GRE)
5. DTI data, including regional fractional anisotropy (FA) and apparent diffusion coefficient (ADC)

Covariates
Covariates included in our statistical models include: age (years; continuous), sex (male; female), race/field center (MN whites; MD whites; NC whites; NC blacks; MS blacks), smoking status (current; former; never), myocardial infarction, diabetes status, LDL cholesterol levels, and prior history of stroke (defined at ARIC-NCS) and hypertension (by standard ARIC definition) all at ARIC-NCS, except in secondary analyses with Brain MRI CES-D data (when defined from that visit).
Potential Effect Modifiers
We will formally test for interaction by time of onset (for participants with CES-D measurement at the Brain MRI visit as well as ARIC-NCS) as well as by race, sex, and APOE status (0 versus 1 or 2 ε4 alleles).

Statistical Analysis
All statistical analyses will be performed incorporating sampling weights (derived by the ARIC coordinating center) to account for the visit 5 brain MRI selection process that was designed to oversample cognitively impaired individuals (see above). Incorporating sampling weights is particularly important for this analysis, as cognitive impairment is associated both with depression and with brain MRI findings.

We will tabulate participant characteristics for the overall population and by depression groups as defined above. Participant characteristics will be presented as means for continuous variables and as % for categorical variables; we will use t-tests and chi-square analyses to for univariate comparison of the depressed versus the non-depressed group.

We will use adjusted linear regression models to assess the association of depression status with brain volume (total; regional) and WMH volume, adjusted for total intracranial volume. We may need to transform these volume measurements, so will explore distributions of these data as appropriate. We will use adjusted logistic regression models to evaluate presence/absence of vascular lesions or largest quintile of vascular regions or lowest quintile of brain volumes.

We will perform three statistical models:
- Model 1: adjusted for demographic variables: age, sex, educational level, and race/field center.
- Model 2: adjusted for Model 1 + APOE.
- Model 3: adjusted for Models 1 and 2 + vascular risk factors: smoking status, myocardial infarction, diabetes, LDL cholesterol level, hypertension, and prior history of stroke.

Limitations
Although brain MRIs have now been performed on a subset of ARIC participants at three time points (1993-1995, 2004-2006, 2011-2013), we will not be performing analyses of change in brain MRI variables over time. The brain MRIs performed in 1993-1995 and 2004-2006 were only performed in NC and MS, which would limit the sample size for analyses of change over the three brain MRI scans. Additionally, brain MRIs performed in 1993-1995 and 2004-2006 were performed on 1.5 Tesla scanners, while the brain MRIs performed at visit 5 were performed on 3 Tesla scanners, making comparisons across the three scans more challenging.

Another limitation of this study is that we do not have exact measures of depression duration as we do not have dates of diagnosis or reliable data on age at diagnosis. However, the exact date of any diagnosis for depression is inherently arbitrary, as the pathologic changes have likely existed for many months, if not years, prior to clinical presentation and diagnosis.
Lastly, as with any observational study, we will also not be able to rule out the possibility of residual confounding, and with any cross-sectional study, we can only note associations, but cannot make inferences about temporality or causation.

7.a. Will the data be used for non-CVD analysis in this manuscript?
_____ Yes  __X__ No

7.b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _____ Yes  _____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?
__X__ Yes  No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? __X__ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.csc.unc.edu/ARIC/search.php

__X__ Yes  ____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Neuroimaging:
- Knopman DS¹, Griswold ME², Lirette ST², Gottesman RF², Kantarci K², Sharrett AR², Jack CR Jr², Graff-Radford J², Schneider AL², Windham BG², Coker LH², Albert MS², Mosley TH Jr²; ARIC Neurocognitive Investigators. 2015. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. Stroke. 46 (2): 433-40.
- MSP #2266: Associations Between Brain Vascular Imaging Features and Regional Volumetrics (Graff-Radford/Knopman)
- MSP # 3259: Windham BG, Griswold ME, Shibata D, Penman A, Catellier DJ, Mosley TH. 2012. Covert neurological symptoms associated with silent infarcts from
midlife to older age: the Atherosclerosis Risk in Communities study.. Stroke. 43(5):1218-23.


Depression:

Dementia:

11a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes  No

11b. If yes, is the proposal
   __X__ A. primarily the result of an ancillary study (list number* 2008.06)
   ___  B. primarily based on ARIC data with ancillary data playing a minor role
   (usually control variables; list number(s)* ____  __________ ____________)

*ancillary studies are listed by number at http://www.csc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.
12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscce.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.
REFERENCES


