Published in final edited form as:

Int J Geriatr Psychiatry. 2016 March ; 31(3): 316–322. doi:10.1002/gps.4339.

Amyloid-associated depression and ApoE4 allele: longitudinal follow-up for the development of Alzheimer's disease

Wei Qiao Qiu^{1,2,3}, Haihao Zhu², Michael Dean², Zhiheng Liu^{2,6}, Linh Vu², Guanguang Fan^{2,6}, Huajie Li^{2,7}, Mkaya Mwamburi⁵, David C. Steffens⁸, and Rhoda Au⁴

¹Department of Psychiatry, Boston University, Boston, MA, USA

²Department of Pharmacology and Experimental Therapeutics, Boston University, Boston, MA, USA

³Alzheimer's Disease Center, Boston University, Boston, MA, USA

⁴Department of Neurology, Boston University, Boston, MA, USA

⁵Department of Public Health and Family Medicine, Tufts University, Boston, MA, USA

⁶Departments of Anesthesiology, the Second People's Hospital of Shenzhen, China

⁷Department of Neurology, the First People's Hospital of Chang Zhou, China

⁸Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT, USA

Abstract

Background—Amyloid-associated depression is associated with cognitive impairment cross sectionally. This follow-up study was to determine the relationship between amyloid-associated depression and the development of Alzheimer's disease (AD).

Methods—Two hundred and twenty three subjects who did not have dementia at baseline were given a repeat cognitive evaluation for incident AD. Depression was defined by having a Center for Epidemiological Studies Depression (CES-D) score ≥ 16 , and non-amyloid vs. amyloid-associated depression by having a low vs. high plasma amyloid- β peptide 40 (A β 40)/A β 42 ratio. Apolipoprotein E (ApoE) genotype was determined, and antidepressant usage was documented.

Results—Fifteen subjects developed AD (7%) after an average follow-up time of 6.2 years. While none of those with non-amyloid depression developed AD, 9% of those with amyloid-associated depression developed AD. Further, among those with amyloid-associated depression, ApoE4 carriers tended to have a higher risk of AD than ApoE4 non-carriers (40% vs. 4%, $p=0.06$). In contrast, 8% of those who did not have depression at baseline developed AD, but ApoE4 carriers and non-carriers did not show a difference in the AD risk. After adjusting for age, the interaction between ApoE4 and amyloid-associated depression ($\beta=+0.113$, $SE=0.047$, $P=0.02$) and the interaction between ApoE4 and antidepressant use ($\beta=+0.174$, $SE=0.064$, $P=0.007$) were associated with the AD risk.

Correspondence to: W. Q. Qiu, MD, PhD, wqiu67@bu.edu.

Conflict of interest

None declared.

Conclusions—Amyloid-associated depression may be prodromal depression of AD especially in the presence of ApoE4. Future studies with a larger cohort and a longer follow-up are warranted to further confirm this conclusion.

Keywords

amyloid-associated depression; Alzheimer's disease; apolipoprotein E4 allele (ApoE4)

Introduction

Depression increases the risk or is an early symptom of Alzheimer's disease (AD) in the elderly (Ownby *et al.*, 2006; Saczynski *et al.*, 2010). Late life depression is a clinical syndrome with different subtypes and not all depressed elderly will develop dementia (Steffens *et al.*, 1997; Dal Forno *et al.*, 2005). Thus, it is important for clinical practice to identify depression subtypes that are predictive of the onset of AD. Our cross-sectional study showed that depression with a high amyloid- β peptide 40 (A β 40)/A β 42 ratio determined by high A β 40 and low A β 42 in plasma is associated with cognitive impairment, especially memory domain, suggesting a distinct depression subtype, which we have termed "amyloid-associated depression" (Sun *et al.*, 2008). Yet, the longitudinal relationship between amyloid-associated depression and AD has not been previously determined.

Plasma A β 42 declines significantly at a pre-clinical or early stage of AD (Pomara *et al.*, 2005), suggesting a biomarker for a prodrome of the disease. In Amyloid Precursor Protein (APP) transgenic mice, plasma A β 42 declines significantly before the formation of AD pathology in the brain (Kawarabayashi *et al.*, 2001; DeMattos *et al.*, 2002). Elevated plasma A β 40 is correlated with cerebral microvascular pathology, which is linked with both late life depression and AD (van Dijk *et al.*, 2004; Gurol *et al.*, 2006). Thus, it is possible that the combination of high A β 40 and low A β 42 in plasma can be utilized as a biomarker of pathological change in the brain to determine prodromal depression of AD. The Apolipoprotein E4 (ApoE4) allele is the major genetic risk factor of late-onset AD (Strittmatter *et al.*, 1993). ApoE4 is associated with higher amyloid plaque burden composed mainly of A β 42 in AD brains compared to those carrying ApoE2 and E3 (Gearing *et al.*, 1996). The interaction between ApoE4 allele and amyloid-associated depression increases the AD risk, however, is yet unknown.

We hypothesized that a high plasma A β 40/A β 42 ratio plus clinical symptoms of depression may represent a prodromal depression signaling imminent cognitive deterioration leading to development of AD, especially in the presence of ApoE4. In order to test this hypothesis, we conducted a second cognitive evaluation of subjects who were not demented at baseline and examined the longitudinal relationships between amyloid-associated depression and the development of incident AD.

Methods

Study population and recruitment

The *Nutrition, Aging and Memory in the Elderly (NAME)* study is population-based study of homecare elderly from four homecare agencies in the Boston area that were recruited between 2003 and 2006 for baseline assessment (Scott *et al.*, 2006). For an original sample (n=1248), 223 participants who did not have dementia at baseline were invited for a repeat cognitive evaluation between 2009 and 2013. The Boston University Institutional Review Board approved the study. All participants provided written informed consent to participate in this follow-up study. Each subject engaged in two home visits conducted by a trained examiner, who administered the cognitive battery during the first visit, and by a research physician who drew a fasting blood sample and collected data on medical conditions during the second visit.

Depression status at baseline

At the study's inception, participants were given the Center for Epidemiological Studies Depression Scale (CES-D) to measure presence of depressive symptoms at baseline (Radloff, 1977). A CES-D score of 16 was used as the cut-off point for clinical depression (Fuhrer and Rouillon, 1989). Of the 106 subjects with baseline CES-D scores greater than the cut-off, there was a sensitivity of 0.90 and a specificity of 0.83 for the DSM-IV diagnosis of major depression by a board-certified psychiatrist.

Amyloid-associated depression—Those subjects with a CES-D score 16 and a plasma A β 40/A β 42 ratio > median (7.1) were defined as having amyloid-associated depression. Those with a CES-D score 16 and a plasma A β 40/A β 42 ratio median were defined as having non-amyloid depression (Sun *et al.*, 2008).

ApoE4 genotyping and clinical information

A 244 bp of the ApoE gene, which included the two polymorphic sites, was amplified by PCR using a robotic Thermal Cycler (ABI 877, Perkin-Elmer/Applied Biosystems). The PCR products were digested with five units of Hha I, and the fragments were separated by electrophoresis on 8% polyacrylamide non-denaturing gel. The specific allelic fragments were: E2, E3 and E4. ApoE4 was defined by E4/4, E3/4 or E2/4 (Lahoz *et al.*, 1996).

Subjects were classified as having cardiovascular disease (CVD) according to whether they had been previously informed by a doctor that they had congestive heart failure, coronary heart disease, angina pectoris or a heart attack. Diabetes was defined as the use of anti-diabetic medication or fasting glucose greater than 126 mg/dl (available on 96% of the samples). Self-reported stroke history was also recorded.

Diagnoses of dementia and Alzheimer's disease

Research assistants, trained by a neuropsychologist, administered the cognitive tests including WMS-III Logical Memory, WMS-III Word List Learning, Digit Symbol, WAIS-III Block Design, Trails A and B at both baseline and repeat evaluations. Based on these neuropsychological scores and clinical information, consensus diagnosis was made for each

participant during a consensus diagnosis meeting attended by the psychiatrist, neuropsychologist and research assistants. The diagnosis of dementia was based on the DSM-IV criteria. NINCDS-ADRDA guidelines (McKhann *et al.*, 1984) were used to determine whether criteria were met for a diagnosis of possible or probable AD.

Statistical analysis

Statistical analysis was performed using SAS (version 9.1). For analyses of baseline characteristics, the Chi-Square test (X^2 test) was used to compare proportions for binary and categorical variables. Continuous variables were presented as mean $\pm$ SD and compared using T-tests or ANOVA analyses. To account for non-independence of repeated measures in the longitudinal analyses, generalized estimation equations (GEE) logistic regression with first order autoregression (AR(1)) covariance matrix structure was used to examine associations between presence of AD at the end of the interval vs. presence of ApoE4 or amyloid-associated depression or antidepressant use while adjusting for age. The interactions between ApoE4 and amyloid-associated depression or antidepressant use were explored in the logistic regression models. Because the number of incident AD cases was small, we only controlled for age for each multivariate analysis. For all analyses, the two-tailed alpha level of 0.05 was used.

Results

The average follow-up time was 6.2 years, and 15 (7%) of the participants developed AD (Table 1). Among those who developed AD, 12 subjects did not have depression, three subjects had amyloid-associated depression and none of them had non-amyloid depression at baseline. Seven out of 15 who developed AD had been taking antidepressants. In the presence of amyloid-associated depression, two subjects who were ApoE4 carriers developed AD (6.3%), while one subject was ApoE4 non-carriers developed AD (3.1%) ($p=0.06$) (Figure 1). In contrast, in the absence of depression there was no statistical difference in the AD development between ApoE4 carriers and non-carriers.

Compared with those who did not develop AD, those who developed AD were older (mean $\pm$ SD: 71.3 ± 7.5 vs. 78.0 ± 5.5 , $p=0.0005$), had less education and tended to be men and having a higher rate of cardiovascular disease (Table 1). At baseline, 155 subjects did not have depression, 36 had non-amyloid depression and 32 had amyloid-associated depression (Table 2). There were no differences in the demographic except age (mean $\pm$ SD) among those without depression (72.6 ± 7.7), those with non-amyloid depression (68.0 ± 6.6) and those with amyloid-associated depression (72.3 ± 8.0) ($p=0.002$). There were no differences between the two depressed and non-depressed groups in clinical variables including diabetes, cardiovascular disease and stroke. There was also no difference in the frequency of ApoE4 carriers or average MMSE scores among the three subgroups. Because of the sample size, and because age was shown to be a major risk for AD in this study (Tables 1 and 2), we used multivariate regression analysis to study the relationships between different factors and the risk of developing AD after adjusting for age. We found that the interaction between ApoE4 allele and amyloid associated depression was associated with an increased risk of AD ($\beta=+0.113$, $SE=0.047$, $P=0.02$) after adjusting for age (Table 3), but there were no

relationship between ApoE4 or amyloid-associated depression alone and the AD development in this model.

Twenty-eight percent of those without depression, 58% of those with non-amyloid depression and 44% of those with amyloid-associated depression had been taking antidepressants ($p=0.002$). Because there were significant different rates of taking antidepressants among the three subgroups (Table 2), we next studied the relationship between antidepressant usage and the AD development (Table 4). After adjusting for age, antidepressant usage tended to be associated with the risk of developing AD (Model I, $p=0.07$), and the interaction between ApoE4 allele and antidepressant usage was significantly associated with the development of AD (Model II: $\beta=+0.174$, $SE=0.064$, $P=0.007$) (Table 4). Among ApoE4 carriers, 20% of taking antidepressants vs. 6% of those who did not take this class of medication developed AD. Among ApoE4 non-carriers, 5% developed AD regardless of antidepressant usage.

Discussion

There is growing evidence in the literature that depression can be either a risk factor (Devanand *et al.*, 1996; Geerlings *et al.*, 2000; Paterniti *et al.*, 2002; Kumar *et al.*, 2006; Ownby *et al.*, 2006) or an early symptom of AD (Steffens *et al.*, 1997; Berger *et al.*, 1999; Cervilla *et al.*, 2000; Ritchie *et al.*, 2000; Wilson *et al.*, 2002; Lopez *et al.*, 2003). However, not all depressed elderly developed dementia, and thus clinically it is necessary and likely important for a physician to make differential diagnoses of depression subtypes and predict prognoses in the elderly. We proposed that plasma A β might be useful for differentiating different depression subtypes and predictive of a prodromal stage of AD.

This longitudinal study provided some evidence supportive of our hypothesis that amyloid-associated depression increased the risk of developing AD in the presence of ApoE4 allele (Figure 1 and Table 3), although it did not reach statistical significance because of the lack of a large number of subjects. Several studies suggest that amyloid deposits in the brain are associated with late life depression, but not with early onset depression (Butters *et al.*, 2008; Pomara and Sidtis, 2010; Tatenio *et al.*, 2014; Chung *et al.*, 2015; Pietrzak *et al.*, 2015). The brain amyloid imaging plus mood symptoms including depression and anxiety predict the risk of AD development (Pietrzak *et al.*, 2015). There is ample evidence suggesting that CSF A β and tau proteins (Perrin *et al.*, 2009; Pomara *et al.*, 2012; Vanderstichele *et al.*, 2012; Weiner *et al.*, 2012) enhance diagnostic accuracy and likely are surrogate markers of AD pathology in the brains of elderly depressed patients. In contrast to the A β biomarkers in central nervous system (CNS), peripheral A β biomarkers for AD prognosis in late life depression are variable among different studies (Osorio *et al.*, 2014). For example, while some study samples show that high plasma A β 42 is associated with late life depression (Pomara and Murali Doraiswamy, 2003; Blasko *et al.*, 2010), others show that low plasma A β 42 or high A β 40/42 ratio is associated with late life depression in some elders (Qiu *et al.*, 2007; Baba *et al.*, 2012; Namekawa *et al.*, 2013). Despite that the brain amyloid imaging and CSF reflect the brain pathology of AD better than peripheral A β , the cost of using PET scan to screen for the AD prognosis among all depressed elderly will be considerably high and that depressed patients tend to refuse lumbar puncture. Thus it is still necessary to develop

some blood tests, probably by using other peripheral biomarkers or the combination of peripheral biomarkers including A β , for the prognosis and diagnosis of AD.

Our cross-sectional study found that ApoE4 carriers had lower plasma Abeta42 and higher Abeta40/Abeta42 ratio than ApoE4 non-carriers regardless the depression status (Sun *et al.*, 2009). Results from this longitudinal study suggested that ApoE4 carriers with these A β biomarkers plus depressive symptoms indicate an imminent prodromal stage of AD (Figure 1 and Table 2). The ApoE4 allele is the major genetic risk factor of late-onset AD (Strittmatter *et al.*, 1993), and is associated with higher amyloid plaque burden (Gearing *et al.*, 1996), probably through reduced clearance or accelerated aggregation of the peptide. Previous studies reported that among the elderly, aged 80 and older, who are at much higher risk of AD and suffer from compared to those who are younger, a relationship between ApoE4 and depression has been observed (Krishnan *et al.*, 1996; Steffens *et al.*, 2003). However, some other studies with younger elders have shown that late life depression is not generally associated with ApoE4 (Mauricio *et al.*, 2000; Butters *et al.*, 2003). While late-life depression has different subtypes, it is probable that only the prodromal depression of AD was associated with the ApoE4 allele. Our study suggests that both plasma A β and ApoE genotyping to predict cognitive prognoses of late life depression.

Amyloid-associated vs. non-amyloid depression are probably two depression subtypes of late life depression (Sun *et al.*, 2008). While amyloid-associated depression was linked with a prodromal stage of AD, non-amyloid depression was associated with a cognitive pattern of vascular depression, visuospatial and executive dysfunction (Sun *et al.*, 2008) and did not lead to increased risk in the development of AD (Figure 1). A post-mortem study has shown that history of depression is linked with increased amyloid plaques and neurofibrillary tangles, which are the neuropathological hallmarks of AD (Rapp *et al.*, 2006).

Antidepressants, especially SSRI, are effective drugs against mood symptoms of depression including late life depression (Bruce *et al.*, 2002; Kuzuya *et al.*, 2006). Our longitudinal study showed that usage of antidepressants alone tended to increase the AD risk; however, in the presence of ApoE4, antidepressant use was significantly associated with increased risk for AD (Table 4). For our study, use of antidepressants likely reflected greater severity of depressive symptoms, as many patients with milder depressive symptoms in community are often not prescribed or refuse to take antidepressants. We would thus suggest that severe depression, but not the drug use per se, was related to incident AD in our study. Consistently, it is shown that antidepressant use does not modify cognitive decline during aging process (Saczynski *et al.*, 2015). Studies including ours show that there was no relationship between the antidepressants use and plasma A β 42 (Pomara *et al.*, 2006; Sun *et al.*, 2007), which is the major component of neuritic plaques in the AD brain. While it is possible that antidepressants may not be effective to delay cognitive decline in AD prodromal depression, one study shows that fluoxetine treatment improves cognition in vascular dementia probably through increasing brain derived neurotrophic factor (BDNF) in the brain (Liu *et al.*, 2014).

The major limitation of this study was the sample size and the small number of incident AD cases (7%) during a relatively short follow-up. Although our longitudinal study found that amyloid-associated depression increased the risk of AD in the presence of ApoE4, the longitudinal relationship between amyloid-associated depression alone and AD was not

statistically significant. We will need a large cohort with a longer follow-up period to confirm these initial findings. Other limitations include: (1) depression was based on the CES-D score rather than the DSM-IV criteria, and we had no information about disease onset and its course; (2) although our assays for plasma A β had high sensitivity and specificity (Qiu *et al.*, 2007), the field lacks standard assays of measuring A β 40 vs. A β 42 in plasma for inter-laboratory comparisons in order to be applied in clinical practice. Further studies are needed to examine whether amyloid-associated depression is related to brain pathology, and is causally linked to the onset of cognitive decline and AD in other populations. Nevertheless, our cross-sectional and prospective discoveries have pointed out the existence of a depression subtype that precedes onset of AD and by using plasma A β prodromal depression of AD plus ApoE genotyping could differentiate it from other late-life depression subtypes.

Acknowledgements

We especially thank Dr. Marshal Folstein who had the vision to establish the NAME study more than a decade ago. We also thank the NAME study staff and the Boston homecare agencies for their hard work and acquisition of subjects for the baseline study, which is the foundation for this follow-up study. This work was supported by grant from the NIA, AG-022476 for W.Q.Q.

References

- Baba H, Nakano Y, Maeshima H, et al. Metabolism of amyloid-beta protein may be affected in depression. *J Clin Psychiatry*. 2012; 73(1):115–120. [PubMed: 22152118]
- Berger AK, Fratiglioni L, Forsell Y, Winblad B, Backman L. The occurrence of depressive symptoms in the preclinical phase of AD: a population-based study. *Neurology*. 1999; 53(9):1998–2002. [PubMed: 10599771]
- Blasko I, Kemmler G, Jungwirth S, et al. Plasma amyloid beta-42 independently predicts both late-onset depression and Alzheimer disease. *Am J Geriatr Psychiatry*. 2010; 18(11):973–982. [PubMed: 20808106]
- Bruce ML, McAvay GJ, Raue PJ, et al. Major depression in elderly home health care patients. *Am J Psychiatry*. 2002; 159(8):1367–1374. [PubMed: 12153830]
- Butters MA, Sweet RA, Mulsant BH, et al. APOE is associated with age-of-onset, but not cognitive functioning, in late-life depression. *Int J Geriatr Psychiatry*. 2003; 18(12):1075–1081. [PubMed: 14677138]
- Butters MA, Klunk WE, Mathis CA, et al. Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh Compound-B. *Alzheimer Dis Assoc Disord*. 2008; 22(3):261–268. [PubMed: 18580591]
- Cervilla JA, Prince M, Joels S, Mann A. Does depression predict cognitive outcome 9 to 12 years later? Evidence from a prospective study of elderly hypertensives. *Psychol Med*. 2000; 30(5):1017–1023. [PubMed: 12027039]
- Chung JK, Plitman E, Nakajima S, et al. Lifetime history of depression predicts increased amyloid-beta accumulation in patients with mild cognitive impairment. *J Alzheimers Dis*. 2015; 45(3):907–919. doi: 10.3233/JAD-142931. [PubMed: 25633681]
- Dal Forno G, Palermo MT, Donohue JE, et al. Depressive symptoms, sex, and risk for Alzheimer's disease. *Ann Neurol*. 2005; 57(3):381–387. [PubMed: 15732103]
- DeMattos RB, Bales KR, Parsadanian M, et al. Plaque-associated disruption of CSF and plasma amyloid-beta (A β) equilibrium in a mouse model of Alzheimer's disease. *J Neurochem*. 2002; 81(2):229–236. [PubMed: 12064470]
- Devanand DP, Sano M, Tang MX, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry*. 1996; 53(2):175–182. [PubMed: 8629893]

- van Dijk EJ, Prins ND, Vermeer SE, et al. Plasma amyloid beta, apolipoprotein E, lacunar infarcts, and white matter lesions. *Ann Neurol*. 2004; 55(4):570–575. [PubMed: 15048897]
- Fuhrer R, Rouillon F. French version of CES-D scale: description and translation of self evaluation. *Psychiatr Psychol*. 1989; 4:163–166.
- Gearing M, Mori H, Mirra SS. Abeta-peptide length and apolipoprotein E genotype in Alzheimer's disease. *Ann Neurol*. 1996; 39(3):395–399. [PubMed: 8602762]
- Geerlings MI, Schoevers RA, Beekman AT, et al. Depression and risk of cognitive decline and Alzheimer's disease. Results of two prospective community-based studies in The Netherlands. *Br J Psychiatry*. 2000; 176:568–575. [PubMed: 10974964]
- Gulot ME, Irizarry MC, Smith EE, et al. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. *Neurology*. 2006; 66(1):23–29. [PubMed: 16401840]
- Kawarabayashi T, Younkin LH, Saido TC, et al. Age-dependent changes in brain, CSF, and plasma amyloid (beta) protein in the Tg2576 transgenic mouse model of Alzheimer's disease. *J Neurosci*. 2001; 21(2):372–381. [PubMed: 11160418]
- Krishnan KR, Tupler LA, Ritchie JC Jr, et al. Apolipoprotein E-epsilon 4 frequency in geriatric depression. *Biol Psychiatry*. 1996; 40(1):69–71. [PubMed: 8780857]
- Kumar R, Parslow RA, Jorm AF, et al. Clinical and neuroimaging correlates of mild cognitive impairment in a middle-aged community sample: the personality and total health through life 60+ study. *Dement Geriatr Cogn Disord*. 2006; 21(1):44–50. [PubMed: 16254430]
- Kuzuya M, Masuda Y, Hirakawa Y, et al. High prevalence rate of depression among community-dwelling frail elderly Japanese. *Nippon Ronen Igakkai Zasshi*. 2006; 43(4):512–517. [PubMed: 16937945]
- Lahoz C, Osgood D, Wilson PW, Schaefer EJ, Ordovas JM. Frequency of phenotype-genotype discrepancies at the apolipoprotein E locus in a large population study. *Clin Chem*. 1996; 42(11):1817–1823. [PubMed: 8906082]
- Liu X, Zhang J, Sun D, et al. Effects of fluoxetine on brain-derived neurotrophic factor serum concentration and cognition in patients with vascular dementia. *Clin Interv Aging*. 2014; 9:411–418. [PubMed: 24648723]
- Lopez OL, Becker JT, Sweet RA, et al. Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 2003; 15(3):346–353. [PubMed: 12928511]
- Mauricio M, O'Hara R, Yesavage JA, et al. A longitudinal study of apolipoprotein-E genotype and depressive symptoms in community-dwelling older adults. *Am J Geriatr Psychiatry*. 2000; 8(3):196–200. [PubMed: 10910416]
- McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34(7):939–944. [PubMed: 6610841]
- Namekawa Y, Baba H, Maeshima H, et al. Heterogeneity of elderly depression: increased risk of Alzheimer's disease and Abeta protein metabolism. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013; 43:203–208. [PubMed: 23276885]
- Osorio RS, Gumb T, Pomara N. Soluble amyloid-beta levels and late-life depression. *Curr Pharm Des*. 2014; 20(15):2547–2554. [PubMed: 23859552]
- Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry*. 2006; 63(5):530–538. [PubMed: 16651510]
- Paterniti S, Verdier-Taillefer MH, Dufouil C, Alperovitch A. Depressive symptoms and cognitive decline in elderly people. Longitudinal study. *Br J Psychiatry*. 2002; 181:406–410. [PubMed: 12411266]
- Perrin RJ, Fagan AM, Holtzman DM. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature*. 2009; 461(7266):916–922. [PubMed: 19829371]
- Pietrzak RH, Lim YY, Neumeister A, et al. Amyloid-beta, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. *JAMA Psychiatry*. 2015; 72(3):284–291. [PubMed: 25629787]

- Pomara N, Murali Doraiswamy P. Does increased platelet release of Abeta peptide contribute to brain abnormalities in individuals with depression? *Med Hypotheses*. 2003; 60(5):640–643. [PubMed: 12710895]
- Pomara N, Sidtis JJ. Brain neurotoxic amyloid-beta peptides: their potential role in the pathophysiology of depression and as molecular therapeutic targets. *Br J Pharmacol*. 2010; 161(4): 768–770. [PubMed: 21105218]
- Pomara N, Willoughby LM, Sidtis JJ, Mehta PD. Selective reductions in plasma Abeta 1–42 in healthy elderly subjects during longitudinal follow-up: a preliminary report. *Am J Geriatr Psychiatry*. 2005; 13(10):914–917. [PubMed: 16223971]
- Pomara N, Doraiswamy PM, Willoughby LM, et al. Elevation in plasma Abeta42 in geriatric depression: a pilot study. *Neurochem Res*. 2006; 31(3):341–349. [PubMed: 16583267]
- Pomara N, Bruno D, Sarreal AS, et al. Lower CSF amyloid beta peptides and higher F2-isoprostanes in cognitively intact elderly individuals with major depressive disorder. *Am J Psychiatry*. 2012; 169(5):523–530. [PubMed: 22764362]
- Qiu WQ, Sun X, Selkoe DJ, et al. Depression is associated with low plasma Abeta42 independently of cardiovascular disease in the homebound elderly. *Int J Geriatr Psychiatry*. 2007; 22(6):536–542. [PubMed: 17096467]
- Radloff L. The CES-D scale: a self report depression scale for research in the general population. *Appl Psychol Meas*. 1977; 1:385–401.
- Rapp MA, Schnaider-Beeri M, Grossman HT, et al. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Arch Gen Psychiatry*. 2006; 63(2):161–167. [PubMed: 16461859]
- Ritchie K, Ledesert B, Touchon J. Subclinical cognitive impairment: epidemiology and clinical characteristics. *Compr Psychiatry*. 2000; 41(2 Suppl 1):61–65. [PubMed: 10746906]
- Saczynski JS, Beiser A, Seshadri S, et al. Depressive symptoms and risk of dementia: the Framingham Heart Study. *Neurology*. 2010; 75(1):35–41. [PubMed: 20603483]
- Saczynski JS, Rosen AB, McCammon RJ, et al. Antidepressant use and cognitive decline: the health and retirement study. *Am J Med*. 2015; 128(7):739–746. [PubMed: 25644319]
- Scott TM, Peter I, Tucker KL, et al. The Nutrition, Aging, and Memory in Elders (NAME) study: design and methods for a study of micronutrients and cognitive function in a homebound elderly population. *Int J Geriatr Psychiatry*. 2006; 21(6):519–528. [PubMed: 16645938]
- Steffens DC, Plassman BL, Helms MJ, et al. A twin study of late-onset depression and apolipoprotein E epsilon 4 as risk factors for Alzheimer's disease. *Biol Psychiatry*. 1997; 41(8):851–856. [PubMed: 9099411]
- Steffens DC, Trost WT, Payne ME, Hybels CF, MacFall JR. Apolipoprotein E genotype and subcortical vascular lesions in older depressed patients and control subjects. *Biol Psychiatry*. 2003; 54(7):674–681. [PubMed: 14512206]
- Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A*. 1993; 90(5):1977–1981. [PubMed: 8446617]
- Sun X, Mwamburi DM, Bungay K, et al. Depression, antidepressants, and plasma amyloid beta (Beta) peptides in those elderly who do not have cardiovascular disease. *Biol Psychiatry*. 2007; 62(12): 1413–1417. [PubMed: 17544381]
- Sun X, Steffens DC, Au R, et al. Amyloid-associated depression: a prodromal depression of Alzheimer disease? *Arch Gen Psychiatry*. 2008; 65(5):542–550. [PubMed: 18458206]
- Sun X, Chiu CC, Liebson E, et al. Depression and plasma amyloid beta peptides in the elderly with and without the apolipoprotein E4 allele. *Alzheimer Dis Assoc Disord*. 2009; 23(3):238–244. [PubMed: 19812466]
- Tateno A, Sakayori T, Higuchi M, et al. Amyloid imaging with [F]florbetapir in geriatric depression: early-onset versus late-onset. *Int J Geriatr Psychiatry*. 2014; 30(7):720–728. [PubMed: 25335941]
- Vanderstichele H, Bibl M, Engelborghs S, et al. Standardization of preanalytical aspects of cerebrospinal fluid biomarker testing for Alzheimer's disease diagnosis: a consensus paper from the Alzheimer's Biomarkers Standardization Initiative. *Alzheimers Dement*. 2012; 8(1):65–73. [PubMed: 22047631]

- Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. *Alzheimers Dement*. 2012; 8(1 Suppl):S1–S68. [PubMed: 22047634]
- Wilson RS, Barnes LL, Mendes de Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. *Neurology*. 2002; 59(3):364–370. [PubMed: 12177369]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Key points

- Late life depression may have different subtypes such as vascular depression and prodromal depression of AD. It is important to identify the biomarkers for different depression subtypes.
- Amyloid-associated depression is associated with cognitive impairment cross-sectionally. This follow-up study showed that amyloid-associated depression may be prodromal depression of AD especially in the presence of ApoE4 allele.

Figure 1.

Longitudinal study on ApoE4 allele, the depression subtypes and the development of Alzheimer's disease. Subjects were divided into three groups based on the baseline depression status: those without depression, those with non-amyloid depression and those with amyloid-associated depression. Within each group, ApoE4 non-carriers (ApoE4-) and carriers (ApoE4+) were further divided. Frequencies and numbers of subjects who developed AD with statistical significance are shown.

Table 1

Demographic, medical and depression status in the subgroups with and without the development of Alzheimer's disease

Follow-up	No AD n = 208	AD n = 15	P value
Follow-up, year, mean $\pm$ SD	6.2 $\pm$ 0.6	6.2 $\pm$ 0.5	0.69
Age, year, mean $\pm$ SD	71.3 $\pm$ 7.5	78.0 $\pm$ 5.5	0.0005
Female, n/total (%)	171/208 (82%)	10/15 (67%)	0.17
High school and above, n/total (%)	160/208 (77%)	11/15 (73%)	0.09
African Americans, n/total (%)	62/208 (30%)	2/15 (13%)	0.56
ApoE4, n/total (%)	44/206 (21%)	5/14 (36%)	0.32
Diabetes, n/total (%)	58/205 (28%)	4/15 (27%)	0.99
CVD, n/total (%)	73/204 (36%)	7/12 (58%)	0.13
Stroke, n/total (%)	25/206 (12%)	2/14 (14%)	0.68
MMSE score, mean $\pm$ SD	27.0 $\pm$ 2.4	26.1 $\pm$ 2.5	0.16
CES-D score, mean $\pm$ SD	11.3 $\pm$ 9.8	10.6 $\pm$ 6.9	0.87
Antidepressant usage, n/total (%)	71/207 (34%)	7/15 (47%)	0.40
Depression status			0.18
No depression	143/208 (69%)	12/15 (80%)	—
Non-amyloid depression	36/208 (17%)	0/15 (0%)	—
Amyloid-associated depression	29/208 (14%)	3/15 (20%)	—

Mean $\pm$ SD with t-Test or n/total (%) with Chi Square test are presented. The values between those with and without the development of AD are compared, and p values for statistical significance are shown. CVD = Cardiovascular disease; MMSE = Mini-Mental State Exam; CES-D = the Center for Epidemiological Studies Depression Scale.

Table 2

Baseline comparisons among three subgroups based on depression status

Depression status	None n = 155	Non-amyloid n = 36	Amyloid-associated n = 32	P value
Follow-up, year, mean $\pm$ SD	6.2 $\pm$ 0.7	6.1 $\pm$ 0.5	6.2 $\pm$ 0.6	0.67
Age, year, mean $\pm$ SD	72.6 $\pm$ 7.7	68.0 $\pm$ 6.6	72.3 $\pm$ 8.0	0.002
Female, n/total (%)	125/155 (81%)	29/36 (81%)	27/32 (84%)	0.88
High school and above, n/total (%)	121/155 (78%)	24/36 (67%)	26/32 (81%)	0.13
African Americans, n/total (%)	44/155 (28%)	12/36 (33%)	8/32 (25%)	0.78
ApoE4, n/total (%)	37/153 (24%)	7/36 (19%)	5/31 (16%)	0.55
Diabetes, n/total (%)	41/153 (27%)	13/35 (37%)	8/32 (25%)	0.42
Cardiovascular disease, n/total (%)	57/150 (38%)	11/35 (31%)	12/31 (38%)	0.75
Stroke, n/total (%)	19/153 (12%)	5/36 (13%)	3/31 (10%)	0.87
Antidepressant usage, n/total (%)	45/154 (28%)	21/36 (58%)	14/32 (44%)	0.002
MMSE score, mean $\pm$ SD	27.0 $\pm$ 2.3	26.4 $\pm$ 3.1	26.6 $\pm$ 3.1	0.43

No depression was defined by having a CES-D score < 16, non-amyloid depression was defined by having a CES-D score $\geq$ 16 and plasma A β 40/A β 42 ratio $\leq$ 7.1 and amyloid-associated depression was defined by having a CES-D score $\geq$ 16 and plasma A β 40/A β 42 ratio > 7.1. Mean $\pm$ SD with ANOVA test or n/total (%) with Chi Square test are presented. P values for statistical significance are shown. MMSE = Mini-Mental State Exam.

Table 3

Influences of ApoE4 and amyloid-associated depression on the development of Alzheimer's disease

Development of Alzheimer's disease (<i>n</i> = 15)	Model I <i>n</i> = 219		Model II <i>n</i> = 222		Model III <i>n</i> = 219	
	β estimate (SE)	P value	β estimate (SE)	P value	β estimate (SE)	P value
Age, years	+0.007 (0.002)	0.001	+0.007 (0.002)	0.001	+0.007 (0.002)	0.001
ApoE4	+0.044 (0.039)	0.26	—	—	—	—
Amyloid-associated depression (0, 1 and 2)	—	—	−0.001 (0.022)	0.96	—	—
ApoE4 $\times$ amyloid-associated depression	—	—	—	—	+0.113 (0.047)	0.02

Each regression model is adjusted for age. Amyloid-associated depression variables were defined as no depression = 0 (CES-D score < 16), non-amyloid depression = 1 (CES-D score $\geq$ 16 and plasma A β 40/A β 42 ratio $\leq$ 7.1) and amyloid-associated depression = 2 (CES-D score $\geq$ 16 and plasma A β 40/A β 42 ratio > 7.1). The interaction between ApoE4 allele and amyloid-associated depression variables was used. P value < 0.05 is considered significant.

Table 4

Influence of ApoE4 on the development of Alzheimer's disease among those without and with depression at baseline

Development of Alzheimer's disease	Model I n = 221		Model II n = 218	
	β estimate (SE)	P value	β estimate (SE)	P value
Age, years	+0.008 (0.002)	0.0003	+0.008 (0.002)	0.0003
Antidepressant use	+0.064 (0.035)	0.07	—	—
ApoE4 $\times$ antidepressant use	—	—	+0.174 (0.064)	0.007

Each regression model is adjusted for age. The interaction between ApoE4 allele and antidepressant use was used. P value < 0.05 is considered significant.