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Soluble Amyloid-β Levels and Late-Life Depression

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Abstract

Late-Life Major Depression (LLMD) is a complex heterogeneous disorder that has multiple pathophysiological mechanisms such as medical comorbidity, vascular-related factors and Alzheimer's disease (AD). There is an association between LLMD and AD, with LLMD possibly being a risk factor for, or early symptom of AD and vascular dementia. Whether depression is an etiologic risk factor for dementia, or part of the dementia prodrome remains controversial. AD has a long prodromal period with the neuropathologic features of the disease preceding the onset of clinical symptoms by as much as 15–20 years. Clinicopathological studies have provided robust support for the importance of Aβ42 in the pathogenesis of AD, but several other risk factors have also been identified. Given the relationship between Aβ42 and AD, a potential relationship between Aβ42 and LLMD would improve the understanding of the association between LLMD and AD. We reviewed 15 studies that analyzed the relationship between soluble Aβ42 and LLMD. For studies looking at plasma and/or cerebrospinal fluid (CSF) levels of Aβ42, the relationship between LLMD and soluble Aβ42 was equivocal, with some studies finding elevated Aβ42 levels associated with LLMD and others finding the opposite, decreased levels of Aβ42 associated with LLMD. It may be that there is poor reliability in the diagnosis of depression in late life, or variability in the criteria and the scales used, or subtypes of depression in late life such as early vs. late onset depression, vascular-related depression, and preclinical/comorbid depression in AD. The different correlations associated with each of these factors would be causing the inconsistent results for soluble Aβ42 levels in LLMD, but it is also possible that these patterns derive from disease stage-dependent differences in the trajectory of CSF Aβ42 during older age, or changes in neuronal activity or the sleep/wake cycle produced by LLMD that influence Aβ42 dynamics.

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CONFLICT OF INTEREST

Ricardo Osorio and Tyler Gumb do not have any conflicts of interest to disclose.
Dr. Pomara has a joint patent and patent application with the NYU School of Medicine related to the material described in this article.

Keywords

Late-life depression; Aβ42; amyloid; plasma; cerebrospinal fluid; Alzheimer's disease; biomarkers; elderly; dementia; ApoE4

INTRODUCTION

Late-life Depression

Late-life major depression (LLMD) is one of the most frequent and under diagnosed psychiatric conditions in the elderly population [1]. There is some consensus about LLMD being less frequent among older adults than at middle age [2–5], and more commonly mild and in the context of medical comorbidity [6, 7]; but it has a significant impact on physical, cognitive or social functioning, and risk for suicide, all of which are associated with increased mortality [1, 8, 9]. An individual's first depressive episode can occur at any stage of life. Several studies have reported differences in etiology and symptoms between early-onset depression (EOD) and late onset depression (LOD) (defined as an age of onset of the first episode after an age that varies between 50 to 60 years)[10–12], with LOD being associated with a lower family load for depressive disorder [10], fewer premorbid personality disturbances [13], and more vascular risk factors [14]. (Although the cut-off value between EOD and LOD is still considered somewhat arbitrary and the onset of depression difficult to identify, especially when mild)[15].

LLMD is therefore heterogeneous, with multiple pathophysiological mechanisms contributing to depression [12, 16]. Several studies suggest that LLMD is particularly associated with ventricular enlargement, volume loss in the frontal lobes, hippocampi and other subcortical areas [17, 18]; white-matter hyperintensities (WMH) on MRI scans [19, 20]; and neuropsychological impairments in the domains of processing speed, memory, and executive functioning [21]. In some cases, LLMD results in a reversible '*pseudodementia*' presentation in which patients exhibit symptoms consistent with dementia [22], but more importantly, depression may be a risk factor for, or an early symptom of Alzheimer's disease (AD) and Vascular dementia [23–25]. Some authors have described that depression coincides with the onset of dementia in some patients [26–29], but most studies and several meta-analyses have concluded that depression precedes dementia and is associated with approximately a 2-fold increase in the risk of developing cognitive impairment and dementia [23, 24, 30–34]. It remains controversial however, whether depression reflects an etiologic risk factor for dementia or if it is part of the dementia prodrome, as neuropathologic features of AD can precede the onset of clinical symptoms by 15–20 years [35, 36].

Soluble Amyloid-β Levels

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by global deficits in cognition, daily function and behavior [37, 38]. The provisional diagnosis of Alzheimer's disease (AD) is based on a combination of several evaluations, such as clinical history, neuroimaging and cognitive testing; while the definitive diagnosis of AD requires post mortem examination, established on the neuropathological hallmarks of the disease: phosphorylated tau (P-tau) intracellular neurofibrillary tangles, amyloid beta (Aβ)

deposition in the form of extracellular senile plaques and blood vessel deposits, neuronal and synaptic loss, reactive gliosis and neuroinflammation [39–41]. The role of each of these lesions is poorly understood, although clinicopathological studies provide robust support for the importance of Aβ in the pathogenesis of AD. All 3 genes now known to cause AD have been shown to increase Aβ production (amyloid precursor protein [APP], Presenilin-1, Presenilin-2), while Down syndrome patients, who invariably develop classical AD pathology by age 50, produce too much Aβ from birth and begin to get amyloid plaques long before they get P-tau tangles and other AD lesions.

Aβ is a secreted peptide normally present in the plasma and cerebrospinal fluid (CSF), derived from APP through the sequential processing with two proteases. Most of the secreted Aβ contains 40 amino acids (Aβ40), but a small percentage contains 42 (Aβ42). An initiating factor in AD pathogenesis occurs when soluble, monomeric Aβ undergoes a conformational change and converts into forms such as oligomers, protofibrils, and fibrils. Aβ42 aggregates much more easily than Aβ40 due to the presence of two additional hydrophobic amino acids, being the initial species deposited in the brain. Aβ peptides are continuously produced in the brain and cleared to the plasma via the CSF and the blood-brain barrier (BBB). Platelets also produce APP and secrete Aβ in plasma [41, 42], and the APP molecule is expressed in peripheral tissues such as heart, liver, pancreas, lymph nodes, spleen, skeletal muscle, skin, intestines, leukocytes, and thyroid or adrenal glands [43]. Plasma Aβ levels do not generally correlate with CSF Aβ levels nor with other biochemical or pathological measures of cerebral Aβ deposition in normal elderly [44–47], and there is insufficient evidence to permit a conclusion regarding the use of plasma Aβ40, Aβ42, or the ratio of Aβ42/Aβ40 in the diagnosis or assessment of risk of sporadic AD [48]. Nevertheless, there is suggestive evidence that changes in plasma Aβ40, Aβ42, or the ratio of Aβ42/Aβ40 may be associated with individuals at risk for developing AD [49, 50]. On the contrary, reduced levels of CSF Aβ42 do associate with Aβ deposition in brain senile plaques [51, 52] and in conjunction with elevated P-tau levels, are able to differentiate patients with AD from control subjects with high accuracy, as well as those who might be at risk for the developing AD in the preclinical stages of the disease [53].

However, the sensitivity/specificity of CSF levels of Aβ40 and Aβ42 as single markers in AD against non-AD dementias is low [54–56], as decreases in CSF Aβ42 levels have also been found in idiopathic normal pressure hydrocephalus [57], frontotemporal dementia (FTD) [58], dementia with Lewy bodies (DLB) and Parkinson's disease (PD) dementia [59], showing a substantial overlap between some CSF biochemical markers in AD and non-AD conditions, with some authors recommending the use of Aβ42/Aβ40 ratio or the combination of Aβ42, P-tau and T-tau when differentiating AD from non-AD dementias [54, 59]. Plasma Aβ peptides have also been investigated for their diagnostic value in differential diagnosis of AD, with reported disease-specific changes in patients with vascular dementia (increase in plasma Aβ40 paralleled by decreased Aβ38)[60], acute cerebral ischemia (decrease of plasma Aβ40 and increase in Aβ38/Aβ40), diffuse subtype of small vessel disease (increase in plasma Aβ40)[64], lacunar infarcts and white matter lesions (increases in plasma Aβ40 and Aβ42)[62, 63], cerebral amyloid angiopathy (increases in plasma Aβ40 and Aβ42)[64] and atrophy of the medial temporal lobe structures (decrease in Aβ42)[65]. These

observations may be explained by broad clinical and neuropathological similarities between dementia diseases, co-morbid vascular pathology, or highly prevalent common neuropathological features found in both demented and non-demented elderly controls, especially in the oldest old [66, 67], but they may also reflect the effect of potential specific activities of Aβ peptides that are associated with each disease or its interaction with blood homeostasis, blood vessels [42, 68], or brain activity [69].

The presence of soluble levels of CSF and plasma Aβ peptides in LLMD has been a focus of the growing literature on biomarkers in Geriatric Psychiatry since we first hypothesized that sustained elevations of Aβ peptides might occur in individuals with depression [42], but studies to date have varied substantially in their design, criteria for LLMD, scales used, sample size and study populations, making it difficult to interpret the overall data. Therefore, we performed a systematic review to evaluate the scientific literature, asking whether plasma and CSF Aβ levels are associated with the development of depression, and if they play a role in the pathophysiology of LLMD.

METHODS

A systematic literature search was performed in *PubMed*, *Embase* and *Web of Knowledge* (*WoK*) using the following keywords: *depression*, *amyloid beta*, *cerebrospinal fluid (CSF) and plasma*. The search was run on August 12th, 2012. No limitation in the search strategy was inserted. Reference lists from all relevant literature were hand-searched for additional relevant articles overlooked by the database search. Our initial search produced 32 results from *PubMed*, 18 from *Embase*, and 52 from WoK. After reviewing these articles, 15 studies were selected for inclusion in the review. Studies were selected in a 2 stage process. The same inclusion criteria were used for both stages. Inclusion criteria for the review required the study to fulfill 2 primary criteria: included a sample of subjects with late-life depression or depressive symptoms (including subsyndromical depressive symptoms and dysthymia), and measured relevant plasma or CSF amyloid beta (Aβ40, Aβ42, and/or Aβ42/Aβ40 ratio). In the first stage the title and abstract of each article were reviewed and in the second stage the full text was reviewed. No languages were excluded from the search. Data on the following variables was collected on each of the papers and recorded in a systematic fashion: (i) the number of subjects (ii) the type of population (iii) the mean age of subjects (iv) whether the subjects were actively depressed at the time of study or not (v) the depression scale used (vi) the score on the scale that was used as the cut-off point for depression in the study (vii) the differences in soluble Aβ40, Aβ42, and/or Aβ42/Aβ40 ratio between groups (see Table 1).

RESULTS

Plasma and Serum Aβ40 and Aβ42 Cross-sectional Studies

The findings for the association between levels of plasma/serum Aβ42 and depression are conflicting with reports of positive, inverse or no associations between Aβ42 and LLMD (Table 1). The first study reporting positive associations was performed by us in a subset of 47 in/outpatients with Late Life Major Depressive Disorder (LLMD) based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-IV) (mean age: 80.0±7.4

years) who participated in a double blind randomized comparison of antidepressants [70], with plasma Aβ42 levels elevated by approximately 30% in the LLMD group compared to the 30 younger controls (mean age: 69.1±4.4 years)[70]. The second study included 123 community dwelling Korean elderly (mean age of LLMD subjects: 75.60±6.97 years) in which they analyzed plasma Aβ42, LLMD and cognitive function. The subjects were drawn from a population-based sample intended to screen individuals older than 65 for early detection of depression and dementia [71]. There was a negative correlation between Mini-Mental State Examination (MMSE)[72] and Aβ42, and a positive correlation between the Geriatric Depression Scale (GDS)[73] and Aβ42, with the depressed group only having 2% higher plasma levels of Aβ42 than the controls ($p<0.1$)[71]. Of interest, none of the two studies could differentiate subjects according to the presence of cardio/cerebrovascular disease, and in Pomara's study the Aβ42/Aβ40 ratio was associated with increased severity of the white matter hyperintensity burden, while the LLMD group were significantly older (plasma Aβ42 levels have been reported to increase with age)[74], although analyses performed on age and sex-matched subgroups produced results similar to the overall group analyses [70].

In contrast, several cross-sectional studies performed in the same cohort (Nutrition, Aging and Memory in the Elderly [NAME]) found the opposite association, lower plasma levels of Aβ42 in depressed subjects compared with controls [75–78]. These studies all had a relatively large number of subjects, which were drawn from a cohort of homebound elderly from the Boston area aged 60 and older, using a Center for Epidemiologic Studies Depression Scale (CES-D)[79] score of ≥16 as the cut-off point to distinguish for clinical depression. The first study analyzed the association of low plasma Aβ42 and depression controlling for cardiovascular disease (CVD; congestive heart failure, coronary heart disease, angina pectoris, or heart attack)[75]. This study used the first 527 homebound elders participating in the NAME study, and found that CES-D scores were inversely related to plasma Aβ42 levels when the subject had no CVD. In the presence of CVD, the association disappeared. Subsequent analyses from the same cohort on samples of 324 [76], 995 [78], and 1060 [77] elders (with and without CVD) confirmed the finding that subjects with depression had 13.5% lower median plasma Aβ42 levels and a higher Aβ40/Aβ42 ratio than did those without depression [78]. Another finding from this cohort was that only in the absence of the ApoE4 allele, depressed subjects had significantly lower plasma Aβ42 and a higher Aβ40/Aβ42 ratio than those without depression. When subjects with CVD were excluded from this subset of non-ApoE4 carriers, the differences in plasma Aβ42 concentration in those with and without depression became more significant [77]. Mean age of LLMD subjects in this cohort was 73.8±8.5 years and the sample was comprised of homebound elderly with multiple concomitant chronic diseases. Additionally, the same difference in Aβ40/Aβ42 ratio was found in a cross-sectional study on 60 Japanese inpatient young and old depressed subjects [80], in which serum Aβ40 levels were significantly higher in young depressed patients compared to young controls (<60 years) and the Aβ40/Aβ42 ratio was significantly higher in both young and elderly depressed (≥60 years) patients compared to non-depressed controls (mean age of LLMD: 68.2±5.6 years), although the Hamilton Rating Scale for Depression (HAM-D)[81] score did not correlate by itself with Aβ40, Aβ42 levels or Aβ40/42 ratio. These findings were replicated on a larger sample of

193 inpatient young (<40 years), middle age (≥40 to <65) and old depressed subjects (≥65) and 413 controls. Serum Aβ42 levels were significantly lower in elderly subjects compared with controls and trended toward being lower in young and middle-aged patients. Furthermore, the Aβ40/42 ratio was significantly higher in depressed patients than in controls in all age groups. These findings were also observed in a separate analysis in ApoE4 non-carriers [82].

Finally, in a longitudinal study of 988 community-dwelling elders from Pittsburgh, Pennsylvania, Memphis and Tennessee, part of a "*healthier*" cohort (Health Aging and Body Composition; Health ABC) (mean age: 74.0±3.0 years), that had no difficulties performing activities of daily living or walking, no differences were found between LLMD and controls in plasma Aβ42 and Aβ42/Aβ40 ratio levels at baseline irrespective of the presence of the ApoE4 allele [83]. CES-D scores were used to screen for depressive symptoms. Presence of diabetes mellitus, hypertension, stroke or transient ischemic attack, and myocardial infarction were used as comorbidity variables in the analysis.

Plasma and Aβ40 and Aβ42 Longitudinal Studies

Two studies have analyzed the association between plasma levels of Aβ42 and prediction of LLMD at follow-up. The first was an Austrian study that enrolled 331 subjects who fulfilled the criteria of having no previous history of depression, nor having dementia or depression at baseline, from the Vienna Transdanube Aging study (mean age at baseline 75.8±0.5 years)[84]. Subjects were assessed for cognitive functioning and depressive symptoms three times, at baseline, and then at follow up at 2.5 and 5 years. The onset of a depressive episode was diagnosed at each follow-up by interview and the GDS. Levels of plasma Aβ42 at baseline in new converters to LLMD at the 5-year follow-up were significantly higher, when compared with persons without any depression at any time (OR= 1.7, 95% CI: 1.1–2.7). The presence of the ApoE4 allele was not found to be a significant predictor of LLMD. Additionally, irrespective of the presence of mild cognitive impairment (MCI) at baseline, higher plasma Aβ42 at baseline was also found to be a significant predictor of probable or possible AD at 5-year follow up [78].

The second study is the mentioned Health ABC study that had a larger sample size of 988 community-dwelling elders [83]. The study measured Aβ42 and Aβ42/Aβ40 at baseline and at 9-year follow up (mean age at baseline 74.0±3.0 years). Depression was measured using the CES-D (10-item version)[85] with a score of ≥10 as the cut-off point to distinguish for clinical depression. Aβ42 and Aβ42/Aβ40 levels were organized in low, medium, and high tertiles. Initially at baseline, no correlations were found between Aβ42/Aβ40 or Aβ42 and depression. There was also no significant association found between Aβ42/Aβ40 among subjects when ApoE4 status was accounted for [83]. At 9-year follow-up however, low Aβ42/Aβ40 at baseline was associated with an increased risk of developing depression over time but only in ApoE4 carriers (HR=2.14, 95% CI: 1.06–4.34). No association was found between Aβ42/Aβ40 and depression in ApoE4 non-carriers [77].

Cerebrospinal Fluid (CSF) Aβ40 and Aβ42 Studies

CSF levels of Aβ have also been studied in conjunction with LLMD in elderly individuals but the findings have also been inconsistent (Table 2). The first study that analyzed total CSF Aβ (Aβ40 and Aβ42) in LLMD, was a German community-dwelling elderly study that compared 28 AD patients (mean age: 66.8±10.7 years) with 17 non-demented LLMD patients (mean age: 73.4±8.8 years) that were used as the control group [86]. In AD patients, CSF levels of Aβ were inversely correlated with a functional measure of dementia severity but were not different in AD than in LLMD subjects [86]. In a similar study, CSF levels of Aβ42 were studied in a group of Swedish patients with FTD (n=17), AD (n=60), subcortical white-matter dementia (SWD; n=24), Parkinson's disease (PD; n=23), dysthymia (n=19), and in non-depressed age-matched controls (n=32)[87]. CSF Aβ42 was significantly decreased in AD and SWD as compared to non-depressed controls and in AD compared to FTD, but did not differ in AD as compared to the dysthymic group. Similar findings were reported by us in a recent study in which CSF was obtained from 28 non-demented community-dwelling elderly with LLMD (mean age: 66.5±5.4 years) and 19 healthy controls (mean age: 68.1±7.3 years)[89]. The presence of a major depressive episode was based on clinical evaluation and the SCID-IV band the severity of depression was evaluated by the HAM-D [81]. CSF Aβ42 levels were significantly reduced in the LLMD group, similarly to individuals with Alzheimer's disease [88]. The differences in Aβ42 levels were still present when all individuals with the ApoE4 allele were excluded. Importantly, there was an inverse correlation between Aβ42 levels and HAM-D scores, in both the whole sample and in the LLMD group when compared alone, indicating that lower levels of Aβ42 were associated with greater depressive symptom severity. Furthermore, in a subsequent study performed by us in a larger sample of 112 non-depressed (HAM-D≤10), cognitively normal elderly (mean age: 62.0±11.9 years), we observed a two-way interaction between subsyndromical depressive symptoms and low CSF Aβ42. HAM-D depressive symptoms had also an inverse correlation with Aβ42, but only in the 71 ApoE4 non-carriers [89].

In contrast, a Swedish study analyzed 11 non-demented depressed elderly women and compared them to 70 controls (mean age: 72.6±3.1 years) for CSF levels of Aβ42 and its correlation with LLMD [90]. The presence of a depressive episode was diagnosed by clinical interview and the Montgomery-Åsberg Depression Rating scale (MADRS) [91]. Women with LLMD had higher levels of CSF Aβ42 than comparison subjects. Another Swedish study, performed in a total of 183 participants (66.7% female) included 91 patients with AD (31 depressed and 60 non-depressed) and 92 subjects with subjective cognitive impairment (SCI; 41 depressed and 51 non-depressed) (mean age: 67.6±7.4 years) [92]. Depression was assessed using the Cornell Scale for Depression in Dementia [93], using a cut-off score of >6 to define depression. Depression scores were not associated with reduced Aβ42 in the AD or the SCI non-demented subjects [92]. ApoE4 status was not accounted for in any of the two studies.

The Effects of ApoE4 Status on Plasma and CSF Aβ42 and LLMD

The ApoE4 allele is a known genetic risk factor for AD. Although, the exact mechanisms whereby ApoE4 influences the development of AD are not fully understood, there has been some evidence to suggest an interaction with Aβ. CNS lipoprotein metabolism could have an

important effect on the disposition to increased Aβ net production [94], Aβ fibrillogenesis [95], and/or Aβ clearance [96, 97]. Several studies have found that the ApoE4 allele is strongly associated with reduced CSF levels of Aβ42 in both AD and non-demented control populations [98, 99]. In normal aging ApoE4 non-carriers, Aβ42 tends to rise followed by a slight decrease that is more pronounced in senile subjects over 80 years old [100]. In contrast, in ApoE4 carriers the concentration of Aβ42 tends to decline slightly in younger subjects, and then the rate of decline increases rapidly between ages 50 and 60 years. Thus, the slope of the decline is markedly greater in ApoE4 carriers compared to non-carriers [101, 102]. Considering the *"ApoE4 effect"* on age of onset and CSF Aβ42 in aging individuals, it is likely that the ApoE4 allele causes a low plateau in CSF Aβ42 concentrations at an early stage of clinical disease progression, and worsening of cognition is not associated with a worsening of CSF Aβ42 in these subjects [95]. Alternatively, in ApoE4 non-carriers the relationship between CSF Aβ42 and cognition remains linear until lower levels of cognitive performance [95]. The same biomarker finding (inverse relationship between LLMD and Aβ42 but only in young ApoE4 or ApoE4 non-carriers) could be present with depressive symptoms as some CSF studies seem to suggest when the ApoE4 allele is accounted for [89]. A similar relationship between ApoE4 and plasma Aβ42 levels as in CSF has been reported in the NAME cohort [77], with ApoE4 carriers being more likely to show low Aβ42, and to confound the association between Aβ42 and LLMD [77]. A recent unselected all-age autopsy series demonstrated that ApoE4 does shift the onset of Aβ accumulation to an earlier age relative to ApoE4 non-carriers [103], indicating that some of the interactions between ApoE4 and LLMD described in the literature might in fact point out to cases in which LLMD precedes dementia as part of the *prodromal* phase of AD.

DISCUSSION

The relationships between plasma or CSF Aβ42 levels, late life depression (LLMD), and Alzheimer's disease (AD) remain unknown. Alzheimer's disease is an age-dependent neurodegenerative disease where definitive diagnosis is only possible after autopsy and where there is a long prodromal or preclinical phase of more than 15 years [35, 36]. In contrast, LLMD is a *heterogeneous disorder with* multiple pathophysiological (and not exclusive) mechanisms contributing to depression such as early-onset depression, vascular-related factors, subsyndromical depression in the context of medical comorbidity, inflammation, and preclinical/comorbid depression in AD amongst others. To describe the association between lower levels of Aβ42 and LLMD, Sun *et al* [78], in their studies of homebound elders participating in the NAME study, proposed the terms "*Amyloid-associated Depression*," which would be an early symptom of AD [78], and *"Nonamyloid Depression,"* which would be a more vascular-related type of depression [78]. However, this is not an acceptable explanation to depict the seemingly conflicting results with other studies in which depressed patients had higher or similar levels of plasma $A\beta_{42}$ than the control groups [70, 75, 83]. The results from the NAME studies must be interpreted with caution as this cohort used a sample of homebound elders with high risk for cognitive decline [70, 75, 104], that includes subjects with multiple concomitant chronic diseases such as obesity, diabetes, hypertension and renal insufficiency; as well as Mild Cognitive

Impairment (MCI). (On the preliminary data from the first 300 subjects from this cohort about one third had a diagnosis of MCI)[104]. A similar study in the Health ABC cohort, which included a large sample of community-dwelling elderly, who were not homebound, did not find this association at cross-section. At 9-year follow up though, the ABC study found that possessing one or more ApoE4 alleles and low Aβ42/Aβ40 would place the subject at an increased risk for developing LLMD, but no further results have been published to demonstrate that these subjects were free of dementia in subsequent visits, and as the study noted, older individuals who possessed both low plasma Aβ42/Aβ40 and the ApoE4 allele were also at an increased risk for AD. Regardless of ApoE4 status, no significant association was found for Aβ42 levels and depression at 9-year follow up [77].

The relationship between soluble Aβ42 and LLMD is also equivocal in CSF studies, with four studies reporting results that are compatible with low Aβ42 in subjects with depressive symptoms, one showing that Aβ42 concentrations were higher among women with LLMD compared to non-depressed women, and another study suggesting that CSF Aβ42 does not contribute to depression in normal elderly subjects without AD but with subjective cognitive impairment (SCI). None of the two Swedish studies controlled for ApoE4, and the study by Kramberger *et al* included as a control group SCI subjects, which one study has reported that they could present with a CSF *"AD profile"* [105]. Still, amyloid PET imaging also provides another means of exploring the association between depression and brain Aβ burden [52, 106, 107], but the findings have also been conflicting. In one such study, PIB retention in 2 depressed subjects with normal cognitive ability was in the range of non-depressed cognitively normal subjects, while PIB retention in 3 of the 6 depressed subjects with MCI fell in the range of subjects with AD [108]. In another study, PIB retention was measured in a sample of 28 elderly patients (mean age 61 years, range 51–75), with onset of first depressive episode more than 6 years ago but now remitted from depression and 18 healthy subjects (mean age 61 years, range 50–76). Depressed subjects did not have increased levels of PIB binding compared with healthy subjects [109]. Additionally, in a recent population-based clinicopathologic study of non-demented elderly, no association between *AD-type* changes and depression could be observed [110].

Collectively, the existing studies do not fully support the notion that subsyndromal depressive symptoms or LLMD are a risk factor for developing AD through an increase or decrease of soluble Aβ42 but they do not exclude the possibility of an "*amyloid pathway*" (or an effect of LLMD on Aβ42 dynamics) completely, as these patterns could derive from disease stage-dependent differences of soluble Aβ42 that span through older adult age, and change depending on the presentation or criteria used for LLMD (early onset vs. late onset or acute vs. chronic) and/or the presence of presymptomatic AD or the ApoE4 allele. Conclusive evidence is limited by the lack of longitudinal data spanning the continuum from healthy young adult age through the onset of AD and/or the presence of late onset LLMD. If proven to be true, a decrease in plasma/CSF levels of Aβ42, as shown by some of the studies, not accompanied by concomitant increases in total amyloid burden, as described by the PIB PET/neuropathology studies or Baba *et al* findings [82], would be intriguing, and might also indicate the presence of other mechanisms of decreased production of Aβ, that are not dependent on increased amyloid deposition. Although the physiological function of

Aβ is unknown, some reports indicate that the production of this peptide may be associated with neuronal and synaptic activity [69] and regulated by the sleep/wake cycle [111, 112] (which can be affected by depression)[113]. Therefore, we propose that lower plasma/CSF levels of Aβ42 in LLMD in the absence of increased amyloid burden or the ApoE4 allele could also reflect loss of Aβ42 circadian rhythmicity [114, 115]; or changes in neuronal activity that would reduce the number of viable neurons that produce Aβ42, or increase Aβ42 clearance/degradation. These would represent novel pathways by which depressive symptoms and LLMD might influence Aβ42 dynamics. Lower or higher plasma/CSF levels of Aβ especially Aβ42 might also influence the pathogenesis of depression and if confirmed, could serve as potential molecular therapeutic targets.

In summary, no conclusive evidence supports soluble Aβ42 as the potential mechanism underlying the association between LLMD and AD, but there is some evidence that LLMD might influence Aβ42 dynamics in subjects without amyloid burden [82] or the ApoE4 allele. More multimodality and longitudinal biomarker studies including cognitive testing, CSF, FDG and PIB PET imaging to analyze these types of depressed subjects, as well as standard and more reliable definitions of major depression in general (and LLMD in particular) are needed to understand these relationships and their potential implications for the pathophysiology and treatment of depression.

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ABBREVIATIONS

LLMD	Late-life major depression
EOD	Early-onset depression
LOD	Late onset depression
WMH	White-matter hyperintensities
AD	Alzheimer’s disease
Aβ	Amyloid beta
APP	Amyloid precursor protein
CSF	Cerebrospinal fluid
Aβ40	Aβ containing 40 amino acids
Aβ42	Aβ containing 42 amino acids
BBB	Blood–brain barrier
FTD	Frontotemporal dementia
DLB	Dementia with Lewy bodies
WoK	*Web of Knowledge*

MMSE	Mini-Mental State Examination
GDS	Geriatric Depression Scale
NAME	Nutrition, Aging and Memory in the Elderly
CES-D	Center for Epidemiologic Studies Depression Scale
CVD	Cardiovascular disease
HAM-D	Hamilton Rating Scale for Depression
Health ABC	Health Aging and Body Composition
MCI	Mild cognitive impairment
SWD	Subcortical white-matter dementia
PD	Parkinson's disease
MADRS	Montgomery-Åsberg Depression Rating scale
SCI	Subjective cognitive impairment

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Table 1

Crosssectional characteristics of Aβ2 plasma/serum studies.

Author	n=	% female	mean age	Depression Scale	Mean Score of Aβ42	% of Aβ42 difference between depressed and controls	ApoE4 status
Baba, 2012	606	58.0%	56.38(14.7)	HAM-D	2.5 pg/ml	−15.4%	Differences were observed in the whole sample and in non-carriers
Metti, 2012	988	55.20%	74	CES-D	33.9pg/ml	no difference	No differences in carriers or non-carriers
Moon, 2011	123	26%	76	GDS	18.9pg/ml	+1.71%	n/a
Blasko, 2010	331	56.50%	75.8	GDS	n/a	n/a	n/a
Kita, 2009	120	57.50%	55.8	HAM-D	3.3 pmol/l**	−2.1%	n/a
Sun, 2009	1060	76%	75.3	CES-D	18.8 pg/ml*	−12.3%	Differences were observed only in non-carriers
Sun, 2008	995	61%	75.3	CES-D	18.7 pg/ml*	−13.5%	n/a
Sun, 2007	324	75%	75	CES-D	16.9 pg/ml*	−37.2%	n/a
Qiao Qiu, 2006	515	77%	75.7	CES-D	33.1 pg/ml	−23.5%	n/a
Pomara, 2006	82	69.50%	75.3	HAM-D	14.51 pg/ml+	+30%	n/a

* median used in measurements;

** measurements from the elderly subgroup,

+ LLMD subjects only

Table 2

Crosssectional characteristics of Aβ2 CSF studies.

Author	n=	% female	mean age	Depression Scale	Mean Score of Abeta 42	% of Aβ42 difference between depressed and controls	ApoE4 status
Pomara, 2012	47	46.50%	67.1	HAM-D	269.5 pg/mL	−49.2%	Differences were still significant when the ApoE4 carriers were excluded
Osorio, 2012	112	64%	62	HAM-D	544.1 ng/L	n/a	Depressive symptoms had an inverse correlation with Aβ42 but only in ApoE4 non-carriers
Kramberger, 2012	183	67%	67.6	CSDD	686.1 ng/L*	+2.9%	n/a
Gudmundsson, 2007	84	100%	72.6	MADRS	818.3 ng/L	+18%	n/a
Hock, 1998	45	55.5%	69.3	n/a	n/a	n/a	n/a

* median used in measurements