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Featured Article

# Plasma amyloid levels within the Alzheimer's process and correlations with central biomarkers

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**Abstract**

**Backgrounds:** Diagnostic relevance of plasma amyloid β (Aβ) for Alzheimer's disease (AD) process yields conflicting results.

**Objectives:** To assess plasma levels of $A\beta_{42}$ and $A\beta_{40}$ in amnestic mild cognitive impairment (MCI), nonamnestic MCI, and AD patients and to investigate relationships between peripheral and central biomarkers.

**Methods:** One thousand forty participants (417 amnestic MCI, 122 nonamnestic MCI, and 501 AD) from the Biomarker of AmyLoïd pepTide and AlZheimer's diseAse Risk multicenter prospective study with cognition, plasma, cerebrospinal fluid (CSF), and magnetic resonance imaging assessments were included.

**Results:** Plasma $A\beta_{1-42}$ and $A\beta_{1-40}$ were lower in AD (36.9 [11.7] and 263 [80] pg/mL) than in amnestic MCI (38.2 [11.9] and 269 [68] pg/mL) than in nonamnestic MCI (39.7 [10.5] and 272 [52] pg/mL), respectively ($P = .01$ for overall difference between groups for $A\beta_{1-42}$ and $P = .04$ for $A\beta_{1-40}$). Globally, plasma $A\beta_{1-42}$ correlated with age, Mini–Mental State Examination, and APOE ε4 allele. Plasma $A\beta_{1-42}$ correlated with all CSF biomarkers in MCI but only with CSF $A\beta_{42}$ in AD.

**Conclusion:** Plasma Aβ was associated with cognitive status and CSF biomarkers, suggesting the interest of plasma amyloid biomarkers for diagnosis purpose.



*Keywords:* Alzheimer's disease; Mild cognitive impairment; CSF biomarkers; Amyloid β peptides; Plasma biomarkers; Dementia; Cohort study

## 1. Introduction

Alzheimer's disease (AD) is preceded by a very long presymptomatic or prodromal phase. Biomarkers able to detect the in vivo changes of the amyloid β (Aβ) peptides, and tau proteins improve diagnosis and detection of at-AD-risk subjects. Among these biomarkers, cerebrospinal fluid (CSF) $A\beta_{42}$, tau, phosphorylated tau (p-Tau), and cortical amyloid–positron emission tomography (PET) scans have been included in the International Guidelines for AD diagnosis in clinical research settings [1]. CSF $A\beta_{42}$ is reduced at least 15 years before symptoms' onset [2], and the relevance of CSF amyloid has been confirmed for positive [3], differential [4], and early phases (mild cognitive impairment [MCI] and prodromal AD) [5]. A strong correlation is observed between CSF $A\beta_{42}$ and cortical amyloid-PET in AD. Lumbar puncture remains an invasive technique, and amyloid-PET is still expensive and not a screening tool. This highlighted the need of less invasive and expensive biomarkers that could predict central amyloid status. The most promising biomarker seems to be the plasma $A\beta_{42}$, although previous studies have controversial results. Elderly nondemented participants with a higher plasma $A\beta_{42}$ level and a lower plasma $A\beta_{42}/A\beta_{40}$ ratio at baseline have an increased risk of dementia [6]. A decrease of plasma $A\beta_{42}$ level is associated with the progression from controls and MCI to AD [7]. Others studies yield conflicting results regarding the predictive value of plasma $A\beta_{42}$ for AD diagnosis and for cognitive decline in at-AD-risk population [4,6,8–19]; meanwhile, the combination of plasma $A\beta_{42}$ levels and others biomarkers might improve the predictive value [14,20]. Recently, innovative technique allows the quantification of amyloid in plasma with complex proteomics techniques, so far hardly implementable in routine [21]. Although discrepancies between studies can be explained by many factors, the missing link remains the understanding of the relationship between peripheral and central biomarkers at early stage of the disease.

Therefore, the aim of this study was (1) to assess the plasma levels of amyloid $A\beta_{1-42}$ and $A\beta_{1-40}$ in a large clinically based cohort of amnestic MCI (aMCI), nonamnestic MCI (naMCI), and AD patients and (2) to investigate the relationships between plasma $A\beta_{1-42}$, $A\beta_{1-40}$, CSF, and brain imaging biomarkers in a large prospective cohort taking into account potential confounding factors.

## 2. Methods

### 2.1. Study population

BALTAZAR (Biomarker of AmyLoïd pepTide and AlZheimer's diseAse Risk) is a multicenter (23 memory centers) prospective cohort study (ClinicalTrials.gov Identifier #NCT01315639) including participants with MCI or AD at baseline from September 2010 to April 2015 and with an ongoing 3-year follow-up. All participants were Caucasian, community-dwellers and had caregivers. Inclusion criteria