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Cognitive impairment and decline in cognitively normal older adults with high amyloid-β: A meta-analysis

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Abstract

Introduction: This meta-analysis aimed to characterize the nature and magnitude of amyloid (Aβ)-related cognitive impairment and decline in cognitively normal (CN) older individuals.

Method: MEDLINE Ovid was searched from 2012 to June 2016 for studies reporting relationships between cerebrospinal fluid or positron emission tomography (PET) Aβ levels and cognitive impairment (cross-sectional) and decline (longitudinal) in CN older adults. Neuropsychological data were classified into domains of episodic memory, executive function, working memory, processing speed, visuospatial function, semantic memory, and global cognition. Type of Aβ measure, how Aβ burden was analyzed, inclusion of control variables, and clinical criteria used to exclude participants, was considered as moderators. Random-effects models were used for analyses with effect sizes expressed as Cohen's *d*.

Results: A total of 37 studies met inclusion criteria contributing 30 cross-sectional ($N = 5005$) and 14 longitudinal ($N = 2584$) samples. Aβ-related cognitive impairment was observed for global cognition ($d = 0.32$), visuospatial function ($d = 0.25$), processing speed ($d = 0.18$), episodic memory, and executive function (both d's $= 0.15$), with decline observed for global cognition ($d = 0.30$), semantic memory ($d = 0.28$), visuospatial function ($d = 0.25$), and episodic memory ($d = 0.24$). Aβ-related impairment was moderated by age, amyloid measure, type of analysis, and inclusion of control variables and decline moderated by amyloid measure, type of analysis, inclusion of control variables, and exclusion criteria used.

Discussion: CN older adults with high Aβ show a small general cognitive impairment and small to moderate decline in episodic memory, visuospatial function, semantic memory, and global cognition.

Keywords: Cognition; Amyloid-beta; Impairment; Decline; Meta-analysis; Preclinical Alzheimer's disease

1. Introduction

There is now consensus that in cognitively normal (CN) older adults, abnormal levels of amyloid-beta (Aβ+) indicates that the pathophysiological process of Alzheimer's disease

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(AD) has begun, although it may still be up to 20 years before these individuals meet clinical criteria for dementia [1–4]. Neuroimaging and fluid biomarkers allow for *in vivo* measurement of Aβ burden in older individuals using positron emission tomography (PET) and cerebrospinal fluid (CSF) sampling, respectively [5,6]. Studies using these techniques have shown that Aβ burden increases with age, with approximately 10%–20% of CN older adults aged 60–70 years, 20%–30% of those aged 70–80 years, and 30%–40% of those aged 80–90 years being classified as Aβ+ [4,7,8]. Despite their CN classification, prospective studies indicate that cognitive decline is faster and progression to a clinical diagnosis of mild cognitive impairment (MCI) or AD more rapid, in those who are Aβ+ compared to matched CN adults with low Aβ levels (Aβ−) [2,3]. Characterizing preclinical AD is therefore important for understanding the pathogenesis of AD.

Although PET Aβ imaging or CSF sampling identifies reliably the presence of AD pathology in individuals with no overt symptoms, these procedures are expensive, invasive, and must occur in specialized medical centers. Ideally, sensitive and cost-effective clinical measures could be used to identify CN adults who should be referred for these more expensive and invasive testing procedures. Neuropsychological assessment may be useful in this regard, where the presence of a subtle but specific profile of cognitive dysfunction could indicate that Aβ+ would be classified on CSF sampling or PET imaging. However, to date, there is no agreement on what constitutes subtle cognitive decline among individuals with Aβ+. Evidence in support of a cognitive profile indicative of Aβ+ comes from neuropsychological studies that use two types of experimental designs. First are studies that define Aβ+-related cognitive impairment on the basis of the comparison of performance on batteries of neuropsychological tests between Aβ+ CN older adults and Aβ− CN older adults at a single assessment. Such studies generally report only small and statistically nonsignificant differences in neuropsychological test performance between Aβ− and Aβ+ CN older adults [9–13]. Second are studies that define Aβ+-related cognitive decline by evaluating changes in performance on neuropsychological test batteries over time between Aβ+ and Aβ− CN older adults. Studies using this approach have consistently found evidence of Aβ+-related decline on measures of episodic memory, executive function, processing speed, visuospatial function, and language (e.g., [9,11,14–21]). However, although individual studies have identified areas of cognitive impairment and decline associated with Aβ+, there is substantial variation between these studies in terms of the sample sizes enrolled, the domains of cognitive function assessed, the specific neuropsychological or cognitive tests used to measure these domains, and the statistical techniques used to compare Aβ+ and Aβ− groups. Furthermore, in many studies, conclusions about the effects of Aβ+ on cognition have been based only on the presence or absence of statistical significance. Consequently, small but important Aβ+-related effects may have been missed when sample sizes did not provide adequate statistical power to render such differences statistically significant. Meta-analyses of the existing literature on Aβ+-related cognitive impairment, and decline could therefore provide an effective method for overcoming the different limitations of individual studies to provide reliable estimates of Aβ+-related cognitive impairment and decline in preclinical AD.

To date, one meta-analysis evaluated this question and concluded that associations with Aβ burden were strongest for episodic memory (e.g., $r = -0.12$; Hedden et al., 2013 [16]). Additionally, when combining estimates across studies that measured Aβ using CSF, PET, plasma, and histopathologic methods, lower performance in executive function was also related significantly ($r = 0.08$) to Aβ burden. Post hoc analyses indicated that estimates of Aβ+-related cognitive dysfunction were unaffected by the experimental design used, the method of determining Aβ levels, or whether demographic or clinical variables were controlled statistically. Although this initial meta-analysis provides a good basis for understanding the effects of Aβ on cognition in CN older adults, its conclusions are limited because a large number of studies investigating relationships between Aβ+ and neuropsychological test performance have been conducted since its publication. Second, the number of studies using either cross-sectional or longitudinal designs is now sufficient to consider estimates of cognitive impairment and cognitive decline separately. Third, a broader sample of cognitive domains is now available for inclusion in meta-analyses. Finally, samples in studies using longitudinal designs have been followed for longer periods. As such, an updated meta-analysis of this literature is needed to understand the relation between Aβ and cognitive impairment and decline in preclinical AD. The aim of this study was therefore to systematically review the literature on the nature and magnitude of Aβ+-related cognitive impairment and decline in older adults who do not meet clinical criteria for MCI or dementia.

2. Methods

2.1. Study selection

2.1.1. Inclusion/exclusion criteria

Inclusion criteria for the meta-analyses were that (a) the study must include a sample of adults with an average age ≥60 years who did not meet clinical criteria for MCI or dementia and who had undergone assessment with standardized neuropsychological tests; (b) for each participant, Aβ levels were determined using PET or CSF sampling; and (c) studies must have provided sufficient information to allow for the computation of effect sizes.

Studies were excluded from the meta-analysis if they were one of a series of publications from the same specific cohort where, over time, sample sizes or the length of follow-up had increased. For studies meeting this criterion, data for the meta-analyses were taken from that study which was the