Reviewer's report

**Title:** Pre-dementia in Alzheimer's disease

**Version:** 1 Date: 24 August 2010

**Reviewer:** James A. Mortimer

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General comments: This is a well-written and organized manuscript that addresses issues of general interest to those involved in identifying individuals who may progress to Alzheimer's disease.

Major compulsory revisions:

1. The statement is made that "intracerebral amyloidosis precedes the onset of cognitive symptoms in (correct word: by) several years.." Autopsy studies such as those by Braak show that the initial amyloidosis is seen in some subjects while they are still in their 20's and many others by the time they are in their 40's. Viewing Alzheimer's disease as a condition that begins 10 or so years prior to the development of dementia is likely incorrect. The authors need to consider data from studies showing that the earliest changes in this disease may be found in young adulthood.

2. The manuscript would benefit by considering studies addressing markers prior to MCI. There are epidemiologic studies showing cognitive change decades before dementia as well as clinico-pathologic epidemiologic studies showing hippocampal atrophy at very early Braak stages.

3. A statement is made that "most epidemiologic studies do not perform clinical judgement prior to allocating subjects in diagnostic groups..." In fact, most large cohort studies follow a very traditional approach to diagnosis with clinical consensus panel conferences of all persons suspected of dementia or MCI (examples: Framingham, Kame Project, Rotterdam, Chicago Health and Aging Study, Swedish Twin Study of Dementia, Rochester Epidemiologic Project, etc.) The diagnostic approach is likely not the reason for differences slower progression in epidemiologically-detected cases of MCI in comparison to those that are clinically-detected. Rather, cases identified in the clinic are simply further along in the disease process.

4. In the conclusion, the authors state that "a well-defined pattern (of: missing word) CSF and imaging biomarkers can be identified at early stages of the disease process in AD, starting at prodromal and pre-symptomatic stages." The remainder of the conclusion focuses on the prodromal (MCI) stage. Reliance on amyloid PET imaging studies to support pre-symptomatic identification neglects to take into account autopsy-based and non-autopsy based epidemiologic studies that have used structural MRI, functional MRI and subtle cognitive markers to identify individuals at the pre-symptomatic stage.
5. It would be useful for the authors to consider adding information about studies of pre-symptomatic AD (prior to the MCI stage).

Minor Essential Revisions: Although well-written, there are missing words and a few inappropriate uses of English. It is probably easiest to locate these by having one or more fluent English speakers read the manuscript.

**Which journal?:** Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.