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The Wisconsin Registry for Alzheimer's Prevention: A review of findings and current directions

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Abstract The Wisconsin Registry for Alzheimer's Prevention is a longitudinal observational cohort study enriched with persons with a parental history (PH) of probable Alzheimer's disease (AD) dementia. Since late 2001, Wisconsin Registry for Alzheimer's Prevention has enrolled 1561 people at a mean baseline age of 54 years. Participants return for a second visit 4 years after baseline, and subsequent visits occur every 2 years. Eighty-one percent (1270) of participants remain active in the study at a current mean age of 64 and 9 years of follow-up. Serially assessed cognition, self-reported medical and lifestyle histories (e.g., diet, physical and cognitive activity, sleep, and mood), laboratory tests, genetics, and linked studies comprising molecular imaging, structural imaging, and cerebrospinal fluid data have yielded many important findings. In this cohort, PH of probable AD is associated with 46% apolipoprotein E (*APOE*) ε4 positivity, more than twice the rate of 22% among persons without PH. Subclinical or worse cognitive decline relative to internal normative data has been observed in 17.6% of the cohort. Twenty-eight percent exhibit amyloid and/or tau positivity. Biomarker elevations, but not *APOE* or PH status, are associated with cognitive decline. Salutary health and lifestyle factors are associated with better cognition and brain structure and lower AD pathophysiologic burden. Of paramount importance is establishing the amyloid and tau AD endophenotypes to which cognitive outcomes can be linked. Such data will provide new knowledge on the early temporal course of AD pathophysiology and inform the design of secondary prevention clinical trials.

Keywords: Preclinical Alzheimer's disease; Biomarkers; Risk factors

1. Introduction

Although it is widely recognized that Alzheimer's disease (AD) has an extended preclinical stage, the cognitive and neuropathobiological course of changes in late-middle-aged people who may later develop AD dementia are relatively unknown [1]. Such knowledge is crucial if AD is to be identified in its inchoate form, its pathogenesis illuminated, and the tempo and predictors of its progression characterized as a predicate to successful prevention trials.

The Wisconsin Registry for Alzheimer's Prevention (WRAP), established in 2001 [2], is a longitudinal observational cohort of participants who enrolled at midlife (mean age 54), and that is enriched with risk for late-onset AD due to parental history (PH) of AD dementia. The cohort also serves as a registry for linked studies. The overarching goals of the study shown in Table 1 are to identify early cognitive decline and to characterize midlife factors associated with

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Table 1
The major goals of the WRAP study

1	Determine whether AD-related cognitive trajectories can be detected in midlife and distinguished from normal aging using sensitive cognitive assessments.
2	Determine the effect of genetic vulnerability on AD-related cognitive trajectories and biomarkers.
3	Determine the biomarker patterns associated with cognitive trajectories and the development of symptomatic cognitive dysfunction.
4	Examine the influence of health behaviors on risk and resilience to brain pathology and cognitive decline due to AD.

Abbreviations: WRAP, Wisconsin Registry for Alzheimer's Prevention; AD, Alzheimer's disease.

such decline and the contributing underlying biomarkers of AD and related pathology. The present contribution updates the initial description of the cohort, study design, and protocol [2] and provides new data on the effects of family history, apolipoprotein E (*APOE*) genotype, and AD biomarkers on longitudinal cognitive decline over time. Key study findings are summarized, and future directions are presented.

2. Methods

2.1. Study design

To the present, 1561 participants have enrolled over a continuing enrollment window. Recruitment sources included memory clinics in which a parent was diagnosed or treated, limited radio and newspaper advertisements, and word of mouth. Participants generally meet the following inclusion criteria at study entry: age 40–65 years; fluent English speaker; visual and auditory acuity adequate for neuropsychological testing; good health with no diseases expected to interfere with study participation over time. Participants are excluded from enrollment if they have a prior diagnosis of dementia or evidence of dementia at baseline testing (one was excluded due to baseline dementia). The baseline mean age is 54 years, 73% have a parent with AD dementia, and 40% of the total sample are *APOE* ε4 carriers (46% of the PH+ participants and 22% of the PH− participants).

2.2. Determination of PH of AD

The characteristic of PH of AD (PH+) is defined as having at least one biological parent diagnosed with dementia due to probable AD based on the NINDS-ADRDA criteria [3]. Three general methods were used to determine PH. First, direct diagnosis of the parent from study physicians or affiliated faculty, or where medical records for the affected parent were available, a panel of study investigators reviewed the parent's clinical evaluation for dementia to determine whether evidence was sufficient to diagnose probable AD. Second was the neuropathological confirmation of AD in the affected parent. Third, in the absence of sufficient prior information, a Dementia Questionnaire (DQ; [4]) was conducted with the adult child regarding the parent's dementia history and course. The DQ asks about the type of dementia symptoms, the course of progression, and the presence or absence of comorbid conditions that could explain or contribute to the symptoms. Diagnostic classifications based on the DQ show very high sensitivity (100%) and specificity (90%) compared to clinical diagnosis [5]. Eight percent of PH subjects were initially qualified for study entry by a parental autopsy; 83% by medical record review or expert physician diagnosis; and 9% by DQ. Two participants (<1%) were qualified based on self report of PH of AD (but without full DQ or medical record review).

2.3. A comparison group without PH of AD

To understand the role of PH, recruitment of additional participants without PH of probable AD dementia began in 2004. This group now consists of 421 persons who by self-report did not have a parent with dementia due to AD or related cause and who in general have a mother who survived to at least age 75 years and a father to at least age 70 years without dementia.

Because parental status changes over time, it is reassessed at each visit and updated as necessary (e.g., in the case that a previously nondemented parent later developed dementia or, rarely, a parent whose dementia was presumed due to AD was later found by autopsy to be another pathology).

2.4. Study visit procedures

Participants are followed at regular intervals with detailed in-person assessments, questionnaires, and blood collection occurring at each study visit. The first follow-up is approximately 4 years after baseline, and further follow-up visits are approximately every 2 years. Persons will remain in the study until age 85 years, unless they withdraw, convert to dementia, or develop another illness precluding participation or accurate assessment of cognition. Each visit requires approximately 5 hours and comprises the assessments shown in Table 2, that is, cognitive measurement, anthropometric measures, laboratory tests, and questionnaire ratings completed by the participant and an informant including the Quick Dementia Rating System or Clinical Dementia Rating [33]. Reliability and consistency of cognitive testing is established through regular review of aspects of testing procedures at team meetings, biannual individual observations of test administration, through adherence to a standardized manual of procedures, and through blinded rescoring by a separate rater (20% annually for each psychometrist).

2.5. Consent for brain donation

Neuropathologic confirmation is critical for linking cognitive trajectories to disease-related end points. Accordingly, participants are encouraged to enroll in the Wisconsin Brain Donation Program which is administered by the Neuropathology Core of the Wisconsin Alzheimer's Disease Research Center (ADRC). Brain bank enrollment has not been an entry criterion. However, since 2015, brain donation