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Featured Article

Physical activity modifies the influence of apolipoprotein E ε4 allele and type 2 diabetes on dementia and cognitive impairment among older Mexican Americans

I-Fan Shih[a], Kimberly Paul[a], Mary Haan[b], Yu Yu[a], Beate Ritz[a,c,*]

[a]Department of Epidemiology, Fielding School of Public Health, University of California at Los Angeles, CA, USA
[b]Department of Epidemiology and Biostatistics, School of Medicine, University of California at San Francisco, CA, USA
[c]Department of Neurology, School of Medicine, University of California at Los Angeles, CA, USA

Abstract

Introduction: The etiologies of dementia are complex and influenced by genetic and environmental factors including medical conditions.

Methods: We used Cox regression model to estimate the individual and joint effects of physical activity (PA), apolipoprotein E (*APOE*) ε4, and diabetes status on risk of dementia and cognitive impairment without dementia (CIND) among 1438 cognitively intact Mexican American elderly who were followed up to 10 years.

Results: The risk of developing dementia/CIND was increased more than threefold in *APOE* ε4 carriers or diabetics with low levels of PA compared with ε4 noncarriers or nondiabetics who engaged in high PA (ε4: hazard ratio [HR] = 3.44, 95% confidence interval [CI] = 1.85–6.39; diabetes: HR = 3.11, 95% CI = 1.87–5.18); the presence of all three risk factors increased risk by nearly 10-fold (HR = 9.49, 95% CI = 3.57–25.3).

Discussion: PA in elderly Hispanics protects strongly against the onset of dementia/CIND, especially in *APOE* ε4 carriers and those who have diabetes.

Keywords: Mexican American; Physical activity; Apolipoprotein E epsilon 4; Diabetes; Dementia; Cohort study; Cognition

1. Introduction

Cognitive decline and dementia risk are common in old age, and the number of people with dementia is projected to reach 115.4 million in 2050 worldwide [1]. In fast-growing aging populations, this will have a considerable impact on the health care and social systems; thus effective preventative public health strategies are needed. Evidence is accumulating that being physically active has profound effects on the brain's neurochemistry and plasticity and may protect against cognitive decline [2]. Indeed, a meta-analysis including 15 prospective cohort studies, with 30,331 nondemented participants, showed that high levels of physical activity (PA) at baseline versus sedentary lifestyle were associated with decreased cognitive decline during follow-up by as much as 38% [3]. Moreover, many studies show that PA reduces the risk of cardiovascular disease, diabetes, hypertension, and obesity, each contributing to cognitive impairment [4].

Genetic susceptibility may impact the effects of environmental factors [5]. Although the apolipoprotein E (*APOE*) ε4 allele is a well-known genetic risk factor for Alzheimer's disease (AD) and dementia [6], several studies that examined interactions between PA and the *APOE* ε4 genotype reported inconsistent findings [7–12]. For example, a Finnish study found that high levels of PA in midlife were associated with lower risk of dementia/AD among *APOE* ε4 allele carriers [8], whereas in two other studies, late-life

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*Corresponding author. Tel.: +1-310-206-7458; Fax: +1-310-206-6039.

E-mail address: britz@ucla.edu

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PA was inversely associated with dementia risk only among noncarriers in a US population and with risk of cognitive decline in Dutch male allele carriers [7,9]. In addition, a recent German study (participants aged ≥75 years) suggested a possible additive interaction for AD but not general dementia risk [12]. These inconsistencies may partially be because of differences in study design or certain population characteristics such as diabetes status, which has been proposed to possibly modify associations between *APOE* ε4 and AD or dementia [13].

Hispanic population is the most rapidly growing segment of elderly living in the United States, but thus far very few studies have explored risk factors for dementia in this population [14–16]. Our prior work and other studies reported a higher prevalence of type 2 diabetes among Mexican Americans and also suggested an increased risk of dementia/cognitive impairment without dementia (CIND) among participants with diabetes [14]. Although *APOE* ε4 carrier status was strongly associated with risk of AD and dementia, ε4 is less frequent among Mexican Americans [15,16]. To date, no research, however, explored relationships between PA, *APOE* status, diabetes, and cognitive impairment. We specifically focus on PA interactions because different from *APOE* status it is a modifiable behavioral factor that has been shown to prevent several chronic diseases and premature death even in old age [4]. Moreover, populations with a high proportion of individuals with multiple risk factors for cognitive decline might need special encouragement and culturally sensitive programs to remain physically active in older age.

2. Methods

2.1. Study population

All study participants were enrolled in the Sacramento Area Latino Study on Aging (SALSA), a large, prospective cohort study of community-dwelling Mexican Americans. Residents aged more than 60 years at enrollment, resided in California's Sacramento Valley, and self-designated as Latino/-a were eligible to enroll. A detailed description of sampling procedures has been published elsewhere [17]. The overall response rate was 85% for those contacted and about 22% of the total eligible residents in Sacramento County were recruited, that is, 1789 aged 60 to 101 years were recruited and examined in 1998 to 1999 [17]. Cohort members were followed every 12 to 15 months via home visits during which clinical and cognitive assessments were conducted for up to seven times ending in 2008. In a semiannual 10-minute telephone call between home visits we obtained updates on medications, health events, and some additional sociodemographic factors. Participants who (1) did not answer PA questions, (2) did not provide either buccal or blood samples, (3) had a diagnosis with dementia/CIND at baseline, or (4) did not participate in any follow-up visit were excluded from the analyses. A total of 1438 participants are included in this analysis (Fig. 1). SALSA has been approved by the institutional review boards at the University of Michigan, the University of California at San Francisco and Davis, and the University of North Carolina, Chapel.

2.2. Measures

2.2.1. Physical activity

At baseline, participants were asked to report the average number of hours they are spending on 18 different types of activities that are common among older adults during a regular week. We first assigned metabolic equivalents of task (MET) to each activity based on the Compendium of Physical Activities [18], and then multiplied this value with the reported time (hours/week) spent performing the activity (MET-hour/week). We generated moderate to vigorous cumulative PA measures by summing the MET-hour/week values for more than eight activities that required a threefold or more increase over the metabolic rate required by quiet sitting (≥3 METs); specifically walking, dancing, hunting or camping or boating, swimming or engaging in workouts, golfing or other moderate exercise, gardening or yardwork, house repairs, and heavy housework.

2.2.2. APOE *ε4 genotyping*

Serum samples were collected from each participant and were taken to obtain DNA for *APOE* analysis. *APOE* genotype was identified by polymerase chain reaction amplification followed by restriction endonuclease digestion of the polymerase chain reaction product. Participants were considered *APOE* ε4 status positive if they carried at least one ε4 allele. The sequence surrounding the single-nucleotide polymorphisms matched precisely the published sequences.

2.2.3. Diabetes

Diabetes status was based on reports of a physician diagnosis, antidiabetic medication use, or measured fasting glucose level ≥126 mg/dL (7.0 mmol/l), in a blood sample taken at the home visit (not only at baseline). In a medicine cabinet inventory, we recorded diabetes medications and classified them

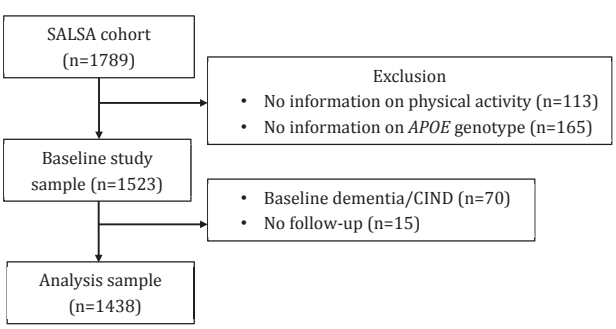

Fig. 1. Flow chart of study participants, Sacramento Area Latino Study on Aging (SALSA), 1998 to 2008. Abbreviations: APOE, apolipoprotein E; CIND, cognitive impaired without dementia.