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

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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 1,438 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 non-carriers or non-diabetics 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—Physical activity 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

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 healthcare 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 non-demented 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]. While 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], while in two other studies, late-life PA was inversely associated with dementia risk only among non-carriers 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 due to 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].

Hispanics are 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 as well as other studies reported a higher prevalence of type 2 diabetes among Mexican Americans, and also suggested an increased risk of dementia/CIND among participants with diabetes [14]. While *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) study, a large, prospective cohort study of community-dwelling Mexican

Americans. Residents over 60 years of age 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; i.e. 1,789 aged 60–101 years were recruited and examined in 1998–1999 [17]. Cohort members were followed every 12–15 months via home visits during which clinical and cognitive assessments were conducted for up to seven times ending in 2008. In a semiannual 10-min phone call between home visits we obtained updates on medications, health events, and some additional sociodemographic factors. Participants who 1) did not answer PA questions, or 2) did not provide either buccal or blood samples, or 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 1,438 participants are included in this analysis (Figure 1). SALSA has been approved by the Institutional Review Boards at the University of Michigan and 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 per week) spent performing the activity (MET-hour/week). We generated moderate to vigorous cumulative PA measures by summing the MET-hour/week values over 8 activities that required a three fold 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 deoxyribonucleic acid (DNA) for *APOE* analysis. *APOE* genotype was identified by polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product. Participants were considered *APOE* ε4 status positive if they carried at least one ε4 allele. The sequence surrounding the single nucleotide polymorphisms (SNPs) 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 according to the Centers for Disease Control and Prevention Ambulatory Care Drug Database (http://www2.cdc.gov/drugs/); fasting glucose tests required no caloric intake for 8-hour or more. Because all participants were age 60 or above, we assumed that most were type 2 diabetes and we will refer to type 2 diabetes in this paper as such [19].

2.2.4. Dementia and Cognitive impairment without dementia (CIND)—Detailed procedures to screen and classify dementia and CIND were described elsewhere [17]. Briefly, each participant was assessed via two cognitive screening tests at baseline and each annual follow-up visit to determine whether they needed a neuropsychological evaluation: the Modified Mini-Mental State Examination (3MSE) and a delayed word recall trial from the Spanish English Verbal Learning Test (SEVLT). Participants were referred for a neuropsychological test battery [20] and a standard neuropsychological examination (Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)) by a geriatrician if 1) their baseline scores on 3MSE or SEVLT fell below the 20th percentile, or 2) had 8-point decreased on the 3MSE or 3-point decreased SEVLT and the scores below the 20th percentile at follow-up [17]. A team of neurologists and a neuropsychologist reviewed all referred cases and classified them as demented, CIND, or cognitively normal on the basis of neuropsychological test battery and IQCODE as well as their history, mental status examination, and findings from the neurologic examination when available. Standard diagnostic criteria were applied for a diagnosis of dementia (DSM-IV) [21], Alzheimer disease (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) [22], and vascular dementia (California Alzheimer's Disease Diagnostic and Treatment Centers) [23]. We combined dementia and CIND partly to improve our statistical power. Given that previous longitudinal studies have reported that people diagnosed with mild cognitive impairment (MCI) are more likely to develop dementia or AD than cognitively normal people [24], the combined outcome allowed us to include clinically important cognitive decline prior to dementia.

2.2.5. Other potential covariates—During the baseline interview we asked participants to report their age, gender, education (years), country of birth, primary language, smoking status (never, current, or ever smoker), and alcohol use (never, daily, weekly, or monthly drinker). Trained interviewers measured participants' standing height and weight and obtained the body mass index (BMI; kg/m^2). Depressive symptoms were evaluated using Center for Epidemiologic Studies Depression Scale (range 0–60). Hypertension was based on measured systolic blood pressure (140 mmHg), self-report of a physician diagnosis, and/or antihypertensive medication use. Information on vascular risk factors and diseases was obtained from self-reports of physician diagnoses such as stroke or myocardial infarction (MI). Morning fasting serum samples were used to test for low density lipoprotein (LDL) cholesterol using the LDL Direct Liquid Select (number 7120; Equal Diagnostics). Statin use was derived from the medicine cabinet inventory [25].

2.3. Statistical analysis

Cox regression models with calendar time as the underlying time scale were used to assess the impact of PA, *APOE ε4* and diabetes on risk of dementia/CIND. Participants who did not return for exams were censored at their last date of contact, or at their time of death if they died. We first categorized PA into tertiles based on the distribution of MET scores: <35 (low), 35–82.5 (medium), 82.5 (high) MET-h/wk. Since the effect estimates for medium and high level of PA were found to be similar, we merged these into one category to increase power for our gene-environmental interaction (GxE) analyses. Age, sex, education, smoking status, history of stroke, and hours of standing or walking at work were entered into all

models as covariates. The main effects of *APOE ε4* allele, diabetes status, and of PA were explored, together with all possible two- and three-way interactions with PA. For each variable included in the regression models, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. We also calculated the relative excess risk due to interaction (RERI) to evaluate interactions on an additive scale [26, 27]. We further conducted analyses for dementia or CIND separately. We also adjusted for hypertension, cardiovascular disease, depressive symptoms, BMI, smoking status, alcohol use, nativity, area of residence, type of occupation and hour of standing or walking at work as potential confounders. Statistical analyses were performed using SAS 9.3. All analyses used an α level of 0.05 for statistical significance (two-tailed).

3. Results

Of 1,438 cognitively intact participants at baseline with at least one follow up, a total of 136 developed dementia/CIND during a mean follow-up time of 6.5 years. Table 1 represents the baseline characteristics of subjects by levels of PA. The proportion of subjects with at least one ε4 allele was slightly higher among participants with high level of PA (14.7% vs. 12.8%), and no one in our population had ε2/ε2. Compared with participants who engaged in low levels of PA, those with higher activity levels were slightly younger, more often male, had more years of education and a lower prevalence of diabetes or history of stroke. They were also less likely to report ever having smoked cigarettes and more likely to be a former smoker.

The results of Cox regression analyses showed as expected that high levels of PA are inversely associated with risk of dementia/CIND, while *APOE* ε4 allele carrier status and diabetes at baseline increase risk (high PA: HR=0.70, P=0.04; ε4: HR=2.30, p<0.001; diabetes: HR=2.20, p<0.001; Table 2). Compared with non-carriers, having one and two ε4 alleles resulted in 2.08 and 11.5 fold increased risks of dementia/CIND, adjusting for multiple potential confounding factors.

When we examined combined effects of PA and *APOE* ε4 status, ε4-carriers who reported low levels of PA had a more than three-fold risk of dementia/CIND compared with highly active non-carriers (Table 3). Compared with physically active *APOE* ε4 non-carriers, we observed a 39% increase in risk for low PA non-carriers, a 120% higher risk for high PA ε4-carriers, and a 244% for low PA ε4-carriers. The same pattern was seen for combined effects of PA and diabetes. Compared with highly active non-diabetics, the HRs for dementia/CIND were 1.55, 2.39 and 3.11 for those reporting low PA, diabetes, and both, respectively. We further evaluated the combined associations of PA, *APOE* ε4 allele and diabetes with risk of dementia/CIND, and observed a nearly 10-fold risk increase for *APOE* ε4 carriers with diabetes and low levels of PA compared with those with high PA who were not diabetics and without a *APOE* ε4 allele (HR = 9.49, 95% CI = 3.57–25.3; Fig.1; Supplementary Table 1). No statistically significant two- or three-way super-additive interactions were found.

In sensitivity analysis, we adjusted for several other potential confounders (eg. nativity, hypertension, cardiovascular disease, depressive symptoms, BMI, smoking status, alcohol use, race, area of residence and type of occupation, LDL and statin) but estimates did not

change substantially; thus, these factors were not included in final models. Analyses in which we considered dementia and CIND separately effect estimates were very similar to those we reported for the combined outcome (i.e. dementia/CIND) (Supplementary Tables 2–4).

4. Discussion

In this longitudinal study of Latino elderly adults, the co-presence of low levels of moderate to vigorous PA with either *APOE* ε4 status or diabetes was associated with a shorter dementia-and CIND-free follow-up time. Moreover, higher PA protected against the onset of dementia/CIND most strongly in those who were *APOE* ε4 carriers with diabetes.

A key finding of the current study is the large (nearly 10-fold) increased risk of dementia/ CIND in *APOE* ε4 carriers who were physically inactive and also had diabetes as compared with non-ε4 carriers, non-diabetic and active individuals. The biological mechanisms underlying these associations are not known but may include inflammation and oxidative stress. Increasing evidence indicates that effects of *APOE* on oxidative stress prevention and anti-inflammation are isoform-specific [6, 28, 29]. Compared with other *APOE* isoforms, the ε4 allele is associated with higher oxidative stress and more likely to overactive pro-inflammatory and/or reduce anti-inflammatory responses [6, 28, 29]. Likewise, oxidative stress is one of the main mechanisms believed to explain insulin resistance in diabetes, and these cellular stresses are also related to inflammation [30]. Indeed, an increased cortical interleukin-6 (IL-6) level and more microvascular infarcts have been associated with risk of dementia in people with diabetes and biomarkers that are related to neuroinflammation [31]. Together, brain inflammation and oxidative stress may accumulate oxidative damage and have detrimental influences on neural tissue, which contribute to cognitive decline and AD [32]. Moreover, inflammation and pro-inflammatory cytokines are known to impair insulin like growth factor 1 (IGF-1) transduction and brain-derived neurotrophic factor (BDNF) signaling in neurons, and low levels of IGF-1 and/or BDNF are associated with cognitive impairment [33]. Regular exercise is known to reduce visceral fat mass and adipose tissue, which contribute to systemic inflammation [34]. With or without fat mass loss, exercise induces IL-6 production from contracting muscle, and stimulates anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1ra) and IL-10 while inhibiting tumor necrosis factor - alpha (TNF-α) production [33, 35–37]. In addition, regular PA can protect against chronic metabolic and cardiorespiratory diseases known to be associated with an increased risk of cognitive decline [34, 38].

As has been reported previously [15, 16], *APOE* ε4 is less frequent among Mexican Americans. However, we found the AD/dementia prevalence to be similar to non-Hispanics, suggesting that other risk factors are more prevalent or that they may increase risk together with *APOE* ε4 [14, 15]. Prior studies of PA and *APOE* ε4 genotype and risk of dementia/AD reported conflicting results, which might have been due to risk modifying characteristics of the study population, or duration of follow-up, assessment and definition of PA and cognitive outcome, or the scale used to assess the interactions (i.e. additive or multiplicative interaction), and thus the comparisons across studies should be made with caution. In addition, previous studies generally presented data in questionnaire-specific

categories (e.g. defining high level of physical activity as participating in leisure-time activities several times a week) but did not provide personal energy expenditure estimates that can be translated into PA levels that correspond to guidelines. The Cardiovascular Health Study (CHS) is the only PA and *APOE* ε4 study that estimated personal energy expenditure (kilocalories/week) and used quartile categories [9]. The PA cutoff (≥ 35 MET hours/week) in our study is slightly higher than this study's highest quartile but followed the Institute of Medicine (IOM) guidelines that recommend at least 60 minutes of moderate activity (approximately 3–6 METs) each day for "active" adults [39]. Our results corroborate previous findings that - regardless of *APOE* ε4 status - being active in late-life benefits cognition [11, 12, 40].

Our findings agree with prospective population-based studies and a meta-analysis indicating that people with diabetes are at increased risk of dementia [41]. However, two studies that recruited Mexican Americans did not support these findings despite the increased prevalence of diabetes [15, 16]. When we examined the combined effects of diabetes and PA, we estimated 3-fold increased risks in diabetics with low levels of PA compared with non-diabetics with high PA levels. To our knowledge, no studies have yet reported on interactions between PA and diabetes for dementia or cognition decline. Nevertheless, a randomized controlled trial suggested that 6 months of aerobic exercise improved executive function and insulin sensitivity in people with prediabetes or newly diagnosed type 2 diabetes [42]. We also observed a 4.26 times higher risk for dementia/CIND among *APOE* ε4 carriers with diabetes, compared with participants who had neither diabetes nor *APOE* ε4; however, we did not find an interaction on an additive scale (supplementary Table 5). While the 2 US studies reported a small but super-additive interaction, for AD they estimated 4-fold joint risks similar in size for diabetes and *APOE* ε4 [13].

SALSA is a longitudinal population-based study cohort of older people of Mexican heritage (N=1,789) from 6 county areas that included metropolitan area as well as surrounding rural counties. This is the only population-based study that assessed dementia in Mexican Americans, a large but understudied ethnic group. The repeated-measures design assessing cognition every 12–15 months for up to seven study visits, enabled us to study incident dementia/CIND over a relatively long period (on average 6.5 years) and assess the influence of baseline PA, diabetes and *APOE* ε4 allele carrier status. Furthermore, we created cumulative PA scores (MET-hour/week) to take both intensity and duration into account, thus measuring PA more comprehensively than prior studies that only presented PA data in specific categories such as whether the participant engaged in leisure-time activities several times a week. Finally, we also assessed and were able to adjust for a large number of demographic and health-related covariates i.e. potential confounders. We previously reported that statin users were less likely to develop dementia/CIND [25], however, further adjusting for baseline statin use in the model did not change the results. In addition, we omitted adjusting for LDL since it can be considered an intermediate in the pathway between PA and cognitive function.

Limitations include that we were unable to assess and/or adjust for changes of PA in relation to cognitive decline because we only collected PA once at baseline. Additionally, our PA measure based on self-reported information is inevitably prone to reporting errors. We did

not evaluate reliability of PA assessment in our SALSA population, however, the PA questionnaire originated from the Alameda County Study [43] and a large number of previous studies found associations between this PA measure and various health outcomes; external validity and internal reliability are high. This measure is also very similar to the Minnesota Leisure Time Physical Activity Questionnaire, which is commonly used among the elderly and has acceptable reliability and validity [44, 45]. Moreover, given that dementia and cognitive impairment occurred during follow-up, it is reasonable to suggest that misclassification of PA level measured at baseline is non-differential and most likely biases our results toward the null. We combined dementia and CIND into one outcome (i.e. dementia/CIND) for purposes of parsimony. Although prior studies reported conflicting associations of PA and *APOE* ε4 with the risk of dementia, AD and cognitive decline, we observed a consistent pattern of associations for all three definitions i.e. for dementia and CIND combined as well as separately (Supplementary Table 2). The 2-way and 3-way interaction results are also consistent in direction and significance for both the combined and separate outcomes (Supplementary Table 3&4). As expected, the smaller cell sample sizes for a single outcome produce wider confidence limits. While we adjusted for a number of demographic and comorbidity related factors, as in all observational studies, residual confounding is a possibility. Although associations between PA and depression have been reported [46], and depression may be a risk factor for dementia [47], we did not observe an interaction of PA and depression on dementia/CIND risk, and baseline depressive symptoms did not confound our results, similar to previous studies [8, 9, 15]. Also, we cannot rule out the possibility that low PA is a proxy of other adverse health outcomes that contributes to cognitive decline. Lastly, compared with healthier participants, those with diabetes or cognitive decline may be more likely to be lost to follow-up. However, our attrition rate was low (5%) and the expected effects of this drop out would have been a bias towards the null.

In conclusion, Mexican Americans who are physically inactive and are *APOE* ε4 allele carriers with diabetes were nearly 10 times more likely to have incident dementia/CIND than active, non-diabetics who do not carry the *APOE* ε4 allele. In light of this rapidly growing elderly population with a very high rate of diabetes, it might be worthwhile targeting *APOE* ε4 carriers with diabetes for programs that increase PA as an effective preventive strategy against cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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RESEARCH IN CONTEXT

1. Systematic review: We reviewed studies that examined physical activity (PA) and Apolipoprotein E (*APOE*) ε4 genotype in relation to Alzheimer's disease (AD) and dementia. Results were inconsistent and we, thus, hypothesized that diabetes status may modify the association, yet no study has previously examined the joint association.

2. Interpretation: Our findings suggest that PA even in late life may reduce risk of dementia and cognitive impairment without dementia (CIND) in elderly Hispanics; the protective effect of PA is especially efficacious among *APOE* ε4 carriers and those who suffer from diabetes.

3. Future directions: Our findings provide important implications for elderly Mexican Americans with a high rate of diabetes. We recommend actions to promote an active lifestyle to help reduce or postpone cognitive decline among this fast-growing underserved population. Additional studies are also needed to better understand the biological mechanisms underlying the associations we observed.

HIGHLIGHTS

- Low PA, *APOE* ɛ4 and diabetes are risk factors for dementia/CIND in older Hispanics.

- Joint associations between PA and ɛ4 or diabetes with dementia/CIND are strong.

- PA protects against cognitive decline in the presence of *APOE* ɛ4 and diabetes.
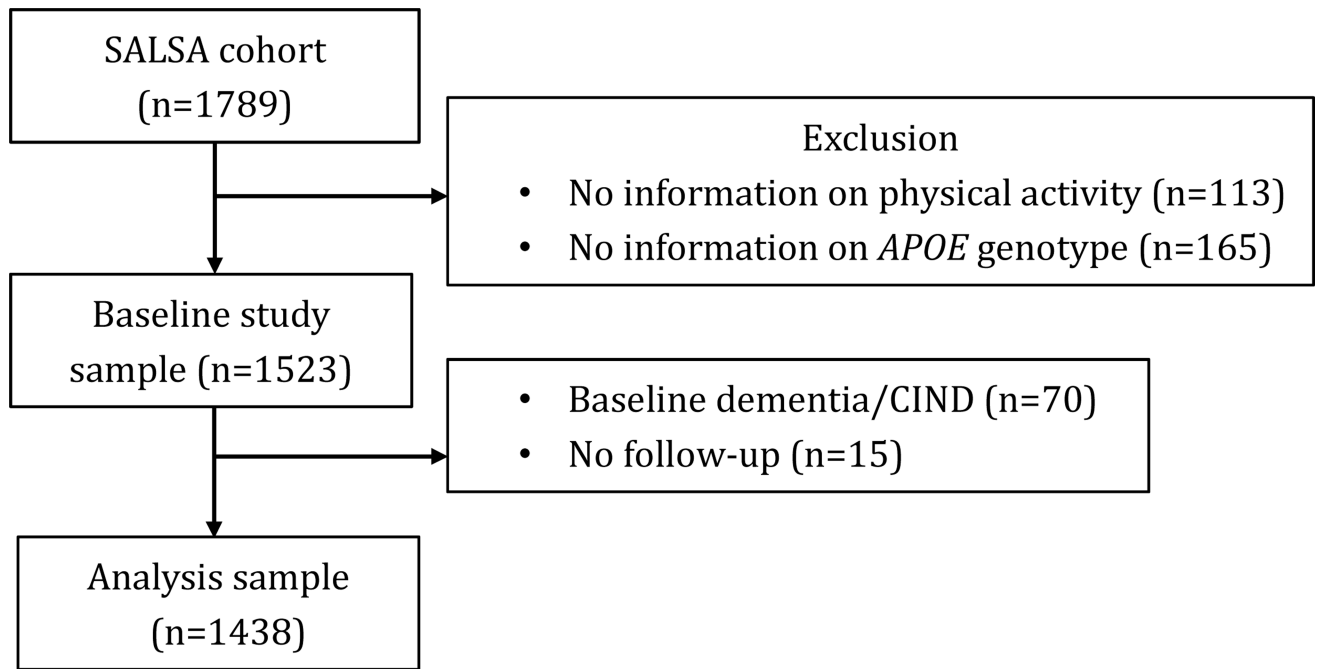
Figure 1.
Flow chart of study participants, Sacramento Area Latino Study on Aging (SALSA), 1998–2008
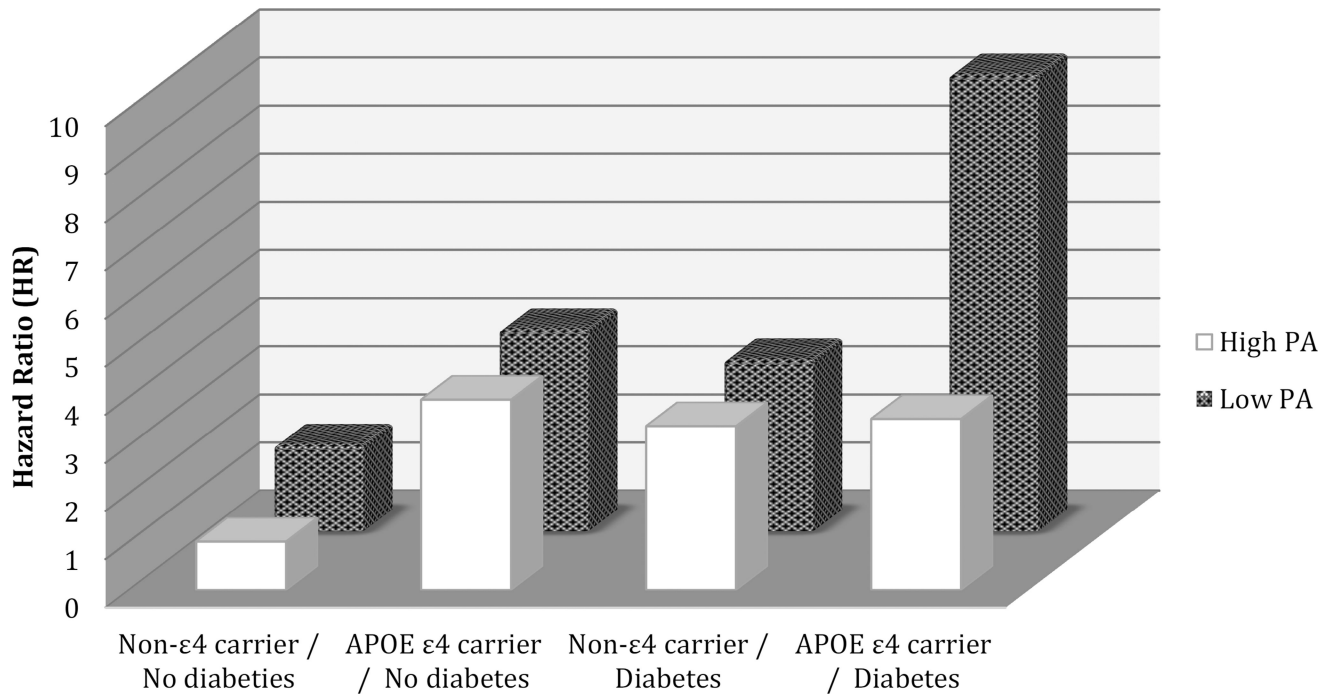
Figure 2.
Three-way interactions of physical activity (PA), apolipoprotein E (*APOE*) ε4 allele and
diabetes status at baseline on risk of dementia and cognitive impaired without dementia
(CIND). Hazard ratios adjusted for gender and baseline age (years), education, smoking
status, history of stoke, and hours of standing or walking at work; relative excess risk due to
interaction (RERI; 95% CI) = 2.34 (−7.03–22.1).

Table 1

Sample characteristics of the study population at baseline by physical activity (PA), Sacramento Area Latino Study on Aging, 1998–2008

| Variable	High PA (n=897)		Low PA (n=541)	
	mean (SD)	n (%)	mean (SD)	n (%)
Demographic				
Age, year	69.7 (6.2)		70.5 (7.2)	
Male		421 (46.9)		177 (32.7)
Education, year	7.7 (5.4)		7.1 (5.3)	
Born in Mexico		392 (43.7)		243 (44.9)
Reside in urban area		777 (86.6)		471 (87.1)
Health-related factors at baseline				
Cardiovascular disease		297 (33.1)		214 (39.6)
Hypertension		600 (66.9)		389 (71.9)
Diabetes		261 (29.1)		195 (36.0)
Stroke		56 (6.2)		57 (10.5)
LDL-C, mg/dl	125.2 (35.0)		119.4 (34.0)	
Statin at baseline		70 (7.8)		58 (10.7)
Behavioral				
Alcohol				
Frequent (daily) drinker		88 (9.8)		38 (7.0)
Moderate (weekly) drinker		129 (14.4)		30 (5.6)
Occasional (monthly) drinker		103 (11.5)		38 (7.0)
Yearly/rarely/never drinker		577 (64.3)		434 (80.4)
Smoking status				
Current		104 (11.6)		57 (10.5)
Former		390 (43.5)		220 (40.7)
Never		403 (44.9)		64 (48.8)
Depression (CESD)	8.6 (9.2)		11.4 (11.7)	
Occupation				
Non-manual		206 (23.2)		106 (19.7)
Manual		550 (62.0)		299 (55.6)
Other (housewives/unemployed)		131 (14.8)		133 (24.7)
Cognitive performance				
3MSE	87.5 (9.4)		85.4 (11.6)	
SEVLT (No. of words)	9.0 (2.8)		8.5 (2.9)	
***APOE* status**				
Any ε4		132 (14.7)		69 (12.8)
ε2/ε3		65 (7.3)		45 (8.3)
ε2/ε4		7 (0.8)		2 (0.4)
ε3/ε3		700 (78.0)		427 (78.9)
ε3/ε4		116 (12.9)		65 (12.0)

	High PA (n=897)		Low PA (n=541)	
Variable	**mean (SD)**	**n (%)**	**mean (SD)**	**n (%)**
ε4/ε4		9 (1.0)		2 (0.4)

Abbreviation: SD, standard deviation; CESD, Center for Epidemiologic Studies Depression Scale; 3MSE, Modified Mini-Mental State Examination; SEVLT, delayed word recall trial from the Spanish English Verbal Learning Test; *APOE*, apolipoprotein E.

[a]PA cutoff = 35 MET-hour/week

Table 2

Cox proportional hazards regression to evaluate the risk of dementia/CIND according to physical activity (PA), *APOE* e4 allele and diabetes status, controlled for baseline covariates

	Model 1		Model 2		Model 1		Model 2	
	Adjust HR (95% CI)	p-value	Adjust HR (95% CI)	p-value	Adjust HR (95% CI)	p-value	Adjust HR (95% CI)	p-value
Physical activity, high vs low	0.66 (0.47–0.92)	0.02	0.70 (0.49–0.99)	0.04	0.64 (0.46–0.91)	0.01	0.68 (0.48–0.97)	0.03
APOE e4 allele (yes vs. no)	2.15 (1.43–3.22)	<.001	2.30 (1.53–3.47)	<.001				
APOE e4 allele (1 vs 0)					1.95 (1.27–2.98)	<.001	2.08 (1.36–3.20)	<.001
APOE e4 allele (2 vs 0)					9.52 (3.42–26.48)	<.001	11.47 (4.08–32.22)	<.001
Diabetes	2.41 (1.71–3.38)	<.001	2.20 (1.56–3.12)	<.001	2.45 (1.74–3.44)	<.001	2.24 (1.58–3.17)	<.001
Age	1.13 (1.10–1.15)	<.001	1.12 (1.09–1.14)	<.001	1.13 (1.10–1.16)	<.001	1.12 (1.09–1.15)	<.001
Male vs. female	0.77 (0.54–1.10)	0.15	0.80 (0.54–1.18)	0.25	0.76 (0.53–1.09)	0.14	0.80 (0.54–1.18)	0.26
Education, year			0.96 (0.92–0.99)	0.01			0.96 (0.92–0.99)	0.01
Former smoker vs never			0.94 (0.63–1.38)	0.74			0.92 (0.62–1.36)	0.68
Current smoker vs never			1.88 (1.10–3.23)	0.02			1.92 (1.12–3.29)	0.02
Stroke			1.89 (1.19–3.02)	0.01			1.92 (1.20–3.07)	0.01
Hours of standing or walking at work			0.95 (0.91–1.00)	0.05			0.95 (0.91–1.00)	0.05

Abbreviation: CIND, cognitive impairment without dementia; *APOE*, apolipoprotein E; HR, hazard ratio; CI, confidence interval.

[a]PA cutoff = 35 MET-hour/week

Table 3

Joint effects between physical activity (PA) and *APOE* e4 allele or diabetic status on incident dementia/CIND[a]

		High level of PA [b]			Low level of PA [b]	
	case/total	Crude HR (95% CI)	Adjust HR (95% CI)	case/total	Crude HR (95% CI)	Adjust HR (95% CI)
APOE e4						
No	52/765	1.00	1.00	52/432	1.79 (1.22–2.63)	1.39 (0.94–2.07)
Yes	19/172	1.96 (1.16–3.32)	2.20 (1.29–3.74)	13/69	2.80 (1.53–5.15)	3.44 (1.85–6.39)
Diabetes						
No	37/636	1.00	1.00	38/346	2.07 (1.32–3.26)	1.55 (0.97–2.48)
Yes	34/261	2.75 (1.73–7.39)	2.39 (1.49–3.84)	27/195	3.13 (1.91–9.15)	3.11 (1.87–5.18)

Measure of interaction on additive scale: RERI (95% CI): PA and e4 = 0.85 (−1.34–3.04); PA and diabetes = 0.16 (−1.40–1.73)

Abbreviation: *APOE*, apolipoprotein E; CIND, cognitive impairment without dementia; HR, hazard ratio; CI, confidence interval; RERI, relative excess risk due to interaction.

[a] Cox proportional model adjusted for gender and baseline age (years), diabetes or *APOE* e4, education, smoking status, history of stroke and hours of standing or walking at work.

[b] PA cutoff = 35 MET-hour/week