HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2023 February 16.

Published in final edited form as:

Alzheimers Dement. 2023 February ; 19(2): 507–517. doi:10.1002/alz.12677.

Modifying effects of race and ethnicity and *APOE* on the association of physical activity with risk of Alzheimer's disease and related dementias

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Abstract

Introduction: We investigated whether the protective association of physical activity with risk of Alzheimer's disease and related dementias (ADRD) has genetic or behavioral variations.

Methods: In the Multiethnic Cohort, we analyzed moderate or vigorous physical activity (MVPA) reported at ages 45 to 75 among 88,047 participants in relation to 13,039 incident diagnoses of late-onset ADRD identified in Medicare claims (1999 to 2014), by five racial and ethnic groups, hours sitting, and in a subset (16%), apolipoprotein E (*APOE*) genotype.

Results: MVPA was inversely associated with ADRD (hazard ratio for ≥14 vs <2.5 hours/week: 0.83, 95% confidence interval [CI]: 0.76 to 0.90 in men; 0.88, 5% CI: 0.81 to 0.95 in women). The association was inverse in all racial and ethnic groups except Black participants (*P*-heterogeneity = 0.52), but stronger in individuals with lower levels of sitting duration or those who do not carry the *APOE* e4 risk allele.

Discussion: The different effects of physical activity by sitting duration and *APOE* genotype warrant further research.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Keywords

Alzheimer's disease; dementia; physical activity; prospective studies; race and ethnicity; sitting

1 | INTRODUCTION

Dementia affects around 50 million people worldwide, imposing substantial health care costs, productivity loss, and caregiving burden.[1] In the United States, 5.8 million adults 65 years of age or older live with late-onset Alzheimer's disease (AD), the most prevalent neurodegenerative disorder in this country's aging population.[2] The amyloid beta (Aβ) deposits and neurofibrillary tangles associated with Alzheimer's pathology are also found at autopsy in the majority of other dementia cases that are diagnosed for vascular, Lewy body, frontotemporal, or non-specific pathology. Therefore, Alzheimer's disease and related dementias (ADRD) are generally studied collectively.[3–6] Given the lack of effective prophylactic and clinical treatments for ADRD,[2,7] identification and better understanding of lifestyle factors and cardiometabolic disorders that contribute to the risk of ADRD are of critical importance for the prevention and management of the disease.[8–10]

Physical activity, in particular, has been consistently associated with a reduced risk of developing ADRD in observational studies.[11–13] In a meta-analysis of 44 prospective cohort studies, physical activity performed for at least 1 hour twice per week was associated with a 23% decrease in all-cause dementia risk and a 32% decrease in AD risk.[11] However, a recent meta-analysis observed a null association when excluding cases diagnosed within 10 years of physical activity assessment and attributed the inverse association to decreased physical activity due to latent dementia among pre-clinical cases.[14] In addition, the results of randomized-controlled interventions of exercise and AD have been inconsistent. Although some interventions resulted in improved cognition among both cognitively healthy older adults and patients with AD,[15,16] evidence for the effect of single-component physical activity interventions on preventing cognitive decline is largely insufficient.[17] Some have suggested that multiple types of exercise were more effective in improving cognitive functions, and in women more than in men.[15] Results from observational studies can help guide the design of future interventions that target at-risk populations. Most studies to date on physical activity and AD or dementia involved a single racial or ethnic population (non-Hispanic White or Asian) and did not allow for comparisons by race and ethnicity. Furthermore, previous studies rarely accounted for sedentary behavior, which by itself may have independent metabolic effects, and thus, should be examined in tandem with moderate or vigorous physical activity (MVPA).[18] In addition, the protective effect of physical activity may moderate the predominant genetic risk for AD conveyed by the apolipoprotein E (*APOE*) genotype that has been associated with a 2-fold risk with each e4 risk allele.[19,20]

In the current study, we investigated the association between physical activity and incident ADRD in the population-based Multiethnic Cohort Study (MEC). Using the MEC-Medicare linkage data, we examined whether physical activity assessed at middle to old age was associated with risk of ADRD later in life and whether the associations varied by race and ethnicity, sedentary behavior, and *APOE* genotypes, as well as the follow-up duration

between the MVPA assessment and ADRD diagnosis, age at diagnosis, and body weight status.

2 | METHODS

2.1 | Study population

More than 215,000 adults 45 to 75 years of age entered the MEC by completing a comprehensive questionnaire including physical activity assessment in 1993 to 1996.[21] The participants consisted primarily of five racial and ethnic groups—Black, Japanese American, Latino, Native Hawaiia and White—living in Hawaii and California. The majority of the MEC Latino participants were of Mexican descent: 35% were born in Mexico and 45% were born in United States; among those who were US-born, 66% had a parent born in Mexico. The institutional review boards of the University of Hawaii and the University of Southern California approved the study. These boards considered that informed consent was implied by the return of the baseline questionnaire that was mailed to potential participants along with a cover letter explaining the study. In addition to annual linkage to Hawaii and California death registries and the National Death Index, the cohort has been linked to the Medicare administrative data for 1999 to 2014.[22] For the current study, the analyses were restricted to the MEC participants who were Medicare Fee-for-Service (FFS) beneficiaries (n = 123,186), for whom claims data are available. Medicare surveillance started at the age the participant enrolled in Medicare FFS or in 1999, whichever came later. We excluded participants who were not from the five main racial and ethnic groups (n = 7511), who were enrolled in Medicare at ages younger than 65 likely due to an early onset disability (n = 4707), and who were enrolled in Medicare FFS for fewer than 2 years (n = 6426). In addition, in order to remove prevalent cases of ADRD to study "diagnostic incidence" for the association with physical activity, we excluded those with a disease claim within the first 2 years after the start of Medicare surveillance (n = 2106) and those who reported AD on the MEC questionnaire at 5-year follow-up (1998 to 2002; n = 221). Finally, we excluded those who had missing information on daily sitting or physical activity (n = 6825) and missing covariates on education, marital status, medical history, weight and height, cigarette smoking, and diet (n = 7343). As a result, a total of 88,047 were included in the analysis. This analytic population had characteristics that were similar to all cohort members ≥65 years of age at the start of Medicare surveillance (n = 110,968) in terms of age, sex, race and ethnicity, body mass index (BMI), education, and smoking status (Table S1).

2.2 | Assessment of physical activity

On the baseline questionnaire at cohort entry (1993 to 1996), participants reported their average weekly or daily time spent in physical activity, sitting, and sleeping during the previous year.[23,24] Three specific categories of physical activity were included: moderate activity (such as housework, brisk walking, golfing, bowling, bicycling on level ground, or gardening), vigorous or strenuous sports (such as jogging, bicycling on hills, tennis, racquetball, swimming laps, or aerobics), and vigorous work (such as moving heavy furniture, loading or unloading trucks, shoveling, weight lifting, or equivalent manual labor). Each activity type was reported in eight duration categories: never, 0.5 to 1, 2 to 3, 4 to 6, 7 to 10, 11 to 20, 21 to 30, and ≥31 hours per week. Total hours of MVPA per week were

calculated as the sum of the midpoints of the categories and used as the physical activity exposure of main interest. Five specific types of sitting activities were queried for: sitting in car or bus, sitting at work, watching TV, sitting at meals, and other sitting activities such as reading, playing cards, or sewing. For each type of sitting activity, participants selected one of seven categories for duration: never, <1, 1 to 2, 3 to 4, 5 to 6, 7 to 10, and ≥11 hours per day. Total daily sitting hours were calculated as the sum of the midpoints of the categories. Sleep duration including naps was asked using six categories: <5, 6, 7, 8, 9, and ≥10 hours per day. Light physical activity was calculated by subtracting the total time spent in MVPA, sitting and sleeping from 24 hours. We also examined metabolic equivalents (METs) for total activities and MET-hours for MVPA per day. In a validation study, the correlation for total energy expenditure based on the MEC physical activity questionnaire and the objective method of doubly labeled water was reasonable for METs (r = 0.29).[25] The same information on physical activity was collected at a 10-year follow-up survey (2003 to 2008), except that moderate activity was separated into questions on recreational (brisk walking, golfing, bicycling on level ground, gardening, dancing, or softball) and work (housework, yard work, restaurant work, sales work, or equivalent moderate physical activity) activities.

2.3 | Covariates

In addition to physical activity questions, the baseline questionnaire collected information on demographic characteristics, education, medical history, weight and height, smoking, and dietary habits using a validated, quantitative food frequency questionnaire (QFFQ) with more than 180 food items.[21,26] The Healthy Eating Index-2015 (HEI-2015) was calculated as a measure of overall diet quality as described previously.[27]

We compiled genotyping array data available from over 20 genome-wide association studies (GWAS) conducted in the MEC,[28] which were then imputed using the Haplotype Reference Consortium. As a result, of the 88,047 participants in the current analysis, 14,332 participants (1973 ADRD cases, or 16%) had *APOE* genotype data, following quality control filtering and imputation (Supplemental Digital Content). The *APOE* genotype, encoding the isoforms of apolipoprotein E, was determined based on two single nucleotide polymorphisms (SNPs; rs429358 and rs7412), for the alleles, e2 (T/T; Cys112, Cys158), e3 (T/C; Cys112, Arg158), and e4 (C/C; Arg112, Arg158).[29]

2.4 | Outcomes

The diagnostic incidence of ADRD during the Medicare linkage period (1999 to 2014) was the primary outcome of interest. A diagnosis of ADRD was identified among FFS beneficiaries based on the International Classification of Disease, Ninth Revision (ICD-9) codes in the claims data: for AD, 331.0; for ADRD, 331.1, 331.11, 331.19, 331.2, 331.7, 331.82, 332.0 and 331.0 (Parkinsonism), 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 290.9, 294.0, 294.10, 294.11, 294.20, 294.21, 294.8, and 797. For the definition of ADRD, we combined the approaches used by Medicare (ie, excluding alcohol-induced dementia [291.2], Jakob-Creutzfeldt disease [046], drug-induced [292.82], Huntington disease [333.4]) and by Goodman et al. (ie, including Lewy body dementia [331.82, 331.0, 332.0], idiopathic dementia [290.9], and unspecified dementia [294.20, 294.21]).[30]

2.5 | Statistical analysis

Cox proportional hazards models with age as the time metric were used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for ADRD for men and women separately. For the current analysis, the follow-up for case ascertainment began 2 years from the start of Medicare surveillance or from January 1, 1999, whichever came later, to account for the minimum enrollment period of 2 years on Medicare. The follow-up ended at the earliest of the following dates: claim's date of service for AD/ADRD, date of death, or Dec 31, 2014. MVPA and total sitting variables were categorized into quintiles based on the distributions in the entire study population. The lowest quintile for MVPA (<2.5 hours per week) was set as a reference group. This cutoff value, 150 minutes per week, is the minimum recommendation for moderate-intensity physical activity for American adults.[31] The tests for a linear trend were performed by modeling sex- and race- and ethnicity-specific median values within the quintile categories as a continuous variable. The proportional hazards assumption was verified by the Schoenfeld residuals method.[32]

Sex-specific models included age at cohort entry and age at start of Medicare surveillance as covariates and race and ethnicity as a strata variable. Models were further adjusted for covariates from the baseline questionnaire, including education (years), marital status (married, not married), history of hypertension (yes, no), history of heart disease (yes, no), history of stroke (yes, no), history of diabetes (yes, no), smoking status (never, former, current), pack-years of cigarette smoking, BMI (kg/m^2), total sitting hours, alcohol consumption (g/day), and HEI-2015 score, as well as Medicare usage, as defined by the average number of inpatient claims (<1, ≥1 per year) and outpatient claims (<1, ≥1 per year). The models for total sitting were mutually adjusted for MVPA. We considered sleeping hours and total energy intake as covariates, but did not retain them in the final model, since they did not affect the main associations. Because the association was similar in men and women, we combined men and women for subgroup analysis with adjustment for sex as a strata variable.

We ran the multivariate models stratified by race and ethnicity, BMI, sitting time, age at cohort entry, follow-up time, and age at ADRD claim. For the 16% of the participants with *APOE* genotype data available, the models were run by *APOE* e4 carrier status (carriers of one to two copies of the e4 allele vs non-carriers). This subset with *APOE* e4 carrier status, compared to the full sample, included proportionally more men, Blacks, Native Hawaiians, and smokers and overweight and more educated participants (Table S1). Heterogeneity of the main association across subgroups was tested by Wald statistics for cross-product terms between the trend variables for physical activity and the subgroup variable in the combined data, except for the subgroups by *APOE* e4 carrier status, for which the indicator variable for ≥2.5 or <2.5 hours per week of MVPA was used instead of the trend variable.

We repeated the analysis in the 41,746 men and women with physical activity and covariate data from the 10-year follow-up survey and without prior ADRD. The outcome was incident ADRD (3885 cases) based on claims after the 10-year follow-up (from 2003 to 2008 through 2014). All statistical tests were two-sided. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

During a mean Medicare surveillance of 10.4 years (range: 2 to 16), 13,039 incident cases of ADRD were identified among 88,047 eligible participants. Table 1 provides the characteristics of participants at cohort entry by levels of MVPA. Men and women who were more physically active were more likely to be Native Hawaiian or White, to have lower BMI, to have a greater intake of alcohol and total energy, to have a higher HEI-2015 score, to be former smokers, and to be married, whereas they were less likely to have history of hypertension, heart disease, stroke, and diabetes, or to make inpatient Medicare claims.

The associations of physical activity in different intensities with risk of ADRD are shown in Table 2. MVPA showed the strongest association with a decreased risk of ADRD in both men and women: HR = 0.83 (95% CI: 0.76–0.90) for the highest versus lowest quintile, *P*-trend <0.001 in men and HR = 0.88 (95% CI: 0.81–0.95), *P*-trend = 0.004 in women. The associations did not differ between men and women (*P*-heterogeneity by sex = 0.52). After disaggregating physical activity levels, moderate activity had stronger associations than did vigorous sports or work activities in both men and women. We repeated the analysis using METs for total activities (accounting for light and sedentary activities, as well as MVPA and sleep) versus MET hours only for MVPA and similarly observed a stronger inverse association for the latter (data not shown). In a sensitivity analysis excluding 1927 cases claimed within the first 3 years of follow-up, the association between MVPA and ADRD risk remained similar (Table S2).

In the analysis for sedentary behaviors (Table 3), total sitting time was not associated with ADRD risk in either men or women. In men, there was no significant association for specific sedentary behaviors. In women, although total sitting was not associated with the risk, sitting in a car or bus (HR = 1.10, 95% CI: 1.00–1.21, for ≥3 vs <1 hour/day, *P*-heterogeneity by sex = 0.14) and sitting to watch TV (HR = 1.13, 95% CI: 1.02–1.24, for ≥5 vs <1 hour/day, *P*-heterogeneity by sex = 0.07) were related to increased risk, whereas sitting at work was associated with decreased risk of ADRD (HR = 0.82, 95% CI: 0.72–0.92, for ≥7 vs 0 hours/day, *P*-heterogeneity by sex = 0.08).

In race- and ethnicity-specific analyses with men and women combined (Table 4), an inverse trend in the MVPA-ADRD association was significant in Japanese American (*P*-trend <0.001) and White (*P* = 0.007) groups and consistent, albeit not reaching statistical significance in Latino (*P* = 0.14) and Native Hawaiian (*P* = 0.23) groups. However, in Blacks, no suggestion of association was observed across MVPA levels (*P*-heterogeneity across racial and ethnic groups = 0.52). When restricting analyses to Black participants without the e4 allele, an inverse association was suggested (HR = 0.86, 95% CI: 0.67–1.11, for ≥2.5 vs <2.5 hours/week of MVPA). For total sitting time, no significant association with ADRD risk was found in any racial and ethnic group. When accounting for deaths from other causes than ADRD as a competing risk, the association between MVPA and ADRD was attenuated but still significant (HR = 0.92, 95% CI: 0.87–0.97, for the highest vs lowest quintile, *P*-trend = 0.02), whereas no substantial change was found for total sitting time (Table S3).

Participants with less total sitting time showed a stronger inverse association of MVPA (*P*-trend <0.001 for ≤6 hours/day and 0.81 for ≥10 hours/day; *P*-heterogeneity = 0.04) (Table 5). The similar joint analysis was performed for each sedentary behavior and none of the heterogeneity tests was significant (data not shown). In analyses by *APOE* e4 carrier status (Table 6), a decrease in ADRD risk was found in all non-carriers with ≥2.5 hours per week of MVPA, whereas no association was found among carriers (*P*-heterogeneity = 0.02).

No heterogeneity in the association between MVPA and ADRD was found across BMI levels (Table S4, *P*-heterogeneity = 0.73), age at cohort entry (Table S5, <65 vs ≥65 years, *P*-heterogeneity = 0.11), or age at ADRD diagnosis (Table S6, <75 vs ≥75 years, *P*-heterogeneity = 0.87). The inverse association was found for the cases with ≥10 years (*P*-trend = 0.001) as well as for those with <10 years (*P*-trend <0.001) between the physical activity assessment and ADRD diagnosis (Table S7, *P*-heterogeneity <0.001). When MVPA was examined at the 10-year follow-up and subsequent ADRD risk in a subset (Table S8), the inverse association for MVPA was stronger than that for MVPA assessed at cohort entry. In addition, the inverse association was found for sports as well as work activities in both men and women.

4 | DISCUSSION

In this population-based prospective study, we replicated the association between higher physical activity and a lower risk of ADRD, providing rare evidence of the important protective relationship in an ethnically diverse population. In the combined data, ≥5 hours weekly (or about ≥40 minutes daily) of MVPA reported at middle or older ages was associated with an ≈15% lower risk of subsequent ADRD, independent of a number of potential confounding factors including sitting duration. We observed that the inverse MVPA-ADRD association was significant or suggestive among all racial and ethnic groups apart from Black participants. In addition, our large data analysis suggests modifying effects by exposures to sedentary behaviors or predominant genetic susceptibility to AD. The risk reduction from MVPA was greater among individuals with a shorter, compared to longer, sitting duration and those who do not carry the *APOE* e4 risk allele. On the other hand, we found similarly protective associations of MVPA by BMI levels, age at diagnosis, or age cohorts.

Our findings are consistent with those of previous prospective studies showing an inverse association between physical activity and AD or dementia.[11,33–36] In particular, our results contradict the recent meta-analysis that attributed the inverse association to decreased physical activity due to latent dementia among pre-clinical cases.[14] The mean duration between the physical activity assessment (1993 to 1996) and the Medicare claim (1999 to 2014) in the MEC was 15.0 (± 3.8) years. For most of the ADRD cases (86%), physical activity was assessed ≥10 years before the Medicare claim and the inverse association was observed when restricting the analysis to those cases. In addition, removing the cases within the first 3 years of follow-up from the analysis did not change the inverse association.

Although our results, overall and in White and Japanese American groups, are consistent with previous reports based respectively on White and East Asian populations in Japan and

China,[11,33–36] we found some suggestion of racial and ethnic differences. A risk reduction was observed in White and Japanese American groups with statistical significance and in Native Hawaiian group with a non-linear trend; however, no association was found in Black and Latino groups for any physical activity level. In the MEC, Black participants tended to be less physically active (mean MVPA: 6.8 hours/week) than the other racial and ethnic groups (mean MVPA range: 7.5 to 10.5 hours/week) and as reported in previous studies,[37] had the highest risk of ADRD. It is conceivable that Black adults need higher levels of physical activity to counter their susceptibility to ADRD. Although Black participants, as well as Native Hawaiian participants, had higher BMI levels, our effect modification analysis by BMI categories and our stratified analysis limited to non-obese participants show no differential associations and do not support BMI as the source of the ethnically heterogeneous association. On the other hand, a higher frequency of *APOE* e4 risk allele was observed in Black participants, and our stratified analysis among Black participants without e4 allele suggested an inverse association between MVPA and ADRD, which warrants further studies with a larger sample size. We also speculate that the lack of significant association in Black and Latino participants might be attributed to potential modifying effects of unmeasured social determinants of health as a result of structural racism and inequities, concurrent or experienced over the life course.[38,39]

Although total sitting time was not associated with ADRD risk in our study, there was a suggestion that the association might vary by type of sedentary activities. Among women, an inverse association was found for sitting at work, whereas the risk was increased with longer sitting time to watch TV. Nonetheless, the risk reduction by MVPA was greater in individuals with shorter total sitting hours. This finding suggests that MVPA may be particularly beneficial for ADRD prevention among less-sedentary people, which is consistent with some previous reports that longer sedentary time eliminates the benefits of physical exercises on individual's cognitive health.[40,41]

One of the main challenges in ADRD research is that accurate diagnosis of AD through imaging and biomarker analysis is often not feasible. Considering this limitation and the common occurrence of mixed-etiology dementia involving AD pathology, we analyzed the physical activity association with ADRD broadly but also examined the association by the predominant genetic risk factor for AD in the *APOE* gene. We found that the association is likely limited to non-carriers of the e4 risk allele. Such a gene-behavioral interaction was suggested[42] but has not been corroborated, for example, for a change in cognitive function in a combined analysis of three European cohorts (n = ≈7200, with 26% as e4 carriers)[43] or in a physical activity intervention (n = 54, with 43% as e4 carriers),[44] which might have been due to some study-specific issues, such as cohort heterogeneity, limited sample sizes, and inadequate follow-up for cognitive assessments. Our finding supports further research that physical activity and other factors may have different associations with the risk of ADRD by the predominant effect of the *APOE* genotype status.

This study has several strengths including the prospective design, a large number of participants and cases over a long-term follow-up, racial and ethnic diversity, and the availability of the *APOE* genotype data and many potential confounders for adjustment. Our study also has several limitations to consider when interpreting the findings. The

ADRD case definition was based solely on Medicare claims data, which may not have fully captured incident cases. The under-detection of cases might occur more often for those with mild symptoms than for severe dementia and yield potentially different risk factor associations compared with those obtained using criterion-standard evaluation.[45] However, Medicare claims have been largely concordant with clinical diagnoses of dementia in an Alzheimer disease registry.[46,47] Indeed, our rate estimates are similar as in clinical studies.[48] It is unlikely that the potential under-detection of ADRD based on Medicare-based ascertainment affected our large prospectively cohort data differently across physical activity levels. The robust association estimates in various subgroup analyses also support this point. Although the physical activity questionnaire used in the MEC was validated in reference to doubly labeled water and found to have reasonable validity,[25] it might not have captured the activities relevant to ADRD comprehensively.[11,49] In addition, even though we observed that the inverse physical activity association was driven more by moderate activities rather than by vigorous sports or work activities, this may have been because moderate intensity is the primary type of physical activity in our mature adult population and may not preclude a stronger protective effect of vigorous physical activity to mitigate cognitive decline and ADRD risks. Finally, despite the large sample size, statistical power might still be limited for some of the subgroups, including for the joint analysis of race and ethnicity and *APOE* genotype on the MVPA-ADRD association.

In summary, our study confirms that higher physical activity levels at middle to old age are associated with a lower risk of ADRD in later life and suggests similarities of the association across racial and ethnic groups and differences by *APOE* e4 and sitting duration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by grants from the National Cancer Institute and a supplement from the National Institute of Aging at the U.S. National Institutes of Health to the Multiethnic Cohort Study (U01 CA164973; CA164973 08S1). The funding organizations played no role in the design and conduct, the management and analysis of the data, the interpretation of results, or the preparation of the article.

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RESEARCH IN CONTEXT

Systematic Review:

Evidence from observational studies consistently showed a protective association of physical activity with risk of Alzheimer's disease and related dementias (ADRD) but has lacked consideration of racial and ethnic diversity and potential modifying factors.

Interpretation:

We found that ≥5 hours weekly (or ≥40 minutes daily) of moderate or vigorous physical activity (MVPA) reported at middle or older ages was associated with an ≈15% lower risk of subsequent ADRD. The inverse MVPA-ADRD association was observed for most racial and ethnic groups, but stronger in individuals with lower levels of sitting duration or those who do not carry the apolipoprotein E (*APOE*) e4 risk allele.

Future Directions:

Further research should assess physical activity interventions in the context of sedentary behaviors and the *APOE* status.

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TABLE 1

Characteristics by physical activity at cohort entry (1993 to 1996) in the Multiethnic Cohort

		Moderate/vigorous activity (hours/week)				
	All	**<2.5**	**2.5 to <5**	**5 to <7**	**7 to <14**	**≥14**
Men, n	39,676	6938	6811	7248	9733	8946
Age at cohort entry, mean ± SD	59.8 ± 8.1	60.4 ± 7.8	60.2 ± 8.2	59.8 ± 8.1	58.9 ± 8.0	59.8 ± 8.3
Age at Medicare surveillance start, mean ± SD	69.7 ± 4.8	69.9 ± 4.8	70.0 ± 5.0	69.8 ± 4.8	69.2 ± 4.5	69.8 ± 4.9
Race/ethnicity (%)						
Black	9.8	15.1	12.0	9.6	7.5	6.6
Japanese American	34.6	29.5	34.1	39.5	34.2	35.2
Latino[a]	20.1	31.2	21.6	17.1	17.5	15.4
Native Hawaiian	7.0	5.16.	6.2	6.4	8.1	8.6
White	28.5	19.1	26.0	27.4	32.7	34.2
Education (years), mean ± SD	13.7 ± 3.2	12.6 ± 3.7	13.7 ± 3.1	14.0 ± 3.0	14.2 ± 3.0	13.9 ± 2.9
Married (%)	79.0	75.3	79.0	80.9	80.4	78.8
History of hypertension (%)	38.0	42.8	41.0	39.3	34.8	34.5
History of heart disease (%)	8.8	10.6	9.2	9.2	7.9	8.0
History of stroke (%)	2.2	3.5	2.5	2.2	1.6	1.6
History of diabetes (%)	10.3	15.0	10.9	9.5	8.8	8.2
Medicare usage						
≥1 inpatient claim/year (%)	3.7	4.9	3.7	3.9	3.3	3.0
≥1 outpatient claim/year (%)	51.3	51.1	51.8	51.6	51.3	50.8
Body mass index (kg/m^2), mean ± SD	26.5 ± 3.9	27.2 ± 4.3	26.7 ± 4.0	26.5 ± 3.9	26.4 ± 3.7	26.1 ± 3.6
Smoking status (%)						
Never	32.0	30.9	32.8	32.2	32.6	31.7
Former	52.1	49.5	51.0	53.1	52.9	53.3
Current	15.8	19.5	16.2	14.7	14.5	15.0
Pack-years among ever smokers, mean ± SD	20.4 ± 16.3	21.0 ± 16.8	20.5 ± 16.5	20.3 ± 16.4	19.3 ± 15.7	21.0 ± 16.3
Sitting hours, mean ± SD	8.1 ± 3.5	7.8 ± 3.9	8.4 ± 3.6	8.4 ± 3.4	8.4 ± 3.4	7.4 ± 3.0
Sleeping hours, mean ± SD	7.0 ± 1.1	7.0 ± 1.2	7.0 ± 1.1	7.0 ± 1.1	7.1 ± 1.1	7.1 ± 1.1
Alcohol intake (g/day), mean ± SD	14.5 ± 30.5	13.7 ± 35.3	13.5 ± 30.7	13.9 ± 29.6	14.7 ± 28.2	16.1 ± 29.6

		Moderate/vigorous activity (hours/week)				
	All	**<2.5**	**2.5 to <5**	**5 to <7**	**7 to <14**	**≥14**
Total energy intake (kcal/day), mean ± SD	2402 ± 1067	2324 ± 1141	2304 ± 1043	2296 ± 1006	2451 ± 1062	2568 ± 1057
Healthy Eating Index-2015, mean ± SD	65.9 ± 10.4	63.5 ± 10.4	65.2 ± 10.2	66.0 ± 10.4	66.8 ± 10.2	67.1 ± 10.3
Women, n	48,371	8579	11,213	10,059	9605	8915
Age at cohort entry, mean ± SD	59.5 ± 8.1	59.8 ± 7.9	59.7 ± 8.2	59.5 ± 8.1	58.7 ± 8.1	59.9 ± 8.0
Age at Medicare surveillance start, mean ± SD	69.6 ± 4.7	69.6 ± 4.8	69.7 ± 4.9	69.6 ± 4.8	69.2 ± 4.6	69.7 ± 4.7
Race/ethnicity (%)						
Black	14.6	18.9	18.4	14.4	11.4	9.5
Japanese American	33.1	27.6	36.2	36.3	32.4	31.7
Latino[a]	17.4	32.4	16.3	14.9	12.5	12.5
Native Hawaiian	7.4	5.7	7.3	7.4	8.3	8.2
White	27.4	15.5	21.8	27.0	35.3	38.0
Education (years), mean ± SD	13.5 ± 3.1	12.1 ± 3.8	13.4 ± 3.0	13.8 ± 2.8	14.1 ± 2.8	13.9 ± 2.7
Married (%)	61.8	52.8	59.7	64.0	64.1	67.9
History of hypertension (%)	35.8	41.7	38.6	35.8	31.7	31.3
History of heart disease (%)	5.6	8.7	5.7	4.9	4.2	4.6
History of stroke (%)	1.7	2.4	1.9	1.7	1.3	1.4
History of diabetes (%)	8.9	12.7	9.8	8.2	6.8	6.9
Medicare usage						
≥1 inpatient claim/y (%)	3.5	4.4	3.7	3.3	3.0	2.9
≥1 outpatient claim/y (%)	62.7	62.6	61.5	63.6	62.4	63.7
Body mass index (kg/m^2), mean ± SD	26.0 ± 5.3	27.3 ± 5.7	26.3 ± 5.5	25.8 ± 5.0	25.4 ± 5.0	25.1 ± 4.8
Smoking status (%)						
Never	57.6	61.7	58.7	57.6	55.2	54.5
Former	29.4	26.4	27.8	29.3	32.2	31.3
Current	13.0	11.9	13.5	13.0	12.6	14.1
Pack-years among ever smokers, mean ± SD	15.5 ± 14.4	14.5 ± 14.2	15.1 ± 14.1	15.1 ± 14.2	15.2 ± 14.0	17.4 ± 15.3
Sitting hours, mean ± SD	8.2 ± 3.6	7.6 ± 4.0	8.4 ± 3.7	8.6 ± 3.5	8.5 ± 3.4	7.6 ± 3.1
Sleeping hours, mean ± SD	7.0 ± 1.1	6.9 ± 1.2	6.9 ± 1.1	7.0 ± 1.1	7.0 ± 1.1	7.0 ± 1.1
Alcohol intake (g/day), mean ± SD	4.5 ± 14.6	3.3 ± 14.0	3.7 ± 12.8	4.4 ± 14.8	5.5 ± 16.2	5.6 ± 15.2
Total energy intake (kcal/day), mean ± SD	1958 ± 918	1972 ± 1030	1924 ± 928	1913 ± 867	1973 ± 886	2023 ± 876

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	All	Moderate/vigorous activity (hours/week)				
		<2.5	**2.5 to <5**	**5 to <7**	**7 to <14**	**≥14**
Healthy Eating Index-2015, mean ± SD	69.4 ± 10.4	66.8 ± 10.4	68.4 ± 10.3	69.9 ± 10.3	70.8 ± 10.2	71.0 ± 10.2

[a]The majority of the MEC Latino participants were of Mexican descent.

TABLE 2

Physical activity and risk of Alzheimer's disease and related dementias

	Men		Women		
	Cases	**HR (95% CI)[a]**	**Cases**	**HR (95% CI)[a]**	***P*-heterogeneity by sex**
Moderate/vigorous activity					
<2.5 hours/week	1078	1.00 (ref)	1482	1.00 (ref)	
2.5 to <5 hours/week	1015	0.96 (0.88–1.05)	1863	0.96 (0.89–1.03)	
5 to <7 hours/week	935	0.83 (0.75–0.90)	1517	0.88 (0.82–0.95)	
7 to <14 hours/week	1223	0.88 (0.81–0.96)	1336	0.89 (0.83–0.96)	
≥14 hours/week	1195	0.83 (0.76–0.90)	1395	0.88 (0.81–0.95)	
P-trend		<0.001		0.004	0.52
Moderate activity					
≤1 hour/week	1431	1.00 (ref)	1556	1.00 (ref)	
2–3 hours/week	1384	0.96 (0.89–1.03)	2097	0.96 (0.90–1.03)	
4–6 hours/week	1037	0.82 (0.75–0.89)	1639	0.90 (0.84–0.97)	
7–10 hours/week	689	0.90 (0.82–0.99)	970	0.90 (0.83–0.98)	
≥11 hours/week	879	0.84 (0.77–0.92)	1299	0.89 (0.83–0.96)	
P-trend		<0.001		0.02	0.09
Vigorous sports activity					
Never	3475	1.00 (ref)	5682	1.00 (ref)	
0.5–1 hour/week	916	1.00 (0.93–1.08)	924	1.01 (0.94–1.08)	
2–3 hours/week	491	1.03 (0.94–1.14)	451	0.86 (0.78–0.95)	
≥4 hours/week	472	0.96 (0.87–1.06)	340	0.95 (0.85–1.06)	
P-trend		0.60		0.03	0.12
Vigorous work activity					
Never	2702	1.00 (ref)	6014	1.00 (ref)	
0.5–1 hour/week	1189	0.92 (0.86–0.99)	781	0.94 (0.87–1.01)	
2–3 hours/week	702	1.01 (0.93–1.10)	323	1.09 (0.97–1.22)	
≥4 hours/week	720	0.94 (0.87–1.03)	197	0.99 (0.86–1.15)	
P-trend		0.36		0.86	0.71

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[a] Adjusted for age at cohort entry, age at Medicare surveillance start, race/ethnicity, education, history of hypertension, history of heart disease, history of stroke, history of diabetes, Medicare usage (in-patient and out-patient claims separately, number per year), marital status, smoking status, pack-years of cigarette smoking, body mass index, total sitting hours, alcohol consumption, and Healthy Eating Index-2015.

TABLE 3

Sedentary behaviors and risk of Alzheimer's disease and related dementias

	Men		Women		
	Cases	**HR (95% CI)[a]**	**Cases**	**HR (95% CI)[a]**	***P*-heterogeneity by sex**
Total sitting					
<5 hours/day	1184	1.00 (ref)	1600	1.00 (ref)	
5 to <7 hours/day	1300	1.00 (0.92–1.08)	1790	1.04 (0.97–1.11)	
7 to <9 hours/day	1160	0.90 (0.83–0.98)	1593	0.99 (0.92–1.06)	
9 to <12 hours/day	1128	0.94 (0.86–1.02)	1599	1.00 (0.94–1.08)	
≥12 hours/day	674	0.96 (0.87–1.06)	1011	1.01 (0.93–1.09)	
P-trend		0.19		0.84	0.58
Sitting in car or bus					
<1 hour/day	3230	1.00 (ref)	4836	1.00 (ref)	
1–2 hours/day	1650	0.99 (0.93–1.05)	2052	1.06 (1.00–1.11)	
≥3 hours/day	414	1.01 (0.91–1.12)	471	1.10 (1.00–1.21)	
P-trend		0.96		0.01	0.14
Sitting at work					
Never	2132	1.00 (ref)	3441	1.00 (ref)	
>0–2 hours/day	1485	0.97 (0.91–1.04)	1686	0.95 (0.89–1.01)	
3–4 hours/day	619	0.92 (0.84–1.01)	619	0.90 (0.82–0.98)	
5–6 hours/day	524	0.90 (0.81–0.99)	591	0.88 (0.81–0.97)	
≥7 hours/day	210	0.96 (0.83–1.11)	316	0.82 (0.72–0.92)	
P-trend		0.06		<0.001	0.08
Sitting to watch TV					
<1 hour/day	644	1.00 (ref)	871	1.00 (ref)	
1–2 hours/day	2059	0.99 (0.90–1.08)	2757	1.01 (0.94–1.09)	
3–4 hours/day	2061	0.96 (0.88–1.05)	2961	1.03 (0.95–1.11)	
≥5 hours/day	592	1.02 (0.91–1.14)	879	1.13 (1.02–1.24)	
P-trend		0.87		0.02	0.07

[a]Adjusted for age at cohort entry, age at Medicare surveillance start, race/ethnicity, education, history of hypertension, history of heart disease, history of stroke, history of diabetes, Medicare usage (in-patient and out-patient claims separately, number per year), marital status, smoking status, pack-years of cigarette smoking, body mass index, moderate or vigorous physical activity, alcohol consumption, and Healthy Eating Index-2015.

TABLE 4

Physical activity and risk of Alzheimer's disease and related dementias by race/ethnicity

	Black		Japanese American		Latino		Native Hawaiian		White		
	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	*P*-heterogeneity by ethnicity
Moderate/vigorous activity											
<2.5 hours/week	566	1.00 (ref)	737	1.00 (ref)	699	1.00 (ref)	116	1.00 (ref)	442	1.00 (ref)	
2.5 to <5 hours/week	616	1.01 (0.90–1.13)	1002	0.91 (0.83–1.00)	468	1.05 (0.93–1.18)	167	1.00 (0.78–1.27)	625	0.90 (0.79–1.01)	
5 to <7 hours/week	416	0.95 (0.84–1.09)	894	0.78 (0.71–0.86)	379	1.03(0.90–1.17)	130	0.71(0.55–0.9217)	633	0.82 (0.73–0.93)	
7 to <14 hours/week	371	1.02 (0.89–1.17)	922	0.87 (0.79–0.96)	309	0.91 (0.79–1.04)	164	0.80 (0.62–1.02)	793	0.81 (0.72–0.92)	
≥14 hours/week	298	0.99 (0.86–1.15)	966	0.79 (0.72–0.87)	270	0.93 (0.81–1.0)	173	0.81 (0.64–1.04)	883	0.81 (0.72–0.91)	
P-trend		0.99		<0.001		0.14		0.23		0.007	0.52
Total sitting											
<5 hours/day	463	1.00 (ref)	895	1.00 (ref)	699	1.00 (ref)	168	1.00 (ref)	559	1.00 (ref)	
5 to <7 hours/day	516	1.11 (0.98–1.26)	1135	1.00 (0.91–1.09)	495	1.01 (0.90–1.13)	173	1.10 (0.89–1.36)	771	0.99 (0.89–1.10)	
7 to <9 hours/day	450	1.02 (0.90–1.16)	1005	0.96 (0.87–1.05)	342	0.86 (0.75–0.98)	1352	0.84 (0.67–1.06)	821	0.97 (0.87–1.08)	
9 to <12 hours/day	486	1.10 (0.96–1.25)	958	0.98 (0.90–1.08)	339	0.92 (0.80–1.05)	16439	0.93 (0.75–1.16)	780	0.93 (0.84–1.04)	
≥12 hours/day	352	1.04 (0.90–1.20)	528	0.93 (0.83–1.03)	250	1.09 (0.94–1.26)	110	0.86 (0.67–1.1026)	445	1.01 (0.89–1.15)	
P-trend		0.61		0.21		0.94		0.12		0.70	0.45

[a]Adjusted for age at cohort entry, age at Medicare surveillance start, sex, education, history of hypertension, history of heart disease, history of stroke, history of diabetes, Medicare usage (in-patient and out-patient claims separately, number per year), marital status, smoking status, pack-years of cigarette smoking, body mass index, alcohol consumption, and Healthy Eating Index-2015. For moderate/vigorous activity, further adjusted for total sitting. For total sitting, further adjusted for moderate/vigorous activity.

TABLE 5

Moderate or vigorous physical activity and risk of Alzheimer's disease and related dementias by sitting time

	Total sitting hours (hours/day)						
	≤6		>6 to <10		≥10		
Moderate/vigorous Activity	**Cases**	**HR (95% CI)[a]**	**Cases**	**HR (95% CI)[a]**	**Cases**	**HR (95% CI)[a]**	***P*-heterogeneity by sitting time**
<2.5 hours/week	1297	1.00 (ref)	684	1.00 (ref)	579	1.00 (ref)	
2.5 to <5 hours/week	1191	0.96 (0.89–1.04)	965	1.00 (0.90–1.10)	722	0.92 (0.82–1.03)	
5 to <7 hours/week	863	0.83 (0.76–0.91)	919	0.93 (0.84–1.03)	670	0.82 (0.73–0.92)	
7 to <14 hours/week	876	0.84 (0.77–0.92)	970	0.95 (0.86–1.05)	713	0.90 (0.80–1.01)	
≥14 hours/week	989	0.79 (0.73–0.87)	1035	0.90 (0.81–0.99)	566	0.92 (0.82–1.04)	
P-trend		<0.001		0.04		0.81	0.04

[a]Adjusted for age at cohort entry, age at Medicare surveillance start, sex, race/ethnicity, education, history of hypertension, history of heart disease, history of stroke, history of diabetes, Medicare usage (in-patient and out-patient claims separately, number per year), marital status, smoking status, pack-years of cigarette smoking, body mass index, alcohol consumption and Healthy Eating Index-2015.

TABLE 6

Moderate or vigorous physical activity and risk of Alzheimer's disease and related dementias by no. of *APOE* e4

	All with *APOE* genotype data		No. of *APOE* e4				
			0		1, 2		
Moderate/vigorous activity	**Cases**	**HR (95% CI)[a]**	**Cases**	**HR (95% CI)[a]**	**Cases**	**HR (95% CI)[a]**	***P*- heterogeneity by *APOE***
<2.5 hours/week	350	1.00 (ref)	243	1.00 (ref)	107	1.00 (ref)	
2.5 to <5 hours/week	431	0.97 (0.84–1.12)	262	0.87 (0.73–1.04)	169	1.14 (0.89–1.46)	
5 to <7 hours/week	352	0.81 (0.69–0.94)	230	0.75 (0.62–0.90)	122	0.91 (0.69–1.19)	
7 to <14 hours/week	422	0.91 (0.79–1.06)	255	0.79 (0.66–0.95)	167	1.13 (0.88–1.45)	
≥14 hours/week	418	0.86 (0.74–1.00)	264	0.76 (0.64–0.92)	154	1.04 (0.80–1.35)	
P-trend		0.23		0.07		0.69	0.02

[a]Adjusted for age at cohort entry, age at Medicare surveillance start, sex, race/ethnicity, education, history of hypertension, history of heart disease, history of stroke, history of diabetes, Medicare usage (in-patient and out-patient claims separately, number per year), marital status, smoking status, pack-years of cigarette smoking, body mass index, total sitting hours, alcohol consumption, and Healthy Eating Index-2015.