CAUSAL EFFECTS OF PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR ON HEALTH DEFICITS ACCUMULATION IN OLDER ADULTS

Esther García-Esquinas, Rosario Ortolá, David Martínez-Gómez, Javier Damián, Matthew Prina, Fernando Rodríguez-Artalejo, Roberto Pastor-Barriuso, Causal effects of physical activity and sedentary behaviour on health deficits accumulation in older adults, International Journal of Epidemiology, Volume 50, Issue 3, June 2021, Pages 852–865.

which has been published in final form at:
https://doi.org/10.1093/ije/dyaa228

Causal effects of physical activity and sedentary behavior on health deficits accumulation in older adults

Esther García-Esquinas,[1,2] Rosario Ortolá,[1,2] David Martínez-Gómez,[1,2,3] Javier Damián,[4,5] Matthew Prina,[6] Fernando Rodríguez-Artalejo,[1,2,3] Roberto Pastor-Barriuso[2,4]

[1] Department of Preventive Medicine and Public Health, Autonomous University of Madrid and Idipaz, Arzobispo Morcillo s/n, 28029, Madrid, Spain

[2] Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Monforte de Lemos 5, 28029, Madrid, Spain

[3] IMDEA Food Institute, Campus de Excelencia Internacional UAM+CSIC, Carretera de Canto Blanco 8, 28049, Madrid, Spain

[4] National Center for Epidemiology, Carlos III Institute of Health, Calle Sinesio Delgado 6, 28029, Madrid, Spain

[5] Consortium for Biomedical Research in Neurodegenerative Diseases (CIBERNED), Monforte de Lemos 5, 28029, Madrid, Spain

[6] Department of Health Service and Population Research, Institute of Psychiatry, Psychology, and Neuroscience, King's College, 16 De Crespigny Park Camberwell, SE5 8AF, London, United Kingdom

Corresponding author

Esther García-Esquinas
Department of Preventive Medicine and Public Health,
School of Medicine.
Universidad Autónoma de Madrid.
Calle del Arzobispo Morcillo 4.
28029 Madrid, Spain
Phone: (+34) 91-497-27-61
E-mail: esther.garciag@uam.es

Summary box

-Most previous studies on physical activity, sedentary behaviors and age-related outcomes have moderate to high risk of bias due to residual confounding, reverse causation and selective withdrawal

- An increasing number of reports suggest differential relationships of mentally-active and passive sedentary time with health outcomes, as well as differential associations by sex. These differences have not been addressed for healthy ageing

-Our study suggests that moderate recreational physical activity (10-25 MET-hours/week) can delay healthy ageing.

-Among women, spending less than 2.5 hours/day watching television, and more than 10 hours/week on mentally-active sedentary activities, are important contributors to successful aging.

ABSTRACT

Background: Increasing physical activity (PA) and reducing sedentary behavior (SB) have been associated with healthy aging, but their effects adjusted for reverse causation and selection bias remain unclear.

Methods: A deficits accumulation (DA) index based on the number and severity of 51 health deficits (0-100%) was calculated at baseline and three biannual follow-up visits in a representative cohort of 3,228 community-dwelling older adults in Spain. Average differences in DA index by previous recreational PA, household PA, mentally-active SB, and passive SB were estimated using marginal structural models with inverse probability of exposure and censoring weights.

Results: Compared to participants with previous recreational PA of 10-19.9 MET-hours/week, average differences in DA index (95% confidence intervals) were 0.19 (−1.09, 1.48), 0.69 (−0.23, 1.61), −0.66 (−1.34, 0.02), −0.87 (−1.59, −0.13), and −0.55 (−1.37, 0.28) for 0, 0.1-9.9, 20-29.9, 30-39.9, and ≥40 MET-hours/week, respectively (*P* for trend=0.006). Household PA showed no effect on subsequent DA after adjusting for reverse causation. Women, but not men, who spent 7-14.9, 15-20.9, and ≥21 hours/week on mentally-active SB had DA decreases of 0.09 (−1.00, 1.19), 1.08 (−0.28, 2.45), and 2.17 (0.58, 3.75) compared with 1-6.9 hours/week (*P* for trend=0.005), whereas women who spent 3-3.9, 4-4.9, and ≥5 hours/day on passive SB showed DA increases of 0.41 (−0.52, 1.35), 1.35 (0.13, 2.57), and 2.13 (0.78, 3.47) compared with 2-2.9 hours/day (*P* for trend=0.001).

Conclusions: The proposed methodology allows estimating the causal effects of PA and SB on aging, by simulating a random assignment, in which all subjects have the same probability of exposure.

Registration: The study was registered under ClinicalTrials.gov (number NCT01133093).

Keywords: causality, health deficits, older adults, physical activity, sedentary behavior

BACKGROUND

Biological aging is the result of heterogeneous damage accumulation in different human tissues over lifetime (1). This cumulative harm increases the risk of chronic morbidities, cognitive decline, physical impairments, and psychological adverse outcomes, all of which are important components of unhealthy aging (2). Because populations are aging rapidly across the world but not all subjects age at the same pace, there is great interest in understanding the individual determinants of unhealthy aging trajectories (3). Identification of these factors may enable behavioral and environmental interventions for healthy aging.

Increasing physical activity (PA) and reducing sedentary time have been proposed as effective strategies to improve health in populations. Specifically, findings from clinical trials in old age have shown that moderate-intensity PA programs improve physical function (4) and decrease the risk for cognitive decline (5), dementia (6), or major mobility disability (7). The evidence from observational studies has also shown beneficial effects of PA on aging-related conditions (8,9)). In a recent meta-analysis of 23 cohort studies including 174,114 participants aged 20 to 87 years, PA was positively associated with healthy aging (9), albeit the high between-study heterogeneity in PA assessments precluded the estimation of a pooled dose-response trend with intensity or the analysis of domain-specific associations. Furthermore, two thirds of the identified studies were characterized as having moderate to high risk of bias due to residual confounding or differential loss to follow-up, and, more importantly, none of them appropriately controlled for time-varying confounding by lifestyle changes or reverse causation, where underlying diseases or frailty conditions may cause decreased PA. Although experimental studies may partially solve these problems, they are not free from caveats. Often generalizability is limited because of restricted admission criteria. Moreover, the benefits of randomization are progressively lost with the passing of time, and long-term behavior is important when studying the effects of PA on ageing. That is why appropriate observational studies that update the information periodically can provide evidence that complements that obtained by experimental designs. In this context, the implementation of causal methods may notably account for the effects of reverse causality and selective withdrawal.

The prospective association between sedentary behavior (SB) and geriatric-relevant health outcomes faces similar challenges as does the PA literature (10). Moreover, its study is further complicated by conflicting results: although non-experimental studies support a positive association between total sedentary time and the risk of certain components of unhealthy aging, such as physical function impairments (11–15), an increasing number of reports suggest differential relationships by SB type. Thus, for example, the time spent in cognitively engaged SB (reading, using the computer) has been associated with a decreased risk of cognitive (16,17) and mental impairments (18,19) in old age, while more passive SBs (television [TV] watching) have shown opposite effects on both cognitive (20,21) and mental health (18,19). Overall, this evidence suggests that the mentally stimulating characteristics of certain SBs may counterbalance their associated low energy expenditure regarding their impact on brain and mental health. To our knowledge, though, no studies have yet evaluated the differential dose-response relations of mentally active and passive SBs with trajectories of healthy aging.

In this context, and to overcome the above mentioned methodological problems (time-varying confounding, reverse causation, and attrition bias), the present study set out to use causal methods including marginal structure models with inverse probability of exposure and censoring weights, with the objective of estimating the effect of recreational PA, household PA, mentally-active SB, and passive SB on the accumulation of health deficits over the 10-year follow-up of a nationally representative cohort of community-dwelling older adults in Spain.

METHODS

Study population and data collection

The Seniors-ENRICA cohort was established in 2008–2010 with 3,289 individuals selected by multi-stage stratified random sampling from the non-institutionalized Spanish population aged 60 years or older (2,22). Of the initial cohort, 61 participants were excluded because they lacked baseline information on health deficits, PA, SB, or other lifestyle factors. The remaining 3,228 participants contributed updated data at 5,316 biannual follow-up visits until 2017, including 2,444 (75.7%), 1,774 (55.0%), and 1,098 (34.0%) participants in the first, second, and third follow-up visits, respectively (**Figure 1**). Attrition rates increased from 24.3% to 38.1% across successive visits, with most participants lost due to non-response. These losses to follow-up were strongly related to the presence of health deficits and lifestyle determinants, and the induced selection bias was corrected through weighting methods based on the inverse probability of censoring (see Statistical Analysis section).

Baseline and follow-up information on sociodemographic, lifestyle, self-rated health, and morbidity was collected using computer-assisted telephone interviews and diet histories. Samples of urine and blood were collected and mental and physical examinations were performed by trained staff in home visits. All participants gave informed consent, and the Clinical Research Ethics Committee of the La Paz University Hospital approved the study (nº HULP 2144).

Health deficits accumulation, physical activity, sedentary behavior

Based on the Rockwood's frailty index (23), a deficits accumulation (DA) index was calculated at baseline and each follow-up visit using a total of 51 health deficits, including 21 impairments in physical and cognitive functioning, 7 self-reported health and vitality problems, 6 mental health conditions, and 17 items on morbidities, polypharmacy, and use of health services (2). Some health deficits were assessed in a dichotomous way (1 point if present and 0 otherwise), while others were graded according to severity (0 points for no deficit, 0.25 to 0.75 points for mild to moderate deficits, and 1 point for severe deficit). A detailed description of the construction of the DA index is provided in **Supplementary Methods** and the complete list of health deficits and associated scores are shown in **Supplementary Table 1**. The overall DA index was calculated as the sum of points assigned to each health deficit divided by the total number of deficits and further multiplied by 100 to obtain a summary range from 0 to 100% deficit (2).

Older adults reported at each visit their participation in different PAs using the validated questionnaire used in the EPIC-Spain cohort (24). Recreational PA included walking (commuting, shopping, or leisure time), cycling (commuting or leisure time), and playing sports (running, playing soccer, doing aerobics, swimming, or playing tennis), while household PA consisted of doing household chores (cleaning, cooking, doing laundry, or children rearing), gardening, and doing home-repair (do-it-yourself activities). Across all waves, walking was the only recreational PA in approximately 60% of the study participants. Compared with the rate of energy expended at rest, the assigned metabolic equivalents of tasks (METs) were 2.5 for walking and household chores and 4.0 for cycling, playing sports, gardening, and home repair (25). Recreational PA was categorized into 0, 0.1–9.9, 10–19.9, 20–29.9, 30–39.9, and ≥ 40 MET-hours/week and household PA into 0, 0.1–19.9, 20–39.9, 40–59.9, 60–79.9, and ≥ 80 MET-hours/week.

Participants also reported the average weekly hours during the preceding year that they were sitting or lying in different activities using the Nurses' Health Study questionnaire validated in Spain (26). These SBs were classified into mentally-active (reading or using the computer) and passive (TV watching). Mentally-active SB was categorized as < 1, 1–6.9, 7–14.9, 15–20.9, and ≥ 21 hours/week and passive SB as < 2, 2–2.9, 3–3.9, 4–4.9, and ≥ 5 hours/day.

Other lifestyle factors were collected at baseline and follow-up visits, including smoking status (never, former, or current), alcohol drinking (never, former, or current), and adherence to the Mediterranean diet (≤ 5, 6, 7, 8, or ≥ 9 points), as determined by the Mediterranean Diet Adherence Screener score (27). Weight and height were measured twice using electronic scales and portable extendable stadiometers with standardized procedures, and the mean of the two readings was used to calculate the body mass index (< 25, 25–29.9, or ≥ 30 kg/m^2) (28).

Statistical analysis

The average differences in DA index at each follow-up visit across activity categories at previous visit (recreational PA, household PA, mentally-active SB, or passive SB) were initially estimated using repeated measures regression models adjusted for age (restricted quadratic splines with knots at 65, 70, 75, and 80 years), sex (men or women), educational level (primary or less, secondary, or university), baseline DA index (restricted quadratic splines with knots at 10, 20, and 30%), and baseline categories of time-varying lifestyle factors, including smoking status, alcohol drinking, Mediterranean diet score, body mass index, and the alternative activity variables. Tests for linear trend in the average DA index were performed by including an ordinal variable with the median of each activity category, and smooth dose-response curves were estimated through restricted quadratic splines of activity variables with the upper tail constrained to be linear and the same non-zero cut-points used for categorical analysis.

To adjust for potential time-varying confounding by lifestyle changes and reverse causation by previous DA index, the above models were then fitted using inverse probability of exposure weights. This method was used since follow-up levels of time-varying lifestyle factors and DA index may simultaneously be confounders for later activity and mediators for earlier activity and thus cannot be appropriately adjusted for by standard methods (29).

Stabilized exposure weights were assigned to each participant-visit as the probability of having the observed activity history up to the previous visit given age, sex, education, and baseline lifestyle factors and DA index, divided by the same probability further conditional on full lifestyle and DA histories through that visit. These probabilities were estimated from pooled polytomous logistic models with activity categories across successive visits as outcome (see **Supplementary Methods** for a formal definition and estimation of exposure weights). The odds of being in a higher category of recreational PA, household PA, and mentally-active SB decreased by 30%, 14% and 16% per 10-percent increase in DA index at the same visit, respectively. Inverse probability of exposure weighting provided an effective adjustment for time-varying confounding since, given baseline lifestyle factors and DA index, the weighted distributions of these confounders at each follow-up visit were virtually identical across activity categories (**Supplementary Tables 2 and 3**).

To control further for selection bias due to differential loss to follow-up with respect to time-varying DA index and its lifestyle determinants, the repeated measures models were finally fitted using the product of both inverse probability of exposure and censoring weights (29). If time-varying lifestyle factors and DA index were affected by earlier activity, standard adjustment for these common predictors of censoring and outcome would provide a biased estimate of the effect of activity on DA index (30). Stabilized censoring weights were allocated to each participant-visit as the probability of remaining uncensored up to the current visit given activity history through the previous visit, age, sex, education, and baseline lifestyle factors and DA index, divided by that probability further conditional on lifestyle and DA histories through the previous visit. The probabilities of being uncensored at each follow-up visit were estimated using pooled logistic models (see **Supplementary Methods** for further details). The odds of remaining uncensored decreased by 33% per 10-percent increase in DA index at previous visit. Inverse probability of censoring weighting controlled properly for selection bias; given baseline lifestyles and DA index, the weighted distributions of these time-varying factors were nearly identical among censored and uncensored participants at subsequent visit (**Supplementary Table 4**). The distribution of final weights at each follow-up visit, which were calculated as the product of inverse probability of exposure and censoring weights, is displayed in **Supplementary Figure 1**.

Specific effects of each activity variable on DA index among men and women were estimated by including interactions between activity categories and sex in repeated measures models with stabilized exposure and censoring weights and tested for heterogeneity by using joint Wald tests. Other potential effect modifications by age group, educational level, and baseline categories of DA index and lifestyle factors were explored in a similar way. All models used robust standard error estimates to account for within-participant correlations induced by repeated measures and weighting (31). Statistical analyses were performed in Stata, version 14 (StataCorp) and graphics were produced in R, version 3 (R Foundation for Statistical Computing).

RESULTS

At baseline, the mean (SD) age and DA index of the 3,228 participants in the Seniors-ENRICA cohort were 69.0 (6.6) years and 16.2 (11.1) percent deficit, and 53.8% were women (**Table 1**). The mean (SD) recreational and household PAs were 21.2 (14.5) and 37.3 (32.1) MET-hours/week and the mean (SD) times spent on mentally-active and passive SBs were 8.0 (9.8) hours/week and 2.6 (1.6) hours/day. Over 10 years of follow-up, a progressively selected sample of 2,444 (75.7%), 1,774 (55.0%), and 1,098 (34.0%) participants attended the first, second, and third follow-up visits, respectively. Among those retained in the third visit, the mean (SD) age and DA index were 75.1 (5.2) years and 19.1 (12.7) percent deficit, with 22.1 (14.6) and 30.7 (27.3) MET-hours/week of recreational and household PA, and 10.9 (12.0) hours/week and 2.8 (1.6) hours/day of mentally-active and passive SB.

An inverse prospective association of recreational PA with DA index was observed in repeated measures models adjusted for baseline sociodemographic, lifestyle factors, and DA index (**Table 2**, model 1), which was slightly attenuated but remained strong after weighting the models to adjust further for time-varying confounding and reverse causation (**Table 2**, model 2) and to control for selection bias due to differential loss to follow-up (**Table 2**, model 3). Participants with low recreational PA of 0 and 0.1–9.9 MET-hours/week had subsequent average increases in DA index (95% confidence intervals) of 0.19 (−1.09, 1.48) and 0.69 (−0.23, 1.61) compared to those with intermediate levels of 10–19.9 MET-hours/week, whereas participants with high recreational PA of 20–29.9, 30–39.9, and ≥ 40 MET-hours/week had subsequent DA decreases of 0.66 (−0.02, 1.34), 0.87 (0.13, 1.59), and 0.55 (−0.28, 1.37), respectively (*P* for linear trend = 0.006). Smooth dose-response analyses showed that the decreasing trend in DA index was particularly marked at middle recreational PA levels between 10 and 25 MET-hours/week (**Figure 2A**). The beneficial effect of recreational PA on DA index was evident in both men and women (*P* for sex interaction = 0.652) (**Table 2**, model 3), as well as for walking and for cycling and playing sports (**Supplementary Table 5**, model 3).

Household PA, however, showed no effect on subsequent DA index after adjusting for time-varying confounding, reverse causation, and selection bias (**Table 2**, model 3 and **Figure 2B**). Compared to participants with intermediate household PA levels of 20–39.9 MET-hours/week, the average DA index changed by 1.27, −0.11, −0.33, 0.06, and −0.33 for participants with 0, 0.1–19.9, 40–59.9, 60–79.9, and ≥ 80 MET-hours/week, respectively (*P* for linear trend = 0.317). This lack of dose-response relation was also observed among women, which displayed much higher household PA (*P* for sex interaction = 0.407).

Results for mentally-active and passive SB varied substantially by sex (*P* values for sex interaction = 0.042 and 0.018, respectively). While there was no association between these

SBs and DA index in men, women who spent more time on mentally-active SB and less time on passive SB showed a slower accumulation of health deficits. In fully-weighted models accounting for time-varying confounding, reverse causation, and differential loss to follow-up, women who spent < 1 hour/week on mentally-active SB had an average increase in DA index (95% confidence interval) of 0.37 (−1.03, 1.13) compared to those who spent 1–6.9 hours/week, whereas women with 7–14.9, 15–20.9, and ≥ 21 hours/week of mentally-active SB had DA decreases of 0.09 (−1.00, 1.19), 1.08 (−0.28, 2.45), and 2.17 (0.58, 3.75), respectively (*P* for linear trend = 0.005) (**Table 3**, model 3). In contrast, women who spent 3–3.9, 4–4.9, and ≥ 5 hours/day on passive SB showed subsequent average increases in DA index (95% confidence intervals) of 0.41 (−0.52, 1.35), 1.35 (0.13, 2.57), and 2.13 (0.78, 3.47) compared to those with 2–2.9 hours/day of passive SB, respectively (*P* for linear trend = 0.001) (**Table 3**, model 3). Among women, the decreasing trend in DA index was more marked above 10 hours/week of mentally-active SB and the increasing DA trend between 2.5 and 5 hours/day of passive SB (**Figure 3B and D**).

In exploratory subgroup analyses, the average decreases in DA index with increasing recreational PA were larger in participants aged 70 years or older (*P* for interaction = 0.004), those with secondary education or more (*P* = 0.012), and non-drinkers at baseline (*P* = 0.017). In addition, the DA increases with increasing passive SB were more marked in non-drinkers (*P* = 0.020), participants with higher adherence to the Mediterranean diet (*P* = 0.024), and those with higher levels of household PA at baseline (*P* = 0.003), which were more prevalent lifestyle factors among women (**Supplementary Figures 2 to 5**).

DISCUSSION

In this cohort of older adults followed with repeated measures for up to 10 years, higher levels of recreational PA, particularly between 10 and 25 MET-hours/week, were associated with reduced age-related DA after controlling for time-varying confounding by reverse causation and selection bias. Moreover, spending less than 2.5 hours/day watching television, and more than 10 hours/week on mentally-active sedentary activities, were important contributors to successful aging among older women.

Strengths of this study include the use of a great number of validated measures of physical function, cognition, and chronic conditions; the use of domain-specific PA and SB; the adjustment for a broad range of time-varying potential confounders; and the implementation of robust methods (29). The main limitation is the use of self-reported exposure information, which is prone to recall and social desirability bias. However, the use of objective measures (i.e. accelerometry) of PA and sedentary time would have prevented us from evaluating specific domains, which, as shown by our results, is essential to correctly address their health effects in older adults. Moreover, in a new cross-sectional study using both objective measures and self-reports in 1111 Spanish participants from the Seniors-Enrica II cohort, we have found similar associations between light or moderate-to-vigorous PA and DAI scores using accelerometer or self-reported PA. Another limitation is that we did not have explicit information on resistance, balance, or flexibility training, which may also have important benefits over specific health deficits (32–34). Additionally, although we adjusted for a great number of confounders, adjustment may not have been sufficient to compensate for differences between participants who reported 'none' vs those who reported 'any' PA, which may limit the interpretation of the dose-response curve at very low levels. Finally, our results cannot be extrapolated to institutionalized populations (35).

Regarding household PA, the present results show that this type of activity is not effective against ageing. The only previous study addressing this association did found an inverse relation in a sample of 900 individuals representative of the older adult population in Germany (36); however the authors pointed out that their findings may have been influenced by reverse causation, which has been confirmed in our analyses.

A recent narrative review has emphasized the need to adequately address sex differences in SB and health outcomes in the elderly (10). This recommendation is sustained by both cross-sectional and prospective studies showing sex-specific associations of SB with cardiovascular (37), functional (38,39) or mental (19) health outcomes, with greater effects usually observed among women. Although there is no *a priori* biological reason to explain these differences, studies have hypothesized that poorer baseline health may make women more susceptible to the detrimental/positive effects of sedentary behaviors (10). Other studies have suggest that sex-related discrepancies in the association between leisure activities and health outcomes may be driven by differences in living arrangement (40); however in our study similar associations were found among individuals living/not living alone, as well as among those spending <8/≥8 hours alone at home (data not shown). In any case, because ours is the first study to evaluate the stratified effect of mentally-active and passive SB on the accumulation of health deficits, results need to be confirmed by further research.

CONCLUSIONS

Our findings provide important evidence for informing public health recommendations. In particular, they suggest greatest reductions in DA with 10 to 25 MET-hours/week of recreational, but not household, PA. Walking appeared to be as beneficial as more vigorous activities, such as cycling or sports. These results also draw attention to the importance of differentiating between mentally-active and passive SB, while contribute to the evidence of sex-related differences of SB on health. Future intervention studies should evaluate whether combining low intensity recreational activities (i.e walking) with mentally-active sedentary activities (i.e. reading) may result in lower DA, particularly among women, which are known to lose function and accumulate morbidities faster than men (2).

Funding: This work was supported by the Instituto de Salud Carlos III, State Secretary of R+D+I and FEDER/FSE [FIS grants 16/609,16/1512, 18/287 and 19/319].

REFERENCES

1. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The Hallmarks of Aging. Cell. 2013;153(6):1194-217.

2. García-Esquinas E, Ortolá R, Prina M, Stefler D, Rodríguez-Artalejo F, Pastor-Barriuso R. Trajectories of Accumulation of Health Deficits in Older Adults: Are There Variations According to Health Domains? J Am Med Dir Assoc. 2019;20(6):710-717.e6.

3. Kralj C, Daskalopoulou C, Rodríguez-Artalejo F, García-Esquinas E, Cosco T, Prince M, et al. Healthy ageing and its risk factors: A systematic review of the literature. Department of Health Service and Population Research King´s College London. 2018;

4. Fielding RA, Guralnik JM, King AC, Pahor M, McDermott MM, Tudor-Locke C, et al. Dose of physical activity, physical functioning and disability risk in mobility-limited older adults: Results from the LIFE study randomized trial. Stepto NK, editor. PLOS ONE. 2017;12(8):e0182155.

5. for the LIFE Study investigators, Liu Z, Hsu F-C, Trombetti A, King AC, Liu CK, et al. Effect of 24-month physical activity on cognitive frailty and the role of inflammation: the LIFE randomized clinical trial. BMC Med. 2018;16(1):185.

6. Santos-Lozano A, Pareja-Galeano H, Sanchis-Gomar F, Quindós-Rubial M, Fiuza-Luces C, Cristi-Montero C, et al. Physical Activity and Alzheimer Disease: A Protective Association. Mayo Clin Proc. 2016;91(8):999-1020.

7. Fanning J, Rejeski WJ, Chen S-H, Nicklas BJ, Walkup MP, Axtell RS, et al. A Case for Promoting Movement Medicine: Preventing Disability in the LIFE Randomized Controlled Trial. J Gerontol A Biol Sci Med Sci. 2019;74(11):1821-7.

8. Dipietro L, Campbell WW, Buchner DM, Erickson KI, Powell KE, Bloodgood B, et al. Physical Activity, Injurious Falls, and Physical Function in Aging: An Umbrella Review. Med Sci Sports Exerc. 2019;51(6):1303-13.

9. Daskalopoulou C, Stubbs B, Kralj C, Koukounari A, Prince M, Prina AM. Physical activity and healthy ageing: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2017;38:6-17.

10. Copeland JL, Ashe MC, Biddle SJ, Brown WJ, Buman MP, Chastin S, et al. Sedentary time in older adults: a critical review of measurement, associations with health, and interventions. Br J Sports Med. 2017;51(21):1539-1539.

11. García-Esquinas E, Andrade E, Martínez-Gómez D, Caballero FF, López-García E, Rodríguez-Artalejo F. Television viewing time as a risk factor for frailty and functional limitations in older adults: results from 2 European prospective cohorts. Int J Behav Nutr Phys Act. 2017;14(1):54.

12. DiPietro L, Jin Y, Talegawkar S, Matthews CE. The Joint Associations of Sedentary Time and Physical Activity With Mobility Disability in Older People: The NIH-AARP Diet and Health Study. J Gerontol A Biol Sci Med Sci. 2018;73(4):532-8.

13. Liao Y, Hsu H-H, Shibata A, Ishii K, Koohsari MJ, Oka K. Associations of total amount and patterns of objectively measured sedentary behavior with performance-based physical function. Prev Med Rep. 2018;12:128-34.

14. Rosenberg DE, Bellettiere J, Gardiner PA, Villarreal VN, Crist K, Kerr J. Independent Associations Between Sedentary Behaviors and Mental, Cognitive, Physical, and Functional Health Among Older Adults in Retirement Communities. J Gerontol A Biol Sci Med Sci. 2015;71(1):78-83.

15. Semanik PA, Lee J, Song J, Chang RW, Sohn M-W, Ehrlich-Jones LS, et al. Accelerometer-monitored sedentary behavior and observed physical function loss. Am J Public Health. 2015;105(3):560-6.

16. Blasko I, Jungwirth S, Kemmler G, Weissgram S, Tragl KH, Fischer P. Leisure time activities and cognitive functioning in middle European population-based study. Eur Geriatr Med. 2014;5(3):200-7.

17. Hui-Xin W, Yinlong J, Hugh C. H, Chaoke L, Lili Y, Yibin C, et al. Late Life Leisure Activities and Risk of Cognitive Decline. J Gerontol A Biol Sci Med Sci. 2013;68(2):205-13.

18. Hallgren M, Owen N, Stubbs B, Zeebari Z, Vancampfort D, Schuch F, et al. Passive and mentally-active sedentary behaviors and incident major depressive disorder: A 13-year cohort study. J Affect Disord. 2018;241:579-85.

19. Andrade-Gómez E, Martínez-Gómez D, Rodríguez-Artalejo F, García-Esquinas E. Sedentary behaviors, physical activity, and changes in depression and psychological distress symptoms in older adults. Depress Anxiety. 2018;35(9):884-97.

20. Falck RS, Davis JC, Liu-Ambrose T. What is the association between sedentary behaviour and cognitive function? A systematic review. Br J Sports Med. 2017;51(10):800-11.

21. Wang JYJ, Zhou DHD, Li J, Zhang M, Deng J, Tang M, et al. Leisure activity and risk of cognitive impairment: the Chongqing aging study. Neurology. 2006;66(6):911-3.

22. Rodríguez-Artalejo F, Graciani A, Guallar-Castillón P, León-Muñoz LM, Zuluaga MC, López-García E, et al. [Rationale and methods of the study on nutrition and cardiovascular risk in Spain (ENRICA)]. Rev Esp Cardiol. 2011;64(10):876-82.

23. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ Can Med Assoc J. 2005;173(5):489-95.

24. Pols MA, Peeters PH, Ocké MC, Slimani N, Bueno-de-Mesquita HB, Collette HJ. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. Int J Epidemiol. 1997;26 Suppl 1:S181-189.

25. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 Compendium of Physical Activities: A Second Update of Codes and MET Values. Med Sci Sports Exerc. 2011;43(8):1575-81.

26. Martínez-González MA, López-Fontana C, Varo JJ, Sánchez-Villegas A, Martinez JA. Validation of the Spanish version of the physical activity questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up Study. Public Health Nutr. 2005;8(7):920-7.

27. Schröder H, Fitó M, Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. J Nutr. 2011;141(6):1140-5.

28. Gutiérrez-Fisac JL, Guallar-Castillón P, León-Muñoz LM, Graciani A, Banegas JR, Rodríguez-Artalejo F. Prevalence of general and abdominal obesity in the adult population of Spain, 2008-2010: the ENRICA study. Obes Rev Off J Int Assoc Study Obes. 2012;13(4):388-92.

29. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550-60.

30. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004;15(5):615-25.

31. White H. A Heteroskedasticity-Consistent Covariance Matrix Estimator and a Direct Test for Heteroskedasticity. Econometrica. 1980;48(4):817.

32. Liu-Ambrose T, Davis JC, Best JR, Dian L, Madden K, Cook W, et al. Effect of a Home-Based Exercise Program on Subsequent Falls Among Community-Dwelling High-Risk Older Adults After a Fall: A Randomized Clinical Trial. JAMA. 2019;321(21):2092-100.

33. Manini TM, Beavers DP, Pahor M, Guralnik JM, Spring B, Church TS, et al. Effect of Physical Activity on Self-Reported Disability in Older Adults: Results from the LIFE Study. J Am Geriatr Soc. 2017;65(5):980-8.

34. Espeland MA, Lipska K, Miller ME, Rushing J, Cohen RA, Verghese J, et al. Effects of Physical Activity Intervention on Physical and Cognitive Function in Sedentary Adults With and Without Diabetes. J Gerontol A Biol Sci Med Sci. 2017;72(6):861-6.

35. Pinto JM, Wroblewski KE, Huisingh-Scheetz M, Correia C, Lopez KJ, Chen RC, et al. Global Sensory Impairment Predicts Morbidity and Mortality in Older U.S. Adults. J Am Geriatr Soc. 2017;65(12):2587-95.

36. Stephan A-J, Strobl R, Müller M, Holle R, Autenrieth CS, Thorand B, et al. A high level of household physical activity compensates for lack of leisure time physical activity with regard to deficit accumulation: Results from the KORA-Age study. Prev Med. 2016;86:64-9.

37. Ford ES, Caspersen CJ. Sedentary behaviour and cardiovascular disease: a review of prospective studies. Int J Epidemiol. 2012;41(5):1338-53.

38. Dunlop DD, Song J, Arnston EK, Semanik PA, Lee J, Chang RW, et al. Sedentary time in US older adults associated with disability in activities of daily living independent of physical activity. J Phys Act Health. 2014;12(1):93-101.

39. Chen T, Narazaki K, Haeuchi Y, Chen S, Honda T, Kumagai S. Associations of Sedentary Time and Breaks in Sedentary Time With Disability in Instrumental Activities of Daily Living in Community-Dwelling Older Adults. J Phys Act Health. 2015;13(3):303-9.

40. Nilsen C, Agahi N, Shaw BA. Does the association between leisure activities and survival in old age differ by living arrangement? J Epidemiol Community Health. 2018;72(1):1-6.

Table 1. Baseline and follow-up characteristics of participants in the Seniors-ENRICA cohort, 2008–2010 to 2017.[a]

Characteristic	Baseline visit (2008–2010)	Follow-up visit		
		First (2013)	Second (2015)	Third (2017)
No. of participants	3,228	2,444	1,774	1,098
Age (years)				
60–64	919 (28.5)	262 (10.7)	2 (0.1)	0 (0.0)
65–69	1,014 (31.4)	789 (32.3)	451 (25.4)	151 (13.8)
70–74	633 (19.6)	647 (26.5)	639 (36.0)	418 (38.1)
75–79	414 (12.8)	424 (17.3)	352 (19.8)	307 (28.0)
≥ 80	248 (7.7)	322 (13.2)	330 (18.6)	221 (20.1)
Sex				
Men	1,492 (46.2)	1,151 (47.1)	854 (48.2)	542 (49.4)
Women	1,736 (53.8)	1,293 (52.9)	920 (51.9)	556 (50.6)
Educational level				
Primary or less	1,851 (57.3)	1,325 (54.2)	890 (50.1)	524 (47.7)
Secondary	759 (23.5)	601 (24.6)	475 (26.8)	302 (27.5)
University	618 (19.2)	518 (21.2)	409 (23.1)	272 (24.8)
Smoking status				
Never	1,878 (58.2)	1,334 (54.6)	910 (51.3)	538 (49.0)
Former	973 (30.1)	904 (37.0)	721 (40.6)	489 (44.5)
Current	377 (11.7)	206 (8.4)	143 (8.1)	71 (6.5)
Alcohol drinking				
Never	1,002 (31.0)	537 (22.0)	357 (20.1)	175 (15.9)
Former	460 (14.3)	398 (16.3)	282 (15.9)	245 (22.3)
Current	1,766 (54.7)	1,509 (61.7)	1135 (64.0)	678 (61.8)
Mediterranean diet score[b]				
≤ 5	664 (20.6)	344 (14.1)	244 (13.8)	169 (15.4)
6	656 (20.3)	483 (19.8)	339 (19.1)	237 (21.6)
7	748 (23.2)	582 (23.8)	405 (22.8)	277 (25.2)
8	609 (18.9)	537 (21.9)	404 (22.8)	245 (22.3)
≥ 9	551 (17.1)	498 (20.4)	382 (21.5)	170 (15.5)
Body mass index (kg/m^2)				
< 25	643 (19.9)	559 (22.9)	471 (26.6)	302 (27.5)
25–29.9	1,529 (47.4)	113 (45.4)	805 (45.4)	501 (45.6)
≥ 30	1,056 (32.7)	772 (31.6)	497 (28.0)	295 (26.9)
Recreational physical activity[c] (MET-hours/week)				
0	269 (8.3)	171 (7.0)	153 (8.6)	59 (5.4)
0.1–9.9	409 (12.7)	325 (13.3)	208 (11.7)	151 (13.7)
10–19.9	1,070 (33.1)	780 (31.9)	586 (33.0)	381 (34.7)
20–29.9	673 (20.9)	566 (23.2)	351 (19.8)	216 (19.7)
30–39.9	451 (14.0)	363 (14.9)	283 (6.0)	170 (15.5)
≥ 40	356 (11.0)	239 (9.7)	193 (10.9)	121 (11.0)
Household physical activity[c] (MET-hours/week)				
0	246 (7.6)	203 (8.3)	142 (8.0)	100 (9.1)
0.1–19.9	1,009 (31.3)	784 (32.1)	524 (29.5)	408 (37.2)
20–39.9	754 (23.4)	612 (25.0)	408 (23.0)	272 (24.8)
40–59.9	518 (16.0)	415 (17.0)	315 (17.8)	154 (14.0)
60–79.9	317 (9.8)	221 (9.0)	174 (9.8)	94 (8.5)
≥ 80	384 (11.9)	209 (8.6)	211 (11.9)	70 (6.4)
Mentally-active sedentary behavior[d] (hours/week)				
< 1	862 (26.7)	576 (23.6)	355 (20.0)	199 (18.1)
1–6.9	1,243 (38.5)	910 (37.2)	654 (36.9)	381 (34.7)

7–14.9	581 (18.0)	475 (19.4)	343 (19.3)	259 (23.6)
15–20.9	273 (8.5)	259 (10.6)	195 (11.0)	105 (9.6)
≥ 21	269 (8.3)	224 (9.2)	227 (12.8)	154 (14.0)
Passive sedentary behavior[d] (hours/day)				
< 2	940 (29.1)	521 (21.3)	333 (18.8)	235 (21.4)
2–2.9	958 (29.7)	679 (27.8)	445 (25.1)	275 (25.1)
3–3.9	592 (18.3)	620 (25.4)	429 (24.2)	286 (26.0)
4–4.9	363 (11.3)	339 (13.9)	281 (15.8)	157 (14.3)
≥ 5	375 (11.6)	285 (11.6)	286 (16.1)	145 (13.2)
Deficits accumulation index[e]				
< 10	1,119 (34.6)	645 (26.4)	448 (25.2)	292 (26.6)
10–19.9	1,147 (35.5)	853 (24.9)	661 (37.3)	382 (34.8)
20–29.9	571 (17.8)	515 (21.1)	339 (19.1)	233 (21.2)
≥ 30	391 (12.1)	431 (17.6)	326 (18.4)	191 (17.4)

[a] Data are number (percentages).
[b] Mediterranean Diet Adherence Screener score, ranging from 0 to 14 points (highest adherence).
[c] Recreational physical activity included walking, cycling, and playing sports and household physical activity included doing household chores, gardening, and home repair. The metabolic equivalents of tasks (METs) were 2.5 for walking and household chores and 4.0 for cycling, playing sports, gardening, and home repair.
[d] Mentally-active sedentary behavior included reading and using the computer and passive sedentary behavior included TV watching.
[e] Percentage of health deficits present out of the 51 health deficits considered, scale ranging from 0 to 100% deficit.

Table 2. Differences in health deficits accumulation by previous recreational and household physical activity among men and women in the Seniors-ENRICA cohort, 2008–2010 to 2017.

Previous physical activity	No. of follow-up visits	Average difference in deficits accumulation index[a] (95% CI)		
		Model 1[b]	Model 2[c]	Model 3[d]
Recreational (MET-hours/week)				
Overall				
0	387	1.57 (0.43 to 2.70)	0.44 (−0.74 to 1.63)	0.19 (−1.09 to 1.48)
0.1–9.9	645	1.30 (0.46 to 2.13)	0.68 (−0.16 to 1.52)	0.69 (−0.23 to 1.61)
10–19.9	1,723	0.00 (reference)	0.00 (reference)	0.00 (reference)
20–29.9	1,146	−0.81 (−1.40 to −0.21)	−0.59 (−1.21 to 0.03)	−0.66 (−1.34 to 0.02)
30–39.9	805	−0.73 (−1.40 to −0.06)	−0.67 (−1.35 to 0.00)	−0.87 (−1.59 to −0.13)
≥ 40	610	−0.56 (−1.34 to 0.22)	−0.40 (−1.20 to 0.39)	−0.55 (−1.37 to 0.28)
P for linear trend[e]		< 0.001	0.010	0.006
Men				
0	135	1.44 (−0.05 to 2.94)	1.17 (−0.77 to 3.10)	1.06 (−0.86 to 2.99)
0.1–9.9	223	0.64 (−0.58 to 1.86)	0.15 (−1.10 to 1.42)	0.44 (−0.96 to 1.84)
10–19.9	736	0.00 (reference)	0.00 (reference)	0.00 (reference)
20–29.9	532	−1.02 (−1.92 to −0.12)	−0.72 (−1.53 to 0.09)	−0.63 (−1.48 to 0.23)
30–39.9	453	−0.68 (−1.63 to 0.28)	−0.50 (−1.41 to 0.42)	−0.54 (−1.48 to 0.41)
≥ 40	468	−0.47 (−1.42 to 0.48)	−0.21 (−1.15 to 0.72)	−0.23 (−1.18 to 0.73)
P for linear trend[e]		0.013	0.192	0.151
Women				
0	252	1.66 (0.51 to 2.81)	0.04 (−1.42 to 1.49)	−0.31 (−1.94 to 1.33)
0.1–9.9	422	1.67 (0.74 to 2.60)	0.96 (−0.14 to 2.05)	0.81 (−0.40 to 2.01)
10–19.9	987	0.00 (reference)	0.00 (reference)	0.00 (reference)
20–29.9	614	−0.63 (−1.45 to 0.19)	−0.47 (−1.37 to 0.44)	−0.65 (−1.68 to 0.37)
30–39.9	352	−0.85 (−1.83 to 0.14)	−0.88 (−1.91 to 0.14)	−1.21 (−2.33 to −0.10)
≥ 40	142	−1.04 (−2.48 to 0.39)	−0.93 (−2.54 to 0.68)	−1.22 (−2.92 to 0.48)
P for linear trend[e]		< 0.001	0.015	0.011
P for sex interaction[f]		0.660	0.579	0.652
Household (MET-hours/week)				
Overall				
0	360	2.00 (0.80 to 3.21)	1.49 (0.14 to 2.84)	1.27 (−0.06 to 2.60)
0.1–19.9	1,641	0.07 (−0.56 to 0.70)	−0.11 (−0.76 to 0.54)	−0.11 (−0.79 to 0.56)
20–39.9	1,293	0.00 (reference)	0.00 (reference)	0.00 (reference)
40–59.9	905	−0.45 (−1.17 to 0.26)	−0.23 (−0.97 to 0.52)	−0.33 (−1.12 to 0.45)

60–79.9	525	−0.07 (−0.99 to 0.85)	0.16 (−0.76 to 1.08)	0.06 (−0.90 to 1.01)
≥ 80	592	−0.42 (−1.30 to 0.46)	−0.24 (−1.16 to 0.68)	−0.33 (−1.27 to 0.61)
P for linear trend[e]		0.035	0.369	0.317
Men				
0	289	2.00 (0.70 to 3.30)	2.16 (0.69 to 3.64)	1.86 (0.42 to 3.30)
0.1–19.9	1,260	0.45 (-0.29 to 1.19)	0.35 (−0.40 to 1.11)	0.34 (−0.47 to 1.14)
20–39.9	581	0.00 (reference)	0.00 (reference)	0.00 (reference)
40–59.9	256	0.52 (−0.50 to 1.54)	0.57 (−0.50 to 1.64)	0.53 (−0.61 to 1.66)
60–79.9	109	0.81 (−0.98 to 2.59)	1.08 (−0.76 to 2.92)	0.96 (−0.86 to 2.79)
≥ 80	52	−0.55 (−2.43 to 1.31)	−0.58 (−2.70 to 1.54)	−0.52 (−2.69 to 1.65)
P for linear trend[e]		0.121	0.215	0.302
Women				
0	71	3.19 (0.22 to 6.15)	−0.09 (−3.30 to 3.11)	0.06 (−3.19 to 3.30)
0.1–19.9	381	−0.39 (−1.52 to 0.75)	−0.62 (−1.78 to 0.54)	−0.60 (−1.79 to 0.59)
20–39.9	712	0.00 (reference)	0.00 (reference)	0.00 (reference)
40–59.9	649	−0.98 (−1.94 to −0.02)	−0.71 (−1.71 to 0.28)	−0.86 (−1.90 to 0.18)
60–79.9	416	−0.48 (−1.60 to 0.64)	−0.31 (−1.42 to 0.80)	−0.41 (−1.57 to 0.75)
≥ 80	540	−0.64 (−1.68 to 0.40)	−0.49 (−1.56 to 0.58)	−0.60 (−1.70 to 0.50)
P for linear trend[e]		0.129	0.801	0.601
P for sex interaction[f]		0.232	0.344	0.407

[a] Average differences in deficits accumulation index at each follow-up visit and 95% confidence intervals (CIs) by category of recreational (resp. household) physical activity at previous visit were obtained from repeated measures regression models with robust standard errors accounting for within-participant correlations induced by repeated measures and weighting. Sex-specific differences were obtained by including interactions between categories of recreational (resp. household) physical activity and sex in repeated measures models.

[b] Model 1 was adjusted for age (restricted quadratic splines with knots at 65, 70, 75, and 80 years), sex (men or women), educational level (primary or less, secondary, or university), and baseline levels of deficits accumulation index (restricted quadratic splines with knots at 10, 20, and 30%), smoking status (never, former, or current), alcohol drinking (never, former, or current), Mediterranean diet score (≤ 5, 6, 7, 8, or ≥ 9 points), body mass index (< 25, 25–29.9, or ≥ 30 kg/m^2), household (resp. recreational) physical activity, mentally-active sedentary behavior (< 1, 1–6.9, 7–14.9, 15–20.9, or ≥ 21 hours/week), and passive sedentary behavior (< 2, 2–2.9, 3–3.9, 4–4.9, or ≥ 5 hours/day).

[c] Model 2 was further weighted by the inverse of the conditional probability of having the observed recreational (resp. household) physical activity history up to the previous visit given follow-up levels of deficits accumulation index, smoking status, alcohol drinking, Mediterranean diet score, body mass index, household (resp. recreational) physical activity, mentally-active sedentary behavior, and passive sedentary behavior through that visit (with the same specifications used for baseline levels).

[d] Model 3 was further weighted by the inverse of the conditional probability of remaining uncensored up to the current visit given follow-up levels of deficits accumulation index, smoking status, alcohol drinking, Mediterranean diet score, body mass index, household (resp. recreational) physical activity, mentally-active sedentary behavior, and passive sedentary behavior through the previous visit (with the same specifications used for baseline levels).

[e] *P* values for linear trend in average deficits accumulation indexes were obtained by using an ordinal variable with the median recreational (resp. household) physical activity in each category.

[f] *P* values for interaction between recreational (resp. household) physical activity and sex were obtained by using joint Wald tests of interaction coefficients.

Table 3. Differences in health deficits accumulation by previous mentally-active and passive sedentary behavior among men and women in the Seniors-ENRICA cohort, 2008–2010 to 2017.

Previous sedentary behavior	No. of follow-up visits	Average difference in deficits accumulation index[a] (95% CI)		
		Model 1[b]	Model 2[c]	Model 3[d]
Mentally-active (hours/week)				
Overall				
< 1	1,131	0.74 (0.00 to 1.47)	0.32 (−0.43 to 1.08)	0.26 (−0.54 to 1.06)
1–6.9	2,017	0.00 (reference)	0.00 (reference)	0.00 (reference)
7–14.9	1,044	−0.26 (−0.90 to 0.39)	0.03 (−0.62 to 0.69)	0.00 (−0.70 to 0.71)
15–20.9	551	−0.45 (−1.24 to 0.34)	−0.17 (−1.02 to 0.68)	−0.23 (−1.10 to 0.65)
≥ 21	573	−0.58 (−1.45 to 0.30)	−0.53 (−1.38 to 0.32)	−0.61 (−1.50 to 0.28)
P for linear trend[e]		0.020	0.143	0.129
Men				
< 1	382	0.32 (−0.76 to 1.42)	0.00 (−1.11 to 1.12)	0.01 (−1.16 to 1.18)
1–6.9	846	0.00 (reference)	0.00 (reference)	0.00 (reference)
7–14.9	573	0.05 (−0.77 to 0.86)	0.23 (−0.61 to 1.08)	0.15 (−0.73 to 1.03)
15–20.9	323	0.44 (−0.56 to 1.44)	0.63 (−0.47 to 1.72)	0.46 (−0.64 to 1.56)
≥ 21	423	0.17 (−0.87 to 1.22)	0.16 (−0.88 to 1.19)	0.05 (−1.03 to 1.13)
P for linear trend[e]		0.796	0.578	0.79
Women				
< 1	749	0.92 (−0.05 to 1.88)	0.46 (−0.52 to 1.45)	0.37 (−1.03 to 1.13)
1–6.9	1,171	0.00 (reference)	0.00 (reference)	0.00 (reference)
7–14.9	471	−0.52 (−1.51 to 0.47)	−0.12 (−1.13 to 0.89)	−0.09 (−1.19 to 1.00)
15–20.9	228	−1.57 (−2.78 to −0.37)	−1.17 (−2.43 to 0.09)	−1.08 (−2.45 to 0.28)
≥ 21	150	−2.22 (−3.77 to −0.70)	−2.10 (−3.55 to −0.64)	−2.17 (−3.75 to −0.58)
P for linear trend[e]		< 0.001	0.002	0.005
P for sex interaction[f]		0.004	0.012	0.042
Passive (hours/day)				
Overall				
< 2	1,349	0.27 (−0.33 to 0.86)	0.21 (−0.39 to 0.81)	0.27 (−0.38 to 0.91)
2–2.9	1,516	0.00 (reference)	0.00 (reference)	0.00 (reference)
3–3.9	1,173	0.14 (−0.46 to 0.75)	0.31 (−0.31 to 0.92)	0.34 (−0.30 to 0.99)
4–4.9	670	0.95 (0.14 to 1.75)	0.79 (−0.03 to 1.62)	0.83 (−0.02 to 1.69)
≥ 5	608	1.26 (0.30 to 2.22)	0.92 (−0.07 to 1.90)	1.07 (0.05 to 2.09)

P for linear trend[e]		0.023	0.073	0.070
Men				
< 2	732	0.42 (−0.37 to 1.20)	0.38 (−0.41 to 1.17)	0.47 (−0.38 to 1.32)
2–2.9	730	0.00 (reference)	0.00 (reference)	0.00 (reference)
3–3.9	561	0.05 (−0.78 to 0.88)	0.22 (−0.62 to 1.07)	0.27 (−0.62 to 1.16)
4–4.9	293	0.56 (−0.56 to 1.68)	0.34 (−0.80 to 1.48)	0.19 (−0.98 to 1.36)
≥ 5	231	0.02 (−1.43 to 1.47)	−0.45 (−1.89 to 0.98)	−0.57 (−2.03 to 0.88)
P for linear trend[e]		0.800	0.479	0.333
Women				
< 2	617	0.05 (−0.86 to 0.97)	−0.02 (−0.94 to 0.89)	−0.03 (−0.98 to 0.93)
2–2.9	786	0.00 (reference)	0.00 (reference)	0.00 (reference)
3–3.9	612	0.22 (−0.66 to 1.11)	0.38 (−0.50 to 1.27)	0.41 (−0.52 to 1.35)
4–4.9	377	1.26 (0.11 to 2.41)	1.16 (−0.01 to 2.33)	1.35 (0.13 to 2.57)
≥ 5	377	2.06 (0.80 to 3.31)	1.80 (0.50 to 3.10)	2.13 (0.78 to 3.47)
P for linear trend[e]		0.001	0.004	0.001
P for sex interaction[f]		0.111	0.067	0.018

[a] Average differences in deficits accumulation index at each follow-up visit and 95% confidence intervals (CIs) by category of mentally-active (resp. passive) sedentary behavior at previous visit were obtained from repeated measures regression models with robust standard errors accounting for within-participant correlations induced by repeated measures and weighting. Sex-specific differences were obtained by including interactions between categories of mentally-active (resp. passive) sedentary behavior and sex in repeated measures models.

[b] Model 1 was adjusted for age (restricted quadratic splines with knots at 65, 70, 75, and 80 years), sex (men or women), educational level (primary or less, secondary, or university), and baseline levels of deficits accumulation index (restricted quadratic splines with knots at 10, 20, and 30%), smoking status (never, former, or current), alcohol drinking (never, former, or current), Mediterranean diet score (≤ 5, 6, 7, 8, or ≥ 9 points), body mass index (< 25, 25–29.9, or ≥ 30 kg/m^2), recreational physical activity (0, 0.1–9.9, 10–19.9, 20–29.9, 30–39.9, or ≥ 40 MET-hours/week), household physical activity (0, 0.1–19.9, 20–39.9, 40–59.9, 60–79.9, or ≥ 80 MET-hours/week), and passive (resp. mentally-active) sedentary behavior.

[c] Model 2 was further weighted by the inverse of the conditional probability of having the observed mentally-active (resp. passive) sedentary behavior history up to the previous visit given follow-up levels of deficits accumulation index, smoking status, alcohol drinking, Mediterranean diet score, body mass index, recreational physical activity, household physical activity, and passive (resp. mentally-active) sedentary behavior through that visit (with the same specifications used for baseline levels).

[d] Model 3 was further weighted by the inverse of the conditional probability of remaining uncensored up to the current visit given follow-up levels of deficits accumulation index, smoking status, alcohol drinking, Mediterranean diet score, body mass index, recreational physical activity, household physical activity, and passive (resp. mentally-active) sedentary behavior through the previous visit (with the same specifications used for baseline levels).

[e] *P* values for linear trend in average deficits accumulation indexes were obtained by using an ordinal variable with the median mentally-active (resp. passive) sedentary behavior in each category.

[f] *P* values for interaction between mentally-active (resp. passive) sedentary behavior and sex were obtained by using joint Wald tests of interaction coefficients.

FIGURE LEGENDS

Figure 1. Flow chart of participants in the Seniors-ENRICA cohort, 2008–2010 to 2017.

Figure 2. Differences in health deficits accumulation as a smooth function of previous recreational (A) and household physical activity (B) among participants in the Seniors-ENRICA cohort, 2008–2010 to 2017.

Curves represent average differences in deficits accumulation index at each follow-up visit (solid lines) and 95% confidence intervals (dashed lines) based on restricted quadratic splines for recreational and household physical activity at previous visit with knots at 10, 20, 30, and 40 MET-hours/week and 20, 40, 60, and 80 MET-hours/week, respectively. The reference values were set at 16.5 and 30.0 MET-hours/week, respectively. Average differences were obtained from repeated measures regression models adjusted for age, sex, educational level, and baseline levels of deficits accumulation index, smoking status, alcohol drinking, Mediterranean diet score, body mass index, household (resp. recreational) physical activity, mentally-active sedentary behavior, and passive sedentary behavior; weighted by the inverse of the conditional probabilities of exposure and censoring given follow-up levels of the above time-varying factors up to the previous visit; and accounting for within-participant correlations induced by repeated measures and weighting. Bars represent the histograms of recreational and household physical activity at previous visit.

Figure 3. Differences in health deficits accumulation as a smooth function of previous mentally-active (A, B) and passive sedentary behavior (C, D) among men and women in the Seniors-ENRICA cohort, 2008–2010 to 2017.

Curves represent average differences in deficits accumulation index at each follow-up visit (solid lines) and 95% confidence intervals (dashed lines) based on restricted quadratic splines for mentally-active and passive sedentary behavior at previous visit with knots at 1, 7, 15, and 21 hours/week and 2, 3, 4, and 5 hours/day, respectively. The reference values were set at 4.0 hours/week and 2.5 hours/day, respectively. Sex-specific average differences were obtained from repeated measures regression models with interactions between spline terms for mentally-active (resp. passive) sedentary behavior and sex; adjusted for age, educational level, and baseline levels of deficits accumulation index, smoking status, alcohol drinking, Mediterranean diet score, body mass index, recreational physical activity, household physical activity, and passive (resp. mentally-active) sedentary behavior; weighted by the inverse of the conditional probabilities of exposure and censoring given follow-up levels of the above time-varying factors up to the previous visit; and accounting for within-participant correlations induced by repeated measures and weighting. Bars represent the histograms of mentally-active and passive sedentary behavior at previous visit among men and women.