Published in final edited form as:

Alzheimers Dement. 2021 December ; 17(12): 1905–1913. doi:10.1002/alz.12359.

Association of Life's Simple 7 with incident dementia and its modification by the apolipoprotein E genotype

Jing Guo, PhD[1], **Adam M. Brickman, PhD**[1,2,3], **Jennifer J. Manly, PhD**[1,2,3], **Christiane Reitz, MD, PhD**[1,2,3,4], **Nicole Schupf, PhD**[1,2,4], **Richard P. Mayeux, MD**[1,2,3,4], **Yian Gu, PhD**[1,2,3,4]

[1]The Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY.

[2]The Department of Neurology, Columbia University, New York, NY.

[3]The Gertrude H. Sergievsky Center, Columbia University, New York, NY.

[4]The Department of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University, New York, NY.

Abstract

Introduction: There is limited and inconsistent reporting on the association between Life's Simple 7 (LS7) and dementia in the elderly population.

Methods: Based on Washington Heights-Inwood Columbia Aging Project (WHICAP) study, LS7 scores were estimated to assess cardiovascular health status. Associations between LS7 scores and incident dementia were investigated by Cox proportional hazards models.

Results: Among 1987 subjects, 291 incident cases of dementia were identified over a median follow-up of 5.84 years. Compared with subjects in the poor cardiovascular health group (scores 0 to 5), those in intermediate (6 to 9) and optimal (10 to 14) groups had lower dementia risk, with the hazard ratio (HR; 95% confidence interval [CI]) being 0.74 (0.54 to 1.00) and 0.59 (0.38 to 0.91), respectively. These results were significant in Apolipoprotein E genotype ε4 (*APOE*-ε4) allele noncarriers but not in carriers.

Discussion: Higher LS7 scores are protective for dementia, especially among the *APOE*-ε4 noncarriers.

Keywords

dementia; cardiovascular health; Life's Simple 7; *APOE*-ε4; epidemiology

1. Introduction

With no effective medical treatments available, dementia remains a global challenge for health and social care [1]. Primary prevention through modifiable risk factors is thus an urgent priority to reduce the incidence of cognitive impairment and dementia [1, 2]. Much of

Corresponding author: Yian Gu, Ph.D., yg2121@cumc.columbia.edu, 630 West 168th Street, P&S Box 16, New York, NY 10032, Phone: 212-305-6684; Fax: 212-342-1838.

the evidence focuses on the individual lifestyle/cardiovascular risk factors [3–6]. However, recent evidence suggests that a multidomain intervention could be required for the optimum preventive effects on cognitive impairment and dementia [7–9].

The Life's Simple 7 (LS7), proposed by the American Heart Association (AHA) for primordial prevention of cardiovascular diseases, comprehensively defines ideal cardiovascular health as presence of four health behaviors (physical activity at moderate levels ≥150 min/wk, or at vigorous levels ≥75 min/wk, or at moderate and vigorous levels ≥150 min/wk, nonsmoking, body mass index [BMI] <25.0 kg/m^2, and healthy diet habits including at least four of the following components: fruits and vegetables ≥4.5 servings/d, sodium <1500 mg/d, fish ≥two 3.5 oz/wk, whole grains ≥3 servings/d, sugar-sweetened beverages <36 oz/wk) and three biological metrics (untreated total cholesterol <200 mg/dL, fasting blood glucose <100 mg/dL, and untreated blood pressure <120/<80 mm Hg) [10]. Emerging evidence indicates that the LS7 is inversely associated with the risks of dementia [11–15] and Alzheimer's disease (AD) [14]. However, nonsignificant associations of LS7 with cognition [16] and dementia [17] have also been reported. Results from a cluster-randomized controlled trial showed that a multidomain vascular care intervention did not lead to a reduction in incidence of all-cause dementia among an elderly population [18].

Apolipoprotein E genotype ε4 (*APOE*-ε4) allele is currently identified as the most important genetic risk factor for late-onset AD [19]. *APOE*-ε4 might lead to increased risk of AD through multiple mechanisms including interference with the clearance of amyloid-beta (Aβ), crosstalk with Aβ, lipid and glucose metabolism, and inflammation [19], many of which are the potential pathways through which LS7 or its components are linked with cognition or dementia [5, 20–22]. Only a few studies have investigated the associations between adherence to a healthy lifestyle clustering and risks of dementia by stratification of *APOE*-ε4 status [23–25], and the results were inconsistent, with both stronger [24] or weaker [23, 25] associations found in *APOE*-ε4 allele carriers than in noncarriers. To the best of our knowledge, no study has examined the effect modification of *APOE*-ε4 carriage on the association between LS7 scores and dementia risk.

Due to the limited and inconsistent evidence, in the present study, we aimed to examine whether LS7 scores were associated with incident dementia risk and whether this association varied by *APOE*-ε4 allele status in a multi-ethnic elderly population.

2. Methods

2.1 Study design and population

The Washington Heights-Inwood Columbia Aging Project (WHICAP) is a multiethnic, community-based, prospective cohort study which is performed to explore risk factors for aging and dementia. Three waves of participants were recruited in 1992, 1999, and 2009 in WHICAP, all using similar study procedures [6, 26]. Briefly, participants were recruited from a probability sample of Medicare recipients who were 65 years and older, socioeconomically and racially diverse, and residing in northern Manhattan. At the study entry, each subject underwent a structured in-person interview of general health and function, followed by a comprehensive assessment including medical and neurological

histories, standardized physical, neurological and neuropsychological examinations. Participants were followed every 18–24 months, repeating similar baseline examinations.

The WHICAP study was approved by the Institutional Review Board at Columbia University Medical Center. Written informed consent was provided by all the participants.

Among all the 4945 subjects at baseline, cases with prevalent dementia were excluded (n = 490) (Figure 1). Subjects were further excluded if they had no follow-up survey (n = 1088), had missing values on variables of interests (LS7 scores [n = 1360], incident dementia [n = 10], education duration [n = 9], *APOE*-ε4 [n = 1]). Finally, a total of 1987 subjects were included in the present study.

2.2 Measurements of LS7 metrics

All the LS7 metrics were categorized into three grades of poor (coded as 0), intermediate (coed as 1), and optimal (coded as 2) according to the AHA criteria [10] with modifications in diet, physical activity and glucose in this study (Supplementary Table S1). Information about BMI, diet, smoking, physical activity, and blood pressure were collected from baseline interviews/examinations, and cholesterol and glucose levels were tested in the follow-up visit. For each LS7 component, the first available assessment at follow-up visit was used if the information is missing at baseline. BMI was calculated, using measured weight and height, as weight in kilograms divided by height in meters squared. Dietary information was collected using semi-quantitative food frequency questionnaire (SFFQ). Due to incomplete information of whole grain intake captured by this SFFQ, whole grain intake was not included in the construction of the diet metric. Leisure time physical activity (LTPA) was assessed using Godin physical activity form, and total LTPA dose was measured by metabolic equivalents (METs)-minutes/2-weeks. As in this older population the majority of subjects (nearly 85%) had the lowest levels of physical activity defined by the original AHA criteria, we modified the LTPA category cutoffs as low (no LTPA), middle and high levels, with the latter two levels based on median value of 1260 MET-minutes/2 weeks among those who reported non-zero LTPA. This method for LTPA categorization has a high capacity to predict incident AD in older adults [6]. After resting quietly in a seated position, blood pressure levels (mmHg) on the right arm were consecutively examined for three times every three minutes over nine minutes, and the third measurement was used [27]. Subjects who had ever smoked ≥ 1 cigarette per day for a period of one year or more were regarded as smokers [27], and were subsequently classified as past smokers when they had quit smoking, or current smokers when they were still smoking. Levels of total cholesterol, glucose, and HbA1c were measured according to standard research procedures [27]. Fasting plasma total cholesterol levels were tested using standard enzymatic techniques. HbA1c was quantified using boronate affinity chromatography with the Primus CLC 385 (Primus, Kansas City, MO). Glucose metric was preferentially assessed by the blood glucose, and was secondarily assessed by HbA1c levels if the glucose values were missing. HbA1c levels were categorized into poor, intermediate and ideal at the cut-off points of 6.5% and 5.7% [28].

The LS7 scores were calculated as the sum of seven components, ranging from 0 to 14 with higher scores meaning better cardiovascular health. LS7 scores were then categorized

as poor for scores ranging from 0 to 5 (< mean - standard deviation [SD]), intermediate for scores ranging from 6 to 9 (≥ mean - SD and < mean + SD), and optimal for scores ranging from 10 to 14 (≥ mean + SD) as suggested in the literature [15].

2.3 Clinical diagnosis of dementia

The primary outcome was all-cause dementia which was determined based on *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria* [29]. At each WHICAP visit, participants underwent a standardized neuropsychological battery including measures of memory, language, orientation, abstract reasoning, and visuospatial ability [30]. Dementia was diagnosed through diagnostic consensus conferences attended by a panel of neurologists, psychiatrists, and neuropsychologists, using results from the neuropsychological battery and evidence of impairment in social or occupational function. Incident dementia was identified when the subjects were firstly clinically diagnosed with dementia during the follow-up study among those with a previous diagnosis with no dementia.

2.4 Covariates

Demographics including age (years), sex (male, female), ethnicity (White, Black, Hispanic, and others) and education duration (years) were collected from baseline interviews. Daily calories intake (kcal) was obtained from the SFFQ administered at baseline. Depression status (yes, no) was assessed via the 10-item Centre for Epidemiological Studies Depression Scale (CES-D), and a cut-off score of 4 was used to identify individuals with major depression [31]. *APOE*-ε4 genotype was defined based on absence or presence (either 1 or 2) of ε4 alleles.

2.5 Statistical analysis

Characteristics of subjects across the categories of LS7 scores were compared using the analysis of variance and Chi-square test for the continuous and categorical variables, respectively. Associations of LS7 scores with risks of incident dementia were examined by the Cox regression models. The survival-time metrics were years of follow-up from the first survey through the last visit or diagnosis of incident dementia (whichever came first). Model 1 was adjusted for age, sex, and ethnicity, and Model 2 was further adjusted for education duration, cohort wave, daily calories intake, depression, and *APOE*-ε4 possession. Both categorical (setting the poor as reference) and continuous LS7 scores were used to fit Cox regression models. The method of scaled Schoenfeld residuals was used to check the validity of proportional hazards (PH) assumption for Cox regression models.

Interactions were examined by the product term between LS7 (continuous) and *APOE*-ε4 allele status (dichotomous) in the fully adjusted model, followed by stratified analyses by *APOE*-ε4 allele status. Analyses on the associations between individual LS7 components and dementia were performed with similar methods.

Sensitivity analyses were conducted when removing subjects with follow-up time less than two years (n = 1831); when additionally adjusting for history of comorbidities including

hypertension, diabetes, and heart diseases at baseline. The association analysis was also performed by using the Weibull regression model.

All the data analyses were performed with R (version 3.6.1). Two-sided p values less than 0.05 were statistically significant.

3. Results

3.1 Characteristics of the study participants

The 1987 eligible subjects included in the present study were followed up over a median of 5.84 (ranging from 0.94 to 17.68) years, for a total of 13555.64 person-years. Among them, a total of 291 incident dementia cases were identified.

As shown in Table 1, the mean age was 75.33 (SD = 5.98) years, and about one third of the participants were males. About one quarter of the subjects were carriers of an *APOE*-ε4 allele. Subjects with higher levels of LS7 scores were more likely to be males, to be White, to have a higher degree of education, to have lower prevalence of depression, hypertension, diabetes, and heart diseases, and to have a lower proportion of incident dementia.

3.2 Associations between LS7 scores and incident dementia

Decreased incidence rate of dementia was observed with improved levels of LS7 metrics (Table 2). After full adjustments, compared with subjects with poor cardiovascular health, decreased risks of incident dementia was found in the intermediate (hazard ratio [HR] = 0.74, 95% CI = 0.54 to 1.00) and optimal (HR = 0.59, 95% CI = 0.38 to 0.91) groups ($p_{\text{trend}} = 0.020$). An increase of one point in LS7 scores was significantly related with a decreased risk of dementia of 8% (HR = 0.92, 95% CI = 0.86 to 0.98). The PH assumption was not significantly violated for continuous ($p = 0.101$) and categorical ($p = 0.086$) LS7 scores in the fully adjusted Cox regression models.

3.3 Examination of effect modification by APOE-ε4 allele status

The interaction between LS7 and *APOE*-ε4 allele status was not statistically significant ($p_{\text{interaction}} = 0.249$). The association between LS7 and dementia risk was significant in *APOE*-ε4 noncarriers but not in carriers (Table 2).

3.4 Associations between LS7 components and incident dementia

Among all the subjects, with improved levels of physical activity, the risks of dementia significantly decreased. Other factors were not associated with dementia risk.

The interactions between smoking scores and *APOE*-ε4 allele status were statistically significant ($p_{\text{interaction}} = 0.020$), while no interaction was found for *APOE* with other LS7 components. In *APOE*-ε4 allele carriers, LS7 components, except for physical activity, were not associated with dementia risk. Among subjects who had no *APOE*-ε4 allele, those at the optimal levels of physical activity, smoking, and glucose had significantly lower dementia risk.

3.5 Sensitivity analyses

Similar associations of LS7 scores with risks of dementia were observed when excluding subjects whose follow-up duration was less than two years (Supplementary Table S2), and when the history of comorbidities at baseline were additionally adjusted (Supplementary Table S3). Robust results were found by using the Weibull regression models for association analysis (Supplementary Table S4).

4. Discussion

Results in the current study indicated that ideal LS7 cardiovascular health was associated with decreased risks of all-cause dementia in the elderly population. In addition, improved levels of LS7 scores and the LS7 components of smoking and blood glucose were significantly associated with reduced dementia risk in the *APOE*-ε4 allele noncarriers but not in carriers. Decreased risks of dementia associated with physical activity were found regardless of *APOE*-ε4 status.

Lifestyle factors may affect the dementia risk through cardiovascular and neurodegenerative brain pathologies including vascular, oxidative stress, inflammatory, and neurotoxic processes [8]. Due to the complex and heterogeneous nature of dementia, multidomain intervention targeting different risk factors and mechanisms simultaneously is recommended to achieve optimal preventive effects [7]. Higher LS7 scores at midlife was reported to be related with higher volumes of grey matter and whole brain [15], and with reduced cognitive decline in late life [32]. Consistent with previous studies [11, 15], the current study demonstrated that higher LS7 scores were associated with decreased risks of dementia. However, evidence from other observational studies indicated nonsignificant associations among mid-aged adults in Germany [17], and with cognitive function in the elderly population in Chile [16]. Besides, results from randomized controlled trials demonstrated that a 2-year multidomain intervention (diet, cognitive training, exercise, and vascular risk monitoring) could maintain or improve the cognitive function for elderly population in Finland [7], but a 6-year multidomain vascular care intervention (diet, physical activity, weight, smoking, and blood pressure) did not reduce the incidence of dementia for older people in Netherlands [18]. Overall, it seems that inconsistent associations of cardiovascular health with dementia risk can be due to multiple reasons, including difference in measuring outcomes and LS7, length of follow up time, and population characteristics such as age, race/ethnicity, and genetic background.

We found that associations of LS7 scores with dementia were significant among *APOE*-ε4 noncarriers, but was nonsignificant among carriers. Our findings were in line with the evidence from other studies [23, 25]. Among the Japanese-American men (mean age = 52 years), the composite effects of lifestyles including BMI, smoking, diet, and physical activity on dementia risk were statistically significant for *APOE*-ε4 allele noncarriers, but not for the carriers [23]. A clustering of healthy lifestyle factors was also found to be related to decreased dementia risk among the *APOE*-ε4 negative participants of the Rotterdam study only (mean age = about 69 years), but not in *APOE*-ε4 carriers [25]. However, inconsistent results were observed that *APOE*-ε4 allele carriers, rather than noncarriers, in the Finnish adults (mean age = 50.6 years) had lower risks of dementia associated with a

combination of healthy lifestyle factors [24]. A retrospective cohort study concluded that a favorable lifestyle pattern was related to lower dementia risk among Europeans (mean age = 64.1 years) with high polygenic risk scores [33]. In a randomized clinical trial study, the effects of multidomain intervention on cognitive change was not significantly different among *APOE*-ε4 allele carriers and noncarriers [34].

Subjects in our study (mean age at baseline = 75.33 years) were older than some of the abovementioned epidemiological studies. *APOE*-ε4 allele contributes to neuronal degeneration through the acceleration of Aβ deposition and neurotoxicity [35]. The effects of *APOE*-ε4 allele on dementia vary at different age stages [36] and accumulate with advancing age, ultimately showing more detrimental effects in older individuals. The health benefits of favorable lifestyle factors may be offset and masked by the accumulated detrimental effects in older *APOE*-ε4 allele carriers, which may explain the significantly protective associations of LS7 with dementia in *APOE*-ε4 allele noncarriers but not in carriers in the present study. Besides, because *APOE*-ε4 allele are related with earlier onset of dementia and premature mortality [19], and the mean of LS7 scores was not statistically different between *APOE*-ε4 carriers and noncarriers in this study ($p = 0.816$), the dementia risk in surviving, nondemented, and older *APOE*-ε4 carriers is likely to be less affected by the lifestyle factors later in life [25]. Additionally, we used LS7 scores which contains both health behaviors and biological metrics to assess the cardiovascular health comprehensively, while the biological components of LS7 such as hypertension, glucose, and cholesterol were not included in previous studies [23–25, 33]. As mechanisms underlying the modification effects of *APOE*-ε4 allele are not yet fully understood, more biological measurements may help better understand the relevant mechanisms.

Similar to our findings, only three LS7 components, including physical activity, smoking status, and glucose, were identified to be significantly associated with dementia risk in German adults [17]. Subjects with higher levels of physical activity had reduced risks of dementia regardless of *APOE*-ε4 allele status in our study [6]. Physical activity can ameliorate the metabolic and vascular factors and psychological stress, and can favor amyloid clearance and improve cognitive reserve [8]. Our results are consistent with several large epidemiological studies reporting benefits of LTPA and lack of interaction between LTPA and *APOE* on cognitive function [37, 38]. A recent study did find AD patients who were *APOE* ε4 carriers benefitted more from the exercise intervention by preservation of cognitive performance [39]. However, the study was over-represented by *APOE*-ε4 carriers (72% of all subjects) and included only 55 noncarriers. Thus, the null results in noncarriers may be limited by small sample size. Overall, current evidence suggests that LTPA might be an important intervention target for dementia prevention among *APOE*-ε4 carriers.

Our data demonstrated significant associations of favorable smoking status (never smoking *vs.* current smoking) with reduced dementia risk in *APOE*-ε4 noncarriers but not in carriers. Similarly, in previous studies from WHICAP as well as other large population-based studies, current smokers had lower cognitive function [40, 41] and elevated AD risk [3, 21] compared with nonsmokers, and the association was stronger among elderly *APOE*-ε4 allele noncarriers than carriers. However, significant results of smoking have also been found in

APOE-ε4 allele carriers rather than noncarriers in other previous studies with limited sample size [42] or younger participants [20].

Higher levels of glucose have been reported to be related with elevated risks of dementia [43]. In the current study we found similar association between glucose and dementia risk in *APOE*-ε4 allele noncarriers only. Levels of insulin, glucose, and Homeostatic Model Assessment-Insulin Resistance were related with increased AD risks or lower cognitive function among *APOE*-ε4 negative but not ε4 positive subjects based on data from prospective cohort [5, 44] and cross-sectional studies [45], which were consistent with our findings.

The present study did not find blood pressure to be related with risk of dementia in the elderly population. Hypertension in midlife but not late life has been proposed to be associated with increased risk of cognitive impairment and dementia [46]. Consistent with our findings, a previous WHICAP study reported that hypertension after age 65 years is not associated with the risk of cognitive decline and AD [47]. Results from other cohort studies also demonstrated that elevated blood pressure levels in late life are not significantly associated with risk of all-cause dementia [48] and cognitive decline [49].

Several limitations need to be noted in our study. A single measurement of LS7 scores may not capture the average levels of cardiovascular health during the whole follow-up period. Self-reported information on lifestyle may lead to a bias in LS7 scores. The lifestyle may also be affected by the preclinical dementia and other chronic conditions. However, when we excluded subjects with a short follow-up time below two years and additionally adjusted for other comorbidities to reduce potential reserve causality, we found robust results. Some subjects were excluded due to missing data or lack of follow-up visits, which might also induce selection bias. Influence of missing data on LS7 scores was likely to be limited because no significant differences in LS7 scores between the subjects excluded and included were found ($p > 0.05$). The weak association of LS7 scores with dementia among *APOE*-ε4 carriers should be interpreted with cautious due to a relatively small sample size of *APOE*-ε4 carriers and small numbers of incident dementia cases among them.

There are many advantages in this study. Our study makes timely contributions as the field of dementia prevention now moves toward multifactorial interventions. Guided by potential biological mechanisms and increasing interest in precision prevention, we *a priori* decided to perform stratified analyses by *APOE* status so our results can be valuable for future studies looking for prevention measures for at-risk populations. The generalizability of our findings is improved by the multiethnic and community-based participants. The incident dementia was identified based on the standard criteria and consensus diagnosis.

5. Conclusions

In conclusion, a favorable cardiovascular health was related to lower risks of dementia in the elderly population, especially for the *APOE*-ε4 allele noncarriers. Continued search for protective factors among *APOE*-ε4 carriers for dementia prevention is highly warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Data collection and sharing for this project was supported by the Washington Heights-Inwood Columbia Aging Project (WHICAP, PO1AG007232, R01AG037212, RF1AG054023, R01AG059013, R56AG060156, AG061008) funded by the National Institute on Aging (NIA) and by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1TR001873. C.R. was funded by NIH grants RF1AG054080, P30AG066462, R01AG064614, and U01AG052410.

This manuscript has been reviewed by WHICAP investigators for scientific content and consistency of data interpretation with previous WHICAP Study publications. We acknowledge the WHICAP study participants and the WHICAP research and support staff for their contributions to this study.

References

[1]. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet. 2017;390:2673–734. [PubMed: 28735855]

[2]. Kivipelto M, Mangialasche F, Snyder HM, Allegri R, Andrieu S, Arai H, et al. World-Wide FINGERS Network: A global approach to risk reduction and prevention of dementia. Alzheimers Dement. 2020;16:1078–94. [PubMed: 32627328]

[3]. Ott A, Slooter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. Lancet. 1998;351:1840–3. [PubMed: 9652667]

[4]. Barberger-Gateau P, Samieri C, Feart C, Plourde M. Dietary omega 3 polyunsaturated fatty acids and Alzheimer's disease: interaction with apolipoprotein E genotype. Curr Alzheimer Res. 2011;8:479–91. [PubMed: 21605054]

[5]. Hughes TM, Craft S, Baker LD, Espeland MA, Rapp SR, Sink KM, et al. Changes in metabolic risk factors over 10 years and their associations with late-life cognitive performance: The Multi-Ethnic Study of Atherosclerosis. Alzheimers Dement (Amst). 2017;8:18–25. [PubMed: 28435852]

[6]. Ogino E, Manly JJ, Schupf N, Mayeux R, Gu Y. Current and past leisure time physical activity in relation to risk of Alzheimer's disease in older adults. Alzheimers Dement. 2019;15:1603–11. [PubMed: 31587996]

[7]. Ngandu T, Lehtisalo J, Solomon A, Levalahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015;385:2255–63. [PubMed: 25771249]

[8]. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol. 2018;14:653–66. [PubMed: 30291317]

[9]. Dhana K, Evans DA, Rajan KB, Bennett DA, Morris MC. Healthy lifestyle and the risk of Alzheimer dementia: Findings from 2 longitudinal studies. Neurology. 2020;95:e374–e83. [PubMed: 32554763]

[10]. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010;121:586–613. [PubMed: 20089546]

[11]. Samieri C, Perier MC, Gaye B, Proust-Lima C, Helmer C, Dartigues JF, et al. Association of Cardiovascular Health Level in Older Age With Cognitive Decline and Incident Dementia. JAMA. 2018;320:657–64. [PubMed: 30140876]

[12]. Atkins JL, Delgado J, Pilling LC, Bowman K, Masoli JAH, Kuchel GA, et al. Impact of Low Cardiovascular Risk Profiles on Geriatric Outcomes: Evidence From 421,000 Participants in Two Cohorts. J Gerontol A Biol Sci Med Sci. 2019;74:350–7. [PubMed: 29982474]

[13]. Gardener H, Wright CB, Dong C, Cheung K, DeRosa J, Nannery M, et al. Ideal Cardiovascular Health and Cognitive Aging in the Northern Manhattan Study. J Am Heart Assoc. 2016;5:e002731. [PubMed: 26984255]

[14]. Pase MP, Beiser A, Enserro D, Xanthakis V, Aparicio H, Satizabal CL, et al. Association of Ideal Cardiovascular Health With Vascular Brain Injury and Incident Dementia. Stroke. 2016;47:1201–6. [PubMed: 27073239]

[15]. Sabia S, Fayosse A, Dumurgier J, Schnitzler A, Empana JP, Ebmeier KP, et al. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. BMJ. 2019;366:l4414. [PubMed: 31391187]

[16]. Garcia-Hermoso A, Ramirez-Velez R, Ramirez-Campillo R, Izquierdo M. Relationship Between Ideal Cardiovascular Health and Disability in Older Adults: The Chilean National Health Survey (2009–10). J Am Geriatr Soc. 2017;65:2727–32. [PubMed: 29067687]

[17]. Hessler JB, Ander KH, Bronner M, Etgen T, Forstl H, Poppert H, et al. Predicting dementia in primary care patients with a cardiovascular health metric: a prospective population-based study. BMC Neurol. 2016;16:116. [PubMed: 27459854]

[18]. Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet. 2016;388:797–805. [PubMed: 27474376]

[19]. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol. 2019;15:501–18. [PubMed: 31367008]

[20]. Rusanen M, Rovio S, Ngandu T, Nissinen A, Tuomilehto J, Soininen H, et al. Midlife smoking, apolipoprotein E and risk of dementia and Alzheimer's disease: a population-based cardiovascular risk factors, aging and dementia study. Dement Geriatr Cogn Disord. 2010;30:277–84. [PubMed: 20847559]

[21]. Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. The influence of smoking on the risk of Alzheimer's disease. Neurology. 1999;52:1408–12. [PubMed: 10227626]

[22]. Livny A, Ravona-Springer R, Heymann A, Priess R, Kushnir T, Tsarfaty G, et al. Long-term Variability in Glycemic Control Is Associated With White Matter Hyperintensities in APOE4 Genotype Carriers With Type 2 Diabetes. Diabetes Care. 2016;39:1056–9. [PubMed: 27208321]

[23]. Gelber RP, Petrovitch H, Masaki KH, Abbott RD, Ross GW, Launer LJ, et al. Lifestyle and the risk of dementia in Japanese-american men. J Am Geriatr Soc. 2012;60:118–23. [PubMed: 22211390]

[24]. Kivipelto M, Rovio S, Ngandu T, Kareholt I, Eskelinen M, Winblad B, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med. 2008;12:2762–71. [PubMed: 18318693]

[25]. Licher S, Ahmad S, Karamujic-Comic H, Voortman T, Leening MJG, Ikram MA, et al. Genetic predisposition, modifiable-risk-factor profile and long-term dementia risk in the general population. Nat Med. 2019;25:1364–9. [PubMed: 31451782]

[26]. Gu Y, Beato JM, Amarante E, Chesebro AG, Manly JJ, Schupf N, et al. Assessment of Leisure Time Physical Activity and Brain Health in a Multiethnic Cohort of Older Adults. JAMA Netw Open. 2020;3:e2026506. [PubMed: 33211111]

[27]. Reitz C, Guzman VA, Narkhede A, DeCarli C, Brickman AM, Luchsinger JA. Relation of Dysglycemia to Structural Brain Changes in a Multiethnic Elderly Cohort. J Am Geriatr Soc. 2017;65:277–85. [PubMed: 27917464]

[28]. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43:S14–S31. [PubMed: 31862745]

[29]. Bell CC. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. JAMA. 1994;272:828–9.

[30]. Stern Y, Andrews H, Pittman J, Sano M, Tatemichi T, Lantigua R, et al. Diagnosis of dementia in a heterogeneous population. Development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. Arch Neurol. 1992;49:453–60. [PubMed: 1580806]

[31]. Irwin M, Artin KH, Oxman MN. Screening for depression in the older adult: criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). Arch Intern Med. 1999;159:1701–4. [PubMed: 10448771]

[32]. Gonzalez HM, Tarraf W, Harrison K, Windham BG, Tingle J, Alonso A, et al. Midlife cardiovascular health and 20-year cognitive decline: Atherosclerosis Risk in Communities Study results. Alzheimers Dement. 2018;14:579–89. [PubMed: 29268079]

[33]. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hypponen E, Kuzma E, et al. Association of Lifestyle and Genetic Risk With Incidence of Dementia. JAMA. 2019.

[34]. Solomon A, Turunen H, Ngandu T, Peltonen M, Levalahti E, Helisalmi S, et al. Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention: A Subgroup Analysis of a Randomized Clinical Trial. JAMA Neurol. 2018;75:462–70. [PubMed: 29356827]

[35]. Roda AR, Montoliu-Gaya L, Villegas S. The Role of Apolipoprotein E Isoforms in Alzheimer's Disease. J Alzheimers Dis. 2019;68:459–71. [PubMed: 30775980]

[36]. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 1997;278:1349–56. [PubMed: 9343467]

[37]. Folley S, Zhou A, Llewellyn DJ, Hypponen E. Physical Activity, APOE Genotype, and Cognitive Decline: Exploring Gene-Environment Interactions in the UK Biobank. J Alzheimers Dis. 2019;71:741–50. [PubMed: 31450492]

[38]. Rodriguez FS, Schroeter ML, Arelin K, Witte AV, Baber R, Burkhardt R, et al. APOE e4-genotype and lifestyle interaction on cognitive performance: Results of the LIFE-Adult-study. Health Psychol. 2018;37:194–205. [PubMed: 29215900]

[39]. Jensen CS, Simonsen AH, Siersma V, Beyer N, Frederiksen KS, Gottrup H, et al. Patients with Alzheimer's disease who carry the APOE epsilon4 allele benefit more from physical exercise. Alzheimers Dement (N Y). 2019;5:99–106. [PubMed: 31011620]

[40]. Reitz C, Luchsinger J, Tang MX, Mayeux R. Effect of smoking and time on cognitive function in the elderly without dementia. Neurology. 2005;65:870–5. [PubMed: 16186526]

[41]. Carmelli D, Swan GE, Reed T, Schellenberg GD, Christian JC. The effect of apolipoprotein E epsilon4 in the relationships of smoking and drinking to cognitive function. Neuroepidemiology. 1999;18:125–33. [PubMed: 10202267]

[42]. Durazzo TC, Mattsson N, Weiner MW, Alzheimer's Disease Neuroimaging I. Interaction of Cigarette Smoking History With APOE Genotype and Age on Amyloid Level, Glucose Metabolism, and Neurocognition in Cognitively Normal Elders. Nicotine Tob Res. 2016;18:204–11. [PubMed: 25847292]

[43]. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, et al. Glucose levels and risk of dementia. N Engl J Med. 2013;369:540–8. [PubMed: 23924004]

[44]. Schrijvers EM, Witteman JC, Sijbrands EJ, Hofman A, Koudstaal PJ, Breteler MM. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology. 2010;75:1982–7. [PubMed: 21115952]

[45]. Ekblad LL, Rinne JO, Puukka PJ, Laine HK, Ahtiluoto SE, Sulkava RO, et al. Insulin resistance is associated with poorer verbal fluency performance in women. Diabetologia. 2015;58:2545–53. [PubMed: 26276262]

[46]. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. Ageing Res Rev. 2009;8:61–70. [PubMed: 19063999]

[47]. Posner HB, Tang MX, Luchsinger J, Lantigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology. 2002;58:1175–81. [PubMed: 11971083]

[48]. Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J, et al. Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. Hypertension. 2011;58:22–8. [PubMed: 21555680]

[49]. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA Neurol. 2014;71:1218–27. [PubMed: 25090106]

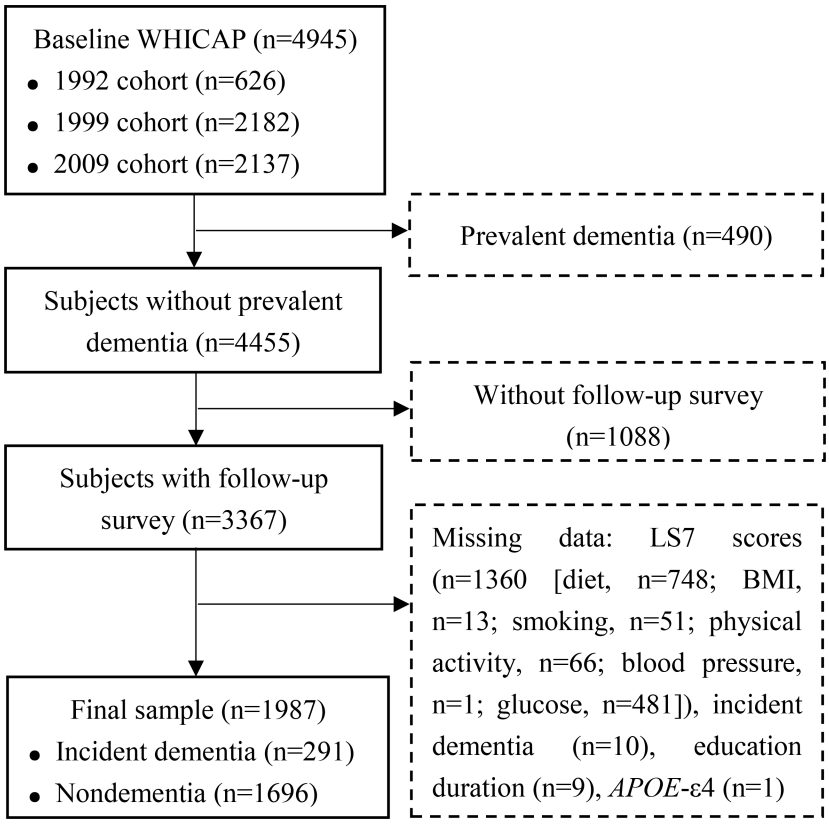

Figure 1.
Flow chart of subject selection.

Table 1.

Characteristics of subjects across LS7 categories.

Characteristics	LS7 categories			Total (n = 1987)	*p* value
	Poor (n = 279)	Intermediate (n = 1367)	Optimal (n = 341)		
Age (years), mean (SD)	74.97 (5.76)	75.52 (5.96)	74.87 (6.24)	75.33 (5.98)	0.112
Gender, n (%)					0.002
Male	72 (25.81)	429 (31.38)	132 (38.71)	633 (31.86)	
Female	207 (74.19)	938 (68.62)	209 (61.29)	1354 (68.14)	
Race/ethnicity, n (%)					< 0.001
White	56 (20.07)	350 (25.60)	155 (45.45)	561 (28.23)	
Black	93 (33.33)	408 (29.85)	84 (24.63)	585 (29.44)	
Hispanic	127 (45.52)	579 (42.36)	96 (28.15)	802 (40.36)	
Others	3 (1.08)	30 (2.19)	6 (1.76)	39 (1.96)	
Education duration (years), mean (SD)	9.99 (4.92)	10.63 (4.91)	12.97 (4.62)	10.94 (4.95)	< 0.001
Cohort wave, n (%)					< 0.001
1992 cohort	50 (17.92)	165 (12.07)	32 (9.38)	247 (12.43)	
1999 cohort	149 (53.41)	694 (50.77)	120 (35.19)	963 (48.47)	
2009 cohort	80 (28.67)	508 (37.16)	189 (55.43)	777 (39.10)	
Dietary calories (kcal), mean (SD)	1380.59 (568.31)	1403.39 (500.04)	1391.20 (447.96)	1398.09 (501.61)	0.757
Depression, n (%)					0.008
No	189 (67.74)	1019 (74.54)	268 (78.59)	1476 (74.28)	
Yes	90 (32.26)	348 (25.46)	73 (21.41)	511 (25.72)	
History of hypertension, n (%)					< 0.001
No	26 (9.32)	185 (13.53)	116 (34.02)	327 (16.46)	
Yes	253 (90.68)	1182 (86.47)	225 (65.98)	1660 (83.54)	
History of diabetes, n (%)					< 0.001
No	127 (45.52)	966 (70.67)	312 (91.50)	1405 (70.71)	
Yes	152 (54.48)	401 (29.33)	29 (8.50)	582 (29.29)	
History of heart diseases, n (%)					0.001
No	144 (51.61)	739 (54.06)	219 (64.22)	1102 (55.46)	
Yes	135 (48.39)	628 (45.94)	122 (35.78)	885 (44.54)	
APOE-ε4 allele, n (%)					0.392
Noncarrier	205 (73.48)	1016 (74.32)	241 (70.67)	1462 (73.58)	
Carrier	74 (26.52)	351 (25.68)	100 (29.33)	525 (26.42)	
LS7 scores, mean (SD)	4.42 (0.82)	7.49 (1.06)	10.57 (0.82)	7.59 (1.98)	< 0.001
Incident dementia, n (%)					0.003
No	224 (80.29)	1165 (85.22)	307 (90.03)	1696 (85.35)	
Yes	55 (19.71)	202 (14.78)	34 (9.97)	291 (14.65)	

Abbreviations: *APOE*-ε4, apolipoprotein E genotype ε4; LS7, Life's Simple 7; SD, standard deviation; %, proportion.

Table 2.

Associations between LS7 scores and incident dementia.

Subgroups	Categories of LS7 scores				
	Poor (0 to 5)	**Intermediate (6 to 9)**	**Optimal (10 to 14)**	p_{trend}	**Continuous LS7 scores**
All (n = 1987)					
No. of cases/total No.	55/279	202/1367	34/341		
Incidence rate per 1000 person-years (95% CI)	27.54 (20.27, 34.82)	21.33 (18.39, 24.27)	16.28 (10.81, 21.76)		
Absolute rate difference per 1000 person-years (95% CI)	Reference	−6.22 (−14.07, 1.64)	**−11.26 (−20.37, −2.15)**		
HR (95% CI) in Model 1 [a]	Reference	**0.73 (0.54, 0.99)**	**0.56 (0.36, 0.87)**	**0.010**	**0.92 (0.86, 0.97)**
HR (95% CI) in Model 2 [b]	Reference	**0.74 (0.54, 1.00)**	**0.59 (0.38, 0.91)**	**0.020**	**0.92 (0.86, 0.98)**
APOE-ε4 carrier (n = 525)					
No. of cases/total No.	16/74	62/351	12/100		
Incidence rate per 1000 person-years (95% CI)	30.75 (15.68, 45.82)	26.32 (19.77, 32.88)	22.26 (96.66, 34.86)		
Absolute rate difference per 1000 person-years (95% CI)	Reference	−4.43 (−20.86, 12.00)	−8.49 (−28.13, 11.15)		
HR (95% CI) in Model 1 [a]	Reference	0.82 (0.47, 1.42)	0.84 (0.39, 1.84)	0.688	0.95 (0.85, 1.06)
HR (95% CI) in Model 2 [b]	Reference	0.77 (0.43, 1.35)	0.75 (0.34, 1.64)	0.495	0.93 (0.83, 1.05)
APOE-ε4 noncarrier (n = 1462)					
No. of cases/total No.	39/205	140/1016	22/241		
Incidence rate per 1000 person-years (95% CI)	26.41 (18.12, 34.71)	19.68 (16.42, 22.93)	14.20 (8.27, 20.14)		
Absolute rate difference per 1000 person-years (95% CI)	Reference	−6.74 (−15.65, 2.17)	**−12.21 (−22.41, −2.02)**		
HR (95% CI) in Model 1 [a]	Reference	0.70 (0.49, 1.00)	**0.47 (0.27, 0.80)**	**0.006**	**0.90 (0.84, 0.97)**
HR (95% CI) in Model 2 [b]	Reference	0.72 (0.50, 1.03)	**0.49 (0.28, 0.83)**	**0.009**	**0.90 (0.83, 0.97)**

Abbreviations: LS7, Life's Simple 7; HR, hazard ratio; CI, confidence interval; *APOE*-ε4, apolipoprotein E genotype ε4.

[a]Model 1 was adjusted for age, sex and race.

[b]Model 2 was adjusted for terms in Model 1 plus education, cohort wave, calories intake, depression and *APOE*-ε4. *APOE*-ε4 allele status was not adjusted within each subgroup of *APOE*-ε4 noncarriers and carriers.

Values in bold mean statistically significant ($p < 0.05$).

Table 3.

HR (95% CI) for incident dementia associated with LS7 components.

Subgroups	Categorical LS7 components			Continuous LS7 components	$p_{interaction}$ [a]
	Poor (0)	Intermediate (1)	Optimal (2)		
All (n = 1987) [b]					
Diet	Reference	0.89 (0.69, 1.14)	0.69 (0.33, 1.44)	0.87 (0.7, 1.09)	0.865
Physical activity	Reference	**0.67 (0.51, 0.87)**	**0.59 (0.43, 0.80)**	**0.75 (0.64, 0.88)**	0.614
Smoking	Reference	0.73 (0.46, 1.14)	0.67 (0.43, 1.04)	0.86 (0.71, 1.04)	**0.020**
Blood pressure	Reference	0.93 (0.73, 1.19)	0.79 (0.49, 1.29)	0.91 (0.75, 1.11)	0.932
Glucose	Reference	0.82 (0.60, 1.10)	0.77 (0.57, 1.03)	0.88 (0.76, 1.02)	0.260
Total cholesterol	Reference	0.87 (0.58, 1.30)	0.96 (0.66, 1.40)	1.02 (0.85, 1.21)	0.602
BMI	Reference	1.08 (0.82, 1.43)	1.29 (0.94, 1.76)	1.13 (0.97, 1.33)	0.512
APOE-ε4 carrier (n = 525) [c]					
Diet	Reference	0.96 (0.62, 1.49)	0.25 (0.03, 1.91)	0.84 (0.57, 1.25)	-
Physical activity	Reference	**0.59 (0.36, 0.96)**	**0.46 (0.25, 0.83)**	**0.66 (0.49, 0.89)**	-
Smoking	Reference	1.58 (0.47, 5.31)	1.55 (0.46, 5.16)	1.07 (0.73, 1.57)	-
Blood pressure	Reference	0.98 (0.61, 1.57)	0.74 (0.28, 1.95)	0.92 (0.63, 1.34)	-
Glucose	Reference	0.99 (0.55, 1.76)	1.00 (0.57, 1.76)	1.00 (0.76, 1.33)	-
Total cholesterol	Reference	0.87 (0.43, 1.75)	0.78 (0.39, 1.53)	0.89 (0.65, 1.21)	-
BMI	Reference	1.20 (0.73, 1.97)	1.40 (0.78, 2.53)	1.19 (0.89, 1.59)	-
APOE-ε4 noncarrier (n = 1462) [c]					
Diet	Reference	0.85 (0.63, 1.15)	0.96 (0.43, 2.11)	0.89 (0.67, 1.16)	-
Physical activity	Reference	**0.68 (0.49, 0.94)**	**0.59 (0.40, 0.86)**	**0.75 (0.63, 0.91)**	-
Smoking	Reference	0.62 (0.38, 1.02)	**0.54 (0.33, 0.87)**	**0.78 (0.62, 0.97)**	-
Blood pressure	Reference	0.94 (0.70, 1.27)	0.77 (0.44, 1.34)	0.91 (0.72, 1.14)	-
Glucose	Reference	0.75 (0.52, 1.07)	**0.68 (0.48, 0.96)**	**0.82 (0.69, 0.98)**	-
Total cholesterol	Reference	0.79 (0.47, 1.31)	0.93 (0.59, 1.48)	1.03 (0.83, 1.28)	-
BMI	Reference	1.01 (0.72, 1.42)	1.24 (0.85, 1.80)	1.11 (0.92, 1.34)	-

Abbreviations: LS7, Life's Simple 7; HR, hazard ratio; CI, confidence interval; *APOE*-ε4, apolipoprotein E genotype ε4.

[a] Interactions were tested by adding a product term between scores of LS7 component (continuous) and *APOE*-ε4 allele status (dichotomous) in the adjusted Cox regression model.

[b] Cox regression models were adjusted for age, sex, race, education, cohort wave, calories intake, depression and *APOE*-ε4 allele status.

[c] Cox regression models were adjusted for age, sex, race, education, cohort wave, calories intake and depression.

Values in bold mean statistically significant ($p < 0.05$).