Association between Life’s Simple 7 and cerebrospinal fluid biomarkers of Alzheimer’s disease pathology in cognitively intact adults: the CABLE study

Yong-Li Zhao¹, Ya-Nan Ou¹, Ya-Hui Ma¹, Yu-Yuan Huang², Yan-Lin Bi³, Lan Tan¹* and Jin-Tai Yu²*

Abstract
Introduction: This study sought to explore the association between Life's Simple 7 (LS7) and cerebrospinal fluid (CSF) Alzheimer's disease (AD) pathological biomarkers in the cognitively normal northern Chinese population.

Methods: From the Chinese Alzheimer's Biomarker and LifestylE (CABLE) study, 1106 cognitively normal participants were enrolled. The mean age was 62.34 years, and 39.6% were female. LS7 scores were summed with each metric assigned 0, 1, or 2 scores. The multiple linear regression models were used to investigate the association between LS7 scores and CSF AD biomarkers.

Results: We found that LS7 scores were significantly associated with CSF AD pathologies, including Aβ42/40 (β = 0.034, \( P = .041 \)), p-tau181 (β = −0.043, \( P = .006 \)), and t-tau (β = −0.044, \( P = .003 \)). In subscales, the biological metrics (blood pressure, cholesterol, glucose) were significantly related to CSF tau-related biomarkers. These associations were observed in the APOE ε4 allele non-carriers, yet not in carriers. The relationship of behavior metrics was found in the middle age and males.

Conclusion: Improving LS7 scores might do a favor to alleviate the pathology of AD in the preclinical stage, especially among the APOE ε4 allele non-carriers.

Keywords: Life’s Simple 7, Cerebrospinal fluid, Biomarkers, Alzheimer’s disease, Pathogenesis

Introduction
As the most common form of dementia, Alzheimer’s disease (AD) is a multifactorial neurodegenerative disease, featured by extracellular amyloid β plaques (Aβ) and intracellular tau neurofibrillary tangles of the brain which could have changed decades before the clinical stage and can be detected by biomarkers of positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) [1, 2]. Since there is no effective treatment, prevention remains the most preferred and earliest strategy. Most studies have focused on a single factor of individual lifestyle and vascular risks, which have been identified as modifiable factors and could only approximately attribute a third of dementia cases [3]. However, recent evidence suggested that multidomain intervention simultaneously might play more roles in preventing cognitive decline and dementia [4, 5].
The Life's Simple 7 (LS7) was proposed as an assessment of cardiovascular health by the American Heart Association (AHA), based on 4 health behaviors (physical activity, body mass index [BMI], diet, and smoking) and 3 biological metrics (blood pressure [BP], fasting blood glucose [FBG], and total cholesterol [TC]) [6]. Emerging proofs suggested that ideal LS7 was associated with better cognition [7–9]. Moreover, it was related to reduced risks of dementia and AD [5, 10–12]. Nonetheless, insignificant relationships between LS7 and cognition, dementia, and AD were also observed [13–16]. The correlations between LS7 and white matter hyperintensity, silent brain infarct, cerebral volume, and higher total brain and gray matter volumes have been observed [10, 17]. However, the relationships between LS7 and AD core pathologies have not been examined, including Aβ42, total tau (t-tau), and phosphorylated tau (p-tau) which could be well reflected in CSF with decreased Aβ42 and increased t-tau and p-tau181 levels [18]. Nonetheless, the heterogeneity of CSF Aβ42 levels was thought significant [19], and Aβ42/40 ratio was believed to improve the accuracy of discriminating AD compared to Aβ42 [20].

CSF AD biomarkers assessments and APOE-ε4 genotyping

The fasting CSF sample was extracted via a standard operating procedure with the discarding of the first 1–2 mL and processed within 2 h. After centrifuging at 2000 × g for 10 min, it was stored in an enzyme-free EP (Eppendorf) tube at −80 °C. The thaw/freezing cycle was limited to two times or less. CSF Aβ42, Aβ40, p-tau181, and t-tau levels were determined with the ELISA kits (Innotest β-AMYLOID (1–42) [catalog number: 81583]; β-AMYLOID (1–40) [catalog number: 81585]; PHOSPHO-TAU (181p) [catalog number: 81581]; hTAU-Ag [catalog number: 81579]; Fujirebio, Ghent, Belgium). All measurements were performed by professional experimenters who were blind to clinical information. The within-batch coefficient of variation (CV) was <5% (mean CV 4.5% for Aβ42, 3.7% for Aβ40, 2.5% for p-tau181, and 4.4% for t-tau). The inter-batch CV was <20% (mean CV 5.3% for Aβ42, 3.4% for Aβ40, 2.4% for p-tau181, and 4.8% for t-tau).

Using the QiAamp® DNA Blood Mini Kit (250), DNA was drawn from fasting blood samples. Next, it was separated and stored in an enzyme-free EP tube at −80 °C until the APOE genotyping was completed in this study. Two specific loci related to APOE status (rs7412 and rs429358) were selected for genotyping with restriction fragment length polymorphism technology. Participants were classified as APOE ε4 non-carriers and APOE ε4 carriers (individuals with at least one copy of the APOE ε4 gene).

Materials and methods

The populations

All individuals in this study were enrolled in the Chinese Alzheimer's Biomarker and Lifestyle (CABLE) study, a large-scale ongoing study from 2017 exploring the genetic and environmental factors and biomarkers of AD in the 40- to 90-year-old northern Han Chinese population [23]. The subjects were recruited from the city of Qingdao, Shandong province, China, with a convenient sample from hospitalized patients of Qingdao Municipal Hospital. The exclusion criteria were (a) infection of the central nervous system, epilepsy, head trauma, major neurological disorders, or other neurodegenerative diseases rather than AD (e.g., Parkinson’s disease); (b) major psychological disorders; (c) severe systemic diseases (e.g., malignant tumors); and (d) family history of genetic diseases. The Institutional Ethics Committee of Qingdao Municipal Hospital approved the CABLE study, and it was carried out following the Declaration of Helsinki. All subjects or their proxies gave written consent.

A total of 1106 cognitively intact subjects with adequate data of CSF biomarkers and LS7 measurements were enrolled in this cross-sectional study. All individuals underwent comprehensive clinical, psychiatric neuropsychological examinations; biochemical testing; and biological samples (blood and CSF sample) collections at study entry. The basic information of age, sex, years of education, and medical history was obtained through a structured questionnaire and supplemented by an electronic medical record system. Global cognitive function was examined by the China Modified Mini-mental State Examination (CM-MMSE). Depression and anxiety were assessed using the Hamilton Rating Scale for Depression (HAMD) and Hamilton Rating Scale for Anxiety (HAMA), respectively. The population diagnosed with cognitive impairment (CM-MMSE ≤ 24) for >6 years of education, ≤ 20 for no more than 6 years of education, ≤ 17 for no education), significantly depression (HAMD > 7), or anxiety (HAMA > 7) were excluded.

Measurements of LS7 metrics

We looked into each indicator of LS7 and categorized them into poor (score as 0), intermediate (score as 1),...
and ideal (score as 2) qualities leaning on the AHA criteria and with modifications in terms of diet and physical activity (Additional file 1: Table S1). All of the behavior metrics including BMI, smoking, diet, and physical activity were measured through a self-reported questionnaire and medical record system. The biological metrics of BP, cholesterol, and glucose levels were tested by professionals in the laboratory.

We obtained BMI by the calculation of weight divided by height squared. Subjects who were smoking were regarded as current smokers, and those who had quit smoking were regarded as past smokers with different quitting times. Compared with the AHA criteria, our diet metric only involved two components of fruit and fish, and with the information of frequency through a questionnaire, yet lacking quantitative data. Moreover, the whole grain, sodium, and sugar-sweetened beverage intake were not included since insufficient information was collected. For each ingredient, the daily frequency was coded as 2, once or several times a week coded as 1, and never or occasionally coded as 0, and the sum of the two ingredients was used to ultimately categorize the diet metric (Additional file 1: Table S1). The measurement of physical activity during leisure time was examined through a questionnaire looking at the frequency of exercise, with a major limitation of lacking intensity and duration. We assigned daily frequent as 2 scores, once a week or several times a week as 1 score, and never or occasionally as 0 scores. BP was measured in triplicate every morning when the participants were resting and in a sitting position during their first 5 days of hospitalization, and the mean of measurements was used to divide the metric. After fasting for at least 8 h, the enzymatic method and the glucose hexokinase (HK) method were used to test the fasting plasma total cholesterol and glucose levels, respectively.

The composite LS7 scores were calculated from the sum of 7 components, ranging from 0 to 14. It was further ranked as poor (scores 0–5, < mean – standard deviation [SD]), intermediate (scores 6–10, > mean – SD and < mean + SD), and optimal (scores 11–14, ≥ mean + SD) levels.

Statistical analysis
The baseline characteristics were compared using the chi-square test (for categorical variables) and the analysis of variance or Kruskal–Wallis test (for continuous variables). We normalized the level of CSF AD biomarkers by the Box–Cox transformations using the “car” package of the R software and standardized them by Z-scale in case of skewed distribution. Extreme values outside the 3 SD of CSF AD biomarkers were excluded.

Across the three categories of LS7 scores, differences in CSF AD biomarkers were compared using analysis of variance, and the cognition test was compared using the Kruskal–Wallis test. We applied multiple linear regression (MLR) models to explore the association between total LS7 scores and CSF Aβ42, Aβ42/40, Aβ40, t-tau, and p-tau181 biomarkers, with the adjustment of age, sex, education, and APOE ε4 allele statuses. Moreover, the subscale of the biological metrics (the summary scores of BP, total cholesterol, and glucose), behavior metrics (the summary scores of BMI, smoke, diet, and physical activity), and individual components of LS7 was investigated. Interactions were tested in regression models by the terms of APOE genotype, age, and sex with LS7 score, and followed by stratified analyses by different APOE ε4 allele statuses (non-carrier or carrier), mid-life (< 65 years), or late life (≥ 65 years), male or female. Lastly, sensitivity analyses were performed by (1) additionally adjusting for the comorbidities of coronary heart disease and stroke to control relevant confounders and (2) analyzing the relatively healthy population with no history of hypertension, diabetes, and hyperlipemia, who were in an early stage of disease, to validate the association between LS7 score and CSF AD biomarkers.

The packages “car,” “ggplot2,” and “lm” in the R 4.0.3 software were used for statistical analyses and illustrations (R Project for Statistical Computing: http://www.r-project.org). P values of less than 0.05 were considered significant.

Results
Characteristics of participants
We totally included 1106 subjects with a mean age of 62.34 (SD = 10.27), ranging from 40 to 89, which were shown in Table 1. About one-third (39.6%) of the participants were female, and 137 (13.92%) were APOE ε4 carriers. A total of 639 were in their middle age (<65 years), and 467 were in late age (≥ 65 years). The mean LS7 score was 7.99 (SD = 2.05), and the distribution was exhibited in Additional file 1: Fig. S1. Individuals with higher levels of LS7 scores were younger and better educated (Table 1).

Association between LS7 scores and CSF AD biomarkers
Across the three LS7 categories, the group with an optimal level of LS7 scores was proved to have lower CSF t-tau and p-tau181 levels (Fig. 1). Associations between higher LS7 scores and decreased CSF p-tau181 (β = −0.043, P = 0.006), t-tau (β = −0.044, P = 0.003), and increased Aβ42/40 (β = 0.034, P = 0.041) biomarkers were significantly revealed when adjusting for age, sex, education, and APOE ε4 allele (Fig. 2). In subscales, the biological metrics was significantly associated with p-tau181 (β = −0.073,
Besides, the relationships between the total LS7 score and the biological metrics with Aβ40 were also found (Additional file 1: Table S2). Yet, we did not record any association of behavior metrics. There were no significant associations with CSF Aβ42 (Fig. 2). Individually, we observed that the metrics of BP, glucose, and physical activity were related to CSF AD biomarkers (Additional file 1: Table S3).

Interactions and stratified analyses by APOE ε4 allele statuses, age, and genders

Interaction between age and behavior metrics was found \( (P = 0.0243, \text{Additional file 1: Table S4}) \). In the mid-age, both biological and behavior metrics were significantly related to CSF tau-related biomarkers, whereas in the late age, only the biological metrics were noticed to be associated with CSF biomarkers (Fig. 3, Additional file 1: Table S5). Besides, significant associations between LS7 scores and CSF Aβ42/40 \( (\beta = 0.039, P = 0.029) \), p-tau181 \( (\beta = -0.049, P = 0.003) \), and t-tau \( (\beta = -0.050, P = 0.004) \) biomarkers were revealed among the APOE ε4 non-carriers, yet not among carriers (Fig. 3). Moreover, LS7 scores were associated with CSF AD biomarkers in both males and females, and the behavior metrics were observed to be associated with CSF Aβ42/40 in males (Fig. 3).

Table 1 Characteristics of participants across LS7 categories

| Characteristics                          | LS7 categories | Total | \( P \) value |
|------------------------------------------|----------------|-------|--------------|
|                                          | Poor           | Intermediate | Optimal |
| \( N \)                                  | 128            | 852               | 126    | 1106  | –                          |
| Age (years), mean (SD)                    | 62.12 (9.74)   | 62.89 (10.15)     | 58.84 (10.96) | 62.34 (10.27) | .0002*                     |
| Gender, female (%)                       | 44 (34.37)     | 334 (39.20)       | 60 (47.61)  | 438 (39.60) | .0861                      |
| Education (years), mean (SD)              | 9.35 (4.33)    | 9.61 (4.21)       | 10.90 (3.83) | 9.73 (4.20)  | .0031*                     |
| APOE ε4, yes (%)                         | 19 (16.10)     | 104 (13.79)       | 14 (12.50)  | 137 (13.92) | .7163                      |
| CM-MMSE, mean (SD)                       | 27.85 (2.26)   | 27.90 (2.06)      | 28.33 (1.77) | 27.94 (2.05) | .0942                      |
| LS7 score, mean (SD)                     | 4.47 (0.78)    | 8.01 (1.28)       | 11.44 (0.70) | 7.99 (2.05)  | <.0001*                     |
| CSF AD biomarkers                        |                |                   |          |      |                           |
| \( \text{Abeta42, mean (SD)} \)          | 187.19 (97.19) | 202.61 (112.61)   | 182.53 (91.32) | 198.64 (108.95) | .1920                      |
| \( \text{Abeta40, mean (SD)} \)          | 6116.46 (2834.65) | 5880.47 (2650.43) | 5014.28 (2349.72) | 5808.7 (2653.89) | .0015*                     |
| \( \text{Abeta42/40, mean (SD)} \)      | 0.0401 (0.0423) | 0.0404 (0.0289)   | 0.0411 (0.0213) | 0.0404 (0.0300) | .2090                      |
| \( \text{P-TAU181, mean (SD)} \)        | 38.46 (10.45)  | 37.68 (9.30)      | 34.25 (6.95)  | 37.36 (9.26)  | .0005*                     |
| \( \text{T-TAU, mean (SD)} \)           | 183.77 (78.51) | 177.72 (83.35)    | 149.44 (65.18) | 175.21 (81.43) | .0001*                     |

The statistically significant results have been bolded

\*The difference among the groups was examined by the analysis of variance

\*The difference among the groups was examined by the chi-square test

\*The difference among the groups was examined by the Kruskal-Wallis test

Sensitivity analyses

We performed sensitivity analyses by additionally adjusting for the comorbidities of coronary heart disease and stroke and produced similar results of the associations between LS7 scores and CSF Aβ42/40, p-tau181, and t-tau biomarkers (Additional file 1: Table S6). Additionally, in the relatively healthy population with no history of hypertension, diabetes, and hyperlipemia, there was only a significant association between the biological metrics and CSF Aβ40 biomarker (Additional file 1: Table S7).

Discussion

This study is the first to examine the association between LS7 scores and CSF AD biomarkers in the cognitively intact population. Our results demonstrated that LS7 scores, especially the biological metrics, were significantly related to CSF Aβ42/40 and tau-related pathology. These relationships were significant among the APOE ε4 non-carriers, yet not in the carriers. These findings provided supports for the linkage between LS7 cardiovascular health and AD risks.

Given the complicated nature of dementia, the interventions of LS7, which could control for multiple risk factors and underlying mechanisms at the same time, have been noticed to promote brain health and prevent dementia [4]. A 2-year randomized controlled trial demonstrated that multidomain intervention of vascular...
risks was beneficial to cognitive functioning for the at-risk elderly people [24]. In France, a cohort study by Samieri et al. indicated that optimal LS7 could reduce the incidence of dementia [25]. Other longitudinal studies from England, America, and Finland also suggested the associations between LS7 and cardiovascular health with dementia [10–12, 26]. Moreover, the relationship between a composite healthy lifestyle and risks of AD was observed in 2 longitudinal studies in Chicago [5]. Besides, the ideal cardiovascular health was found relevant to better cognitive performance [8, 9, 27], and less decline [7, 8, 25]. Nevertheless, not all results were consistent. In the Netherlands, a 6-year multidomain intervention of vascular care did not bring older people to a reduction of dementia. In that study, the population was not selected aged 70 years or older with modest cardiovascular risks at the baseline, which might be the reason for insignificance [16]. Also, no significant association between LS7 and dementia was found in Germany, which lacked the diet metric of their LS7 assessments [15]. Notably, there was still no examination of the relationship between LS7 and the pathology of AD.

In our CABLE study, we firstly revealed the relationship between LS7 scores and CSF Aβ42/40 even after additionally adjusting for the complications of coronary heart disease and stroke. That supported the correlations between LS7 score and AD risks despite the no significance with Aβ42, since many lines of evidence have suggested that CSF Aβ42/40 ratio performed better for discrimination of AD, which balanced the total

![Fig. 1 Differences in CSF biomarkers between the three LS7 categories. Differences in CSF Aβ42, Aβ42/40, p-tau181, and t-tau levels were examined by the analysis of variance. LS7, Life’s Simple 7; CSF, cerebrospinal fluid; Aβ, amyloid beta, P-tau181, phosphorylated tau181; T-tau, total tau](image)
production of amyloid beta peptides [28]. Besides, the decreased p-tau181 and t-tau indicated the relationship between LS7 scores and incipient AD risks. As CSF p-tau181 reflected the phosphorylation state of tau in brain, it is considered specific to AD pathologies. Total tau in CSF presented the neuronal damage and degeneration with less specificity for AD [29]. In our study, we have excluded the population with acute neurological disorders and other neurodegenerative diseases to reduce the potential heterogeneity. In sum, our findings provided pathological support for the association between LS7 and potential AD risks. Here, we involved all the 7 metrics of LS7, while the diet and physical activity metrics were limited to frequency. The population in the current study was relatively younger with intact cognitive function, which could represent the preclinical stage of AD. The correlations between LS7 and dementia and AD risks were verified, and the underlying mechanisms of accumulation of neurodegenerative pathology and the reduction of clearance may be involved in multiple pathways, including vascular risks, inflammatory, oxidative stress, and mitochondrial dysfunction [11, 30–33].

A few studies gazed into the summary and separate components of LS7, which could provide additional insights into the relationships. Both behavior and biological metrics of midlife were related to dementia incidence in London [10]. Based on a longitudinal cohort study in the USA, metabolic changes had a significant influence on late-life cognition [34]. Similarly, the biological metrics were suggested to be associated with cognitive decline and dementia in other two cohort studies, rather than the behavior metrics [7, 35]. In our study, the subscale of biologics was significantly associated with CSF Aβ and tau-related biomarkers. Yet, we did not find the relationship of behavior metrics in the total population. The biological metric could reflect the metabolism of the human body objectively, which can be involved
inflammatory and immune mechanisms, and interact with genetic risks to activate neuropathology. Subjectivity in the measurements of behaviors might cause bias, and the effects of behavior metrics on cognition may involve other mechanisms such as psychological factors and cognitive reservation [36, 37]. Besides, the interaction between age and behavior metrics was found. In the mid-age, we found that both biological metrics and behavior metrics were relevant to CSF biomarkers, while in the late age, there was only biological metrics revealed significant association, which might be due to the complex effects of BMI on dementia attenuating the significance of behavior metrics in late life [38, 39]. Also, the association of biological metrics was only found in males, which could be derived from the different distribution of LS7 scores between the genders (Additional file 1: Fig. S1).

The genetic risks have been known as important factors contributing to the pathogenesis of dementia [40]. However, the interaction between lifestyle and genetic risk remains unclear [41]. From a series of longitudinal studies, associations between a composed lifestyle and dementia, AD, and cognition decline were suggested regardless of the APOE ε4 allele [5, 25, 42]. A 2-year multidomain intervention was found beneficial for both APOE ε4 non-carriers and carriers (Solomon et al. 2018). However, research in Rotterdam displayed the protective effects on dementia among low and intermediate genetic risk populations [41]. Also, significant associations between LS7 scores and composite lifestyles with dementia were observed only among APOE ε4 allele non-carriers, yet not in the carriers [11, 14]. The relationship between metabolic risk profile and cognitive performance was suggested stronger among APOE ε4 allele non-carriers [34]. In our CABLE study, we found the associations between LS7 scores, as well as the biological metrics and CSF AD biomarkers only among the APOE ε4 non-carriers, yet we failed to record these associations in the carriers. The population in our study was relatively younger (mean age = 62.71 years), and the influences of the APOE ε4 allele on dementia were suggested different, attenuating with increasing age, which might explain part of the non-significant interactions [43]. Nonetheless, the number of APOE ε4 carriers in our study was limited and only 137 (13.92%), which might lead to a false negative. More researches with an ample sample size and a sufficiently long follow-up period are necessary.

Limitations

Some limitations should be noted. This study was cross-sectional. The information on diet and physical activity metrics were based on frequency lacking quantitative data with only two dietary ingredients of fruit and fish, which were major weaknesses comparing with the standard AHA criteria. Besides, there was only a significant association with Aβ40 in the sensitivity analyses of the relatively healthy population without histories of hypertension, diabetes, and hyperlipemia. Moreover, in these populations, the opposite relationship with Aβ42 existed, which may be due to the bias by poor efficacy of LS7 for discrimination, and the longitudinal studies with the large sample are needed for further exploration. All analyses were performed on people recruited from the hospital, which can be further researched with a community-based population in the future.

Conclusions

In summary, LS7 scores were significantly associated with CSF Aβ42/40, p-tau181, and t-tau biomarkers of AD in the cognitively intact population, which offered a pathological verification of multidomain intervention. Therefore, putting efforts into improving LS7 cardiovascular health might be helpful to prevent AD, especially in...
the APOE e4 non-carriers. More longitudinal researches with a larger sample size as well as randomized controlled trials are anticipated in the future.

Abbreviations
LS7: Life’s Simple 7; CSF: Cerebrospinal fluid; AD: Alzheimer’s disease; CABLE: Chinese Alzheimer’s Biomarker and LifestyIE study; APOE: Apolipoprotein E genotype e4; Aβ: Amyloid β plaques; p-tau181: Phosphorylated tau181; t-tau: Total tau; AHA: American Heart Association; CV: Coefficient of variation; SD: Standard deviation; CM-MMSE: China Modified Mini-Mental State Examination; HAMD: Hamilton Rating Scale for Depression; HAMA: Hamilton Rating Scale for Anxiety; BMI: Body mass index; BP: Blood pressure; TC: Total cholesterol.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13195-022-01019-2.

Additional file 1: Table S1. Modified measurements of Life’s Simple 7 in our study. Table S2. Associations between LS7 scores with CSF AD biomarkers. Table S3. Associations between individual component of LS7 with CSF AD biomarkers. Table S4. Interaction analyses by APOE e4 genotype, age, and genders. Table S5. Subgroup analyses of associations between total LS7 and subscales with CSF AD biomarkers. Table S6. Sensitivity analyses of associations between LS7 scores with CSF AD biomarkers additionally adjusting for comorbidities. Table S7. Sensitivity analyses of associations between LS7 scores with CSF AD biomarkers in the population with no history of hypertension, diabetes, and hyperlipemia. Fig. S1. The distribution of each component scores of LS7.

Acknowledgements
The authors thank all the participants of the present study as well as all the members of the staff of the CABLE study for their role in data collection.

Authors’ contributions
JTY conceptualized the study and revised the manuscript. YLZ and YNO analyzed and interpreted the data, drafted and revised the manuscript, did the statistical analysis, and prepared all the figures. YHM participated in the collection and organization of the data. All authors contributed to the writing and revisions of the paper and approved the final manuscript.

Funding
This study was supported by grants from the Science and Technology Innovation 2030 Major Projects (2022ZD021600), the National Natural Science Foundation of China (82071201, 91849126), the National Key R&D Program of China (2018YFC1314702), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and Zhangjiang Lab, Tianqiao and Chrissy Chen Foundation, Shanghai, China. This study was supported by grants from the Science and Technology Innovation 2030 Major Projects (2022ZD021600), the National Natural Science Foundation of China (82071201, 91849126), the National Key R&D Program of China (2018YFC1314702), Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and Zhangjiang Lab, Tianqiao and Chrissy Chen Foundation, Shanghai, China.

Availability of data and materials
The datasets used and analyzed in the current study are available from the corresponding authors on reasonable request.

Declarations
Ethics approval and consent to participate
The CABLE study was approved by the Institutional Ethics Committee of Qingdao Municipal Hospital and carried out following the Declaration of Helsinki. All subjects or their proxies gave written consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Neurology, Qingdao Municipal Hospital, Qingdao University, No. 5 Donghai Middle Road, Qingdao, China. 2 Department of Neurology and Institute of Neurology, State Key Laboratory of Medical Neurobiology and MOE Frontier Center for Brain Science, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China. 3 Department of Anesthesiology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China.

Received: 14 January 2022 Accepted: 16 May 2022

Published online: 26 May 2022

References
1. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CE. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement. 2011;7(3):263–9. https://doi.org/10.1016/j.jalz.2011.03.005.
2. Hodson R. Alzheimer’s disease. Nature. 2018;559(7715):S1. https://doi.org/10.1038/41856-018-05717-6.
3. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames O, Ballard C, Banerjee S, Burns A, Cohen‑Manfroid J, Cooper C, Fox N, Gitlin LN, Howard R, Kales HC, Larson EB, Ritchie K, Rockwood K, Sampol ES, Samus Q, Schneider LS, Seldon G, Teri L, Mukadam N. Dementia prevention, intervention, and care. Lancet (London, England). 2017;390(10113):2673–734. https://doi.org/10.1016/S0140-6736(17)31365-6.
4. Kivipelto M, Mangalam D, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol. 2018;14(11):653–66. https://doi.org/10.1038/s41582-018-0070-3.
5. 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(4):e374–83. https://doi.org/10.1212/wnl.0000000000009586.
6. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomasselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. 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(4):586–613. https://doi.org/10.1161/CIRCULATIONAHA.109.192703.
7. González HM, Tarraf W, Harrison K, Windham BG, Tingle J, Alonso A, Griswold M, Heiss G, Knopman DS, Mosley TH. Midlife cardiovascular health and 20-year cognitive decline: atherosclerosis risk in communities study results. Alzheimers Dement. 2018;14(5):579–89. https://doi.org/10.1016/j.jalz.2017.11.002.
8. Gardener H, Wright CB, Dong C, Cheung K, DeRosa J, Papp L, Van Horn L, Greenland K, Daniels S, Nichol G, Tomasselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. 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(4):586–613. https://doi.org/10.1161/CIRCULATIONAHA.109.192703.
9. González HM, Tarraf W, Gouskova N, Rodriguez CJ, Rundek T, Grober E, Pirzada A, González P, Lutsey PL, Camacho A, Daviglus ML, Wright C, Mosley TH. Life’s Simple 7 cardiovascular health metrics are associated with Hispanic/Latino neurocognitive function: HCHS/SOL results. J Alzheimers Dis. 2016;53(3):955–65. https://doi.org/10.3233/JAD-151125.
10. Sabia S, Fayosse A, Dumurgier J, Schnitzler A, Empana JP, Ebmeier KP, Dugravot A, Kivimäki M, Singh-Manoux A. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25-year follow-up of Whitehall II cohort study. BMJ (Clinical research ed). 2019;366:j44114. https://doi.org/10.1136/bmj.j44114.
11. Guo J, Brickman AM, Manly JJ, Reitz C, Shupf N, Mayeux R, Gu Y. Association of Life’s Simple 7 with incident dementia and its modification by the apolipoprotein E genotype. Alzheimers Dement. 2021. https://doi.org/10.1002/abz.12359.
12. Atkins JL, Delgado J, Melzer D. Life’s Simple 7 likely to be associated with dementia risk reduction in both midlife and older age groups. BMJ (Clinical research ed). 2019;366:i5491. https://doi.org/10.1136/bmj.i5491.
13. Jeon YJ, Jung SJ, Kim HC. Does serum vitamin D level affect the association between cardiovascular health and cognition? Results of the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) study. Eur J Neurol. 2021;28(1):48–55. https://doi.org/10.1111/ene.14496.

14. Gelber RP, Petrovitch H, Masaki KH, Abbott RD, Ross GW, Launer LJ, White LR. Lifestyle and the risk of dementia in Japanese-American men. J Am Geriatr Soc. 2012;60(1):118–23. https://doi.org/10.1111/j.1532-5415.2011.03768.x.

15. Hessler JB, Ander KH, Brönnner M, Eiten G, Förstl H, Poppert H, Sander D, Bickel H. Predicting dementia in primary care patients with a cardiovascular health measure: a prospective population-based study. BMC Neurol. 2016;16:116. https://doi.org/10.1186/s12883-016-0466-8.

16. Moll van Charante EP, Richard E, Eurelings LS, van Dalen JW, Ligthart S, de Lange J, Smit JH, van Boxtel MP, Deurenberg P, Verstraete M, de Groot LC. A 2-year multidomain lifestyle 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 (London, England). 2016;388(10046):79–85. https://doi.org/10.1016/S0140-6736(16)30956-3.

17. Gardener H, Caunca M, Dong C, Cheung YK, Alperin N, Rundek T, Elkind MM, Qiu C. Cardiovascular health metrics from mid- to late-life and risk of late-life cognitive performance: the multi-ethnic study of atherosclerosis. JAMA. 2020;323(1):52–60. https://doi.org/10.1001/jama.2019.17720.

18. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. J Intern Med. 2018;284(6):643–63. https://doi.org/10.1111/joim.12816.

19. Moore JH, Ylikoski M, Ylikoski J, Brönnner M, Förstl H, Poppert H, Sander D, Bickel H. Predicting dementia in primary care patients with a cardiovascular health measure: a prospective population-based study. BMC Neurol. 2016;16:116. https://doi.org/10.1186/s12883-016-0466-8.

20. Xiao Y, Xu W, Tan L, Su BJ, Yu H, Bi YL, Yue XF, Dong Q, Yu JT. Sleep characteristics of 6-year multidomain vascular care intervention to prevent dementia (preDVA): a cluster-randomised controlled trial. Lancet (London, England). 2016;388(10046):79–85. https://doi.org/10.1016/S0140-6736(16)30950-3.

21. Gardener H, Caunca M, Dong C, Cheung YK, Alperin N, Rundek T, Elkind MM, Qiu C. Cardiovascular health metrics from mid- to late-life and risk of late-life cognitive performance: the multi-ethnic study of atherosclerosis. JAMA. 2020;323(1):52–60. https://doi.org/10.1001/jama.2019.17720.

22. Lewczuk P, Lelental N, Spitzer P, Maler JM, Kornhuber J. Amyloid-β 42/40 ratio and total tau. Neurobiol Aging. 2004;25(3):273–81. https://doi.org/10.1016/j.neurobiaging.2003.08.012.

23. Xu W, Tan L, Su BJ, Yu H, Bi YL, Yue XF, Dong Q, Yu JT. Impact of low cardiovascular risk factors and risk of incident dementia: longitudinal cohort and Mendelian randomization analyses in the UK Biobank. Alzheimer's Dement. 2021. https://doi.org/10.1007/alz.12120.

24. Rodriguez-Ayllón M, Cadenas-Sánchez C, Estévez-López F, Muñoz NE, Mora-Gonzalez J, Miguéles JH, Molina-García P, Henriksson H, Mena-Molina A, Martínez-Viccaíno V, Catena A, LoF M, Erickson KJ, Lubans DR, Ortega FB, Esteban-Cornejo J. Role of physical activity and sedentary behavior in the mental health of preschoolers, children and adolescents: a systematic review and meta-analysis. Sports Med (Auckland, NZ). 2019;49(9):1383–410. https://doi.org/10.1007/s40279-019-01099-5.

25. Taylor AH. Routledge handbook of physical activity and mental health. Ment Health Phys Act. 2013;6(2):101–2. https://doi.org/10.1016/j.mhpa.2013.06.003.

26. Qu Y, Hu HY, Ou YN, Shen XN, Xu W, Wang ZT, Dong Q, Tan L, Yu JT. Association of body mass index with risk of cognitive impairment and dementia: a systematic review and meta-analysis of prospective studies. Neurosci Biobehav Rev. 2020;115:189–98. https://doi.org/10.1016/j.neubiorev.2020.05.012.

27. Huang SJ, Ma YH, Bi YL, Shen XN, Hou XH, Cao XP, Ou YN, Zhao B, Dong Q, Tan L, Yu JT. Metabolically healthy obesity and lipids may be protective factors for pathological changes of Alzheimer’s disease in cognitively normal adults. J Neurochem. 2021;157(3):834–45. https://doi.org/10.1111/jnc.15306.

28. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol. 2021;20(1):68–80. https://doi.org/10.1016/S1474-4422(20)30412-9.

29. Licher S, Ahmad S, Karamujić-Čomić H, Voortman T, Leening MJG, Ikram KM. Changes in metabolic risk factors over 10 years and their associations with late-life cognitive performance: the multi-ethnic study of atherosclerosis. JAMA. 2019;322(5):430–7. https://doi.org/10.1001/jama.2019.8757.

30. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14(10):576–90. https://doi.org/10.1038/s41574-018-0059-4.

31. Saphis S, Borys JM, Levy E. Metabolic syndrome as a multifaceted risk factor for oxidative stress. Antioxid Redox Signal. 2017;29(9):445–61. https://doi.org/10.1089/ars.2016.6756.

32. Atkins JL, Delgado J, Pilling LC, Bowman K, Masoli JAII, Kuchel GA, Ferrucci L, Melzer D. 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(3):350–7. https://doi.org/10.1093/gerona/gly083.

33. Hughes TM, Craft S, Baker LD, Espeland MA, Rapp SR, Sink KM, Bertoni AG, Burke GL, Gottesman RF, Michos ED, Luchsinger JA, Fitzpatrick AL, Hayden MW. Changes in metabolic risk factors over 10 years and their associations with late-life cognitive performance: the multi-ethnic study of atherosclerosis. Alzheimers Dement (Amsterdam, Netherlands). 2017;8:18–25.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.