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Original Article

Association of life's simple 7 with cognitive function in a multi-ethnic cohort

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ABSTRACT

Background and objectives: Multiple lifestyle and health factors could contribute to cognitive health, while not many studies examined the factors in a combined way, especially in Asian population. This study aims to examine the association of Life's Simple 7 (LS7) with cognitive function and its change in a multi-ethnic Asian population.**Methods:** Longitudinal data were drawn from the Singapore Multi-Ethnic Cohort, involving 2601 participants (45–86 years). LS7 at baseline was calculated by summing seven metrics, and a higher LS7 (range: 0–7) score indicates a healthier lifestyle. Cognitive function was measured at two revisits with Mini-Mental State Examination (MMSE). Association of baseline LS7 with MMSE percentiles (10th, 30th and 50th) and its change over time were examined using linear quantile mixed model. Interactions between LS7 and age group, sex, ethnicity, education level and marital status were also explored.**Results:** Higher LS7 was significantly associated with higher MMSE scores at 10th ($\beta = 0.11$, 95% CI 0.01, 0.20), 30th ($\beta = 0.12$, 95% CI 0.05, 0.19), and 50th ($\beta = 0.07$, 95% CI 0.03, 0.11) percentiles. These associations were particularly pronounced among currently unmarried individuals, participants aged 60 and above, those with education above primary school and Chinese ethnicity. No significant association was found between LS7 and MMSE change over time.**Discussion:** Higher LS7 was significantly associated with better cognition particularly among older, unmarried individuals and participants with higher education or of Chinese ethnicity. These findings highlight the value of composite lifestyle scores for cognitive impairment risk modification in Asian populations.

1. Introduction

The substantial increase in life expectancy in recent decades has significantly impacted on the incidence of non-communicable diseases, particularly dementia, a disease strongly associated with aging. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) report projected that global number of people with dementia will increase from 57.4 million in 2019 to 152.8 million in 2050 [1]. Cognitive impairment, as a spectrum and precursor to dementia when an individual starts having trouble with memory, learning, concentration, is usually more than twice as prevalent as dementia [2–4]. In Singapore, a multi-ethnic urban Asian population, the prevalence of cognitive impairment among

adults aged 60 and above ranged from 15.2 % to 27.3 % across ethnicities [5–7]. Despite the high disease burden and substantial investment in drug development, there is currently no cure for dementia [8]. This underscores the urgent need for risk factor intervention and primary prevention strategies to mitigate its impact.

Several socioeconomic, lifestyle and psychological factors have been found to be associated with dementia, including education, physical activity and depression [9,10]. While each factor independently contributes only a modest proportion to overall dementia risk, the aggregated effect of multiple risk factors may account for a substantially greater proportion of the risk. As the same factors that increase risk for heart disease also damage blood vessels in the brain, a composite score

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proposed by the American Heart Association (AHA) for cardiovascular disease prevention, the Life's Simple 7 (LS7), could also be relevant for dementia prevention [11]. Several studies have shown that higher LS7 (healthier lifestyle and better health metrics) was significantly associated with lower dementia risk and better cognitive function [12–15]. In a Swedish study, higher LS7 was significantly associated with better cognitive function and slower cognitive decline in the young-old (aged 60 to 72), but not in the old-old (aged 78 and above), suggesting that such association may be modifiable by age [15]. A study conducted in the UK has demonstrated that each one score higher LS7 was associated with 10 % reduced hazard of dementia [13].

However, the relationship between LS7 and cognitive health are not always consistent, and the strengths of association vary across different studies. In a national health survey of Chile, people who scored higher on LS7 showed lower odds of cognitive impairment than those who scored lower on LS7, but this difference was not significant [16]. Similarly, in a German cohort of 3547 individuals, there was no significant association between LS7 and dementia risk, although it was significant for the individual metrics (smoking, physical activity and fasting glucose) [17].

Most existing studies assessing the relationship between LS7 with cognitive function were conducted in non-Asia populations. There is also a lack of studies focusing on middle-aged Asian populations, despite evidence suggesting that cognitive decline may begin earlier in life [18]. A cross-sectional study of Chinese ($n = 297$) recruited older adults (aged 65 and above) and found that optimal LS7 score was significantly associated with 66 % lower odds of mild cognitive impairment [12]. This raises concerns about the generalizability of LS7 to Asian populations, where lifestyle pattern and risk profiles may differ significantly.

In this study, we aim to examine the association between LS7 and cognitive function as well as its change over time using a multi-ethnic

cohort of Singaporean middle- and old-aged adults. We hypothesize that combination of favorable lifestyle factors (LS7), including non-smoking, optimal BMI, adequate physical activity, a healthy diet, and optimal levels of blood cholesterol, glucose and blood pressure are associated with better cognitive performance and slower cognitive decline.

2. Methods

2.1. Study population

This study employed longitudinal data from the Multi-Ethnic Cohort Phase 1 (MEC1), a prospective population-based cohort conducted to assess the factors contributing to non-communicable disease development in the three major Asian ethnic groups: Chinese, Malay, and Indians living in Singapore [19]. Between 2004 and 2010, MEC1 enrolled Singaporean citizens and permanent residents who were at least 21 years of age. Participants were subsequently invited for the first revisit during 2011 and 2016 and the second revisit during 2016 and 2020. At baseline and revisits, participants underwent home interviews to collect data on demographics, medical and family history, as well as lifestyle factors. Participants were also given the option to take a health assessment which included blood biomarkers, physical measurements, and cognitive function evaluations. All studies were approved by the Institutional Review Board of the National University of Singapore, and all participants provided written informed consent prior to their involvement in the study [19].

As shown in Fig. 1, among 14,467 recruited participants, 4908 were excluded for the following reasons: other ethnicity ($n = 43$), baseline age below 45 ($n = 4730$), stroke history ($n = 94$), missing education level ($n = 35$), missing working status ($n = 1$), missing marital status ($n = 5$). Additionally, 3946 participants were excluded for missing health

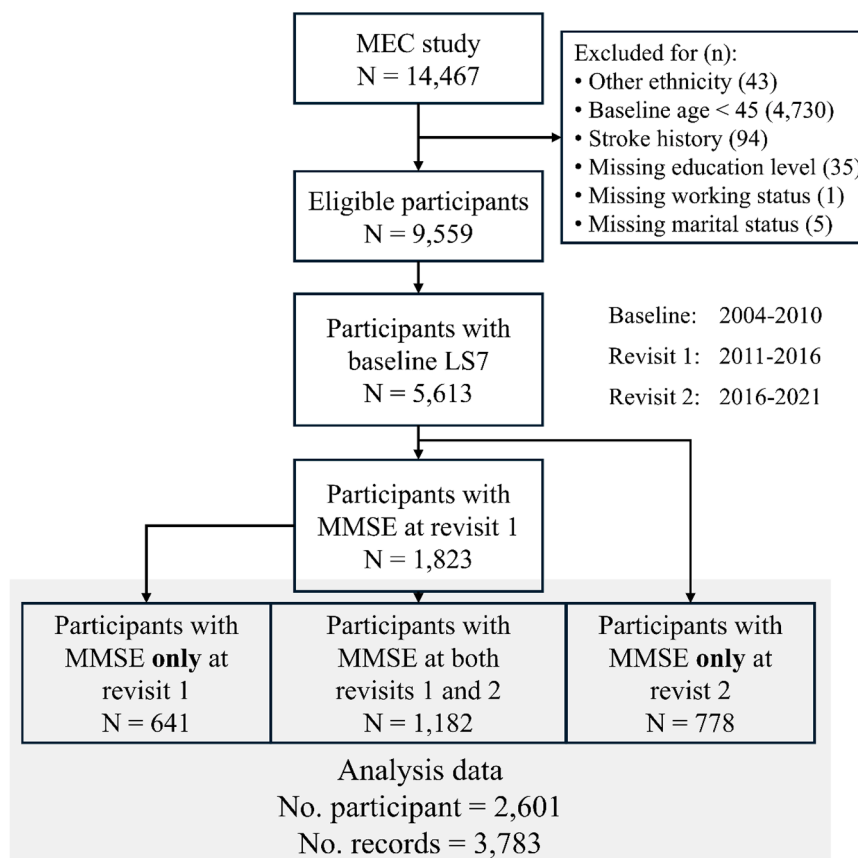


Fig. 1. Flowchart of eligible MEC1 Revisit participants in this study's analyses.

metrics and the remaining 5613 participants had baseline Life's Simple 7 (LS7) data. In total, 1823 participants underwent the Mini-Mental State Examination (MMSE) at first revisit, with a median follow-up duration of 6 years (interquartile range [IQR]: 5–8 years). At the second revisit, 1182 of those who had MMSE in the first revisit had a second MMSE assessment, while an additional 778 participants had MMSE assessment only at the second revisit but not at the first revisit. The median duration from baseline to the second revisit was 11 years (IQR: 10–12 years). This study included data from 2601 participants (641 with MMSE at first revisit only, 1182 with MMSE at both revisits and 778 with MMSE at second revisit only), yielding 3783 MMSE records for analysis.

2.2. Lifestyle behavioral factors

At each visit, smoking habits were inquired using two questions: "Have you ever smoked at least 100 cigarettes in your lifetime?" and "Do you smoke cigarettes currently?" Based on responses to these questions, participants were classified as never smokers, ever smokers or current smokers.

The SP2PAQ (SP2 physical activity questionnaire) was administered to collect information on the type, frequency and duration of various domains of physical activities, including transportation, occupation, leisure time and household activities [20]. Since intensity varies across different activities, metabolic equivalents (MET) values were assigned to each activity to quantify energy expenditure in a standardized manner. MET values refer to the amount of energy expended by a given activity relative to sitting still for the same duration. The total volume of moderate-to-vigorous physical activity (MVPA) and vigorous physical activity (VPA) was computed as sum of individual activity volumes in MET-minutes per week [19].

Dietary patterns were evaluated using a validated 163-item semi-quantitative Food Frequency Questionnaire (FFQ), specifically designed for the diverse adult population of Singapore [21]. This questionnaire captured information on the participants' average consumption frequency and portion sizes of various food and beverage items over the previous year, including staple foods, meats, vegetables and drinks. To estimate energy and nutrient intakes, data from the FFQ were analyzed using the Food Information and Nutrient Database for Singapore. The amount of specific food group consumption (fruits and vegetables, fish, whole grains, and sugar-sweetened beverages) was quantified based on this database, with further methodological details described elsewhere [21].

2.3. Physical examination and blood biomarkers

At each visit, participants were given an option to attend a physical examination, which included measurements of weight, height, blood pressure and blood taking. Height (without shoes) was measured to the nearest 0.1 cm and body height (with empty pocket) was measured to the nearest 0.1 kg, as detailed elsewhere [19]. Body mass index (BMI) was then calculated as weight (kg) divided by height squared (m^2).

Before blood pressure measurement, participants were instructed to rest for at least five minutes. Systolic and diastolic blood pressure were then measured using an automated digital blood pressure monitor (Dinamap Carescape V100, General Electric). Two readings were recorded initially, and if the first two readings were different by more than 5 mmHg in both SBP and DBP or 10 mmHg in either SBP or DBP, a third reading was taken. The final SBP and DBP values were calculated as the average of the recorded readings.

During physical examinations, blood samples were collected on the same day, prior to which participants were instructed to fast for 8–12 hours. Assessed biomarkers include blood glucose, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL-C), creatinine, low-density lipoprotein cholesterol (LDL-C) and glycated hemoglobin A1c (HbA1c).

2.4. Life's simple 7 score at baseline

LS7 is a composite score proposed by American Heart Association as an indicator of cardiovascular health [22]. It consists of four modifiable behavioral factors (smoking, BMI, physical activity and diet) and three cardiometabolic factors (blood lipid, fasting glucose, and blood pressure) [23]. Participants receive one point for each factor if they meet the corresponding favorable criterion, and the LS7 score is calculated as the sum of all factors with higher LS7 indicates healthier lifestyle. The criteria for each component are as follows: 1) not smoking (never smoked or ever smoked but stopped); 2) normal BMI: $<23 \text{ kg/m}^2$; 3) adequate physical activity; 4) healthy diet; 5) blood cholesterol $<200 \text{ mg/dL}$; 6) fasting glucose $<100 \text{ mg/dL}$; and 7) normal blood pressure: SBP $<120 \text{ mmHg}$ and DBP $<80 \text{ mmHg}$ (Supplementary Table 1) [23, 24]. Commonly used criterion for adequate physical activity is $\geq 150 \text{ min/week}$ moderate intensity or $\geq 75 \text{ min/week}$ vigorous intensity or $\geq 150 \text{ min/week}$ moderate and vigorous intensity, while in this study an equivalent value of 500 MET-min/week is used as the criterion [25]. Healthy diet is defined as meeting at least 3 of following criteria: fruits or vegetables ($\geq 450 \text{ g/day}$), fish ($\geq 198 \text{ g/week}$), whole grains ($\geq 85 \text{ g/day}$) and sugar sweetened beverages ($\leq 1 \text{ L/week}$). Previous studies also included a criterion of sodium ($<1500 \text{ mg/d}$), but sodium intake data was not collected in the MEC study and this item was excluded [23]. LS7 was then classified into levels of poor (0–2), intermediate (3–4) and ideal (5–7).

2.5. Cognitive function and cognitive impairment

At both revisits, a validated Singapore-modified version of the Mini-Mental Status Examination (MMSE) was administered to participants aged 40 and above to assess their cognitive function [26]. The MMSE comprises six domains: orientation, immediate recall, attention, delayed recall, language, and construction. The scores from each domain were summed up to generate an overall MMSE score ranging from 0 to 30, where higher scores indicate better cognitive performance. For the Singapore population, an education-based cut-off has been proposed to identify cognitive impairment, which are <25 for individuals with no education, <27 for those with primary school education, and <29 for participants with secondary school education or above [27].

2.6. Covariates

Covariates were collected through questionnaires, including year of birth, sex, education level, ethnicity, marital and working status. Age at each visit was calculated as the difference between the year of birth and the year of the visit. Participants were asked about their ethnicity as reported in their national registration identity card. Education level was categorized into no formal qualification/lower primary, primary, secondary, Institute of Technical Education/National Technical Certificate (ITE/NTC), "A" level/polytechnic/diploma, and university. Participants were classified into two groups: "above primary school" or "primary school and below". There were 5 responses to the question of marital status: 1) never married; 2) currently married; 3) separated but not divorced; 4) divorced and 5) widowed, according to which participants were classified as currently married and currently unmarried (including never married, separated but not divorced, divorced and widowed). Based on participants' usual work status in the past 12 months, they were categorized as employed or unemployed (student, homemaker/housewife, retired or unemployed).

2.7. Statistical analyses

Association between baseline LS7 and repeated measurements of MMSE from both revisits were analyzed. As MMSE scores typically follow a left-skewed distribution, the widely used normal linear regression model, which assumes modelling errors to be normally

distributed and homoscedastic, may not be appropriate. Instead, quantile regression that does not require assumptions of normality or homoscedasticity is more appropriate. As participants were assessed at multiple time points with repeated MMSE measurements, the linear quantile mixed model (LQMM), an extension of the standard linear mixed model that estimates conditional quantiles instead of means with repeated measurements, which can accommodate longitudinal repeated measures, was used for this analysis [28]. Regression coefficients from linear mixed models represent the changes in mean values of outcome per unit increment of exposure. Similarly, those from LQMM reflect how specific quantiles of the outcome vary with each unit increment of the exposure.

To examine the association between LS7 and MMSE at the revisits, a random intercept was included to account for correlation between MMSE measurements at different time points for the same participant. In purpose of achieving convergence, up to 8000 iterations were allowed. Most adjusted covariates were measured at the baseline visit, including age, sex, ethnicity, education, working status and marital status, as well as the time duration between baseline and revisits. For inferences, confidence intervals for the fixed-effects coefficients were obtained using bootstrap methods at 10th, 30th and 50th percentiles, which demonstrates how the lower and middle bands of MMSE are associated with LS7. MMSE follows a left-skewed distribution with ceiling effect near the maximum score of 30, which limits the variability and sensitivity to exposures of its higher percentiles, thus only the lower percentiles were used in the model. For concerns in overestimation of household activity, a sensitivity analysis was conducted where household category was removed from calculation of total physical activity volume.

To account for potential selection bias due to loss to follow-up, inverse probability weighting (IPW) was applied [29]. The probability of attending a follow-up was estimated using logistic regression with covariates (baseline age, sex, ethnicity, education, working status and marital status). Sampling weight of each participant was calculated as the inverse of the predicted probability of attending follow-up, and incorporated into the linear quantile mixed model to estimate associations between baseline LS7 and quantiles of MMSE at follow-ups. By re-weighting the samples, follow-up becomes independent of these covariates, minimizing selection bias.

Interactions between LS7 and socio-economic factors (age group, sex, ethnicity, education level and marital status) were explored to identify probable effect modifications. In models with interaction term, age was divided into younger (< 60 years) and older groups (\geq 60 years). In addition to interaction model, age group (< 60 years and \geq 60 years) stratified analyses were carried out to examine association between LS7 and MMSE. The associations between individual LS7 components (not smoking, normal BMI, adequate physical activity, healthy diet, normal blood cholesterol, normal fasting glucose and normal blood pressure) were also examined in separate models. Recalibrated LS7 was then computed as sum of each component score times weight by regression coefficients from the 10th percentile model, and finally standardized through its mean and standard deviation to assess the association with MMSE.

In a subset of participants ($n = 1182$) who had MMSE at both revisits, association between baseline LS7 and rate of MMSE change was also examined using LQMM, with adjustment for baseline age, sex, ethnicity, education, working status, marital status and duration between baseline and the revisits of MMSE assessment. In addition, an interaction term (follow-up length \times LS7) was included in the model. The regression coefficient for this term reflects the extent to which the annual change in MMSE differs with each one-point increase in the LS7 score. Associations between LS7 components and MMSE were also examined in the same method. All statistical analyses were conducted using R-4.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and R package lqmm (version 1.5.8) [28].

2.8. Data availability statement

Data used in this study is accessible through request to Singapore Population Healthy Study Scientific Committee (<https://blog.nus.edu.sg/sphs/data-and-samples-request/>).

3. Results

3.1. Participant characteristics at baseline

Table 1 shows the baseline characteristics of the 2601 participants, stratified by baseline LS7 levels with 505 classified as poor LS7, 1520 as intermediate and 576 as ideal (Supplementary Table 1). Among the 2601 participants included in the analysis, 1507 (57.9 %) were female, and the mean (standard deviation) age at baseline was 54.0 (7.0) years. The majority (67.6 %) had attained an education level above primary school, and 52.2 % were Chinese, followed by 27.0 % Indian and 20.7 % Malay. Most participants (86.7 %, $n = 2255$) were currently married, and 63.5 % ($n = 1652$) were employed. For LS7 factors, 9.7 % of participants were current smokers. Participants had a mean BMI of 24.9 (4.5) kg/m² and a median (IQR) MVPA volume of 2397.0 (1050.0–4249.5) MET-minutes/week. Approximately 26.1 % of participants adhered to a healthy diet. In blood biomarkers, participants had a mean total cholesterol of 209.5 (37.6) mg/dL and fasting glucose of 97.0 (31.7) mg/dL. Mean SBP was 133.0 (25.4) and 78.3 (21.0) mmHg for DBP. At the first and second revisits, median (IQR) MMSE scores were respectively 29 (27–30) and 28 (27–29).

Compared to participants in the poor LS7 (score 0–2) group, those with higher LS7 scores were significantly more likely to be female, younger, have education above primary school, be of Chinese ethnicity, be married and be employed. With respect to LS7 components, there were significantly fewer active smokers, lower BMI, higher physical activity volume and better adherence to a healthy diet among groups of higher LS7. These participants also had significantly lower levels of total cholesterol, fasting glucose, SBP and DBP.

3.2. Associations of LS7 with MMSE percentiles

As shown in Table 2, higher baseline LS7 was associated with higher MMSE, which was significant at the 10th ($\beta = 0.11$, 95 % CI 0.01, 0.20), 30th ($\beta = 0.12$, 95 % CI 0.05, 0.19) and 50th ($\beta = 0.07$, 95 % CI 0.03, 0.11) percentiles after adjustments. In sensitivity analysis, household activity was excluded from LS7 calculation and results are similar that higher LS7 was significantly associated with higher MMSE score at all three percentiles (Supplementary Table 2). In models with inverse probability weighting, associations between baseline LS7 and quantiles of follow-up MMSE were similar to unweighted models (Supplementary Table 3). In interaction models, the association between higher LS7 and better MMSE score was found to be modified by age group, ethnicity, education level and marital status, but not by sex (Table 2).

For people aged below 60, the association of higher LS7 with higher MMSE was only significant at 30th ($\beta = 0.06$, 95 % CI 0.01, 0.12) percentile. In contrast, associations between LS7 and MMSE are significantly stronger among older adults (aged 60 and above) at 30th ($\beta = 0.30$, 95 % CI 0.08, 0.51) and 50th ($\beta = 0.37$, 95 % CI 0.20, 0.54) percentiles. Similarly, in analyses stratified by age group, association between LS7 and MMSE was statistically significant even among those <60 years, although the effect was somewhat attenuated compared to older individuals (Supplementary Table 4). For ethnicity, higher LS7 was associated with lower MMSE at 10th ($\beta = 0.14$, 95 % CI 0.02, 0.25) and 30th ($\beta = 0.13$, 95 % CI 0.08, 0.18) percentiles in Chinese, significantly stronger associations than Malays. Association between LS7 and MMSE was only significantly modified by education level at the 10th percentile. Higher LS7 was significantly associated with MMSE at 10th percentile among individuals with education above primary school ($\beta = 0.13$, 95 % CI 0.03, 0.23) but not among people with primary school

Table 1
Baseline characteristics of included participants by LS7 levels.

| Baseline characteristics | Baseline LS7 levels | | | Total sample (N = 2601) | P value |
|---|--------------------------|------------------------------|---------------------------|----------------------------|---------------------|
| | Poor (0–2, N = 505) | Intermediate (3–4, N = 1520) | Ideal (5–7, N = 576) | | |
| Female, n (%) | 271 (53.7) | 879 (57.8) | 357 (62.0) | 1507 (57.9) | 0.02 [†] |
| Age, mean (SD), years | 54.6 (6.9) | 54.3 (7.2) | 52.8 (6.6) | 54.0 (7.0) | <0.001 [#] |
| Above primary school, n (%) | 303 (60.0) | 1025 (67.4) | 430 (74.7) | 1758 (67.6) | <0.001 [†] |
| Ethnicity, n (%) | | | | | <0.001 [†] |
| Chinese | 198 (39.2) | 775 (51.0) | 386 (67.0) | 1359 (52.2) | |
| Malay | 157 (31.1) | 316 (20.8) | 66 (11.5) | 539 (20.7) | |
| Indian | 150 (29.7) | 429 (28.2) | 124 (21.5) | 703 (27.0) | |
| Married, n (%) | 422 (83.6) | 1323 (87.0) | 510 (88.5) | 2255 (86.7) | 0.046 [†] |
| Employed, n (%) | 303 (60.0) | 960 (63.2) | 389 (67.5) | 1652 (63.5) | 0.03 [†] |
| Active smoker, n (%) | 113 (22.4) | 123 (8.1) | 16 (2.8) | 252 (9.7) | <0.001 [†] |
| BMI, mean (SD), kg/m ² | 27.5 (4.4) | 25.2 (4.3) | 22.0 (3.3) | 24.9 (4.5) | <0.001 [#] |
| MVPA, median (IQR), MET-minutes/week | 1516.5 (420.0–3050.9) | 2457.2 (1155.3–4409.9) | 3145.3 (1618.4–5082.3) | 2397.0 (1050.0–4249.5) | <0.001 [#] |
| Healthy diet, n (%) | 20 (4.0) | 374 (24.6) | 285 (49.5) | 679 (26.1) | <0.001 [†] |
| Total cholesterol, mean (SD), mg/dL | 225.0 (35.6) | 210.6 (36.8) | 192.8 (34.8) | 209.5 (37.6) | <0.001 [#] |
| Fasting glucose, mean (SD), mg/dL | 113.8 (44.2) | 95.7 (29.7) | 86.1 (11.2) | 97.0 (31.7) | <0.001 [#] |
| SBP, mean (SD), mmHg | 143.7 (27.9) | 134.2 (24.7) | 120.7 (19.4) | 133.0 (25.4) | <0.001 [#] |
| DBP, mean (SD), mmHg | 83.7 (25.2) | 79.0 (21.3) | 71.7 (12.8) | 78.3 (21.0) | <0.001 [#] |
| MMSE at 1st revisit, median(IQR) | 29 (27–30) | 29 (27–30) | 29 (28–30) | 29 (27–30) | <0.001 [‡] |
| MMSE at 2nd revisit, median(IQR) | 28 (26–29) | 28 (27–29) | 29 (27–30) | 28 (27–29) | <0.001 [‡] |

Characteristics were compared across LS7 levels using.

[†] chi-square test.

[#] ANOVA test or.

[‡] Kruskal Wallis test.

education and below ($\beta = -0.03$, 95 % CI -0.18 , 0.12).

Interaction of LS7 with marital status was statistically significant for 10th (P-interaction: 0.04) and 30th (P-interaction: 0.04) percentiles. Among currently married participants, associations of higher LS7 with higher MMSE were marginally significant at 30th ($\beta = 0.10$, 95 % CI 0.00, 0.19) and 50th ($\beta = 0.05$, 95 % CI 0.00, 0.10) but not 10th ($\beta = 0.08$, 95 % CI -0.02 , 0.19) percentiles. These associations were stronger (10th percentile $\beta = 0.27$, 95 % CI 0.07, 0.48; 30th percentile $\beta = 0.28$, 95 % CI 0.08, 0.47; 50th percentile $\beta = 0.23$, 95 % CI 0.03, 0.42) in currently unmarried group.

3.3. Associations of LS7 components and recalibrated LS7 with MMSE

All individual LS7 components except healthy diet were associated with higher MMSE scores (Table 3). At the 10th percentile, normal BMI ($\beta = 0.25$, 95 % CI 0.06, 0.43) was significantly associated with higher MMSE scores. However, association of not smoking ($\beta = 0.20$, 95 % CI -0.06 , 0.46), physical activity ($\beta = 0.06$, 95 % CI -0.16 , 0.29), healthy diet ($\beta = -0.01$, 95 % CI -0.20 , 0.19), normal blood cholesterol ($\beta = 0.04$, 95 % CI -0.12 , 0.21), normal fasting glucose ($\beta = 0.05$, 95 % CI -0.15 , 0.24) or normal blood pressure ($\beta = 0.13$, 95 % CI -0.12 , 0.37) were not associated with MMSE. After recalibration of LS7 based on the weights of individual component associations with 10th percentile of MMSE, per SD increment of LS7 was significantly associated with higher MMSE at 10th ($\beta = 0.17$, 95 % CI 0.04, 0.31), 30th ($\beta = 0.17$, 95 % CI 0.09, 0.24) and 50th ($\beta = 0.09$, 95 % CI 0.03, 0.16) percentiles. When all the LS7 components were jointly included in a model, results are similar to the separate models of individual components (Supplementary Table 5).

3.4. Associations of LS7 components and MMSE change

In the subset of 1182 participants who completed MMSE assessment at both revisits, cognitive scores declined at a mean rate of 0.13 points per year over a mean follow-up duration of 4.3 years. As shown in Table 4, higher LS7 scores were not significantly associated with the rate

of MMSE change at the 10th percentile ($\beta = -0.01$, 95 % CI -0.03 to 0.02), 30th percentile ($\beta = 0.00$, 95 % CI -0.02 to 0.02), or 50th percentile ($\beta = 0.02$, 95 % CI 0.00 to 0.04). Among individual LS7 components, only adherence to a healthy diet was marginally associated with faster MMSE decline at the 10th percentile ($\beta = -0.10$, 95 % CI -0.19 to -0.01).

4. Discussion

In this longitudinal analysis of middle- and old-aged Singaporean Chinese, Malay and Indian, we found that higher (favorable) Life's Simple 7 (LS7), a composite healthy lifestyle score, was associated with better cognitive function measured with MMSE at the 10th, 30th and 50th percentiles but not with its change. Interaction analysis revealed that associations between LS7 and MMSE were significantly modified by marital status, age group, ethnicity and education level. BMI was significantly associated with higher MMSE across models of 10th, 30th and 50th percentiles. After recalibration of the LS7 weighted by the strength of associations between individual components and 10th percentiles of MMSE, a higher LS7 was significantly associated with higher MMSE scores across all percentiles (10th, 30th, and 50th).

Numerous studies have reported the beneficial effects of higher adherence to LS7 scores on better cognitive function [13,15] and lower dementia risk [12,14,16]. One key study, the Whitehall II cohort of British civil service employees examined the association of LS7 measurements with later dementia diagnoses confirmed by medical professionals. Individuals with an intermediate LS7 score had a significantly lower hazard ratio for dementia (HR 0.67, 95 % CI 0.51–0.88) compared to those in the poor LS7 group [13]. Similarly, the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), a longitudinal cohort study with baseline LS7 assessments and repeated cognitive measurements showed that a poor LS7 score was significantly associated with lower cognitive function (regression coefficients ranged between -0.21 and -0.10) in the young-old group (60–72 years), but no such association was observed in the old-old group (78 years and above) [15]. Our study further incorporated middle-aged individuals and reported

Table 2
Association of LS7 with percentiles of MMSE score*.

| Model | Term | Regression coefficients (95 % CI) | | |
|---------|--------------------------------|-----------------------------------|---------------------|---------------------|
| | | P value | | |
| | | 10th percentile | 30th percentile | 50th percentile |
| Model 1 | LS7 | 0.14 (0.05, 0.24) | 0.19 (0.08, 0.31) | 0.15 (0.09, 0.21) |
| | | 0.003 | 0.001 | <0.001 |
| | | | | |
| Model 2 | LS7 | 0.11 (0.01, 0.20) | 0.12 (0.05, 0.19) | 0.07 (0.03, 0.11) |
| | | 0.03 | 0.002 | 0.002 |
| | | | | |
| Model 3 | LS7 (age below 60) | 0.04 (-0.09, 0.17) | 0.06 (0.01, 0.12) | 0.06 (-0.02, 0.14) |
| | | 0.54 | 0.03 | 0.14 |
| | | | | |
| | LS7 (aged 60 and above) | 0.03 (-0.21, 0.27) | 0.30 (0.08, 0.51) | 0.37 (0.20, 0.54) |
| | | 0.81 | 0.01 | <0.001 |
| | | | | |
| Model 4 | P-interaction LS7 (male) | 0.59 | 0.02 | 0.003 |
| | | 0.13 (0.01, 0.25) | 0.11 (0.04, 0.17) | 0.04 (-0.03, 0.11) |
| | | 0.04 | 0.003 | 0.30 |
| | LS7 (female) | 0.09 (-0.01, 0.19) | 0.12 (0.02, 0.22) | 0.08 (0.01, 0.16) |
| | | 0.08 | 0.02 | 0.03 |
| | | | | |
| Model 5 | P-interaction LS7 (Chinese) | 0.55 | 0.71 | 0.40 |
| | | 0.14 (0.02, 0.25) † | 0.13 (0.08, 0.18) † | 0.08 (0.02, 0.14) |
| | | 0.02 | <0.001 | 0.01 |
| | LS7 (Malay) | -0.10 (-0.28, 0.07) | -0.08 (-0.23, 0.07) | -0.07 (-0.26, 0.13) |
| | | 0.23 | 0.30 | 0.51 |
| | | | | |
| | LS7 (Indian) | 0.05 (-0.15, 0.26) | 0.10 (-0.05, 0.25) | 0.12 (-0.03, 0.26) |
| | | 0.60 | 0.19 | 0.11 |
| | | | | |
| Model 6 | LS7 (primary school and below) | -0.03 (-0.18, 0.12) | 0.02 (-0.13, 0.17) | 0.11 (-0.03, 0.26) |
| | | 0.66 | 0.77 | 0.13 |
| | | | | |
| | LS7 (above primary school) | 0.13 (0.03, 0.23) | 0.12 (0.05, 0.20) | 0.06 (0.02, 0.11) |
| | | 0.01 | 0.002 | 0.01 |
| | | | | |
| Model 7 | P-interaction LS7 (unmarried) | 0.02 | 0.17 | 0.55 |
| | | 0.27 (0.07, 0.48) | 0.28 (0.08, 0.47) | 0.23 (0.03, 0.42) |
| | | 0.01 | 0.01 | 0.03 |
| | LS7 (married) | 0.08 (-0.02, 0.19) | 0.10 (0.00, 0.19) | 0.05 (0.00, 0.10) |
| | | 0.13 | 0.04 | 0.04 |
| | | | | |
| | P-interaction | 0.04 | 0.04 | 0.06 |
| | | | | |
| | | | | |

* Linear quantile mixed model, and 10th, 30th and 50th percentiles were selected.

- Model 1: adjusted for baseline age and length of follow-up;
- Model 2: adjusted for baseline age, length of follow-up, sex, education level, working status, marital status and ethnicity;
- Model 3: model 2 + LS7 interaction with baseline age group;
- Model 4: model 2 + LS7 interaction with sex;
- Model 5: model 2 + LS7 interaction with ethnicity.
- † Regression coefficient significantly different from Malay group;
- Model 6: model 2 + LS7 interaction with education level;
- Model 7: model 2 + LS7 interaction with marital status.

similar findings that association of LS7 with better cognitive function was only significant for age group 60 and above but not in the group of age below 60. These findings underscore the potential role of cardiovascular health in mitigating cognitive decline.

Our findings demonstrate evidence that the association between LS7 and MMSE scores was modified by marital status, with a stronger association observed among currently unmarried participants than those who were currently married. Previous studies from Singapore and China have also demonstrated that married individuals tend to have better cognitive function and lower risk of dementia than individuals who were not married [30,31]. One possible explanation for this observation is that married individuals may benefit from additional protective factors,

Table 3
Association of individual components and recalibrated LS7 with percentiles of MMSE score*.

| | Regression coefficients (95 % CI) | | |
|---------------------|-----------------------------------|--------------------|--------------------|
| | P value | | |
| | 10th percentile | 30th percentile | 50th percentile |
| Not smoking | 0.20 (-0.06, 0.46) | 0.17 (-0.06, 0.40) | 0.16 (-0.08, 0.40) |
| | 0.14 | 0.40 | 0.19 |
| Normal BMI † | 0.25 (0.06, 0.43) | 0.25 (0.13, 0.38) | 0.17 (0.01, 0.33) |
| | 0.01 | <0.001 | 0.04 |
| Physical activity † | 0.06 (-0.16, 0.29) | 0.09 (-0.12, 0.30) | 0.08 (-0.08, 0.25) |
| | 0.57 | 0.38 | 0.32 |
| Healthy diet † | -0.01 (-0.20, 0.19) | 0.04 (-0.13, 0.22) | 0.05 (-0.11, 0.20) |
| | 0.95 | 0.61 | 0.55 |
| Blood cholesterol † | 0.04 (-0.12, 0.21) | 0.07 (-0.09, 0.23) | 0.05 (-0.12, 0.23) |
| | 0.62 | 0.37 | 0.54 |
| Fasting glucose † | 0.05 (-0.15, 0.24) | 0.06 (-0.06, 0.19) | 0.03 (-0.12, 0.17) |
| | 0.64 | 0.32 | 0.72 |
| Blood pressure † | 0.13 (-0.12, 0.37) | 0.11 (-0.07, 0.29) | 0.10 (-0.11, 0.31) |
| | 0.31 | 0.23 | 0.34 |
| Recalibrated LS7 # | 0.17 (0.04, 0.31) | 0.17 (0.09, 0.24) | 0.09 (0.03, 0.16) |
| | 0.01 | <0.001 | 0.01 |

* Linear quantile mixed model, and 10th, 30th and 50th percentiles were selected. LS7 components were modelled separately; Adjusted for baseline age, length of follow-up, sex, education level, working status, marital status and ethnicity.

† Normal BMI: <23 kg/m²; Physical activity: moderate-to-vigorous physical activity (MVPA) ≥500 MET-minutes/week; healthy diet: proper amount of at least 3 recommended food items; Blood cholesterol: <200 mg/dL; Fasting blood glucose: <100mg/dL; Blood pressure: SBP <120 mmHg and DBP <80 mmHg.

Recalibrated LS7 = 0.196776658*not smoking + 0.246160596*normal BMI + 0.064029617*physical activity + 0.041057069*blood cholesterol + 0.04641775*blood glucose + 0.125089372*blood pressure. Recalibrated LS7 was standardized according to its standard deviation (SD), so regression coefficient reflects MMSE score difference per 1 SD increment of LS7.

such as greater social support, shared health behaviors and structured daily routines, which could offset the negative effects of a lower LS7 score. As a result, the impact of LS7 on cognitive function appears to be stronger in individuals who are not currently married, who may lack such additional protective mechanisms.

Although most LS7 components showed positive associations with MMSE, only normal BMI was significantly associated with better cognitive performance. The high prevalence of non-smoking (90.3 %) and adequate physical activity (86.0 %) may have resulted in limited variability, which could have reduced statistical power (Supplementary Table 1). Only 35.1 % of participants had a normal BMI, and this component was significantly associated with higher MMSE scores. These findings highlight the importance of maintaining a healthy BMI and suggest that BMI may be a key target for multi-domain intervention strategies aimed at preserving cognitive health among Singaporean adults.

Our study did not find significant association between baseline LS7 and rate of change in MMSE scores. First, the relatively short duration from the 1st to the 2nd revisit (median: 3, IQR 4–5 years) and modest cognitive changes observed may limit the power to detect significant longitudinal effects. Second, the MMSE, while widely used, has limited sensitivity for detecting subtle cognitive decline, particularly among well-educated participants. Third, lifestyle behaviors and health status may change over time, and a one-time LS7 measurement at baseline may not capture dynamic exposures influencing cognitive trajectories. Lastly, unmeasured confounders such as sleep quality, social engagement, or genetic predispositions may have influenced the results. Although our

Table 4
Association of LS7 and individual components with MMSE score change rate*.

| | Regression coefficients (95 % CI) | | |
|---------------------|-----------------------------------|-----------------------------|----------------------------|
| | P value | | |
| | 10th percentile | 30th percentile | 50th percentile |
| LS7 | -0.01 (-0.03, 0.02) 0.56 | 0.00 (-0.02, 0.02) 0.86 | 0.02 (0.00, 0.04) 0.12 |
| Not smoking | -0.02 (-0.14, 0.09) 0.66 | 0.02 (-0.07, 0.10) 0.70 | 0.01 (-0.06, 0.08) 0.70 |
| Normal BMI † | -0.05 (-0.12, 0.03) 0.23 | -0.03 (-0.07, 0.02) 0.25 | 0.03 (-0.02, 0.08) 0.27 |
| Physical activity † | -0.01 (-0.11, 0.10) 0.92 | -0.03 (-0.13, 0.07) 0.52 | 0.00 (-0.08, 0.08) 0.98 |
| Healthy diet † | -0.10 (-0.19, -0.01) 0.04 | -0.01 (-0.10, 0.07) 0.74 | 0.01 (-0.06, 0.08) 0.76 |
| Blood cholesterol † | 0.04 (-0.07, 0.15) 0.49 | -0.03 (-0.10, 0.03) 0.27 | 0.00 (-0.05, 0.06) 0.92 |
| Fasting glucose † | -0.03 (-0.12, 0.06) 0.55 | -0.00 (-0.07, 0.07) 0.96 | 0.05 (-0.01, 0.11) 0.07 |
| Blood pressure † | 0.01 (-0.09, 0.12) 0.78 | 0.03 (-0.05, 0.11) 0.40 | 0.04 (-0.03, 0.12) 0.26 |

* Linear quantile mixed model, and 10th, 30th and 50th percentiles were selected. Subset of 1182 participants who have MMSE at both revisits. Adjusted for baseline age, sex, ethnicity, education, working status, marital status and duration between baseline and revisit.

previous study reported significantly cross-sectional association between better cognitive function for higher adherence to healthy diet pattern [26], this longitudinal analysis found significantly faster cognitive decline for people with healthy diet. This probably reflects weaker association between nutrition and cognition over time, that people with health diet pattern have higher MMSE in earlier visits, but their score tend to drop more in extended time of follow-up.

Although this study identified a statistically significant association between LS7 and MMSE scores, it is important to emphasize that statistical significance does not necessarily equate to clinical significance. The estimated change in MMSE per one-point increase in LS7 ranged from 0.07 to 0.12 points, which is modest when compared to the minimum clinically important difference (MCID) for MMSE of 1.4 points [32]. Several factors may explain this limited effect size. First, the study cohort comprised a relatively healthy population, as indicated by the median MMSE scores of 29 and 28 at the two follow-up visits. In such cognitively intact populations, detecting strong associations with modifiable lifestyle factors is inherently challenging. Second, while LS7 is a validated cardiovascular health metric, it does not encompass some of the more influential predictors of cognitive function, such as genetic predisposition and early-life education—factors that are unmodifiable by midlife and were not captured in this study. Lastly, the strength of association may have been attenuated due to the exclusion of other relevant modifiable risk factors, such as hearing loss and depression, which were not measured in the MEC cohort. Future studies that expand the LS7 framework to include such variables may yield more clinically meaningful associations with cognitive decline.

Of the 9559 eligible participants, only 2601 were included in the final analysis. This was primarily due to missing LS7 metrics from physical examination component and attrition during follow-up assessments. Compared with those included, the excluded participants were younger, more likely to be of Malay ethnicity, less likely to be married or working, and less likely to have education above primary school (Supplementary Table 6). As such, the excluded group likely had lower LS7 and MMSE scores. The underrepresentation of this subgroup in our final

sample may have led to an underestimation of the true association between LS7 and cognitive function. To minimize bias caused by differential follow-up, we conducted an inverse probability weighting analysis and observed results consistent with the unweighted model (Supplementary Table 3). However, the effect sizes were modest (0.07–0.12 MMSE points per LS7 point), suggesting limited clinical impact despite statistical significance. Importantly, small improvements at the individual level may still accumulate into substantial public health benefits at scale, since LS7 factors are modifiable in the general population. Future cohorts with more complete data, longer follow-up, and broader representativeness are needed to clarify the true association and clinical relevance between LS7 and cognitive outcomes.

There are several notable strengths of this study. Firstly, median duration since baseline was 6 (5–8) years for revisit 1 and 11 (10–12) years for revisit 2, which minimized the influence of possible reverse causality. At the same time, our study explored multiple lifestyle behavior factors, including diet quality and physical activity, providing a more holistic evaluation of their combined effects on cognitive health. By examining the associations of these factors together, we gained insights into the potential synergistic effects of the lifestyle behavior factors on cognitive function as well as effect modification by socioeconomic factors. Secondly, the MEC study collected a wide range of variables, allowing us to account for potential confounders. This enabled the adjustments for important factors such as demographics, social and socioeconomic factors that may influence lifestyle behavior factors and cognition. Thirdly, unlike traditional models that estimate mean effects, LQMM enables a more detailed examination of LS7 impact across different percentiles of cognitive function, providing a comprehensive understanding of the association. Most importantly, quantile regression is resistant to extreme values of MMSE (like there were 32 MMSE measurements below 20) and it does not require assumptions about residual distribution, allowing the MMSE score to be analyzed in its original scale, and improving the interpretability of the results.

It is also important to acknowledge several limitations of the present study. Firstly, participants with worse cognitive function may have difficulties accurately recalling their physical activity levels or dietary intake, leading to recall limitation and misclassification. While MMSE is widely used for cognitive impairment screening, its sensitivity in detecting early cognitive decline is limited, particularly among individuals with higher education levels [27]. The absence of sodium intake data in our dataset required modification of the LS7 scoring protocol. Caution should be exercised when comparing our findings with studies that used the original LS7 criteria. Genetic predisposition (like APOE) of dementia was not measured for the participants, thus this study could not differentiate people of high or low risk of dementia. Lastly, other important lifestyle and psychosocial factors known to influence cognitive health, such as sleep duration, social engagement, and cognitive activities, were not included in this study. Future research should incorporate these variables to provide a more comprehensive analysis of lifestyle influences on cognitive function.

5. Conclusion

In conclusion, in this multi-ethnic population of Singaporeans, we found that LS7, a combined score of both lifestyle behaviors and health metrics, was significantly associated with higher MMSE scores with this association being more pronounced among those currently not married, old-age groups those with higher education as well as Chinese and Indians. On top of existing studies from non-Asian population, this study demonstrates that LS7 could work as a target for integral prevention strategy that aims at combining multiple factors together to mitigate cognitive decline in Asian population.

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CRedit authorship contribution statement

Xiangyuan Huang: Writing – original draft, Formal analysis, Conceptualization. **Muhammad Haiman Bin Samad:** Writing – review & editing, Formal analysis. **Gerald Choon Huat Koh:** Writing – review & editing. **Andre Matthias Müller:** Writing – review & editing. **Falk Müller-Riemenschneider:** Writing – review & editing. **Xueling Sim:** Writing – review & editing. **Saima Hilal:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.tjpad.2025.100453](https://doi.org/10.1016/j.tjpad.2025.100453).

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