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A Combined Healthy Lifestyle Score and Mild Cognitive Impairment in the Elderly Chinese: A Cross-Sectional Study

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Abbreviations: BMI: Body Mass Index; CHL: Combined Health Lifestyle; CIs: Confidence Intervals; C-MMSE: Chinese version of Mini-Mental Status Examination; SBP: Systolic Blood Pressure; MCI: Mild Cognitive Impairment

ABSTRACT

Introduction: There was scarce evidence about the combined lifestyle effect on mild cognitive impairment (MCI), a predementia syndrome. We aimed to investigate the relationship between a combined healthy lifestyle score, including five modifiable lifestyle factors and MCI in the elderly Chinese population.

Methods: A cross-sectional study was conducted among 2,213 elderly participants aged 65 and above who lived in an urban community in Shanghai. MCI cases were defined based on the Chinese version of the Mini-Mental Status Examination. Participants received 1 point for each of five self-reported healthy lifestyle factors: never smokers, non-alcohol drinkers, having a balanced diet, normal body weight and regular physical activity; otherwise 0 point was received, which resulted in a combined healthy lifestyle (CHL) score from 1 to 5 points, with a higher score indicating an overall healthier lifestyle pattern. A weighted CHL score estimated based on logistic model-derived parameters and the CHL score excluding diet component were also calculated. Logistic regression models were used to estimate the multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for CHL scores in relation to MCI.

Results: The prevalence of MCI was 12.3% and 21.1% of participants had all five healthy lifestyles. In the multivariable-adjusted model, neither CHL score (OR=1.64, 95%CI=0.90-2.98) or the weighted CHL score (OR=1.16, 95%CI=0.75-1.80) was associated with odds of MCI. The null association was also observed with the non-diet CHL score.

Conclusion: In this elderly Chinese population with healthy lifestyles, no association between a combined lifestyle score and MCI prevalence was identified.

Keywords: Combined Lifestyle Score; Mild Cognitive Impairment; Cross-Sectional Study; Elderly Population

Introduction

Over the past four decades, due to longer life expectancy, China has been experiencing an unprecedentedly fast pace of aging [1]. According to the latest Chinese population census, there were 191 million Chinese people aged 65 and over in 2020, comprising 13.5% of the total population [2]. Cognitive decline is one of the most common physiologic changes closely related to aging. In the pathogenesis progress of cognitive decline, mild cognitive impairment (MCI) is a predementia syndrome, characterized by problems with memory, language, thinking or judgment, which may substantially increase family and medical care burden and reduce the individual quality of life [3,4]. One third of MCI cases will progress to dementia in the next five years if not intervened appropriately [5]. In China, the overall MCI prevalence was estimated to be 15.5% according to a recent nationally representative survey of adults aged 60 and above [6]. However, there are currently no standard treatments or approved medications for MCI. Therefore, identifying modifiable risk factors of MCI to prevent this neurodegenerative disorder effectively has significant public health implications. Several key lifestyle factors have been identified to be related to MCI development in the previous literature, including cigarette smoking [7,8]. Alcohol consumption [9,10] body mass index (BMI) [11,12]. dietary habit [13] and physical activity [14,15]. However, findings have been inconsistent.

There were only a limited number of studies focusing on lifestyle factors in MCI prevention in the Chinese population [16-22]. Lifestyle factors are mostly correlated and interact with each other to affect disease outcomes. Therefore, investigating a combined lifestyle pattern has more advantage than considering only a single lifestyle, especially for a disease with multifactorial etiology such as MCI [23,24]. A combined lifestyle effect on MCI occurrence has been only investigated in few studies [25,26]. Therefore, we aimed to investigate the association between a combined healthy lifestyle score, including five modifiable lifestyle factors (i.e., cigarette smoking, alcohol drinking, physical activity, diet habit and BMI) and the prevalence of MCI, using data from a large cross-sectional study conducted in Shanghai, one of the most rapidly aging cities in China and worldwide. We hypothesized that a healthier lifestyle would be associated lower prevalence of MCI.

Materials and Methods

Study Populations

This cross-sectional study was conducted under the framework of Shanghai Municipal Annual Physical Examination that provides city-level public services, including lifestyle and health status assessment, and physical examination for registered people aged 65 and above. In this study, participants were recruited from registered residents in the Dapu neighborhood community in the Huangpu District, one of the 16 administrative Districts in Shanghai, located in the central business area with the highest elderly population density in the city. Participants were eligible if they met the criteria:

1) 65 years or older with sufficient daily living ability.
2) Had been living in this area for at least 12 months.
3) Willing to participate in the physical examination.

From March to September 2019, a total of 3,575 eligible subjects participated in the physical examination. Among these, we excluded participants who did not provide information regarding cognitive function (n=1,286), smoking status (n=19), alcohol intake (n=12), physical activity (n=1), dietary habit (n=36), or education level (n=8), remaining 2,213 participants in this study. This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the ethics committee of Shanghai Jiao Tong University School of Public Health and School of Nurse, approval number SJUPN-202103-X1. Written informed consent was obtained from all the participants in this study.

Exposure Assessment

A standard questionnaire was administered face-to-face by trained physicians during the physical examination to collect participants' information on demographic characteristics, physical symptoms, lifestyles, occupational exposures, personal medical histories, and medication use. Participants self-reported their habitual lifestyles, including cigarette smoking, alcohol drinking, diet habit, and recreational physical activity. Participants were categorized as never, past or current smokers based on their cigarette smoking history. Past and current smokers were required to report the average number of cigarettes smoked per day. A pack-year was defined as smoking one pack of 20 cigarettes per day for one year. The information on alcohol drinking included alcohol drinking status (never, past and current drinkers), frequency of alcohol drinking, and amount and types of alcoholic beverages consumed over the past year. The total amount of alcohol consumed in grams per week was calculated by multiplying the frequency of alcohol drinking with the amount of alcohol consumed for each alcoholic beverage based on the alcohol content in the respective beverage and summing up all types of alcoholic beverages [27]. A preliminary dietary question was asked to let subjects choose between one of three habitual diet habits they had: a balanced diet (i.e., habitual consumption of a similar amount of plant-based and animal-based foods), a plant-based diet (i.e., habitual consumption of more plant-based foods than animal-based foods), and an animal-based diet emphasizing more animal-based foods intake.

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All participants were asked to report the frequency, type and duration of recreational physical activities over the past year. Metabolic equivalent of task (MET)-hours per day was calculated by summing the products of hours spent per day for each type of physical activity and the corresponding MET value according to the 2011 update compendium of physical activities [28]. Participants' heights and weights were measured by physicians based on a standard protocol. BMI was calculated as weight (kg) divided by the square of height $(m)^2$ and classified as underweight (<18.5 kg/m^2), normal (18.5-23.9 kg/m^2), overweight (24.0-27.9 kg/m^2) and obesity (≥28 kg/m^2) based on the optimal BMI cut-off points recommended for Chinese [29].

Combined Health Lifestyle (CHL) Score and Weighted CHL Score

We firstly assigned a binary score to each of the five lifestyle factors based on literature-identified association for each lifestyle with MCI among the elderly Chinese [30-33] or lifestyle recommendations or guidelines for Chinese [34-36] Participants received one point if they were never smokers [30,33] non-alcohol consumers [30,31] had normal body weight [35] took part in daily recreational physical activity [30,32] or had a balanced diet [34] .otherwise, they received 0 point for each of these factors (Table 1). The binary scoring algorithm was created to be consistent with previous literature on healthy lifestyle pattern analyses [37-40]. We assigned one point to those with daily recreational physical activity and zero to others because summary evidence from a recent large systematic review of 53 studies suggested that physically active older Chinese people had a lower risk of getting cognitive impairment but no evidence was found that type, intensity, or frequency of various physical activities led to a reduced MCI risk [32]. The final CHL score was calculated by adding up the score from each lifestyle, resulting in a total score from 1 (the least healthy lifestyle) to 5 (the healthiest lifestyle) since no participant in this study had five unhealthy lifestyles. The higher CHL score indicated an overall healthier lifestyle pattern.

Table 1: Baseline characteristics of study participants by the combined healthy lifestyle score categories (N=2,213).

Characteristics	All	Combined Healthy Lifestyle Score[a]					P value[b]
		1	2	3	4	5	
No. of Total participants	2213	41	177	655	873	467	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Gender							<0.01
Males	989 (44.7)	41 (100)	143 (80.8)	304 (46.4)	321 (36.8)	180 (38.5)	
Females	1224 (55.3)	0	34 (19.2)	351 (53.6)	552 (63.2)	287 (61.5)	
Educational Level							0.09
Did not complete high school	1061 (47.9)	19 (46.3)	86 (48.6)	323 (49.3)	425 (48.7)	208 (44.5)	
Completed high school	628 (28.4)	15 (36.6)	59 (33.3)	180 (27.5)	250 (28.6)	124 (26.6)	
Above high school	524 (23.7)	7 (17.1)	32 (18.1)	152 (23.2)	198 (22.7)	135 (28.9)	
Body Mass Index							<0.01
Normal weight (18.5-23.9 kg/m^2)	1115 (50.4)	2 (4.9)	37 (20.9)	120 (18.3)	489 (56.0)	467 (100)	
Underweight (<18.5 kg/m^2)	87 (3.9)	1 (2.4)	4 (2.3)	49 (7.5)	33 (3.8)	0	
Overweight (24.0-27.9 kg/m^2)	807 (36.5)	35 (85.4)	109 (61.6)	382 (58.3)	281 (32.2)	0	
Obese (≥28 kg/m^2)	204 (9.2)	3 (7.3)	27 (15.3)	104 (15.9)	70 (8)	0	
Cigarette Smoking Status							<0.01

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Current smokers	217 (9.8)	27 (65.9)	79 (44.6)	86 (13.1)	25 (2.9)	0	
Past smokers	82 (3.7)	14 (34.2)	33 (18.6)	25 (3.8)	10 (1.2)	0	
Never smokers	1914 (86.5)	0	65 (36.7)	544 (83.1)	838 (96.0)	467 (100)	
Alcohol Drinking Status							<0.01
Current drinkers	241 (10.9)	34 (82.9)	86 (48.6)	92 (14.1)	29 (3.3)	0	
Past drinkers	17 (0.8)	6 (14.6)	8 (4.5)	3 (0.5)	0	0	
Never drinkers	1955 (88.3)	1 (2.4)	83 (46.9)	560 (85.5)	844 (96.7)	467 (100)	
Recreational Physical Activity							<0.01
Daily physical activity	1136 (51.3)	1 (2.4)	41 (23.2)	143 (21.8)	484 (55.4)	467 (100)	
No physical activity	1077 (48.7)	40 (97.6)	136 (76.8)	512 (78.2)	389 (44.6)	0	
Diet Habit							<0.01
Balanced intake of plant-based and animal-based foods	2067 (93.4)	37 (90.2)	128 (72.3)	598 (91.3)	837 (95.9)	467 (100)	
More plant-based foods	108 (4.9)	2 (4.9)	34 (19.2)	42 (6.4)	30 (3.4)	0	
More animal-based foods	38 (1.7)	2 (4.9)	15 (8.5)	15 (2.3)	6 (0.7)	0	
Having Medical History							
Hypertension	1646 (74.4)	34 (82.9)	132 (74.6)	502 (76.6)	649 (74.3)	329 (70.5)	0.13
Diabetes mellitus	466 (21.1)	11 (26.8)	44 (24.9)	146 (22.3)	185 (21.2)	80 (17.1)	0.12
Dyslipidemia	1033 (46.7)	25 (61.0)	80 (45.2)	312 (47)	410 (47.)	206 (44.)	0.28
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Age, years	72.3 (0.1)	69.5 (0.8)	71.6 (0.5)	72.8 (0.3)	72.2 (0.2)	72.3 (0.3)	0.01
Body Mass Index, kg/m^2	23.9 (0.1)	25.6 (0.4)	25.4 (0.2)	25.2 (0.1)	23.5 (0.1)	21.9 (0.1)	<0.01
Smoking, Pack-Year	3.8 (0.3)	30.9 (3.2)	20.5 (2.0)	4.3 (0.5)	1.1 (0.2)	0	<0.01
Alcohol Intake, g/week	10.9 (1.1)	114.3 (18.8)	73.3 (11.3)	9.7 (1.6)	2.1 (0.6)	0	<0.01
PA, MET-h/day	0.7 (0.05)	0	0	0	1.3 (0.1)	2.3 (0.1)	<0.01
C-MMSE Score	27.0 (0.1)	27.4 (0.3)	27.5 (0.2)	26.8 (0.1)	27.1 (0.1)	27.1 (0.2)	0.09
Orientation	9.7 (0.02)	9.7 (0.1)	9.8 (0.03)	9.6 (0.04)	9.7 (0.02)	9.8 (0.03)	0.03
Registration	2.9 (0.01)	3 (0)	3 (0.01)	3 (0.01)	2.9 (0.01)	2.9 (0.02)	0.41
Attention and calculation	3.6 (0.04)	3.8 (0.3)	3.8 (0.1)	3.6 (0.1)	3.6 (0.1)	3.6 (0.1)	0.52
Recall	2.4 (0.02)	2.5 (0.1)	2.4 (0.1)	2.4 (0.03)	2.4 (0.03)	2.4 (0.04)	0.79
Language	8.3 (0.1)	8.4 (0.1)	8.5 (0.1)	8.3 (0.0)	8.4 (0.0)	8.4 (0.05)	0.09

Note: [a]Participants received 1 point for each of 5 lifestyle factors if they had any of the following behaviors: never smokers, never drinking alcohol, balanced diet habit, 18.5≤ body mass index <24 kg/m^2, or take part in daily recreational physical activity, otherwise 0 for this lifestyle factor, the total healthy lifestyle factor score was calculated by adding up each lifestyle factor. Higher score means heathier overall lifestyle pattern

[b]P-value was calculated by Chi-square test for categorical variables and general linear model for continuous variables

In addition to the binary score algorithm, a weighted CHL score was generated to take into account the statistical model-derived weight for each lifestyle factor. The weight was calculated as a proportion of the beta coefficient of each factor. To the sum of the beta coefficients from all of the five lifestyle factors in the multivariable-adjusted logistic regression model [38]. The weight (i.e., the proportion multiplied by 100) for each lifestyle component was then assigned to the participant if the subject had the healthy lifestyle factor, otherwise 0 point was received. We added up the weighted scores of all five components to derive the weighted CHL score for each participant with a range from 0 to 100 points with a higher score indicating an overall healthier lifestyle. We categorized the weighted CHL score into five levels to ensure an adequate sample size for each level and similar distribution to the five categories of the CHL score.

Outcome Assessment

MCI was defined based on the score calculated from the Chinese version of Mini-Mental Status Examination (C-MMSE), which was administered face-to-face by trained physicians during the 2019 annual physical examination. C-MMSE contained 19 questions to measure cognitive function on orientation, registration, attention, calculation, recall, and language [25,41]. There were three possible answers for each question on the C-MMSE: correct, wrong and not able to answer. We coded "not able to answer" as "wrong" [25,41]. The total C-MMSE scores ranged from 0 to 30, with higher scores indicating better cognition. Given the cognitive function was closely related to the educational level, MCI cases were defined accounting for the educational level as previously described with the following criteria [42,43]: 1) C-MMSE score≤17 for participants without formal education; 2) C-MMSE score≤20 for participants with primary school; and 3) C-MMSE score≤24 for those with middle school or higher. Otherwise, participants were defined as not having an MCI.

Covariate Assessment

The main covariates of this study included demographic characteristics and medical histories [25,40,44-46]. During the physical examination, participants' height, body weight, waist circumference, pulse, body temperature, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using calibrated instruments by trained physicians based on a standard protocol. After overnight fasting, blood samples were collected from all the participants and tested for biomarkers including lipid panel, glucose, glycated hemoglobin, liver and kidney function markers and hepatitis virus. Hypertension was defined as SBP≥140 mmHg or a DBP≥90 mmHg or taking antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose higher than 7.0 mmol/L or taking antidiabetic agents. Dyslipidemia was defined as total serum cholesterol of 6.2 mmol/L or higher, or serum triglyceride of 2.3 mmol/L or higher, or low-density lipoprotein cholesterol of 4.1 mmol/L or higher, or high density lipoprotein cholesterol lower than 1.0 mmol/L or using lipid lowering agents [47].

Statistical Analysis

Continuous variables were described with means and standard errors (SEs). Categorical variables were described with numbers and percentages. The general linear model and Chi-square test were conducted to compare continuous and categorical variables across five CHL scores respectively with P values reported. The characteristics of the total population were also described. Logistic regression models were fitted to estimate the age and sex-adjusted and multivariable-adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for MCI in relation to each lifestyle factor and the CHL score with subjects possessing each unhealthy lifestyle factor and the lowest CHL score as the referents, respectively. Age, sex, personal medical history including hypertension, diabetes mellitus, dyslipidemia, and lifestyle factors were adjusted for in the multivariable-adjusted model as suggested by prior studies of this topic in the Chinese population [25,44,46]. The same analysis was carried out for the weighted CHL score. Associations between CHL or weighted CHL score and MCI stratified by each effect modifier, including age, sex, medical history of hypertension, diabetes mellitus and dyslipidemia, were conducted. Interaction between CHL score and each effect modifier was examined by adding the cross product in the multivariable-adjusted logistic model. To further examine what component of CHL influenced the CHL-MCI association most, we identified the most common lifestyle pattern for each CHL score and performed a logistic regression analysis to compare

MCI risk between subjects who had the most common lifestyle pattern for a CHL score of 2 to 5 and the subjects with the most common lifestyle for CHL score of 1 as the referent. Since diet habit was the most influential component, we calculated a CHL score excluding diet habit and calculated ORs with 95%CIs for the association between non-diet CHL score and MCI. Several sensitivity analyses were conducted. Five lifestyle factors with refined categories were used to evaluate the association between the combined lifestyle score and MCI prevalence. Smoking status was classified as never, light (<25 pack-years) and heavy (≥25 pack-years) by using the median value of pack-years among ever-smokers. Alcohol drinking was categorized as never, light (<7 drinks/week), moderate (7-14 drinks/week) and heavy (>14 drinks/week), with the cut-offs consistent with previous literature on alcohol intake and MCI risk [27]. Physical activity was grouped as never, moderate (<2.5 MET-h/day) and vigorous (≥2.5 MET-h/day), with the cut-off point chosen as the median MET-h value from all the participants. With these refined categories, we reported both the age and sex-

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adjusted and the multivariable-adjusted associations between each lifestyle and MCI, with participants who had the healthiest lifestyle factor as the respective referent. Secondly, a weight for each lifestyle category was derived based on the corresponding parameter in the multivariable-adjusted logistic model. The weight (i.e., the proportion multiplied by 100) for each lifestyle category was then assigned to the participant who belonged to this category and the total weights of five lifestyles were calculated to obtain the weighted unhealthy lifestyle score for each participant. It was further classified into five levels to calculate its association with MCI. Finally, we excluded the dietary component from this score to see if the association would substantially change. All the statistical analyses were carried out by SAS 9.4 statistical software (SAS Institute, Cary, NC). All the P-values were calculated based on two-sided tests and a P value<0.05 was considered as statistically significant.

Results

In total, 2,213 subjects participated in the survey among whom 12.3% were identified as MCI. Among the five C-MMSE component scores, the average recall score was the lowest with a mean of 2.4, while the orientation score was the highest with a mean of 9.7. In this study population, 86.5% (n=1,914) were never smokers, 88.3% (n=1,955) were never alcohol drinkers, 93.4% (n=2,067) had a balanced diet, 50.4% (n=1,115) had a normal weight, 51.3% (n=1,136) participated in daily recreational physical activity (Supplementary Table S1). According to (Table 1), participants with higher CHL scores were more likely to be females, older, leaner, engage in recreational physical activity, and have a balanced intake of plant-based and animal-based foods. Moreover, they were more likely to consume less alcohol and smoke less. However, other characteristics, including educational level, total C-MMSE score and its components, and medical histories, were not significantly different across the five CHL score groups. In the age and sex-adjusted and fully-adjusted logistic model, never smokers, never alcohol drinkers, individuals with normal BMI, balanced diet consumers, and those who took part in daily recreational physical activity showed no statistically different odds of MCI compared with their respective counterparts (all P>0.05) (Table 2). As shown in (Table 3), we combined CHL scores of 1 and 2 to form the least healthy lifestyle group to ensure adequate case number. Compared to this group, subjects with the healthiest lifestyle pattern did not have a significantly different MCI prevalence in the multivariable-adjusted model (OR=1.64, 95%CI=0.90-2.98).

Table 2: Odds of mild cognitive impairment in relation to single binary lifestyle factor.

Heathy Lifestyle Factor	Score[a]	Number of MCI Cases /Total Sample (%)[b]	Model 1[c]	Model 2[d]	Model 3[e]
Cigarette smoking	0	26/299 (8.7)	1 [Reference]	1 [Reference]	1 [Reference]
	1	247/1914 (12.9)	1.21 (0.76-1.94)	1.25 (0.76-2.04)	1.25 (0.76-2.05)
Alcohol drinking	0	29/258 (11.2)	1 [Reference]	1 [Reference]	1 [Reference]
	1	244/1955 (12.5)	0.94 (0.60-1.46)	0.88 (0.55-1.39)	0.88 (0.55-1.40)
Diet habit	0	18/146 (12.3)	1 [Reference]	1 [Reference]	1 [Reference]
	1	255/2067 (12.3)	0.90 (0.53-1.52)	0.90 (0.53-1.53)	0.90 (0.53-1.52)
BMI	0	140/1098 (12.8)	1 [Reference]	1 [Reference]	1 [Reference]
	1	133/1115 (11.9)	0.92 (0.71-1.19)	0.91 (0.70-1.18)	0.92 (0.71-1.20)
Physical activity	0	133/1077 (12.4)	1 [Reference]	1 [Reference]	1 [Reference]
	1	140/1136 (12.3)	1.13 (0.87-1.46)	1.15 (0.89-1.50)	1.15 (0.88-1.50)

Note: Abbreviation: BMI, body mass index; MCI, mild cognitive impairment

[a]Scoring algorithm is same

[b]This column refers to the proportion of MCI cases among the total sample in the respective score group of each lifestyle factor.

[c]Adjusted for age and sex.

[d]Adjusted for age, sex and other lifestyle factors including smoking status (never or ever smokers), alcohol use (never or ever alcohol drinkers), diet habit (balanced or unbalanced consumption of plant-based and animal-based foods), BMI (normal or abnormal) and daily recreational physical activity (any or none).

[e]Additionally adjusted for medical history of hypertension, diabetes mellitus and dyslipidemia.

Table 3: Odds of mild cognitive impairment in relation to the combined healthy lifestyle score.

CHL Score[a]	Number of MCI Cases/ Total sample (%)	Model 1[b]	P value	Model 2[c]	P value
1+2[d]	16/218 (7.3)	1 [Reference]	-	1 [Reference]	-
3	96/655 (14.7)	1.83 (1.03-3.24)	0.04	1.84 (1.04-3.26)	0.04
4	103/873 (11.8)	1.51 (0.86-2.68)	0.15	1.52 (0.86-2.70)	0.15
5	58/467 (12.4)	1.61 (0.88-2.93)	0.12	1.64 (0.90-2.98)	0.11
P-trend[e]		0.19		0.24	
1+2	16/218 (7.3)	1 [Reference]	-	1 [Reference]	-
3+4	199/1528 (13.0)	1.66 (0.95-2.87)	0.07	1.67 (0.96-2.89)	0.07
5	58/467 (12.4)	1.61 (0.89-2.94)	0.12	1.64 (0.90-3.00)	0.11
P-trend[e]		0.24		0.21	

Note: Abbreviation: CHL, combined healthy lifestyle; MCI, mild cognitive impairment

[a]Scoring algorithm is same as that in Table S1. Total CHL score was calculated by adding up score from each lifestyle factor

[b]Adjusted for age and sex.

[c]Adjusted for age, sex and medical history including hypertension, diabetes mellitus and dyslipidemia.

[d]We combined CHL score 1 and 2 in this category because there were very few cases out of total sample for the score group of 1(3/41) and 2 (13/177) and didn't have participants with score of 0.

[e]P-trend values were calculated using the mean values of each CHL score group as a continuous variable after confirming the linearity assumption was not violated based on the restricted cubic spline method

Table 4: Odds of mild cognitive impairment in relation to weighted combined healthy lifestyle score.

Weighted Combined Healthy Lifestyle Score[a]	Number of Cases / Total Sample (%)	Model 1[b]	P value	Model 2[c]	P value
Q1	46/452 (10.2)	1 [Reference]	-	1 [Reference]	-
Q2	60/428 (14.0)	1.16 (0.74-1.82)	0.51	1.16 (0.74-1.82)	0.51
Q3	58/446 (13.0)	1.17 (0.75-1.83)	0.48	1.18 (0.75-1.84)	0.47
Q4	51/420 (12.1)	1.15 (0.73-1.80)	0.55	1.14 (0.73-1.79)	0.57
Q5	58/467 (12.4)	1.15 (0.74-1.78)	0.54	1.16 (0.75-1.80)	0.5
P-trend[d]		0.56		0.53	
Q1+Q2	106/880 (12.1)	1 [Reference]	-	1 [Reference]	-
Q3+Q4	109/866 (12.6)	1.06 (0.79-1.44)	0.69	1.06 (0.79-1.43)	0.69
Q5	58/467 (12.4)	1.05 (0.74-1.50)	0.78	1.07 (0.75-1.52)	0.73
P-trend[d]		0.71		0.67	

Note: [a]The weight for each factor was calculated by the proportion of the β of each lifestyle factor to the sum of β from all five factors in the logistic model with all five factors and confounding factors included. The weighted CHL was calculated by adding up the weights (100*proportion) from all the factors the subject had and categorized to quintiles

[b]Adjusted for age, sex

[c]Adjusted for age, sex and medical history including hypertension, diabetes mellitus and dyslipidemia.

[d]P-trend values were calculated by using the mean value of each quintile of weighted CHL score as a continuous variable after confirming the linearity assumption was not violated.

Supplementary Table 1: Scoring algorithm of five lifestyle factors of the combined healthy lifestyle score.

Healthy Lifestyle Factors	Score	Interpretation of the Score	Proportion (%)
Cigarette smoking[a]	0	Current or past smokers	13.5
	1	Never-smokers	86.5
Alcohol drinking[b]	0	Current or past alcohol drinkers	11.7
	1	Never drinkers	88.3
Diet habit[c]	0	Unbalanced intake of plant-based and animal-based foods	6.6
	1	Balanced intake of plant-based and animal-based foods	93.4
BMI[d]	0	Abnormal weight: BMI<18.5 kg/m^2 or ≥24 kg/m^2	49.6
	1	Normal weight: 18.5≤BMI≤23.9 kg/m^2	50.4
Physical activity[e]	0	No recreational physical activity	48.7
	1	Any daily recreational physical activity	51.3

Note: Abbreviation: BMI, body mass index.

[a]Cigarette smoking status was dichotomized into never and ever smokers which included current and past smokers.

[b]Alcohol drinking status was dichotomized into never and ever alcohol drinkers which included current and past smokers.

[c]Dietary habit was defined according to the single dietary habit question from the questionnaire and we combined higher intake of animal-based foods or plant-based foods into unbalanced diet habit group.

[d]BMI was categorized to normal and abnormal level according to the Chinese optimal BMI cut-off points recommended by the Working Group on Obesity in China.

[e]This refers to recreational physical activity. Recreational physical activity was dichotomized into no or any recreational physical activity

Supplementary Table 2: Odds of mild cognitive impairment in relation to the most common lifestyle pattern for each score.

Combined Healthy Lifestyle Score[a]	Number of Cases /Total Sample (%)[b]	Score for Each Lifestyle Factorc					Model 1[d]	Model 2[e]
		Smoking	Alcohol	Diet	BMI	Physical activity		
1	2/37 (5.4)	0	0	1	0	0	1 [Reference][f]	1 [Reference][f]
2	1/40 (2.5)	0	1	1	0	0	0.33 (0.03-3.91)	0.33 (0.03-3.96)
3	60/428 (14.0)	1	1	1	0	0	1.60 (0.36-7.17)	1.60 (0.36-7.18)
4	46/389 (11.8)	1	1	1	1	0	1.42 (0.31-6.42)	1.42 (0.31-6.40)
5	58/467 (12.4)	1	1	1	1	1	1.62 (0.36-7.21)	1.61 (0.36-7.18)

Note: [a]Scoring algorithm is same

[b]This column represents the MCI case proportion among total sample for the identified most common lifestyle patten for the respective score category

[c]The score of 1 point never indicated smokers, never drinkers, balanced dietary habit, normal BMI and any daily recreational physical activity for the respective factors

[d]Adjusted for age and sex.

[e]Additionally adjusted for medical history including hypertension, diabetes mellitus and dyslipidemia.

[f]The subjects in the most common lifestyle pattern for CHL score of 1 were treated as reference

There was no significant difference in the trend of MCI across the CHL scores (P-trend=0.24). No association was found after we further grouped CHL scores of 3 and 4 into one group (OR5 vs.1+2=1.64, 95%CI=0.90-3.00, P-trend=0.21). When investigating the weighted CHL score with quintiles, there was no association identified either (ORQ5 VS. Q1=1.16, 95%CI=0.75-1.80) (Table 4). There were no associations observed between CHL or weighted CHL score and MCI in the stratified analysis by any effect modifier we examined, and no significant interaction was found (data not shown). To further explain the observed null association between combined lifestyle pattern and MCI, we investigated the most common lifestyle pattern for each CHL score. Based on the results in (Supplementary Table 2). diet habit appeared as the only lifestyle component in the most common lifestyle pattern for each CHL score. The adjusted ORs comparing each higher versus the lowest CHL score were similar to ORs comparing subjects in the most common lifestyle patterns identified for the two corresponding scores in comparison, which indicated diet might play a key role in the CHL and MCI relationship. Therefore, we investigated the MCI association with CHL score excluding the diet component. Similarly, compared to subjects with the least healthy lifestyle excusing diet, those with a healthier lifestyle were not related to MCI after adjusting for confounders (Supplementary Table 3). In the sensitivity analyses, with the refined categories of each lifestyle factor, there was no single lifestyle factor associated with MCI (Supplementary Table 4). The weighted unhealthy lifestyle score calculated based on the logistic model-derived parameters was not significantly related to MCI (Supplementary Table 5). The weighted unhealthy lifestyle score excluding diet, was not associated with MCI either (data not shown).

Supplementary Table 3: Odds of mild cognitive impairment in relation to combined healthy lifestyle score excluding diet.

Combined Healthy Lifestyle Scorea	Number of Cases / Total Sample (%)[b]	Model 1[c]	P value	Model 2[d]	P value
0	2/37 (5.4)	1 [Reference]	-	1 [Reference]	-
1	12/132 (9.1)	1.44 (0.30-6.84)	0.65	1.44 (0.30-6.86)	0.65
2	85/647 (13.1)	1.76 (0.41-7.63)	0.45	1.78 (0.41-7.71)	0.44
3	114/894 (12.8)	1.79 (0.41-7.75)	0.43	1.81 (0.42-7.83)	0.43
4	60/503 (11.9)	1.67 (0.38-7.30)	0.5	1.70 (0.39-7.45)	0.48
P-trend[e]		0.75		0.71	
0+1	14/169 (8.3)	1 [Reference]	-	1 [Reference]	-
2+3	199/1541 (12.9)	1.32 (0.72-2.39)	0.37	1.33 (0.73-2.41)	0.36
4	60/503 (11.9)	1.24 (0.65-2.35)	0.52	1.26 (0.66-2.39)	0.48
P-trend[e]		0.79		0.74	

Note: [a]Subjects received 1 point for each of 4 lifestyle factors if they were: never smokers, never alcohol drinkers,18.5≤ body mass index <24 kg/m^2, or they took part in daily recreational physical activity, otherwise 0 for corresponding lifestyle factor, the total non-diet CHL score ranged from 0 to 4 with higher score indicating healthier lifestyle.

[b]This column represents the mild cognitive impairment case proportion among total sample of respective score category

[c]Adjusted for age and sex.

[d]Adjusted for age, sex and medical history including hypertension, diabetes mellitus and dyslipidemia.

[e]P-trend was calculated using the mean values of each no-diet CHL score group as a continuous variable in the fully-adjusted model

Supplementary Table 4: Associations between each healthy lifestyle factor with refined categories and odds of MCI.

Lifestyle Factors	Subgroup	Score	Number of Cases / Total Sample (%)	Model 1[a]	Model 2[b]
Smoking[c]	Never	0	238/1861 (12.8)	1 [Reference]	1 [Reference]
	Light	1	11/123 (8.9)	0.82 (0.42-1.62)	0.82 (0.42-1.62)
	Heavy	2	12/130 (9.2)	0.98 (0.51-1.89)	0.99 (0.52-1.91)

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Alcohol drinking[d]	Never	0	239/1916 (12.5)	1 [Reference]	1 [Reference]
	Light	1	10/103 (9.7)	0.85 (0.42-1.70)	0.84 (0.42-1.68)
	Moderate	2	6/52 (11.5)	1.20 (0.49-2.93)	1.20 (0.49-2.93)
	Heavy	3	6/43 (14.0)	1.93 (0.78-4.80)	1.96 (0.79-4.88)
Dietary habit[e]	Balanced	0	243/1973 (12.3)	1 [Reference]	1 [Reference]
	Unbalanced	1	18/141 (12.8)	1.06 (0.63-1.8)	1.07 (0.63-1.82)
BMI[f]	Normal	0	126/1060 (11.9)	1 [Reference]	1 [Reference]
	Underweight	1	7/86 (8.1)	0.66 (0.29-1.48)	0.67 (0.30-1.52)
	Overweight	2	98/769 (12.7)	1.11 (0.83-1.48)	1.09 (0.81-1.46)
	Obesity	3	30/199 (15.1)	1.33 (0.85-2.07)	1.29 (0.83-2.02)
Physical activity[g]	Vigorous	0	70/578 (12.1)	1 [Reference]	1 [Reference]
	Light-to- Moderate	1	61/493 (12.4)	0.88 (0.60-1.28)	0.88 (0.60-1.28)
	None	2	130/1043 (12.5)	0.85 (0.61-1.17)	0.85 (0.61-1.17)

Note: Abbreviation: BMI, body mass index, MET, metabolic equivalent of task

[a]Adjusted for age and sex.

[b]Adjusted for age, sex, other lifestyle factors, and medical history including hypertension, diabetes mellitus and dyslipidemia.

[c]Smoking was categorized to never, light smokers (<25 pack-years), heavy smokers (≥25 pack-years) with cut-off points determined as the median of pack-years in all the ever-smokers.

[d]Light, moderate and heavy alcohol drinking levels were defined as ≤7 drinks/week, 7-14 drinks/week, and >14 drinks/week, respectively.

[e]According to the single diet question from the questionnaire, unbalanced diet habit included subjects consumed either more animal-based or plant-based foods

[f]BMI was categorized to underweight, normal, overweight and obesity defined as <18.5 kg/m^2, 18.5-23.9 kg/m^2, 24-27.9 kg/m^2, and ≥28 kg/m^2, respectively.

[g]Physical activity was categorized to vigorous level (≥2.5 MET-hours/day) and light to moderate (<2.5 MET-hours/day) and none with cut-off pints determined as the mean of total physical activity in all participants.

Supplementary Table 5: Odds of mild cognitive impairment in relation to weighted unhealthy lifestyle score.

Weighted combined unhealthy lifestyle score [a]	Number of cases / total sample (%)	Model 1[b]	P value	Model 2[c]	P value
Q1	27/249 (10.98)	1 [Reference]	-	1 [Reference]	-
Q2	51/425 (12.00)	0.97 (0.58-1.61)	0.91	0.95 (0.57-1.59)	0.85
Q3	72/588 (12.24)	0.99 (0.61-1.60)	0.96	0.98 (0.60-1.59)	0.93
Q4	68/432 (15.74)	1.26 (0.77-2.06)	0.35	1.24 (0.76-2.02)	0.4
Q5	27/423 (10.98)	0.88 (0.52-1.48)	0.63	0.87 (0.51-1.46)	0.59
P-trend[d]		0.75		0.72	
Q1+Q2	78/671 (11.62)	1 [Reference]	-	1 [Reference]	-
Q3+Q4	140/1020 (13.73)	1.13 (0.83-1.53)	0.44	1.09 (0.83-1.43)	0.56
Q5	43/423 (10.17)	0.90 (0.60-1.35)	0.6	1.12 (0.83-1.52)	0.46
P-trend[e]		0.58		0.56	

Note: [a]A weighted unhealthy lifestyle score was calculated by first deriving the proportion of the β for each category of each factor to the sum of β from all the categories of factors in the logistic model and summed up by all the five factors for an individual. Nonsmoking, non-alcohol use, balanced dietary quality, normal body weight and vigorous physical activity was used as reference category for each lifestyle factors.

[b]Adjusted for age and sex.

[c]Adjusted for age, sex and medical history including hypertension, diabetes mellitus and dyslipidemia.

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[d]P-trend was calculated by using the mean value of each quintile as the continuous variable

[e]P-trend was calculated using the mean value of Quintiles "1+2" and Quintiles "3+4" and Quintile "5" to allow for more sample size in each group.

Discussion

In this large cross-sectional study conducted in urban Shanghai with participants possessing relatively healthy lifestyles, we failed to identify a combined effect of multiple lifestyle factors on MCI occurrence. The null association was confirmed by using different scoring algorithms to calculate the CHL score and by the CHL score after removing the most influential component of diet habit, the null association was also robust in the stratified analyses. The prevalence of MCI was 12.3% in this study, which was comparable to that of 15.5% estimated from a recent large national health survey which included 46,011 participants aged 60 years and older representative of all socioeconomic and geographical regions in China [6]. In this study, 21.1% of participants possessed all five healthy lifestyles, and never-smokers, never-alcohol drinkers and balanced diet consumers made up over 80% of all the participants, respectively, representing an overall healthy profile of this study population. The low prevalence of smoking (13.5%) and alcohol use (11.7%) observed in this study was consistent with the reported rates from previous studies conducted in other urban districts in Shanghai [48-50] .which were lower than other cities of China and Western countries, partly due to heightened health awareness of Shanghai urban residents toward alcohol drinking and smoking as a result of city-wide long-term public health education as well as the strict tobacco control regulation recently adopted in first-tier cities in China. The 2016 Chinese dietary guideline has emphasized having a balanced diet as a major dietary quality indicator [34], partially explaining the high proportion of balanced diet consumers in this study [51,52].

However, the only one question regarding whether an individual had a habitual balanced intake of plant-based and animal-based foods is less sufficient to reflect an individual's overall diet quality. Our findings of no association between a single lifestyle factor and MCI were in line with some previous studies, but the associations of these lifestyles with MCI were overall inconsistent in previous literature. Studies investigating smoking and MCI among elderly participants reported both null association [53,54] and positive association [6,45,55]. While a large systematic review including 53 studies concluded a reduced risk of getting cognitive-related diseases through physical activity [20] another review pointed out the effectiveness of single-component physical activity intervention was largely insufficient so far [56]. Previous studies on the effects of different dietary patterns on cognitive impairment among older adults have also been inconsistent, evidence from dietary patterns other than Mediterranean diet was still limited [57] Obesity was found to have no association with cognitive impairment in this study. Two Chinese studies with adults' mean ages older than 65 years both indicated a significantly decreased risk of cognitive impairment with overweight, but not with obesity [11,58]. The inconsistent findings we observed in our study might be attributable to cross-sectional study design, limited sample size and MCI cases, different cut-offs to categorize lifestyle factors, and assessment methods.

Importantly, as we stated previously, our study population residing in urban Shanghai had the unique feature of a relatively homogeneously healthy lifestyle, especially on low prevalence of smoking, alcohol use and a high proportion of having a balanced diet, the inadequate contrast in these lifestyle exposures could be a key factor leading to the null associations we observed. Given that lifestyle factors are interacted with each other, we generated a combined healthy lifestyle score of five important factors to assess how a combined lifestyle pattern may impact MCI occurrence. However, we observed no association between CHL and MCI in this study, no matter which CHL score we used. In contrast, Chinese Longitudinal Healthy Longevity Survey (CLHLS) that comprised 5,716 older Chinese participants with an average age of 82 years reported a higher lifestyle score combining diet quality, tobacco use, alcohol consumption, and outdoor exercise was associated with a significantly better cognitive function assessed with MMSE [25]. In the same CLHLS genetic sub study including 6,160 oldest old subjects (mean age=90), a healthy lifestyle score calculated based on same factors as our study found that participants with intermediate and healthy lifestyle profiles were associated with 28% (95%CI=16%-38%) and 55% (95% CI=44%-64%) lower adjusted odds of cognitive impairment respectively, compared to least healthy participants [59]. In another cross-sectional study consisting of 4,579 community-dwelling Chinese individuals aged 60 years or older living in a city near Shanghai, Qian, et al. [60].

Investigated all the possible combinations of three lifestyle factors which included tea consumption, physical activity, and siesta (afternoon nap or rest) in relation to odds of cognitive impairment, which found physical activity and siesta could synergistically reduce cognitive impairment risk to the greatest extent [60]. Compared to these results, the finding of null combined lifestyle effect from our study could be due to several reasons. Firstly, the limited number of cases, especially the small number of cases in the least healthy lifestyle group, could have limited statistical power to generate significant results. Second, the lifestyles of these elderly populations living in Shanghai were relatively healthy without adequately large contrast in the exposure of interest. Third, assessing lifestyle factors based on self-reported responses and using only one crude diet habit question to assess diet may have misclassified participants. In addition, participants diagnosed with cognitive impairment or having related symptoms were more likely to have a healthier lifestyle due to more care obtained from family members and increased self-awareness, that is, reverse causality might bias the observed association towards null. Finally, our study population was younger (mean age of 72) than the previous two Chinese studies reporting the significant effect of combined lifestyle [25,59]. However, we still cannot exclude the possibility of no association in truth. The mechanisms underlying the relationship between lifestyle factors and cognitive function are not yet fully understood.

Several hypotheses have been proposed that highlight the involvement of vascular dysfunction, inflammation, oxidative stress, neurotoxic and psychosocial processes, which might be potential links between lifestyle risk factors and the vascular and neurodegenerative brain pathologies that contribute to cognitive impairment [61]. Physical activity has been associated with increased levels of brain-derived neurotrophic factors to promote cognitive function [62]. A healthy diet habit could modulate oxidative stress and chronic inflammation, maintain neuronal membrane integrity and upregulate neurotrophic factors [63] Although the mechanisms by which smoking affects cognitive decline remain unclear, smoking could influence executive function, which controls complex cognitive processes through vascular pathways, leading to periventricular and subcortical white matter lesion progression [64]. Alcohol-related brain damage can be caused by neurotoxicity, neuroinflammation and amyloid aggregation [65]. Obesity may adversely affect cognitive function through lip toxicity, insulin resistance and metabolic inflammation, leading to alterations in hippocampal structure and function [66]. However, how these lifestyles interact and exert combined biological effects to influence MCI was largely unknown. This study had several strengths. Firstly, this study provided first evidence of the combined lifestyle effect on cognitive impairment in a rapidly aging Chinese population, with participants' age range closely related to the MCI development window.

Second, our study population could well represent urban community-dwelling residents in a metropolitan city in China given nearly all the eligible subjects living in the study community participated in the study and residents in this community represent urban Shanghainese in terms of demographics and lifestyles. Moreover, the findings of all the analyses in this study were consistent. No matter which CHL score we used, i.e., either CHL score developed based on model-derived statistical weights or arbitrary scores from literature evidence, non-diet CHL score which removed diet-related information bias, or combined lifestyle score based on a more refined categorization of all lifestyles, we all consistently produced null associations between combined lifestyle pattern and MCI, supporting the null association in this study population. This study had several limitations. This study used a cross-sectional design, which precluded a causal inference. Second, the inadequate sample size with a limited number of MCI cases and a homogeneously healthy lifestyle of the study population may have resulted in a failure to detect a significant association. Future large prospective studies conducted among various populations with different lifestyle profiles are warranted to replicate our findings. Third, self-reported responses to some lifestyle questions, especially the lack of a dietary questionnaire to assess diet quality, were prone to information bias and may have biased the association. Fourth, residual confounding factors may still exist, although we adjusted for various potential confounders.

Information on sleeping, psychological factors and social support was not available in this study but was reported to be associated with cognitive function [67-69]. The use of MMSE to characterize cognitive functioning may be associated with ceiling effects and inadequate sensitivity in detecting subtle cognitive impairment [70]. Furthermore, this study was conducted among relatively healthy urban residents living in an economically developed metropolitan city in China, pointing to limitations in generalizing the study's findings to other populations. In summary, in this large cross-sectional study of an elder Chinese population living in a metropolitan city who had relatively healthy lifestyles, no association between a combined lifestyle score and MCI prevalence was identified. Future large prospective studies among populations with adequate variation in lifestyle factors and refined lifestyle measurements are warranted to replicate our findings.

Statements

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Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the ethics committee of

Shanghai Jiao Tong University School of Public Health and School of Nurse, approval number SJUPN-202103-X1. Written informed consent was obtained from all the participants in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jiali Zheng designed the study; Nannan Feng, Xiaofei Ye, Yiyi Zhang, Jiaye Gong, Xiaohong Zhang and Li Hua contributed to data collection; Ying Jin, Huiyong Cai and Feng Zhou contributed to data management; Xiaofei Ye and Yiyi Zhang conducted the data analyses; Jiali Zheng, Xiaofei Ye and Nannan Feng contributed to data interpretation. Xiaofei Ye, Jingwen Dong, Nannan Feng, Xiaonan Wang and Jiali Zheng drafted the manuscript. Jiali Zheng, Nannan Feng, Xiaofei Ye, Yiyi Zhang, Jiaye Gong, Xiaohong Zhang, Li Hua, Ying Jin, Huiyong Cai, Jingwen Dong, Xiaonan Wang, Feng Zhou revised and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from Jiali Zheng upon reasonable request.

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