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Posted Date: 4 April 2024

doi: 10.20944/preprints202404.0345.v1

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Cognitive Function, Healthy Diet, and All-Cause Mortality among Chinese Older Adults: A Longitudinal Prospective Study

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Abstract: Background: Both of cognitive decline and unhealthy lifestyle have been associated with an increased risk of mortality in older people. We aimed to investigate whether lifestyle behaviors might modify the association between cognitive function and the risk of all-cause mortality in Chinese older populations. **Methods:** The study included 5,124 individuals free of dementia in the Chinese Longitudinal Healthy Longevity Survey from 2011 to 2018. Cognitive function was measured using the Mini-Mental State Examination in 2011. A lifestyle score was calculated on the basis of five lifestyle factors including smoking, alcohol consumption, physical activity, diet and body mass index. Cox proportional hazards models were performed to examine the association between baseline cognitive function and all-cause mortality, with an interaction term of cognitive function and lifestyle score being added to the models. **Results:** During a median follow-up of 6.4 years, we documented 1,461 deaths. Both higher cognitive function (HR: 0.96; 95% CI: 0.96–0.97) and healthier lifestyle (HR: 0.92; 95% CI: 0.87–0.97) were significantly associated with a lower risk of mortality. We found that lifestyle significantly modified the association of cognitive function with mortality (P for interaction = 0.004). The inverse association between high cognitive function and mortality was more prominent among participants with healthier lifestyle. Of note, among the lifestyle scores component, diet showed a significant interaction with mortality (P for interaction = 0.003), with the protective HR of the all-cause mortality associated with higher MMSE scores was stronger among participants with healthy diets compared with unhealthy diets**. Conclusion:** Our study indicates that cognitive decline is associated with an increased risk of mortality, and such relations are modified by overall lifestyle, with healthy diet being the major contributor.

Keywords: cognitive function; healthy lifestyle; healthy diet; mortality; older adults

1. Introduction

Dementia is one of the major predictor of mortality in old age [1,2]. It is estimated that by 2050, there will be 131.5 million individuals living with dementia [3], presenting a major challenge for health care and social support systems. Cognitive as fundamental function of daily life that continuously declines with increasing age, has been shown to be the most prevalent cause of dementia [4,5]. Numerous previous prospective studies have demonstrated that lower cognitive function was associated with an increased risk of mortality in middle-aged and older populations [6–9]. Thus, the prevention and intervention of cognitive decline in older individuals is paramount for longevity and later-life quality. Fortunately, cognitive decline is potentially mutable and preventable through various established contributing factors.

Notably, emerging evidence has linked various lifestyle factors with cognitive function [10–12]. For example, population-based and experimental studies have identified a beneficial effect of

 doi:10.20944/preprints202404.0345.v1

physical activity on cognition and brain function [13,14]. In addition to dietary patterns, high nutrient adequacy has been found to be associated with better cognitive performance [15]. Previous studies have indicated that smoking, alcohol consumption and body mass index (BMI) are also related to an increased risk of cognitive decline among old people [16,17]. In addition, it is consistently reported that unhealthy lifestyle is associated with an increased risk of mortality [18–20]. Given their intertwined relationship, we hypothesized that lifestyle factors might modify the association between cognitive function and the risk of mortality. While several studies have examined associations of cognitive function, healthy lifestyle with mortality, the modification effect of healthy lifestyle on the relationship between cognition function and mortality in prospective cohorts is less investigated.

In the present prospective cohort study of older adults from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), we aimed to examine the association between cognition function and all-cause mortality, and particularly investigate the modification effects of lifestyle factors including smoking status, alcohol consumption, physical activity, diet and BMI on the association.

2. Materials and Methods

The Study Design and Participants

The CLHLS is an ongoing population-based prospective cohort study, which aimed to study determinants of healthy ageing among Chinese older adults. The survey applied a multistage, stratified cluster sampling, and conducted in randomly selected counties and cities from 23 of the 31 provinces in Mainland China. Health-related information was collected through structured questionnaires and anthropometric measurements by trained interviewers at each wave of the CLHLS. More detailed information about study design and data collection have been published previously [21–24].

The present analysis includes data cross the three recent waves, each approximately three years apart from the next, from 2011/2012 to 2018. The 2011 survey wave including 9,765 total respondents was treated as the baseline survey. In the current study, we excluded participants who were lost to follow-up or died during 2011-2014 (n=3699). In accordance with previous studies [25], older adults were defined as those aged 65 years or above. Hence, those younger than 65 years old were excluded (n=57). Moreover, participants with self-reported dementia at baseline (n=67) or those with missing values on cognitive function or lifestyle (n=818) at baseline were excluded, leaving a total of 5,124 participants in the final analysis. The detailed study flowchart of participant inclusion and exclusion is provided in the supplemental material Figure S1. Written informed consent was obtained from all participants, and ethical approval was obtained from the Research Ethics Committee of Peking University (IRB00001052–13074).

Measurement of Cognitive Function

The Mini Mental State Examination (MMSE) continues to be the most widely used instrument in assessing cognitive function [26,27]. Cognitive function was measured using the validated Chinese version of 24-item MMSE [23,28]. The 24 items covers six dimensions: (1) orientation (5 items), (2) registration (3 items), (3) naming (1 item), (4) attention and calculation (5 items), (5) recall (3 items) and (6) language (7 items), with the total score ranging from 0 to 30. A higher MMSE score indicates better cognitive function. Based on the literature [28], we treated responses of "unable to answer" as "wrong". Participants were categorized into three groups according to the total MMSE score: low ≤ 24; moderate 25–28; high ≥ 29.

Measurement of Healthy Lifestyle

A lifestyle score was constructed on the basis of five factors, including smoking status, alcohol consumption, physical activity, diet and BMI in accordance with previous studies [20,29,30]. Self-reported information on smoking status (never, former, and current), alcohol consumption (never, former, and current) and regular exercise (yes/no) were collected by trained interviewers at baseline. The participants who never smoked, never drank and exercised regularly were defined as healthy.

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Dietary consumption was assessed by self-reported diversity score according to the World Health Organization recommendations and previous research [31,32]. The respondents were asked to report their current intake frequency of various food groups including vegetables, fruits, legumes and its products, meat, fish, eggs, milk products, nuts and tea. In the analysis, participants received a score of 1 point if the response for one food group was 'almost every day', 'once per week at least' or 'once per month at least' and scored 0 point if the response was 'occasionally' or 'rarely or never'. Especially for the frequency of fruit and vegetable intake, participants scored 1 point if the response was 'almost every day', 'almost every day except in winter" or 'quite often', otherwise received a score of 0. The dietary diversity score was equal to the sum of the points for all nine food groups mentioned above. The score ranged from 0 to 9, with a higher score indicating better dietary diversity. A healthy diet was defined as the dietary diversity score at or above the mean value in accordance with previous studies [33,34]. Height and weight were measured directly by trained investigators and used to calculate BMI as weight in kilograms divided by height in meters squared. BMI was categorized as underweight (< 18.5 kg/m2), normal weight (≥ 18.5 kg/m2 and < 24.0 kg/m2), overweight (≥ 24.0 kg/m2 and < 28.0 kg/m2), or obese (≥ 28 kg/m2). We defined a healthy body weight as individuals with normal weight. Participants scored 1 point for each favorable behavior (no smoking, no alcohol consumption, regular exercise, healthy diet and normal weight), otherwise received a score of 0. The total lifestyle score ranged from 0 to 5, with a higher score indicating a healthier lifestyle. Participants were categorized into three groups according to the total lifestyle score: unhealthy ≤ 2; intermediate = 3; healthy ≥ 4.

3. Results

The outcome of interest in this analysis was all-cause mortality occurring in the 2014 and 2017/2018 waves. The participants' vital status and date of death were collected from officially issued death certificates whenever available, and otherwise through interviews with the next-of-kin. Duration of follow-up was calculated as the time from baseline to death or the censoring time depending on which occurred first.

During a median follow-up of 6.4 years, a total of 1,461 deaths were observed. We found that higher MMSE scores were significantly associated with a lower risk of mortality (Table 2). In the age- and sex-adjusted model, a 1-point increase of MMSE scores was associated with a 5% reduction in the risk of mortality (95% CI 4–5%). After further adjustment for age, sex, education, residence, marital status, living pattern, self-rated of economic status, ADL in disability, history of chronic disease (diabetes, heart diseases, cancer and stroke), and lifestyle, MMSE scores were inversely associated with the risk of mortality. The HR (95% CI) of mortality was 0.96 (0.96–0.97) for a 1-point increase of MMSE scores; and a 39% lower risk was observed in the highest quintile compared with the lowest quintile of MMSE scores (P for trend <0.001).

In addition, we found that healthier lifestyles were significantly associated with a lower risk of mortality (Table 3). In the age- and sex-adjusted model, a 1-point increase of lifestyle scores was associated with a 13% reduction in the risk of mortality (95% CI 9–17%). After further adjustment for MMSE scores and all covariates, healthy lifestyles were inversely associated with the risk of mortality. The HR (95% CI) of mortality was 0.92 (0.87–0.97) for a 1-point increase of lifestyle scores; and a 20% lower risk was observed in the group with healthy lifestyle compared with the group with unhealthy lifestyle (P for trend <0.001).

Table 2. Adjusted HRs and 95% CIs for the MMSE scores with all-cause mortality.

	MMSE scores			HR (95% CI) for 1-point increase	*P* for trend
	Low	Moderate	High		
Model 1[a]	**1.00**	0.61 (0.54-0.70)	0.49 (0.43-0.56)	0.95 (0.95-0.96)	<0.001
Model 2[b]	1.00	0.62 (0.55-0.71)	0.51 (0.44-0.58)	0.96 (0.95-0.96)	<0.001
Model 3[c]	1.00	0.72 (0.63-0.83)	0.60 (0.52-0.69)	0.96 (0.96-0.97)	<0.001
Model 4[d]	1.00	0.73 (0.64-0.83)	0.61 (0.53-0.71)	0.96 (0.96-0.97)	<0.001

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[a] Adjusted for age and sex. [b] Adjusted for age, sex, and lifestyle. [c] Adjusted for all the covariates, including age, sex, education, residence, marital status, living pattern, self-rated of economic status, ADL in disability, and history of chronic disease (diabetes, heart diseases, cancer and stroke). [d] Adjusted for lifestyle and all the covariates, including age, sex, education, residence, marital status, living pattern, self-rated of economic status, ADL in disability and history of chronic disease (diabetes, heart diseases, cancer and stroke). MMSE, Mini-Mental State Examination; HR, hazard ratio; CI, confidence interval; ADL, activities of daily living; BMI, body mass index.

Table 3. Adjusted HRs and 95% CIs for the lifestyle with all-cause mortality.

	Lifestyle			HR (95% CI) for 1-point increase	*P* for trend
	Unhealthy	Intermediate	Healthy		
Model 1[a]	1.00	0.91 (0.81-1.03)	0.69 (0.60-0.79)	0.87 (0.83-0.91)	<0.001
Model 2[b]	1.00	0.93 (0.83-1.05)	0.74 (0.65-0.85)	0.90 (0.86-0.94)	<0.001
Model 3[c]	1.00	0.95 (0.84-1.07)	0.78 (0.68-0.90)	0.90 (0.86-0.95)	<0.001
Model 4[d]	1.00	0.96 (0.85-1.08)	0.80 (0.70-0.93)	0.92 (0.87-0.97)	0.001

[a] Adjusted for age and sex. [b] Adjusted for age, sex, and MMSE scores. [c] Adjusted for all the covariates, including age, sex, education, residence, marital status, living pattern, self-rated of economic status, ADL in disability, and history of chronic disease (diabetes, heart diseases, cancer and stroke). [d] Adjusted for MMSE scores and all the covariates, including age, sex, education, residence, marital status, living pattern, self-rated of economic status, ADL in disability, and history of chronic disease (diabetes, heart diseases, cancer and stroke). MMSE, Mini-Mental State Examination; HR, hazard ratio; CI, confidence interval; ADL, activities of daily living; BMI, body mass index.

A stratified analysis was conducted according to the lifestyle scores to evaluate whether overall lifestyle modified the association between MMSE scores and the risk of all-cause mortality. We found a significant interaction between MMSE scores and lifestyle scores on the risk of mortality (P for interaction = 0.004), in which the protective HR of high MMSE scores was more evident among participants with a healthier lifestyle. The HR (95% CI) of mortality associated with 1-point increase of MMSE scores was 0.98 (0.96–0.99) among participants with a healthy lifestyle, 0.96 (0.95–0.97) among participants with an intermediate lifestyle, and 0.95 (0.93–0.96) among participants with an unhealthy lifestyle, respectively. Similar interaction patterns were observed in the analysis on the quintiles of MMSE scores (Figure 1).

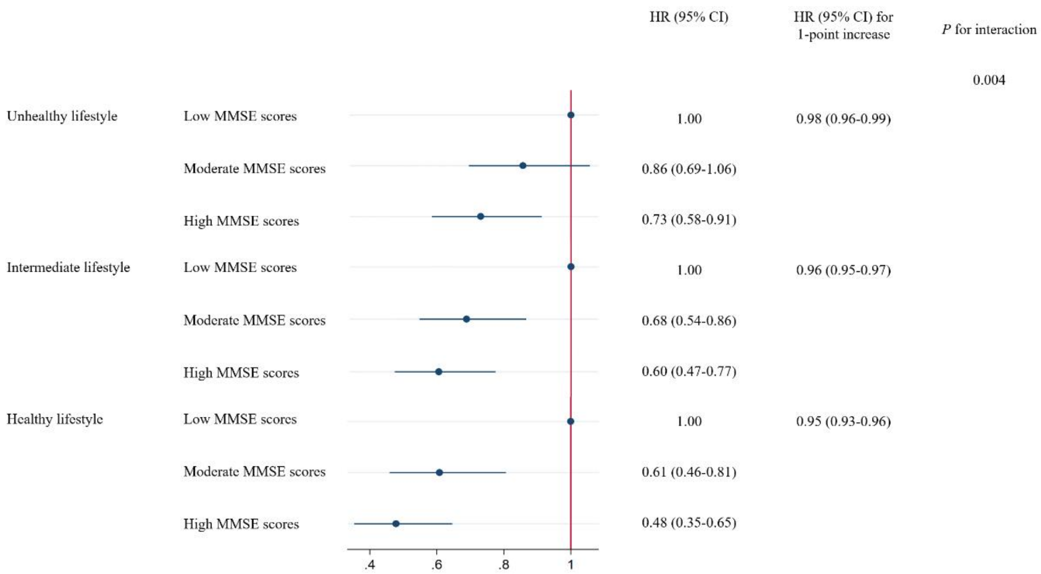

Figure 1. Associations of the MMSE scores with mortality stratified by lifestyles.—Associations between MMSE scores and all-cause mortality stratified by lifestyles. Results were adjusted for age,

sex, education, residence, marital status, living pattern, self-rated of economic status, ADL in disability, and history of chronic disease (diabetes, heart diseases, cancer and stroke). MMSE, Mini-Mental State Examination; HR, hazard ratio; CI, confidence interval.

We further tested the interaction between MMSE scores and each lifestyle behavior separately on the risk of all-cause mortality. Table S1 reported the risks of all-cause mortality by per 1-point increase in MMSE scores, stratified by five lifestyle behaviors. We found that diet showed a significant interaction with MMSE scores for mortality (P for interaction = 0.003). A 1-point higher MMSE scores showed more prominent associations with the risk of mortality among participants with healthy diet (HR 0.956 [95% CI 0.944-0.967]) than those with unhealthy diet (HR 0.969 [95% CI 0.959-0.979]). In particular, the negative HRs of mortality for quintiles 2–3 groups compared with quintile 1 group of MMSE scores were also attenuated among participants with healthier diet (Figure 2). For other lifestyle behavior, although a 1-point higher MMSE scores also showed stronger associations with the risk of mortality among participants with healthy behavior than those with unhealthy behavior, the interactions were not statistically significant.

The sensitivity analysis showed that the cognitive-lifestyle interactions remained significant on mortality after excluding participants with diabetes, heart diseases, cancer or stroke at baseline (Figure S2).

4. Discussion

Maintaining cognitive function and favorable lifestyle are essential for healthy ageing. In this prospective cohort study of the Chinese elderly, we found that both cognitive function and lifestyle were inversely associated with the risk of all-cause mortality. We also observed that overall lifestyle significantly modified the relations between cognitive function and mortality risk, with healthy die being the main contributor. The associations between cognitive decline and increased risks for mortality were attenuated in people with a healthy lifestyle, especially in those with a healthy diet.

The findings from our data suggest that low cognitive function was inversely associated with longevity in older populations, which is consistent with results from several prospective cohort studies in developed countries [7,9,38]. A previous systematic review showed that severity levels of cognitive impairment gave rise to an elevated mortality risk [39]. Similar findings of the inverse association between cognitive function and mortality was also found among the oldest-old Chinese 80 years of age and above [40]. In addition, a previous study also suggests that the faster decline of cognitive function was associated with higher mortality independent of initial cognitive function among Chinese older people [36].

In line with previous studies [19,20,41], we observed that a combination of favorable lifestyle factors is associated with a lower risk of mortality among older Chinese populations. The selection of healthy lifestyle indicators in this study has been largely guided by prior studies, as these indicators are modifiable and universal. Interestingly, we further found a significant modification effect of lifestyle scores combining the five modifiable lifestyle factors on the associations of cognitive function and mortality. Furthermore, these modification effect remained unchanged after excluding participants who had major chronic disease at baseline. The mechanisms underlying the modification effect of lifestyle on the associations between cognitive and the risk of mortality remain unclear, while our findings could be partly explained by the close relationship between lifestyle behaviors and cognitive function. Cognitive function might be associated with healthy literacy, as a consequence, people with lower cognitive function are less able to engage in a healthy lifestyle [6,42]. As the potential mechanisms of cognition-death relationships may be partly explained by health literacy, our study adds to the limited evidence examining the association between cognitive function and healthy lifestyle on all-cause mortality risk. Consistently, mounting evidence highlights the importance of healthy lifestyle in reducing the risk of cognitive decline [11,12,35,43].

Among the individual lifestyle behaviors, we found that healthy diet showed stronger interaction with cognitive function on mortality risk than other lifestyle behaviors. The finding was supported by previous studies that good dietary diversity was associated with a reduced risk of

 doi:10.20944/preprints202404.0345.v1

cognitive impairment among elderly people [31,44–46]. Even though the biological mechanism underlying the interaction was not clear, several plausible explanations have been proposed. First, good dietary diversity has been reported as a proxy indicator of nutrient adequacy [46] that can help reduce the burden of cognitive impairment [47,48]. Second, low dietary diversity is associated with enhanced oxidative stress, which would affect normal brain function and increase the risk of mild cognitive impairment [49,50]. Third, healthy food diversity is correlated with a more diverse gut microbiota [51], which may influence host cognition via the Brain–Gut–Microbiome Axis [52,53]. Further dietary intervention studies are needed to advance current understanding of the mechanistic effects of dietary modification on cognitive function and mortality.

To be noted, although no significant interaction was detected for other lifestyle behaviors, the negative association of high cognitive function with mortality appeared to be more marked among participants with normal weight, no smoking, no alcohol consumption, and regular exercise. Previous studies also showed that smoking, alcohol consumption, regular exercise, and BMI played vital roles in cognitive function [12,54,55].

The study has important implications for the development of new public health intervention strategies to improve healthy aging. To our knowledge, the study is the first to assess the interaction between cognitive function and lifestyle on all-cause mortality among Chinese older adults. More importantly, the study also adds to the limited evidence examining the modification effects of healthy diet on cognitive function and mortality risk. The findings indicate that adherence to a healthy lifestyle may attenuate the adverse association between cognitive decline and mortality risk, highlighting the importance of healthy diet for longevity among the older. These findings, if validated in intervention trials, can be taken as a new supplement to personalized health interventions.

However, the study has several limitations to be addressed. The study was conducted in the CLHLS, in which most participants were Chinese older people. Therefore, the generalizability of our results to other populations should be interpreted with caution. Additionally, unknown residual confounding might still exist even though the vast majority of measurable socio-demographic and potential health-related factors were adjusted. Furthermore, causality could not be determined because of the observational nature of this study, and further randomized clinical trials are required to confirm our findings in the ageing brain.

5. Conclusions

The longitudinal prospective study indicates that higher cognitive function is associated with a lower risk of all-cause mortality, and such relations are modified by lifestyle. Our findings highlight the importance to consider lifestyle factors in investigation of the relation between cognitive function and longevity. Our findings, if confirmed by replications, may have implications for the development of healthy aging strategies targeting improvement of cognitive function among people with unhealthy lifestyle, especially diet.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Acknowledgments: We thank the staff and the participants of the CLHLS study.

Availability of data and materials: The CLHLS questionnaires are available at http://opendata.pku.edu.cn/. The full datasets used in this analysis are available from the corresponding author upon reasonable request.

Authors' contributions: HL designed the study, analyzed and interpreted the data, and wrote the draft manuscript. MW participated in the design of the study and revised the manuscript. All authors revised and approved the final manuscript.

Ethics approval and consent to participate: The CLHLS study was approved by the Research Ethics Committee of Peking University (IRB00001052-13074), and all participants or their proxy respondents provided written informed consent.

Conflicts of Interest: The authors declare that they have no competing interests.

Abbreviations

ADL: activities of daily living; BMI: Body mass index; CI: Confidence interval; CLHLS: Chinese Longitudinal Healthy Longevity Survey; HR: Hazard ratio; MMSE: Mini-Mental State Examination.

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