Is The Association Between Cognitive Decline And Mortality Modified By High Blood Pressure Among The Oldest Old?

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Research Article

Keywords: Cognitive ageing, Epidemiology, Longevity, Hypertension, Oldest old

Posted Date: January 13th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-841728/v2>

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Abstract

Few studies have systematically explored the association between cognitive decline and mortality among the aged (above 80 years old) and also have limited evidence of the potential effect modifiers between them. Therefore, this study included 14,891 aged (mean age: 90.3 ± 7.5 years) and 10,904 aged deaths with 34,486 person-years were observed. Cognitive decline was continuous and stratified into ten categories. Potential effect modifiers were identified as age, sex, blood pressure (BP) and high BP related diseases, including hypertension and cardiovascular disease (CVD) mortality. Cox proportional hazards model was used to evaluate the relationship between them after adjusting for demographic characteristics, socioeconomic status, lifestyle factors, leisure activities and health conditions. Compared to those with maintained high normal cognitive function, participants who have declined to severe cognitive impairment from a high normal cognitive function, low normal cognitive function and mild cognitive impairment have 55%, 56% and 63% mortality risks respectively. The multivariable-adjusted model indicated that the aged with decreasing one more point in MMSE score per year, had around 4% higher risk of mortality. There was a significant association of interaction of cognitive decline-mortality and sex ($P=0.013$) as well as hypertension ($P=0.004$) but with no significant association among age ($P=0.277$), high BP ($P=0.082$), and CVD mortality ($P=0.058$). Our findings suggest that periodic screen cognitive decline and strengthen BP control may be necessary for public health.

Introduction

Cognitive decline, a clinical state between normal cognitive aging and dementia, represents a major and growing health problem worldwide [1–3]. Previous prospective studies were largely confined to the cognitive impairment-mortality relationship, but the association of cognitive decline with mortality was less reported [4–7], and many potential effect modifiers between them are still unclear.

As it stands, pieces of evidence have shown inconsistent results, which may be due to sample size, the variations in analysis strategies, and respondent characteristics such as age, sex, and ethnicity. One 9-year (mean age = 77.6) and 6-year (mean age = 82.5) longitudinal studies showed that 3-year interval cognitive decline measured by Mini-Mental State Examination (MMSE), were related with mortality in the subsequent 6-year or 3-year periods [8, 9]. However, the large confidence intervals indicated inadequate power and the association between cognitive decline with mortality might not be fully assessed in the different stages of cognitive decline due to inaccurate stratification of the median.

In addition, besides age and sex, there might be other important factors such as blood pressure (BP) and high BP related disease outcomes, including hypertension, cardiovascular disease (CVD), which might modify the association between cognitive decline with mortality, meanwhile few of them were reported [10, 11]. Notably, some studies demonstrated that the risk of cognitive impairment-mortality and cognitive decline-mortality decrease with age [8, 9, 12], which might seem counterintuitive and might mislead the public because little is known about how age modified the cognitive decline-mortality risk, especially for the aged (aged 80 and older). In addition, high BP, which affected more than 75% of persons over 75

years and led to the cause of death and disability adjusted life years worldwide, had also been identified as a risk factor for cognitive impairment and dementia [13, 14]. We therefore, formulated a hypothesis that there was the effect modification driven by high BP on the association between cognitive decline with mortality among the aged.

The first objective of the this study was to evaluate the relationship between the cognitive decline, stratified by detailed levels, and followed by mortality based on a large prospective cohort study in China. The second was aimed to assess the effect modification of BP and high BP related disease outcomes, besides age and sex, between the association cognitive decline and mortality.

Methods

Study design and participant

The Chinese Longitudinal Healthy Longevity Survey (CLHLS) is a nationwide survey with the largest sample of participants aged 80 years and above in the world.

Till recently, the program randomly selected half of the cities and counties in 23 provinces of China. It began in 1998, with subsequent follow-up and recruitment of new participants in 2000, 2002, 2005, 2008, 2011, 2014 and followed up till 2018. A more detailed description of the CLHLS has been published elsewhere [15]. The study design of CLHLS and the enrollment of participants are described in Supplementary Materials 1 and 2.

Definition Of Cognitive Decline

Cognitive decline was evaluated using the Chinese version of Mini-Mental State Examination (MMSE), a widely used cognitive test [16]. Cognitive decline was defined as a decline to a lower MMSE category between 2-3 year intervals from baseline [17]. Specifically, baseline MMSE scores were classified into four categories: severe cognitive impairment (0-17), mild cognitive impairment (18-23), low normal cognitive function (24-27) and high normal cognitive function (28-30). When high normal cognitive function declined to 0-3 scores, 4-7 scores, 8-14 scores and below 14 scores, they were defined from high normal cognitive function decline to low normal cognitive function, to mild cognitive impairment, and to severe cognitive impairment, respectively. Similarly, to decline to different stages from high normal cognitive function, there were six types of cognitive decline. Participants in the same cognitive category at both time points and those who maintained the same MMSE scores and transitioned to higher MMSE scores were categorized as maintained cognitive function. Thus, there were four types of maintained cognitive functions. Detailed division are described in Supplementary Material 3. Also, cognitive decline was defined as continuous variable according to the rate of change in MMSE score, which was calculated as the difference between at the baseline cognitive function test and the second cognitive function test divided by follow-up times ((MMSE score at baseline-MMSE score at the second cognitive function test)/the interval between two follow-ups, years).

All-cause Mortality And Cause-specific Mortality

The main outcome was all-cause mortality occurring during the follow-up survey from 1998 to 2018. Survival status was ascertained from family members or relatives of the aged during the follow-up survey in 2018 to assess whether the subjects completed the study, died and the date of death or could not be traced during follow-up. The aged who “lost to follow-up” was not be found and contacted. The aged who survived or lost to follow-up were defined as censored data. Cause-specific (CVD or non-CVD) mortality was ascertained by local doctors during the follow-up survey for deceased.

Covariates Definition

A standardized questionnaire was designed to collect data involving the following variables; demographic characteristics, socioeconomic status, lifestyle factors, leisure activities and health conditions: (1) demographic characteristics included sex (men or women) and age (as continuous variable). (2) socioeconomic status included residence (urban or rural), educational background (illiterate or not), current spouse status (have spouse or have no spouse) marry status (in marriage or not), and living pattern (with family members or not); (3) lifestyle factors included regular exercise(yes/no), current smoke status (yes/no), current drink status (yes/no), dietary diversity (DD) (yes/no); (4) leisure activities were divided into 3 categories (never, sometimes, and often) included doing housework, reading, watching TV and listening to the radio, keeping pet and growing flowers. (5) health conditions included high BP (SBP > 140mmHg or DBP > 90mmHg, yes or no), disability in ADL (yes/not), hypertension (yes or no), and respiratory disease (yes or no). More details are described in Supplementary Material 4.

Statistical analysis

This study reported the hazard ratio (HR) and 95% confidence interval (CI) using Cox proportional hazards model. Stepwise regression was used to determine the independent risk factors of mortality and the important confounders identified by previous studies. Several models were developed: model 1 adjusted for demographic characteristics; model 2 adjusted for the variables in model 1 plus socioeconomic status and lifestyle factors; and model 3 adjusted for the variables in model 2 plus leisure activities; and model 4 adjusted for the variables in model 3 plus health conditions. To exclude the co-linearity, model 4 did not include hypertension. The maintenance of high normal cognitive function was defined as the reference. Kaplan-Meier analysis was used to draw the survival curves according to cognitive status, and the survival curves were compared by the log-rank test. This study tested the suitability of the proportional risk assumption using hypothesis tests based on Schoenfeld residuals and the proportional hazards assumption was not severely violated (Supplementary Material 5, Schoenfeld P =0.08). Follow-up time in years was used as the time axis since enrollment. Additionally, the missing data was less than 1.1% for covariates and mean value imputation methods were applied to correct for the missing covariate values.

Potentially modifiable risk factors were estimated by testing for interactions between cognitive decline-all-cause mortality association and potentially modifiable factors. These modifiable factors included age, sex, BP, hypertension and CVD mortality. Age and BP were the key risk factors and the main research targets in the association between cognitive decline and all-cause mortality and so, this study explored them by cross-stratifying with age-at-enrollment and BP strata (high BP, age 80-89 years (octogenarians); high BP, age ≥ 90 years (nonagenarians); non-high BP, 80-89 years; non-high BP, age ≥ 90 years). In addition, to differentiate from previous studies, we included the younger age group (aged range: 65-79) to verify our hypothesis in appendix materials.

In the further analysis, we conducted the following various analytical strategies to check the robustness of the primary results: (1) Excluding the aged whose cognitive scores increase to a higher MMSE category (2) Stratified analyses were performed, excluding comorbidities (hypertension, heart disease or respiratory disease). (3) Excluding mortality that occurred in the first 0.5, 1 and 1.5 year, due to the possibility that the drops in cognitive performance before mortality and/or disease condition in the last year of life might influence the results. (4) Additionally, to evaluate whether the associations differ for different follow-up times and reverse causation, we stratified across time strata by median (3 years) follow-up periods.

Data analysis was conducted using R version 3.3.4 with package of “survival”. All statistical tests were 2-sided, and statistically significant was judged by *P*-values < 0.05.

Results

Baseline characteristics

Supplementary Materials 1 presents in detail the baseline characteristics of the study participants of six successive and non-overlapping cohorts categorized by detailed cognitive decline. A total of 14,791 aged were included and the mean age was 90.3 years. 10,904 aged deaths with 34,486 persons were observed in the 20-year prospective cohort study. Compared to maintain cognitive function, age tends to be older from 86.4 to 91.3, 87.9 to 92.9 and 90.1 to 93.8 with varying degrees of cognitive decline. Meanwhile, as cognitive decline to varying degrees, the aged was more likely to be female, illiterate, lived in urban, live without family members, not engage in regular exercise, be nonsmokers, be nondrinkers, poor DD, be ADL impairment, not engage in regular leisure activities, and with no high BP.

Association Between Cognitive Decline And Mortality

Table 1 showed that the risk of mortality was increased in parallel with the cognitive decline to a lower score categorized as ten categories (C0 to C9). Compared to those with maintained the high normal cognitive function, cognitive function declined to severe cognitive impairment from a high normal cognitive function, low normal cognitive function and mild cognitive impairment with HRs of 1.55 (95%CI, 1.42, 1.69), 1.56 (95%CI, 1.42, 1.72) and 1.63 (95%CI, 1.47, 1.80) respectively after adjusted demographic characteristics, socioeconomic status, lifestyle factors, leisure activities and health conditions. When

cognitive function declined to mild cognitive impairment from a high normal cognitive function and low normal cognitive function with HRs of 1.25 (95%CI, 1.14, 1.38) and 1.17 (95%CI, 1.05, 1.30).

Table 1
Association of cognitive decline with mortality after adjusting different covariates.

MMSE Score	Hazard Ratio (95% CI)			
	Model 1	Model 2	Model 3	Model 4
Baseline high normal cognitive function				
High normal, maintain function	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
High normal to low normal	1.13(1.04,1.22)	1.12(1.04,1.21)	1.10(1.02,1.19)	1.10(1.02,1.19)
High normal to mild impairment	1.30(1.18,1.42)	1.28(1.17,1.40)	1.26(1.15,1.38)	1.25(1.14,1.38)
High normal to severe impairment	1.61(1.47,1.75)	1.59(1.46,1.73)	1.54(1.41,1.68)	1.55(1.42,1.69)
Low normal, maintain function	1.16(1.08,1.25)	1.15(1.06,1.23)	1.09(1.01,1.18)	1.07(0.99,1.15)
Low normal to mild impairment	1.26(1.14,1.40)	1.25(1.13,1.39)	1.19(1.08,1.32)	1.17(1.05,1.30)
Low normal to severe impairment	1.75(1.60,1.92)	1.72(1.57,1.89)	1.60(1.46,1.76)	1.56(1.42,1.72)
Mild impairment, maintain function	1.25(1.16,1.35)	1.22(1.13,1.32)	1.15(1.06,1.24)	1.10(1.00,1.20)
Mild impairment to severe impairment	1.94(1.78,2.11)	1.89(1.73,2.07)	1.72(1.57,1.88)	1.63(1.47,1.80)
Severe impairment	1.71(1.60,1.83)	1.66(1.55,1.78)	1.50(1.40,1.61)	1.32(1.15,1.53)
Note: Model1: adjusting for demographic characteristics (sex and age); Model2: adjusting for model1 plus socioeconomic status (residence, educational background, current spouse status, marry status marriage and living pattern) and lifestyle factors (regular exercise, current smoke status, current drink status, dietary diversity (DD)); Model3: adjusting for model2 plus leisure activities (housework, reading, watching TV and listening radio, keeping pet and growing flowers); Model4: adjusting for model3 plus health conditions (high blood pressure (BP), disability in activity of daily living (ADL), and respiratory disease).				

Potential Effect Modifiers Of Cognitive Decline-mortality Association

Figure 1 illustrates the association between detailed cognitive decline and mortality, estimated in relation to modify variables (age, sex, high BP, hypertension and CVD mortality). The nonagenarians whose

baseline MMSE score declined to severe impairment from a low normal and mild cognitive impairment suffered from a higher risk of all-cause mortality with the HRs of 1.67 (95% CI, 1.47, 1.89) and 1.68 (95% CI, 1.46, 1.92) than the octogenarians with the HRs of 1.37 (95% CI, 1.16, 1.61) and 1.51 (95% CI, 1.26, 1.82), respectively. Subjects with a high BP had a substantially higher risk of mortality with 1.67 (95% CI, 1.45, 1.93), 1.74 (95% CI, 1.50, 2.02) and 1.67 (95% CI, 1.42, 1.96) than subjects without a high BP condition with 1.49 (95% CI, 1.33, 1.67), 1.46 (95% CI, 1.30, 1.67) and 1.62 (95% CI, 1.41, 1.84). The effect value of the cognitive decline-mortality association was consistent for cross-classifying the data by age and high BP condition. More detailed results were describes in Figure 1.

When cognitive decline was used as continuous variable, the mortality risk is 1.04 (95%CI, 1.04, 1.05). *P*-value of interaction for the continuous cognitive decline-mortality association among age, sex, high BP, hypertension and CVD mortality were 0.277, 0.013, 0.082, 0.004 and 0.058 (Table 2).

Table 2
The interaction effect of the association of cognitive decline, stratified by continuous categories, with mortality after adjusting fully covariates.

Subgroup	No.of patients	HR(95% CI)	P for interaction
Total	14891	1.04(1.04,1.05)	
Age			0.277
Octogenarians	7220	1.05(1.04,1.06)	
Nonagenarians	7671	1.04(1.03,1.05)	
Sex			0.013
Male	6058	1.04(1.03,1.04)	
Female	8833	1.05(1.04,1.05)	
High-BP			0.082
Yes	8589	1.05(1.04,1.06)	
No	6259	1.04(1.03,1.05)	
Hypertention			0.004
Yes	2224	1.06(1.05,1.08)	
No	12667	1.04(1.03,1.05)	
CVD mortality			0.058
Yes	783	1.05(1.04,1.07)	
No	14108	1.04(1.04,1.05)	

In addition, when we included the younger age group (aged 65-79), the statistical difference were observed with <0.05 in age groups. More details were described in Supplementary Materials 7 and 8.

Sensitivity Analysis

After excluding the increased cognitive score, our data still exhibited a robust relationship between cognitive decline and mortality (Supplementary Material 9). There was almost no change in the association when the study excluded the corresponding disease (Supplementary Material 10) and additionally excluded mortality that occurred in the first 0.5, 1 and 1.5 years (Supplementary Materials 11). When the analyses was stratified by follow-up time, the higher risks association of cognitive with mortality was observed in the continuous and ten categories for a follow-up time of more than 3 years, which was in the opposite direction of reverse causation (Supplementary Materials 12).

Discussion

In this nationally representative prospective cohort study including 14,892 aged, we found that cognitive decline was associated with an elevated risk of all-cause mortality, even at a low level of cognitive decline. In addition, our results indicated that low BP, non-hypertension and non-CVD mortality might be potentially beneficial in the cognitive decline-mortality association.

Compared with previous studies, we added new evidence that even a low degree of cognitive decline, it increased the risk of all-cause mortality. Besides, this is the first study, to our knowledge, to explore the association among the aged, stratified by octogenarians and nonagenarians, as well as the combined status of BP and high BP related symptom, illness and death. The initial research detailed the cognitive decline and explored the association between cognitive decline with mortality. However, the large confidence intervals indicate inadequate power, which might be due to small sample size ($n=322$)[8]. The latest research also found that cognitive decline measured by MMSE, was related with mortality in the subsequent 3-year period. However, rough stratification of cognitive decline by the median cannot fully assess the cognitive decline-mortality association [9]. Both researches and others indicated that the cognitive decline-mortality risk decrease with age, stratified similarly aged 65 to 79 and above aged 79 years old, which might mislead the public since they didn't further stratified above aged 79 years old. We also tried the stratification of previous research and did get consistent results (Supplementary Materials 8 and 9). Therefore, this study added new evidence that the cognitive decline-mortality risk might increase with age among the oldest old.

Alternatively, our findings suggested a less-considered mechanism on how cognitive decline might influence the all-cause mortality. The mechanisms for cognitive decline-mortality association with age remain unclear. Previous reverse association about age indicated that it might be linked more closely to an underlying disease that carried an increased mortality risk (e.g., Alzheimer's disease or cardiovascular disease) [18, 19]. This study might not exclude this hypothesis even though, the octogenarians whose baseline MMSE score declined to severe impairment from a low normal and mild cognitive impairment,

suffered from higher mortality risk than the nonagenarians and the trend were the same both in ten categories. This study is intended to suggest that cognitive decline might play a causative role or be a marker of biological ageing, leading mortality over a 20-year follow-up among the aged. Therefore, this study established that rapid decline in cognitive function might be a significant sign, combining with the occurrence of specific diseases with approach of life's end.

Additionally, this study found out that men were more sensitive than women in the association between the cognitive decline and mortality. The possible explanation was that men had more-traditional lifestyle risk factors than women, such as smoking, drinking, and physical inactivity, which contribute to both cognitive decline and all-cause mortality [20]. However, regarding sex stratification, the results of this study were not consistent with previous studies. Females whose baseline MMSE score declined to severe cognitive impairment levels from high normal cognitive function, low normal cognitive function and mild cognitive impairment had higher mortality risk than males in the ten categories and continuous cognitive decline, which might be attributed to less physically activity and emotional disorders [21, 22]. The potential reason was still unclear, and more analogous studies concerning sex and cognitive decline-mortality association were still needed to test our findings.

The higher mortality risk was observed both in older adults and high BP. One of latest result of randomized clinical trial and previous research from CLHLS reported that high BP might lead to poor cognitive function performance [10]. However, our main hypothesis was not to try to explore the etiological chain of BP in the cognitive decline-mortality association, but to explore the modification effect of BP between them. The results as expected in the aged with high BP, cognitive decline had a greater impact on the risk of mortality. There might be a concern about collider-stratification bias. Nevertheless, our results provided evidence of a cognitive decline-mortality association across strata evaluated by age and BP, suggesting that high BP predispose individuals to the adverse health effects of cognitive decline. In the further analysis, this study tried to use high BP related disease and death, including hypertension and CVD mortality, as verification. Interaction effects of the cognitive decline-mortality association were observed in hypertension and CVD mortality. According to previous hypothesis, high BP was known as a sign of increased widespread atherosclerosis and artery stiffness[23, 24], and might cause decrease perfusion of the cerebral white matter, which was one of the main risks of cognitive decline, and ultimately increase the risk for the association between cognitive decline with mortality[25, 26]. Therefore, we believe that this study might provide data support and might be confirmed for future clinical and basic research.

The strength of this study is by far the largest prospective longitudinal design investigating the association between different types of cognitive decline and all-cause mortality, including large sample size, the aged samples, survival analysis to make full use of the observed data, explore the potential effect modifiers, careful establishment and adjustment for potential risk factors, and robust sensitivity analysis results.

However, several limitations should be noted. Firstly, the MMSE was a relatively simple screening tool for cognitive decline with ceiling effect and comprehensive neuropsychological diagnosis to capture all detailed aspects of cognitive function was not available. Secondly, because cause-of-death information provided by village doctors were not based on a formal medical examinations, the records were inevitably incomplete on causes of death and comorbidities contributing to death. This study might not detect a relationship between cognitive decline and mortality among other competing causes of death, although it was adjusted for multiple factors of incident disease (including hypertension and respiratory disease) in our sensitivity analysis. Finally, this study only focused on Chinese aged. Although, it could have been generalized to include other age groups and ethnic groups, such as in western countries, the corresponding covariates were still redefined and reconsidered due to different socio-economic environment and population characteristics.

Conclusions

Cognitive decline was associated with an elevated risk of all-cause mortality among the aged, even at a low level of cognitive decline. The higher mortality risk were observed for cross-classifying of data by the aged and higher BP. Thus, it is necessary to periodical screen cognitive decline and strengthen BP control so as to carry out targeted prevention and intervention for public health.

Declarations

Acknowledgments

We are grateful to all participating people and their families. We acknowledge all staffs for their great contributions to the success of the CLHLS and the CLHLS project team for providing the shared database (<https://opendata.pku.edu.cn/dataverse/CHADS>).

Author contributions

Y.L. designed the study and revised this manuscript. J.D. conducted the literature search, the data collection, the data analysis and drafted the manuscript. NB. S. and SJ. W. revised the manuscript critically for important intellectual content.

Data and materials availability

The CLHLS is an open cohort. We can get the data from the English site <https://sites.duke.edu/centerforaging/programs/chinese-longitudinal-healthy-longevity-survey-clhls/> and the Chinese site <https://opendata.pku.edu.cn/>. In addition, if you want the data that have been cleaned, we are willing to provide it. Don't hesitate to contact the corresponding author.

Competing Interests Statement The authors declare no competing interests.

Ethics approval and consent to participate

The Protection of Human Subjects for the CLHLS was approved by the biomedical ethics committee of Peking University (IRB00001052-13074). The study was performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from all participants and/or their relatives.

Funding: This work was supported by the fund of “San-ming” Project of Medicine in Shenzhen (NO.SZSM201812088).

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Figures

Figure 1

Potential effect modifiers of the association of cognitive decline, stratified ten categories, with mortality after adjusting fully covariates.

Note: Adjusting for demographic characteristics (sex and age), socioeconomic status (residence, educational background, current spouse status, marry status marriage and living pattern), lifestyle factors (regular exercise, current smoke status, current drink status, dietary diversity (DD)), leisure activities (housework, reading, watching TV and listening radio, keeping pet and growing flowers) and health conditions (high blood pressure (BP), disability in activity of daily living (ADL), hypertension, and respiratory disease).

Cognitive decline: Ten categories(C0 to C9, compared to C0): C0: High normal cognitive function, maintain function; C1: High normal cognitive function decline to low normal cognitive function; C2: High normal cognitive function decline to mild cognitive impairment; C3: High normal cognitive function decline to severe cognitive impairment; C4: Low normal cognitive function, maintain function; C5: Low normal cognitive function decline to mild cognitive impairment; C6: Low normal cognitive function decline to severe cognitive impairment; C7: Mild cognitive impairment, maintain function; C8:Mild cognitive impairment, maintain function; C9: Sever cognitive impairment, maintain function.

Supplementary Files

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- [SupplementaryMaterials.doc](#)