



# Superoxide dismutase activity and risk of cognitive decline in older adults: Findings from the Chinese Longitudinal Healthy Longevity Survey



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## ABSTRACT

**Background:** The association between superoxide dismutase (SOD) activity and cognitive decline in older adults remains controversial.

**Objectives:** This study was designed to examine the association between plasma superoxide dismutase (SOD) activity and cognitive decline in older population.

**Method:** We analyzed the follow-up data from 2012 to 2014 waves of the Chinese Longitudinal Healthy Longevity Survey (CLHLS), a community-based longitudinal survey in Chinese longevity areas. A total of 1004 Chinese adults aged 60 years and older were included in this study. Plasma SOD activity was assessed. Cognitive function was evaluated by Mini-Mental State Examination (MMSE) in Chinese version. Modified Poisson regression was performed to investigate the association between plasma SOD activities with cognitive decline. Restricted cubic spline was performed to determine the dose-response relationship.

**Results:** Participants in the highest quartile of SOD activity had an increased risk of cognitive decline compared with those in the lowest quartile (relative risk [RR] = 1.32, 95% confidence interval [CI]: 1.00–1.74,  $P = 0.051$ ). Using cut-off points determined by Chi-square automatic interaction detector analysis (CHAID), the multivariable relative risks (RRs; 95% CI) for the lowest category, second highest, and the highest versus the third highest category of SOD activity were 0.56 (0.34–0.92), 1.26 (1.03–1.54), and 0.96 (0.70–1.31), respectively.

**Conclusions:** Higher SOD activity was associated with elevated risk of cognitive decline among Chinese older adults.

## 1. Introduction

Oxidative stress has long received considerable attention in mechanisms of various age-related diseases. Mounting evidence supports the view that oxidative stress may cause neurodegenerative diseases (Cobleby et al., 2018; Kumar et al., 2018). However, a large meta-analysis found modest evidence of pro-oxidative changes in the brains of patients with Alzheimer's Disease (Zabel et al., 2018). But it is worth noting that levels of oxidative markers in the brain do not necessarily reflect levels in the peripheral circulation. Evidence from another meta-analysis showed redox changes in peripheral blood in patients with Alzheimer's disease and mild cognitive impairment (Schrag et al., 2013). Investigating plasma biomarkers for cognitive decline and the early signs of cognitive impairment may help us better understand the mechanisms of neurodegenerative diseases and identify high-risk

populations.

Superoxide dismutase (SOD) is important in oxidative stress modulation (Sbodio et al., 2018; Bresciani et al., 2015). Based on their metal cofactors and cellular localization, SODs are classified into three isoforms: Mn-SOD/SOD2 (the manganese isoform restricted to mitochondria), SOD1 (Cu/Zn isoform distributed in the cytoplasm) and SOD3 (Cu/Zn isoform present in extracellular space). These enzymes catalyze the superoxide radical into hydrogen peroxide. Subsequently, hydrogen peroxide is converted to water and oxygen by other antioxidant enzymes including glutathione peroxidase (GPx) or catalase (CAT). Therefore, SODs are believed to reduce oxidative damage and decrease vulnerability to aging-related diseases (Dumont et al., 2009; Massaad et al., 2009; Zou et al., 2012). However, it has been found that aged mice with overexpression of SOD including Cu/Zn SOD or Mn-SOD, who have elevated SOD activity, exhibited impaired cognitive function

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(Hu et al., 2007; Lee et al., 2012; Thiels et al., 2000).

Several epidemiological studies have investigated the relationship between SOD activity and cognitive performance. The conclusions were inconsistent (Berr et al., 2004; Sánchez-Rodríguez et al., 2006; Schrag et al., 2013; Talarowska et al., 2014; Wu et al., 2014). Higher SOD activity was associated with impaired cognitive performance in a prospective study of French older adults aged 62–72 years (Berr et al., 2004), but this association was not observed among older participants in a study by Rodríguez et al. (Sánchez-Rodríguez et al., 2006). Moreover, another follow-up study (Zis et al., 2012) found that memory performance was positively associated with SOD function in patients with Down Syndrome. However, only few previous studies were based on relatively large sample sizes using prospective study design. In addition, information on the SOD activity and cognitive decline in community-based older people is scarce.

Therefore, the aim of this study was to investigate the relationship between plasma SOD activity and the risk of cognitive decline prospectively in Chinese older adults using data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), a large, prospective, community-based cohort study.

## 2. Methods

### 2.1. Study design and sample population

We conducted this study with the biomarker sub-study datasets from the CLHLS (Center for Healthy and Development, 2016; Center for Healthy and Development, 2017). This survey has been previously described in details elsewhere (Matchar et al., 2016; Zeng, 2008). Participants in the sub-study were selected from eight longevity areas: Chengmai County of Hainan Province, Laizhou City of Shandong Province, Mayang County of Hunan Province, Rudong County of Jiangsu Province, Sanshui District of Guangdong Province, Xiayi County of Henan Province, Yongfu County of Guangxi Autonomous Area, and Zhongxiang City of Hubei Province. All participants provided a written informed consent. This study was approved by the Ethics Committees of Peking University and Duke University. A total of 2423 participants aged  $\geq 60$  years were included in the baseline study performed in 2012. Follow-up assessments were conducted in 2014 (mean follow-up time is 2.0 years). Both baseline SOD activity levels and baseline Mini-Mental State Examination (MMSE) score were recorded for 2163 individuals. We excluded 492 participants because of missing baseline data on potential confounding variables. Supplementary Fig. S1 displayed missing value patterns for those variables. Among the remaining 1671 participants, 275 died during the follow-up period and 273 were lost during the follow-up. Additionally, we excluded 119 participants without MMSE scores in 2014. The final sample consisted of 1004 participants. Compared with the excluded participants ( $n = 1419$ ), included individuals were prone to be men (47.6% vs 42.6%,  $P < 0.05$ ), younger (median age 81 vs 91 years,  $P < 0.05$ ), and had higher baseline MMSE scores (median score 29 vs 26,  $P < 0.05$ ). Full details on all comparisons are shown in Supplementary Table S1.

### 2.2. Assessment of cognitive function

Cognitive function was evaluated using the Chinese version of the MMSE, which contained four domains of cognitive ability: orientation, calculation, language, and recall. Compared with the original MMSE (Folstein et al., 1975), several items in this Chinese version were modified or deleted to make interviews easier and more practical. The modified MMSE adopted in CLHLS has been previously described in details elsewhere (Lagona and Zhang, 2010; Zhong et al., 2017). According to prior studies (Zhong et al., 2017), the reliability and validity of the modified MMSE were good. MMSE scores ranged from 0 to 30 and higher scores reflected better cognition. Each item was scored 1 if the answer was correct or 0 for incorrect answer. In accordance with

prior research (Xu et al., 2017; Zhang et al., 2008), “unable to answer” was considered as an incorrect answer. As with previous studies (Llewellyn et al., 2010; Matchar et al., 2016), we defined cognitive decline as a loss of MMSE score  $\geq 3$  points.

### 2.3. Assessment of plasma SOD activity

Procedures for the collection and shipment of blood samples were described in detail elsewhere (Matchar et al., 2016). SOD activity was assayed by the xanthine/xanthine oxidase method using commercial assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). The SOD activity was expressed as International Units per milliliter plasma (IU/mL).

### 2.4. Assessment of covariates

CLHLS performed home interviews and collected demographic data including age, gender, education, smoking, alcohol use, leisure activities, and disability (limitations in daily living activities) (Lv et al., 2018). History of smoking including smoking status (current, former, and never), number of cigarettes smoked per day, and duration were also collected. Pack-years (1 pack-year = 20 cigarettes/day for 1 year) was used to quantify tobacco exposure in ever smokers, and it was categorized into never, 0–30 pack-years, and  $\geq 30$  pack-years. Home-based physical examinations were also conducted by trained medical personnel. Moreover, fasting plasma glucose, total cholesterol, 25(OH) D3, high-sensitive C reactive protein and vitamin B<sub>12</sub> were measured with standard medical and laboratory procedures. Details on assay methods were described in previous studies (Matchar et al., 2016; Yin et al., 2012). Malondialdehyde was determined by the thiobarbituric acid (TBA) method using malondialdehyde assay kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg and/or diastolic blood pressure  $\geq 90$  mm Hg. Waist circumference  $\geq 85$  cm indicated abdominal obesity for men and  $\geq 80$  cm for women (Zhou, 2002). According to prior research (Matchar et al., 2016; Yin et al., 2012), Type 2 diabetes mellitus was defined as fasting plasma glucose  $\geq 7.0$  mmol/L. Depressive symptoms were assessed with two self-assessment questions: (1). In the last 12 months, have you felt sad, blue or depressed for 2 weeks or more? (2). In the last 12 months, have you lost interest in things like hobbies, work, or activities that usually give you pleasure? Participants who had at least one positive answer were considered to have symptoms of depression.

### 2.5. Statistical analysis

Categorical variables were described as numbers and percentages, continuous data were expressed as median with interquartile range (IQR). Baseline characteristics among groups were compared with Kruskal–Wallis test or  $\chi^2$  test. Chi-square automatic interaction detector (CHAID) analysis was performed to determine the appropriate cut-off points for discretizing the SOD activity. With merging and splitting steps, CHAID subdivided the data into statistically significant homogeneous subsets based on the relationship between independent and outcome variables. As shown in Fig. 1, the cut-off points were 46.68, 61.41 and 67.28 IU/mL for SOD activity. Thus, individuals were stratified into four categories in further analyses.

The odds ratio (OR) with 95% confidence intervals (CIs) was calculated according to cut-off points mentioned above with unadjusted and adjusted logistic regression models. Besides, logistic regression was repeatedly performed with quartiles of SOD activity as cut-off points. However, the incidence of cognitive decline in our population was relatively high, so differences between the OR and relative risk (RR) might not be negligible. To avoid the possibility of exaggeration and misinterpretation of ORs (Knol et al., 2012), we used the modified Poisson regression approach (Zou, 2004), which combines the Poisson

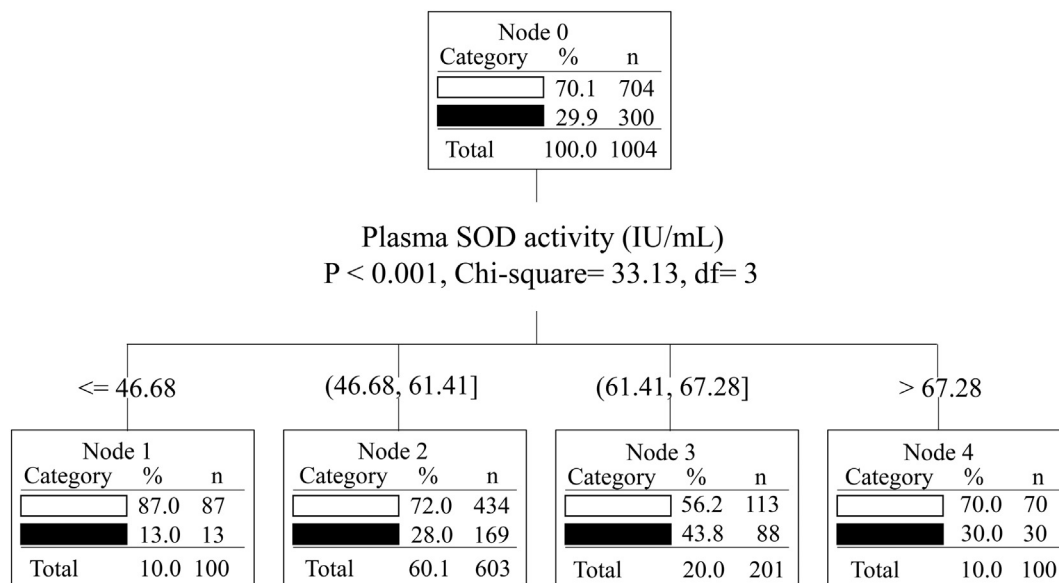


Fig. 1. Homogeneous subgroups of SOD activity from Chi-square automatic interaction detector analysis.

regression model with robust variance estimation, to estimate the RRs and 95% CIs. We performed a Hosmer–Lemeshow test to assess the fit of the logistic regression, and a Pearson Chi-Squared test for the Poisson model, in which  $P > 0.05$  was considered to denote a well-fitting model. Potentially influential observations were identified by the confidence interval displacement diagnostic (C diagnostic) ( $> 1$ ) and the DFbeta diagnostic ( $> 2$ ) as suggested (Hosmer and Lemeshow, 2000; Pregibon, 1981). Parameter estimates will be compared between the regression with all cases and the one without the potentially influential observations. Finally, we used three-knot restricted cubic splines to determine the dose-response relationship of SOD activity for the incidence of cognitive decline.

Multivariate modified Poisson regression was also performed in participants free of cognitive impairment at baseline (MMSE  $\geq 18$ ). To account for excluded observations due to missing information, we used multiple imputation by chained equations (White et al., 2011) to impute missing data five times on variables with missing values (Supplementary Fig. S1). The distributions of observed and imputed values did not differ substantially for all imputed covariates (Supplementary Table S2). For each covariate with missing data, we included all the other covariates in the imputation process to impute missing values. In order to increase the predictive power (White et al., 2011), we further included baseline red blood cell count ( $10^{12}/L$ ) and white blood cell count ( $10^9/L$ ) as predictors. All regression analyses were performed in each imputed dataset and the results were pooled according to Rubin's rules (Rubin, 2008). Following recommendations by White et al., we did not impute the outcomes in order to avoid the increase in data noise (White et al., 2011).

Besides, considering that 275 participants died, 119 participants missed MMSE tests and 273 were lost during the follow-up, to avoid the competing risk, we also performed multivariate modified Poisson regression in each extreme situation. Firstly, we conducted the analysis supposing that all of the participants who died, missed MMSE tests or were lost at follow-up developed cognitive decline and then again, but assuming that all did not develop cognitive decline. The same potential confounding factors were adjusted in all of the above multivariate logistic regression, multivariate modified Poisson regression, and restricted cubic spline models. These confounders included age, gender, years of education, baseline MMSE score, hypertension, central obesity, Type 2 diabetes mellitus, depressive symptoms, total cholesterol (mmol/L), malondialdehyde ( $\mu\text{mol}/L$ ), high-sensitive C reactive protein (mg/L), vitamin B<sub>12</sub> (pmol/L), 25(OH)D<sub>3</sub> (nmol/L), pack-years of

smoking (never, 0–30,  $\geq 30$ ), current alcohol use (yes or no), and physical activities at leisure (yes or no).

Statistical analyses were conducted by SAS 9.3 (SAS Institute, Cary, NC, USA) except for the CHAID model, which were performed with SPSS 24 (IBM Corporation, Armonk, NY, USA). Two-tailed  $P$  values  $< 0.05$  were considered statistically significant.

### 3. Results

#### 3.1. Baseline characteristics of the study participants

The baseline characteristics of study participants were compared according to the subgroups of SOD activity (Table 1). The median age of the total participants was 81 (IQR: 71–91) years and 52.4% were women. Compared with participants with lower SOD activity (category 1 and 2), those with higher level (category 3 and 4) tended to be older female participants with lower baseline MMSE scores on average and fewer years of education.

#### 3.2. Association between plasma SOD activity and risk of cognitive decline

During the follow-up assessments, 300 (29.9%) participants with cognitive decline were identified. These participants, as shown in Fig. 1, accounted for 13.0%, 28.0%, 43.8%, and 30.0% of the lowest to highest SOD activity categories, respectively. There were significant inverse associations between SOD activity and risk of cognitive decline in univariate and multivariate logistic regression models (see Supplementary Table S3). No cases had large C diagnostic and DFbeta values, which suggested that there were no potentially influential observations. Therefore, all cases were included in the reported regression model. After further verification using the modified Poisson regression, the associations were weaker but remained significant. The RRs and 95% CIs for the association between plasma SOD activity and cognitive decline are presented in Table 2. Participants in the highest quartile had an RR of 1.32 for the cognitive decline (95% CI: 1.00–1.74,  $P = 0.051$ ) compared with the lowest quartile of SOD activity. A similar trend was observed when SOD activity was categorized using cut-off points determined by the CHAID analysis. Compared with the third highest subgroup (46.68–61.41 IU/mL), the RRs of cognitive decline were 0.56 (95% CI: 0.34–0.92,  $P = 0.022$ ) for the lowest category ( $\leq 46.68$  IU/mL) of SOD activity, and 1.26 (95% CI: 1.03–1.54,  $P = 0.025$ ) for the second highest (61.41–67.28 IU/mL). However, the association was not

**Table 1**  
Baseline characteristics of the study participants<sup>a</sup>.

Characteristics	All participants	Categories of plasma SOD activity <sup>b</sup>				P value <sup>c</sup>
		1 (n = 99)	2 (n = 604)	3 (n = 201)	4 (n = 100)	
Age (years)	81 (71–91)	76 (70–84)	80 (71–89)	85 (75–98)	83 (76–92)	< 0.001
Female, n (%)	526 (52.4)	41 (41.4)	291 (48.2)	134 (66.7)	60 (60.0)	< 0.001
Years of education (years)	0 (0–4)	2 (0–5)	0 (0–5)	0 (0–3)	0 (0–3)	< 0.001
Hypertension, n (%)	562 (56.0)	62 (62.6)	327 (54.1)	115 (57.2)	58 (58.0)	0.408
Diabetes, n (%)	61 (6.1)	10 (10.1)	38 (6.3)	9 (4.5)	4 (4.0)	0.211
Central obesity, n (%)	441 (43.9)	47 (47.5)	274 (45.4)	85 (42.3)	35 (35.0)	0.215
Depressive symptoms, n (%)	78 (7.8)	9 (9.1)	53 (8.8)	9 (4.5)	7 (7.0)	0.239
Pack-years of smoking, n (%)						
Never	739 (73.6)	68 (68.7)	436 (72.2)	160 (79.6)	75 (75.0)	0.117
0–30	110 (11.0)	14 (14.1)	68 (11.3)	20 (10.0)	8 (8.0)	
≥30	155 (15.4)	17 (17.2)	100 (16.5)	21 (10.4)	17 (17.0)	
Current drinking, n (%)	172 (17.1)	18 (18.2)	117 (19.4)	22 (11.0)	15 (15.0)	0.067
Exercise at leisure, n (%)	166 (16.5)	13 (13.1)	113 (18.7)	27 (13.4)	13 (13.0)	0.157
Vitamin B <sub>12</sub> (pmol/L)	354 (250–503)	330 (248–466)	350 (248–503)	379 (259–545)	373 (245–531)	0.465
Malondialdehyde (μmol/L)	4.9 (3.9–5.9)	4.9 (3.8–5.9)	5.0 (4.0–6.0)	4.7 (3.7–5.8)	4.9 (3.8–5.7)	0.208
High-sensitive C reactive protein (mg/L)	0.8 (0.4–1.9)	0.7 (0.4–1.6)	0.8 (0.4–2.2)	0.7 (0.3–1.8)	0.6 (0.3–1.4)	0.020
25(OH)D <sub>3</sub> (nmol/L)	40.5 (29.4–54.2)	36.7 (28.9–51.9)	40.3 (29.5–52.8)	43.3 (29.5–57.6)	41.6 (29.2–56.5)	0.254
Total cholesterol (mmol/L)	4.3 (3.7–5.0)	4.4 (3.7–4.9)	4.2 (3.6–4.9)	4.4 (3.8–5.0)	4.5 (3.9–5.1)	0.054
Baseline MMSE score	29 (26–29)	29 (27–30)	29 (26–29)	28 (25–29)	28 (23–29)	0.005

SOD, Superoxide dismutase; MMSE, Mini-mental state examination.

<sup>a</sup> Data are presented as median with interquartile range for continuous variables and absolute with proportions for categorical variables.

<sup>b</sup> Category 1, 2, 3 and 4 indicates SOD activity ≤ 46.68, 46.68–61.41, 61.41–67.28 and > 67.28 IU/mL respectively.

<sup>c</sup> Kruskal–Wallis test or  $\chi^2$  test.

significant for the highest category (> 67.28 IU/mL) (RR = 0.96, 95% CI: 0.70–1.31, *P* = 0.788) versus the second category.

### 3.3. The dose-response relationship between plasma SOD activity and risk of cognitive decline

Consistent with the result displayed in Table 2, a non-linear curve was observed for the association of SOD activity with risk of cognitive decline in the analysis using restricted cubic splines (Fig. 2). There was a sharp rise in risk with increasing values of SOD activity until the value approached approximately 64 IU/mL. Beyond this value, the risk of cognitive decline became steady with increasing SOD activity.

### 3.4. Sensitivity analysis

We performed multivariate analysis in participants free of cognitive impairment at baseline (MMSE ≥ 18), which showed similar results. To avoid the competing risk, we also performed multivariate modified Poisson regression in two extreme situations: all of the participants excluded in follow-up developed cognitive decline or none developed.

**Table 2**  
Associations between SOD activity and cognitive decline.

SOD activity (IU/mL)	Events n (%)	Unadjusted modified Poisson regression		Adjusted modified Poisson regression	
		RR (95% CI)	P value	RR (95% CI)	P value
Quartiles <sup>a</sup>					
≤52.02	55 (22.0)	Reference		Reference	
52.02–57.50	63 (24.9)	1.13 (0.82–1.55)	0.443	1.05 (0.78–1.41)	0.759
57.50–62.39	84 (33.5)	1.52 (1.14–2.04)	0.005	1.17 (0.89–1.53)	0.272
> 62.39	98 (39.2)	1.78 (1.35–2.36)	< 0.001	1.32 (1.00–1.74)	0.051
Cutoff <sup>b</sup>					
≤46.68	13 (13.1)	0.47 (0.28–0.79)	0.004	0.56 (0.34–0.92)	0.022
46.68–61.41	169 (28.0)	Reference		Reference	
61.41–67.28	88 (43.8)	1.56 (1.28–1.92)	< 0.001	1.26 (1.03–1.54)	0.025
> 67.28	30 (30.0)	1.06 (0.77–1.48)	0.675	0.96 (0.70–1.31)	0.788

SOD, Superoxide dismutase.

<sup>a</sup> *P* = 0.692 for Pearson Chi-Squared test for the adjusted model.

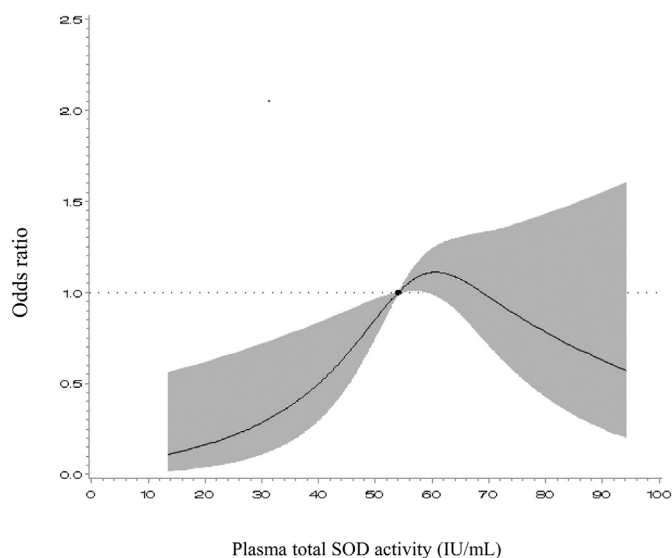
<sup>b</sup> *P* = 0.693 for Pearson Chi-Squared test for the adjusted model.

The Model 2 still showed that high SOD activity was associated with high risk of cognitive decline. However, associations were existed but weaker or even not significant in Model 3. Results of analysis conducted with multiple imputation have been presented in Model 4. Details of the results are described in Supplementary Table S4.

## 4. Discussion

In this prospective community-based study of Chinese older adults, we found that the relationship between plasma SOD activity and risk of cognitive decline was nonlinear; the risk rose with increasing SOD activity at lower values but became steady at relatively high values.

Our results are consistent with a study conducted in French older people (Berr et al., 2004). This prospective community-based study found that higher Cu/Zn-SOD activity was associated with cognitive decline but not reported ORs or RRs. In a study by Zhang et al. (Wu et al., 2014), the association between higher plasma Mn-SOD activity and cognitive impairment was observed in schizophrenia patients (*n* = 923) but not in healthy participants (*n* = 566). This may be attributed to the cross-sectional data and smaller sample size of healthy



**Fig. 2.** The relationship between SOD activity and cognitive decline using adjusted restricted cubic spline models. The reference value for each OR is the midpoint of the reference group (i.e., 54.04 IU/mL). The solid line represented estimated odds ratios and the cloud area indicated 95% CIs.

participants studied. Besides, they found that the association between cognitive impairment and plasma Mn-SOD activity in schizophrenia patients was dependent on the Mn-SOD Ala-9Val polymorphism, which requires validation in further studies. However, there was evidence supporting the association between higher SOD activity and better cognitive performance. A cross-sectional study (Sánchez-Rodríguez et al., 2006) involving community-dwelling older participants ( $n = 189$ ) reported a positive but not significant correlation between SOD activity and MMSE score.

Several mechanisms may explain the higher risk of cognitive decline associated with increased plasma SOD activity in older adults. In pre-clinical studies, transgenic mice overexpressing SODs have become a good tool for studying the relationship between SOD and brain function, whose SOD activity is several folds higher than that of wide-type mice (Maragos et al., 2000; Thiels et al., 2000). It has been shown that overexpression of Cu/Zn-SOD impaired cognitive performance in mutant mice through over-production of hydrogen peroxide. Excess hydrogen peroxide further altered the redox environment and decreased the function of *N*-methyl-D-aspartate receptor (NMDAR) (Lee et al., 2014). Moreover, the redox-mediated decrease in NMDAR function was associated with aging-related cognitive decline (Guidi et al., 2015; Kumar and Foster, 2013). In addition, it is important to note that, although increasing SOD activity may reduce oxidative damage, Lee et al. found that altered redox-sensitive signaling was more significant for age-related memory decline than the level of oxidative damage (Lee et al., 2012). Furthermore, among patients with Down Syndrome, some studies have demonstrated that symptoms of Alzheimer like dementia may be attributed to overexpression of SOD, which stems from triplification of chromosome 21 (Perluigi and Butterfield, 2011; Zana et al., 2007).

Our study has some limitations. First, the missingness problem certainly leads to considerable loss of power, but might also limit the validity of study findings. Moreover, the number of participants with high SOD activity was small, which may not provide sufficient statistical power to detect significant associations. Because of this, our non-linear model showed relatively wide confidence limits at higher levels of SOD activity. The participants were community-dwelling older people from Chinese longevity areas, which might bring some bias in estimating the incidence of cognitive decline. Additionally, the CLHLS oversampled the oldest-old, therefore, it may not be appropriate to

generalize our results to younger populations. Furthermore, the CLHLS dataset did not contain information on the APOE polymorphism, a possible confounding factor. Nevertheless, a study by Berr et al. (Berr et al., 2004), found that the association between SOD activity and cognitive decline remained similar regardless of the Apo E status. Therefore, the APOE polymorphism is expected to have little effect on our results.

In summary, this prospective study indicated that high SOD activity was associated with high risk of cognitive decline among Chinese older adults, although the risk became steady in participants with the highest SOD activity. Future prospective studies should test the non-linear relationship between SOD activity and cognition performance in a more general population of older people and determine whether the association depends on certain genotypes. Furthermore, since SOD works together with catalase and the glutathione pathways, it is essential to fully investigate the association between those antioxidant enzymes and cognitive function so that we may infer the underlying mechanism more accurately and identify more reliable biomarkers.

## 5. Statements

### 5.1. Statement of ethics

This study was approved by the Ethics Committees of Peking University and Duke University. All participants provided informed consent.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.exger.2019.01.010>.

### Conflicts of interest

None.

### Author contributions

D.Q. Sun and L.X. Tao designed this study; Y.Y. Xu and T.J. Wu prepared the data; D.Q. Sun and X.M. Sun analyzed or interpreted the data; D.Q. Sun, X.M. Sun, Y.Y. Xu, T.J. Wu and L.X. Tao drafted the manuscript. L.X. Tao made critical revisions to this paper. All authors read and approved the final manuscript.

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