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Using three statistical methods to analyze the associations between a mixture of multi-nutrients and risk of mild cognitive impairment in an elderly population in Northern China

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Few studies have considered nutrients as a mixture and their impact on Mild Cognitive Impairment (MCI). The generalized linear regression (GLM), weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) models are fitted to estimate the association between intake of a mixture of nutrients and MCI. Comparing the results from these three models, vitamin E and vitamin B6 were identified as the most important factors associated with the risk of MCI. Considering the characteristics of BKMR, it may be more advantageous to use BKMR to estimate the combined the joint effects of nutrients mixture. In the future, studies need to move from a "one nutrient at a time" approach to simultaneous analyses of multiple nutrients intakes in order to understand and quantify the joint effect of nutrients mixture on health.

Keywords Nutrients, MCI, GLM, WQS regression model, BKMR model

The aging of the population and the increasing prevalence of Alzheimer's disease (AD) have caused a huge economic and social burden[1,2]. How to prevent AD has become an important public health problem. Mild cognitive impairment (MCI) is an intermediate state between normal cognition and AD; there is no efficient therapy to prevent or slow the deterioration caused by AD[3]. Therefore, it is important to identify potential protective factors to prevent patients with MCI from further deteriorating.

Previous studies have shown that a healthy lifestyle is an important approach to preventing cognitive decline[4,5]. Diet is one of the most important modifiable risk factors and has attracted more and more attention[6,7]. For example, eating more vegetables, fruits, fish, and nuts was considered a protective factor against decline of cognitive ability[8–10]. The latest meta-analysis showed that, in cross-sectional and prospective studies, close adherence to the Mediterranean diet pattern reduced the risk of overall cognitive decline in non-dementia elderly[11]. B vitamin supplementation may delay cognitive decline in the elderly[12]. Higher serum vitamin D levels may be associated with protection against cognitive decline[13].

However, most of these studies focused on the effect of a single nutrient or a group of similar nutrients at one time. But in reality, the average person takes various nutrients simultaneously. This can lead to interactions between coadministered nutrients. Consequently, most researchers support the need to study the joint effect of common nutrients[7,11,12]. The complex diet pattern, high correlation, and complicated interactions among nutrients require a tailored strategy to assess the mixed effects of nutrients.

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In this present study, we collected data on dietary intake levels of fifteen nutrients in an elderly population in northern China who took part in Community-based Cohort Study on Nervous System Diseases (CCSNSD) from 2018 to 2019. Then we fitted the models of generalized linear regression (GLM), weighted quantile sum (WQS) regression, and Bayesian kernel machine regression (BKMR) to evaluate mixed nutrients in relation to MCI levels in an elderly population in northern China. In particular, we examined (1) whether the associations between certain nutrients and MCI levels are more pronounced than others; and (2) whether the nutrients interact with each other.

Materials and methods

Study population

We extracted our data from the CCSNSD, an ongoing longitudinal study established by the National Institute of Nutrition and Health of the Chinese Center for Disease Control and Prevention in 2018–2019, focusing on potential risk factors associated with epilepsy, Parkinson's disease and AD. The program was approved by the Institutional Review Board of the National Institute of Nutrition and Health (No. 2017020, November 6, 2017). All participants received and signed informed consent before the investigation.

We recruited the study's cohort from Hebei Province. In our analysis we included the following samples: (1) permanent residents over fifty-five years old; (2) subjects with AD without clinical diagnosis at baseline; (3) subjects free from comorbidities that could affect assessment, such as congenital or acquired intellectual disability, MCI, and visual/hearing abnormalities; and (4) subjects with basic abilities for daily living as assessed by the Activity of Daily Living Scale. We included 612 participants with complete information on sociodemographic characteristics, disease history, and physical activity status, and we obtained the results from cognitive examination, food frequency questionnaire (FFQ), psychological assessment, and physical measurement (Fig. 1).

Assessment of cognitive function

We used the Montreal Cognitive Assessment (MoCA) to evaluate cognitive function, and the total score was reflected in the overall cognitive function of participants[14]. The MoCA includes ten tests and fifty-two questions that include an alternate connection test, visual space structure (cube)/(clock), naming, repeat number width in proper/reverse sequence, alertness, continuous subtraction of seven, retell the sentence, word fluency, abstraction, and orientation. The possible scores ranged from 0 to 30 points, and thirty-two questions were scored. The higher score represented the better cognitive function. The criteria for MCI were a MoCA score of ≤ 13 for illiterate individuals, ≤ 19 for individuals with primary school, or ≤ 24 for individuals with high school or higher[15].

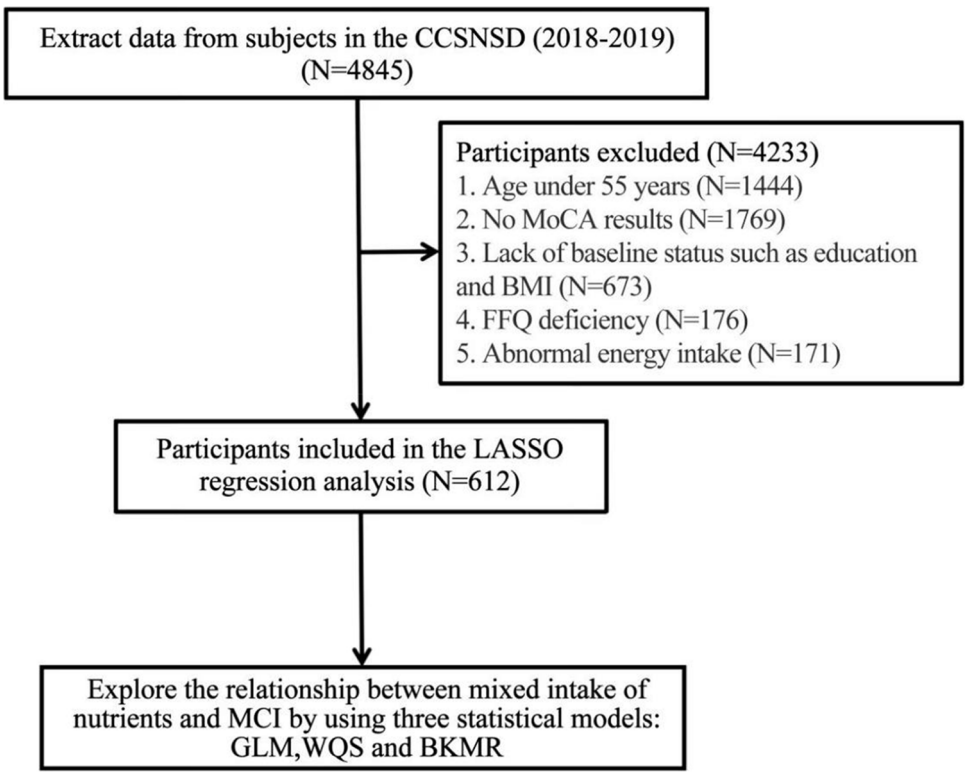

Figure 1. Selection process of subjects.

Assessment of dietary intake

A previously validated semiquantitative FFQ was used to assess diet[16]. The participants were asked about the frequency and intake of 81 food items/food groups in the past 12 months. For each item, participants were asked to specify how often they consumed food or beverages on average in the previous year. The frequency of consumption response was divided into never, < 1 time/month, 1–3 times/month, 1 time/week, 2–4 times/week, 5–6 times/week, 1 time/day, 2–3 times/day, 4–5 times/day, and ≥ 6 times/day[17]. Intake was the raw weight of the edible portion of the food consumed each time. In this study, the average daily intake of various foods obtained through FFQ survey. Energy and nutrient intake were calculated by multiplying the frequency of consumption per unit of food by the energy and nutrient content of a specified serving. The content of a certain nutrient in each food can be known through the Chinese food content database, then we can calculate the amount of a certain nutrient consumed from various foods. The total daily intake of a nutrient can be obtained by adding the nutrient intake from various foods together. In this study, the data with incomplete dietary information were excluded. Finally, the intake of 15 nutrients were calculated.

Assessment of covariates

Interviewers were required to have an undergraduate degree in medicine or public health and to have been trained by national experts and professionals. Those who passed a qualification test were appointed to collect information by questionnaires on sociodemographic and health-related factors, including age, education level (illiterate, primary school, or secondary school and above), resident area (rural or urban), current employment (yes or no), smoking (never or ever/current), alcohol intake (never or ever/current), daily energy intake (kcal), physical activity (yes or no), diabetes (yes or no), hypertension (yes or no), and BMI (< 18.5 kg/m^2, 18.50–23.9 kg/m^2, 24–28 kg/m^2, and ≥ 28 kg/m^2).

Statistical analysis

We expressed data as mean (SD) and *n* (%) for continuous variables and categorical variables, respectively. We used T-test and χ^2 test to compare the differences between groups.

We selected three methods for the present study: (1) the generalized linear regression (GLM) (2) the Least Absolute Shrinkage and Selection Operator (LASSO) regression and (3) BKMR. These methods were selected because they were suitable for use in this dateset, given that the variables are correlated (shows Fig. 2)[10,12,13].

Generalized linear regression

First, we assessed the association between individual nutrient and the risk of MCI by comparing the second, third, and fourth quartiles to the first quartile of a nutrient's level, using multivariate logistic regression as adjusted for age, gender, resident area, education level, employment status, tobacco smoking, drinking status, daily energy intake, LTPA, BMI, hypertension, and diabetes mellitus. We further fitted a logistic regression model for each micronutrient, adjusting additionally for the level of other nutrients.

Weighted quantile sum (WQS) regression

We used LASSO to select variables, then put these selected variables into WQS model to evaluate the relationship between mixed nutrients and MCI.

Least absolute shrinkage and selection operator regression Considering the multicollinearity of the multiple nutrients, LASSO regression with a logit link and the Gaussian family was used to select nutrients highly associated with MCI. The LASSO model is a shrinkage method that can actively select from a large and potentially multicollinear set of variables in the regression, leading to a more relevant and interpretable set of predictors[18]. This method uses the L1 penalty to reduce the coefficient to zero. The penalty parameter λ, also known as the tuning constant, controls the intensity of the penalty. In this study, the optimal LASSO solution was selected based on 5-fold cross-validation to minimize Root Mean Square Error, and in order to reduce biased estimates as much as possible and include as many variables as possible to reduce information loss, the cutoff value of lambda.min was selected.

Weighted quantile sum (WQS) regression The WQS regression model is a method that combines the quantile weighted score of independent variables with linear (continuous results) or logical (binary results) regression[19]. First, the value of each variable in the mixture was coded according to quantile, such as 1st, 2nd, 3rd, 4th, and the quantiles were coded as q i = 1, 2, 3, 4, respectively. By assigning a weight w i to each component of the mixture and calculating the regression coefficient β i of the weighted quantile sum index (WQS index), to assess the overall effect of variables. This method included all selected nutrients and assumed that the association between nutrients in the model and MCI had the same positive direction. By dividing different nutrients into ordered variables (quartiles), we obtained a weighted linear index representing the overall load of all nutrients through weighted calculation. The weight of each nutrient indicated the contribution of that nutrient to the overall effect. In this analysis, the function of WQS is expressed as follows:

$$g(\mu) = \beta_0 + \beta_1 \left(\sum {}^{5}_{i=0} \omega_i q_i \right) + z' \Phi$$

Where $g(\mu)$ represents any monotonic link function, μ is the predictable variable, ω is the weight of the ith components to be estimated, q_i represents the quartile of nutrient intake level (q_i =1, 2, 3, 4 represented the 1st, 2nd, 3rd, or 4th quartile, respectively), and $(\sum {}^{5}_{i=0} \omega_i q_i)$ represents the weighted quantile sum of the set of five components of interest. Furthermore, β_1 denotes the regression coefficient for the weighted quantile sum, β_0

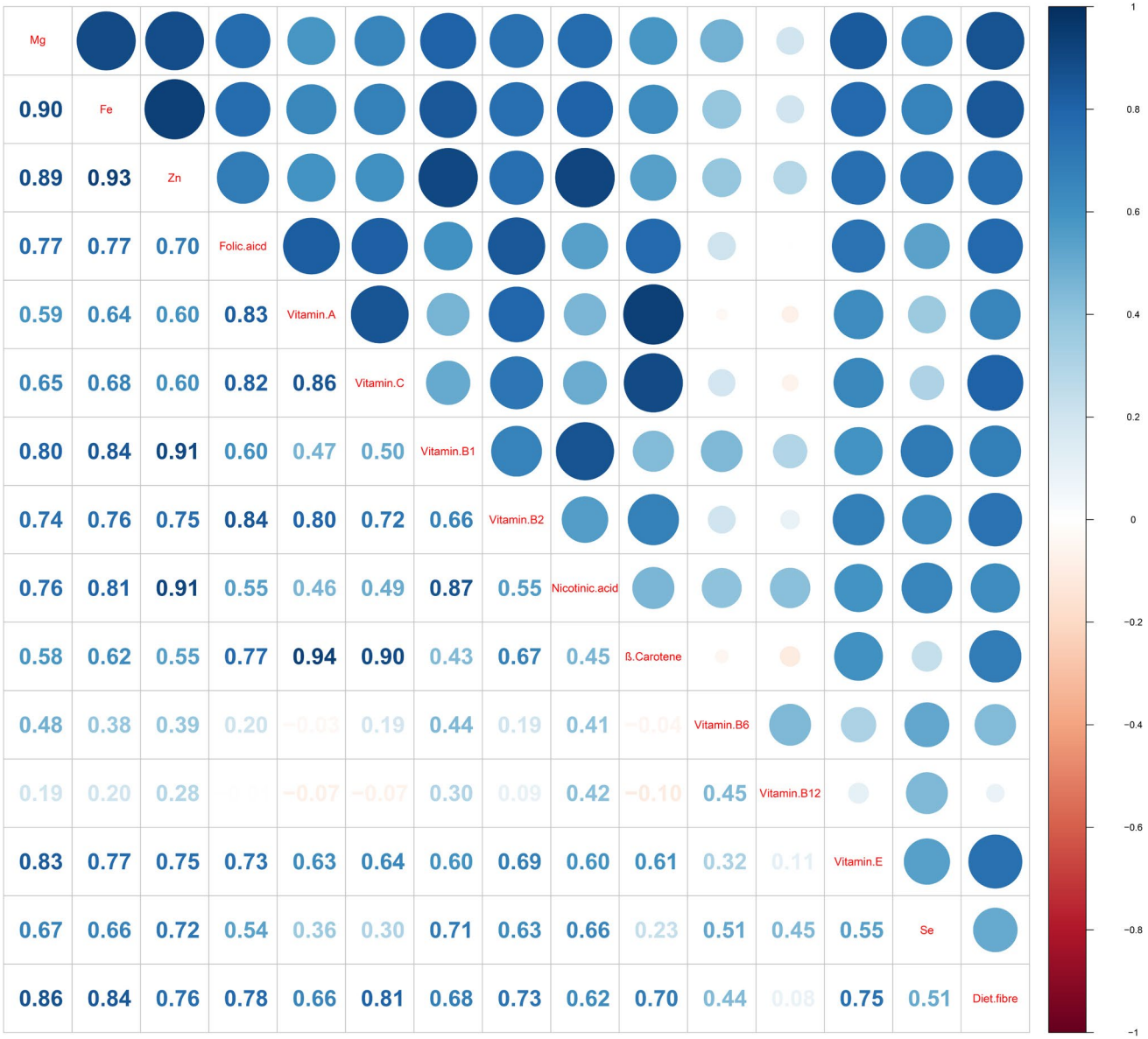

Figure 2. Pairwise Pearson correlations among intake of 15 nutrients ($N=612$). All the correlations were statistically significant ($P<0.05$), except those of folic acid and vitamin B12. Blank: $P>0.05$.

is the intercept, z' refers to the covariates, including risk factors and confounders, and Φ is the coefficient for the covariates. We estimated the weights at between 0 and 1 and added them up to 1. We divided the data into the training set (40%) and the validation set (60%); We also set β_1 to be negative. We bootstrapped the training set 10,000 times and got the estimated weights, which maximized the likelihood of the nonlinear model. In this study, we fitted two WQS models, one is an empty model and the other is adjusted for age, gender, resident area, education level, employment status, tobacco smoking, drinking status, LTPA, BMI, hypertension, and diabetes.

Bayesian Kernel Machine Regression (BKMR)

Kernel machine regression is a popular tool in machine learning, which flexibly simulates the relationship between a large number of variables to a specific result, by mapping or projecting one data sequence to another in a one-to-one manner. The BKMR model utilizes a non-parametric approach to flexibly model the association between exposures and healthy outcomes, including the nonlinear and interactions in the exposure-outcome association[20]. The model used in this study is below:

$$Y_i = h(z_i) + \chi_i \beta + e_i$$

Where Y is the health outcome, i refers to the individual ($i=1, 2, 3\ldots n$), the function $\hbar()$ is a kernel exposure-response function that accommodates interactions among the nutrients and potential nonlinear relationships between nutrients and MCI, z_i is the intake of nutrients, X_i is the potential confounders, and β represents the effect of the covariates. The residual is e_i[21].

Based on Pearson correlation coefficient values ($r>0.8$, shows Fig. 2) and their classification of nutrients, we grouped Magnesium, iron, and zinc into group 1, vitamin A, vitamin C, vitamin B2, vitamin B3, folic acid, and β carotene into group 2, vitamin B1 into group 3, vitamin B6 × 100 into group 4, vitamin B12 into group 5, vitamin E into group 6, selenium into group 7, and Diet fiber into group 8.

$$\begin{aligned} Y_i = \hbar(&\text{group1} = (\text{magnesium, iron, zinc}), \text{group2} = (\text{vitamin A,} \\ &\text{vitamin C, vitamin B2, vitamin B3, Folic acid, β carotene}), \text{group3} \\ &= (\text{vitamin B1}), \text{group4} = (\text{vitamin B6x100}), \\ &\text{group5} = (\text{vitamin B12}), \text{group6} = (\text{vitamin E}), \text{group7} \\ &= (\text{selenium}), \text{group8} = (\text{Diet fiber})) + \chi_i\beta + e_i \end{aligned}$$

Because the nutrients in our analysis were highly correlated, we conducted a hierarchical variable selection method with 10,000 iterations by a Markov chain Monte Carlo algorithm. In the hierarchical variable selection analyses of the BKMR, firstly, we calculated the group posterior inclusion probability (group PIP), which represents the importance of the mixed group for the outcome. A PIP threshold of 0.5 is usually used to determine whether it is important[22]. In other words, the mixed group(group PIP > 0.5) could be included in the model. Based on group PIP, we calculated the conditional posterior inclusion probability (cond PIP), which represented the probability that a particular chemical within the group was included in the model. In a mixed group, the nutrient with the largest cond PIP was included in the model (shows Table 5). Finally, the nutrients included in the model were iron(group 1), vitamin C(group 2), vitamin B6(group 4), vitamin E(group 6), diet fiber(group 8). The model of the hierarchical variable selection analyses is below:

$$\begin{aligned} Y_i = \hbar(&\text{group1} = \text{iron}, \text{group2} = \text{vitamin C}, \text{group4} = \text{vitamin B6}, \text{group6} = \\ &\text{vitamin E}, \text{group8} = \text{Diet fiber}) + \chi_i\beta + e_i \end{aligned}$$

All statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and R software (version 4.1.1; R Core Team). The WQS and BKMR models were implemented with R packages "gWQS" and "BKMR" respectively. Bilateral $P<0.05$ was considered statistically significant.

Approval for human experiments

Confirms that all experiments were performed in accordance with relevant named guidelines and regulations.

Results

Population characteristics

A total of 612 participants were included in this study; 253 (41.3%) were diagnosed with MCI. The characteristics of participants are shown in Table 1. The average age of the participants was 66.84 ± 7.39 years, including 260 males (42.5%) and 352 females (57.5%). Compared with non-MCI people, those with MCI were more likely to be men, living in rural areas, smokers, and doing physical exercise.

Intake of nutrients and their correlation

Fifteen nutrients were calculable in the study population. There was no statistical difference in the intake of the 15 nutrients between those at risk for MCI and those without MCI (Table 2). We found significant correlations ($P<0.05$) among 13 chemicals (Fig. 2), except for the correlation between folic acid and vitamin B12. There were positive correlation between other compounds, except for a nearly no correlation of vitamin C with vitamin B12 ($r=-0.07$), vitamin A with vitamin B6 ($r=-0.03$), vitamin A with vitamin B12 ($r=-0.07$), β carotene with vitamin B6 ($r=-0.04$), and β carotene with vitamin B12 ($r=-0.10$).

Generalized linear regression model to assess the association between levels of fifteen nutrients and MCI

In the multivariable logistic models, including all the 15 nutrients, after adjusting for all the covariates, the folic acid, vitamin E, vitamin B6, magnesium, diet fiber, and iron were found to have a significant association with the risk of MCI (fourth vs. first quartile, Model 1). Meanwhile, there were significant associations only between Vitamin B6 and MCI after additional adjustment for other levels of fifteen nutrients (OR (95% CI): 0.514(0.283,0.933)), (fourth vs. first quartile, Model 2), (Table 3).

WQS model to assess the association between levels of nutrients and MCI

LASSO regression model to assess the association between levels fifteen nutrients and MCI

Fifteen nutrients were included in LASSO regression(Fig. 3A). As shown in Fig. 3B, 0.01934 was chosen as the optimal value of λ with the minimum MSE, at which folic acid, vitamin E, vitamin B6, dietary fiber and magnesium were identified as the optimal subset of variables that can explain the relationship between 15 nutrients and MCI.

Characteristics	Total Group ($n=612$)	Non-MCI ($n=359$)	MCI ($n=253$)	*P* value
Age (years)	66.84 ± 7.39	67.14 ± 7.39	66.41 ± 7.39	0.898
Gender; n(%)				0.048
Male	260(42.5)	142(39.6)	118(46.6)	
Female	352(57.5)	217(60.4)	135(53.4)	
Daily energy intake(kcal)	1369.42 ± 344.67	1384.65 ± 335.10	1347.81 ± 357.36	0.193
Resident area; n(%)				<0.001
Urban	166(21.7)	124(34.5)	42(16.6)	
Rural	466(72.9)	235(65.5)	211(83.4)	
Education level; n(%)				
Illiteracy	172(28.1)	113(31.5)	59(23.3)	0.081
Primary school	193(31.5)	106(29.5)	87(34.4)	
Junior high school/above	247(40.4)	140(39.0)	107(42.3)	
Employment n(%)				0.39
No	533(87.1)	311(86.6)	222(87.7)	
Yes	79(12.9)	48(13.4)	31(12.3)	
Tobacco Smoking; n(%)				<0.001
No	506(82.7)	314(87.5)	192(75.9)	
Yes	106(17.3)	45(12.5)	61(24.1)	
Alcohol Drinking; n(%)				0.115
No	561(91.7)	333(92.8)	228(90.1)	
Yes	51(8.3)	26(7.2)	25(9.9)	
LTPA; n(%)				0.012
No	408(63.0)	226(71.9)	182(66.7)	
Yes	204(37.0)	133(28.1)	71(33.3)	
BMI; (kg/m^2)	24.91 ± 3.75	25.28 ± 3.75	24.37 ± 3.68	0.06
Hypertension; n(%)				0.07
No	245(40.0)	153(36.4)	92(42.6)	
Yes	367(60.0)	206(63.6)	161(57.3)	
Diabetes; n(%)				0.061
No	517(84.5)	296(82.5)	221(87.4)	
Yes	95(15.5)	63(17.5)	32(12.6)	

Table 1. Characteristics of the participants. Note: LTPA, leisure-time physical activity.

WQS model to assess the association between levels of nutrients and MCI

We used the WQS model to further explore the relationship between the overall effect of five nutrients(selected by LASSO) and MCI. The results showed that the overall mixing effect of the five nutrients was significantly negatively associated with MCI, regardless of whether the covariates were adjusted, Model 1: OR = 0.788, 95% CI: (0.628, 0.989), Model 2: OR = 0.756 95% CI: (00.541, 0.976) (Table 4). Regardless of whether the covariates were adjusted, the results showed that vitamin E, magnesium, and vitamin B6 had a greater influence on MCI in both models, although the order of their weights had changed (Fig. 4A and B). In addition, we found that the weights of folic acid and dietary fiber were relatively small.

BKMR model to assess the association between levels of fifteen nutrients and MCI

Show the Supplementary material for details.

The hierarchical variable selection analyses of the BKMR

In the hierarchical variable selection analyses, the group-PIP for eight groups were 0.58, 0.56, 0.627, 0.45, 0.5, 0.36, 0.57, 0.47, and 0.73 respectively, providing evidence that one of the nutrients within each group should be included according to the criteria of overall posterior probability ≥ 0.5. The conditional-PIP further indicated that iron (PIP = 0.39), vitamin C (PIP = 0.38), vitamin B6 (PIP = 1.00), vitamin E (PIP = 1.00), and Diet fiber (PIP = 1.00) had the highest PIPs within each group and were then selected as significant nutrients associated with MCI (Table 5).

Joint effect (95% CI) of the five nutrients on MCI in the hierarchical variable selection analyses of the BKMR

The five variables selected by the hierarchical variable selection analyses were included in the BKMR model for analysis. The overall effect between the five nutrients and MCI is shown in Fig. 5. Although credible intervals were wide, however, We can see that the risk of MCI decreases with the level of nutrients intake, when all metabolites are at or above their sixtieth percentile, compared to when all metabolites are at their median value.

Elements	Total Group $n=612$	Whether MCI		P value
		NO($n=359$)	YES($n=253$)	
Iron(Fe)	16.29 ± 4.64	16.60 ± 4.57	15.85 ± 4.72	0.897
Zinc(Zn)	7.37 ± 2.00	7.48 ± 1.98	7.21 ± 2.02	0.774
Magnesium(Mg)	222.25 ± 69.35	228.47 ± 69.91	213.41 ± 67.11	0.397
Folic acid	123.50 ± 48.83	127.04 ± 49.38	118.47 ± 47.68	0.632
vitamin A	508.67 ± 293.26	512.80 ± 286.75	502.82 ± 302.74	0.227
vitamin C	61.20 ± 41.31	62.50 ± 40.00	59.37 ± 43.13	0.21
vitamin B2	0.70 ± 0.23	0.70 ± 0.23	0.69 ± 0.23	0.483
vitamin B3	9.17 ± 2.82	9.33 ± 2.78	8.93 ± 2.86	0.776
β carotene	1965.06 ± 1543.10	2005.16 ± 1496.13	1908.18 ± 1608.68	0.152
vitamin B1	0.76 ± 0.23	0.77 ± 0.23	0.74 ± 0.23	0.591
vitamin B6 × 100	7.47 ± 3.21	7.76 ± 3.28	7.05 ± 3.06	0.215
vitamin B12	0.25 ± 0.15	0.25 ± 0.15	0.25 ± 0.15	0.966
Vitamin E	12.17 ± 4.91	12.57 ± 11.59	11.59 ± 4.85	0.957
Selenium(Se)	41.42 ± 11.73	42.16 ± 12.37	40.38 ± 10.69	0.065
Diet fiber	9.44 ± 3.51	9.73 ± 3.44	9.02 ± 3.57	0.582

Table 2. Intake of nutrients in the study population.

The trends of intake-response functions of the five nutrients in the hierarchical variable selection analyses of the BKMR

When all the other nutrients were at their median levels vitamin E, vitamin B6, and dietary fiber showed decreasing associations with MCI, whereas vitamin C showed a inverse relationship and iron showed a U-shaped relationship with MCI (Fig. 6).

Joint effects of bivariate on MCI in the hierarchical variable selection analyses of the BKMR

In the hierarchical variable selection analyses of the BKMR, The pairwise interactions among the significant nutrients (iron, vitamin C, vitamin B6, vitamin E, and diet fiber), which visualized how one micronutrient modifies the effect of the other on MCI were shown in Fig. 7. A potential interaction between diet fiber and iron was detected, with the associations between diet fiber and MCI being weaker at higher levels of iron (cell: row 2, column 1). The associations between diet fiber and MCI were stronger at lower levels of vitamin C (cell: row 4, column 1). The U-shaped relationship between iron and MCI being more visible at higher levels of vitamin B6, vitamin E(cell: row 3, column2 / cell: row 5, column2), however, vitamin C is the opposite (cell: row 4, column 2). The protective effect of vitamin B6 on MCI and the impact of vitamin C on MCI was enhanced when iron intake was fixed at 50% (cell: row 2, column3 / cell: row 2, column4). The intake-response curves for some other pairs (e.g., dietary fiber–vitamin B6, dietary fiber–vitamin E, iron–dietary fiber, vitamin C–dietary fiber) were not perfectly parallel, but showed less empirical evidence of interaction. For other pairs (e.g., vitamin B6–vitamin C, vitamin B6–vitamin E, vitamin C–vitamin E), the curves were parallel, suggesting no evidence of interaction (Fig. 7).

Discussion

We divide our statistical analysis of the health effects of mixtures into three aspects: dimension reduction, variable selection, and smooth curve fitting. We first fitted a traditional generalized linear regression model, then we further used the WQS and BKMR models, which have been recently developed to analyze the effects of mixtures on health.

The results of GLM showed that without considering the interaction between nutrients, the intake level of folic acid, vitamin E, vitamin B6, magnesium, dietary fiber, and iron were significantly negatively correlated with MCI, which was consistent with previous reports[12,23,24]. However, after adjusting other nutrients, we found that only vitamin B6 was significantly correlated with MCI, which may due to the collinearity or interactions between the nutrients.

In the LASSO regression analysis using 5-fold cross-validation, folic acid, vitamin E, vitamin B6, dietary fiber and magnesium were identified as the optimal subset of variables that can explain the relationship between 15 nutrients and MCI. The WQS regression model empirically obtains the the distribution of nutrients' weights based on the bootstrap resampling process to evaluate their effects on the body[25], which can well explain the complex effect of multiple nutrients on the body. In this study, both models showed that vitamin E, vitamin B6, and magnesium had larger weightings to MCI. However, after covariates adjustment, we found that the ranking of their weights had changed greatly. A possible reason may be that the WQS model assumes that there is no interaction between the included chemicals. Another reason may be that WQS cannot simultaneously evaluate the combined effects of chemicals with different action directions[19]. In the WQS model, we defined the effects of five nutrients on MCI as same protective effects, but In the previously published literature, the effects of vitamin E and magnesium on MCI are inconsistent[26–31]. In addition, we found that, contrary to previously reported results, folic acid had little effect on MCI in the WQS model, possibly due to a strong interaction[15]. The

Elements	Quartile1	Quartile 2		Quartile3		Quartile4	
		OR(95%CI)	*P* value	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Folic acid							
Model 1	Ref	0.676(0.414,1.102)	0.117	0.607(0.368,1.001)	0.05	0.578(0.350,0.953)	0.032
Model 2	Ref	0.798(0.471,1.352)	0.402	0.838(0.445,1.579)	0.584	0.881(0.406,1.916)	0.75
Vitamin E							
Model 1	Ref	0.951(0.588,1.538)	0.836	0.418(0.247,0.707)	0.001	0.487(0.286,0.827)	0.008
Model 2	Ref	1.026(0.590,1.784)	0.928	0.470(0.240,0.920)	0.028	0.550(0.240,1.261)	0.158
Vitamin B6							
Model 1	Ref	0.883(0.541,1.439)	0.617	0.588(0.353,0.980)	0.041	0.487(0.280,0.848)	0.011
Model 2	Ref	0.862(0.525,1.415)	0.556	0.606(0.360,1.020)	0.06	0.514(0.283,0.933)	0.029
Magnesium							
Model 1	Ref	0.770(0.473,1.255)	0.295	0.515(0.301,0.882)	0.016	0.411(0.231,0.734)	0.003
Model 2	Ref	0.880(0.495,1.564)	0.662	0.681(0.309,1.501)	0.34	0.618(0.219,1.746)	0.364
Diet fiber							
Model 1	Ref	0.647(0.391,1.070)	0.09	0.475(0.279,0.809)	0.006	0.473(0.247,0.816)	0.007
Model 2	Ref	0.306(0.426,1.307)	0.747	0.645(0.316,1.317)	0.645	0.713(0.291,1.746)	0.731
Iron(Fe)							
Model 1	Ref	0.647(0.388,1.079)	0.095	0.664(0.388,1.135)	0.134	0.415(0.227,0.758)	0.004
Model 2	Ref	0.667(0.3,1.482)	0.32	0.765(0.27,2.162)	0.613	0.546(0.146,0.146)	0.369
Zinc(Zn)							
Model 1	Ref	0.907(0.552,1.49)	0.7	0.915(0.535,1.563)	0.744	0.6(0.331,1.087)	0.092
Model 2	Ref	1.773(0.716,4.391)	0.216	2.502(0.707,8.858)	0.155	2.135(0.45,10.139)	0.34
Selenium(Se)							
Model 1	Ref	0.91(0.554,1.497)	0.711	0.896(0.531,1.512)	0.681	0.716(0.411,1.246)	0.237
Model 2	Ref	0.867(0.471,1.595)	0.646	0.94(0.469,1.884)	0.862	0.883(0.382,2.044)	0.772
Vitamin A							
Model 1	Ref	0.949(0.583,1.543)	0.831	0.74(0.453,1.21)	0.23	0.955(0.587,1.554)	0.853
Model 2	Ref	1.646(0.731,3.707)	0.229	2.402(0.721,8.004)	0.154	2.609(0.585,11.642)	0.209
Vitamin C							
Model 1	Ref	0.9(0.553,1.464)	0.672	0.63(0.382,1.039)	0.07	0.785(0.479,1.286)	0.336
Model 2	Ref	1.185(0.552,2.544)	0.664	1.252(0.458,3.422)	0.662	1.594(0.487,5.218)	0.441
Vitamin B1							
Model 1	Ref	0.949(0.572,1.576)	0.841	0.788(0.464,1.341)	0.38	0.569(0.313,1.035)	0.065
Model 2	Ref	1.204(0.592,2.447)	0.608	1.02(0.421,2.474)	0.965	0.742(0.242,2.281)	0.603
Vitamin B2							
Model 1	Ref	0.853(0.52,1.398)	0.527	0.763(0.459,1.268)	0.297	0.92(0.553,1.53)	0.747
Model 2	Ref	1.19(0.565,2.509)	0.647	1.375(0.515,3.667)	0.525	2.041(0.666,6.256)	0.212
Vitamin B12							
Model 1	Ref	1.096(0.681,1.765)	0.705	1.043(0.63,1.727)	0.869	1.212(0.728,2.016)	0.46
Model 2	Ref	1.323(0.752,2.327)	0.331	1.421(0.782,2.581)	0.249	1.443(0.735,2.832)	0.287
Vitamin B3							
Model 1	Ref	0.616(0.371,1.022)	0.061	0.89(0.526,1.506)	0.665	0.579(0.324,1.034)	0.065
Model 2	Ref	0.591(0.27,1.294)	0.188	0.99(0.369,2.657)	0.984	0.875(0.267,2.861)	0.825
β carotene							
Model 1	Ref	0.904(0.559,)	0.68	0.533(0.324,0.879)	0.014	0.807(0.498,1.307)	0.383
Model 2	Ref	0.918(0.442,1.904)	0.817	0.46(0.153,1.384)	0.167	0.518(0.127,2.117)	0.36

Table 3. Adjusted odds ratios [95% CI] for MCI according to the quartiles of fifteen nutrient intakes. Model 1 was adjusted for age, gender, resident area, education level, employment status, tobacco smoking, drinking status, LTPA, BMI, daily energy intake, hypertension, and diabetes mellitus. Model 2 was additionally adjusted for intake of other nutrients.

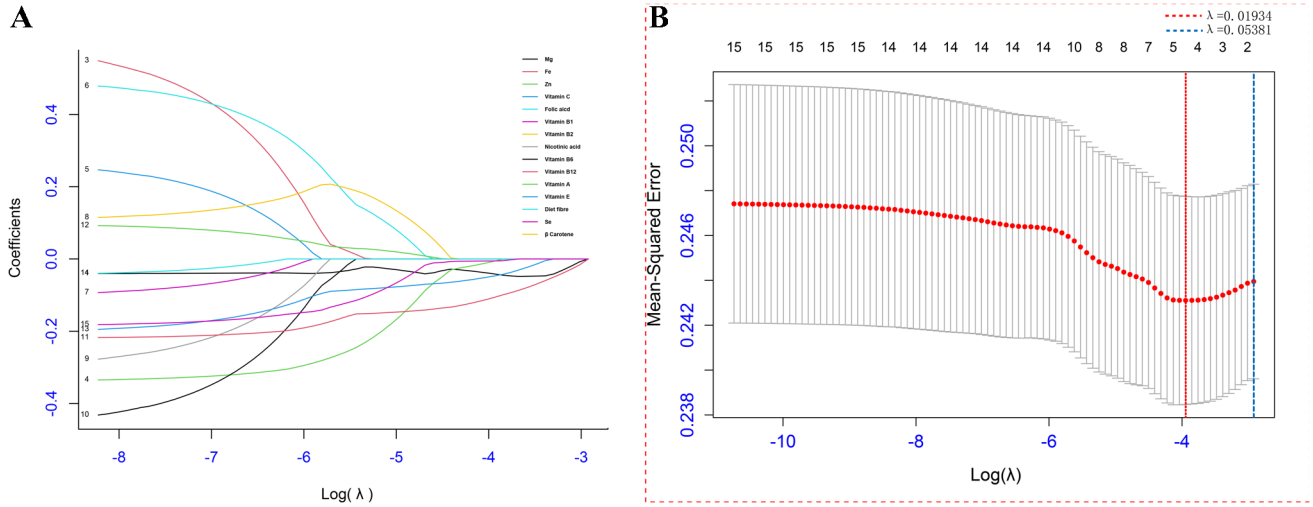

Figure 3. **A**. LASSO coefficient distribution of fifteen nutrients. Generate coefficient distribution map for log (lambda) sequence. **B**. Optimization parameters of LASSO model (lambda). By cross-validation selection, the mean square error is plotted relative to log (lambda), and a vertical line is drawn at the value selected by cross-validation. The black dotted and its error bars represent the cross-validation curve at different values of λ. The red dotted line represented the optimal value of λ, at which the minimum mean squared error (MSE) was identified. In order to reduce biased estimates as much as possible and include as many variables as possible to reduce information loss, the cutoff value of lambda.min was selected, λ = 0.01934.

WQS	OR	95% CI	*P* value
Model 1	0.788	(0.628,0.989)	0.04
Model 2	0.756	(0.541,0.976)	0.034

Table 4. Association between the WQS index and MCI. Model 1: Empty model. Model 2 was adjusted for age, gender, resident area, education level, employment status, tobacco smoking, drinking status, LTPA, BMI, hypertension, and diabetes.

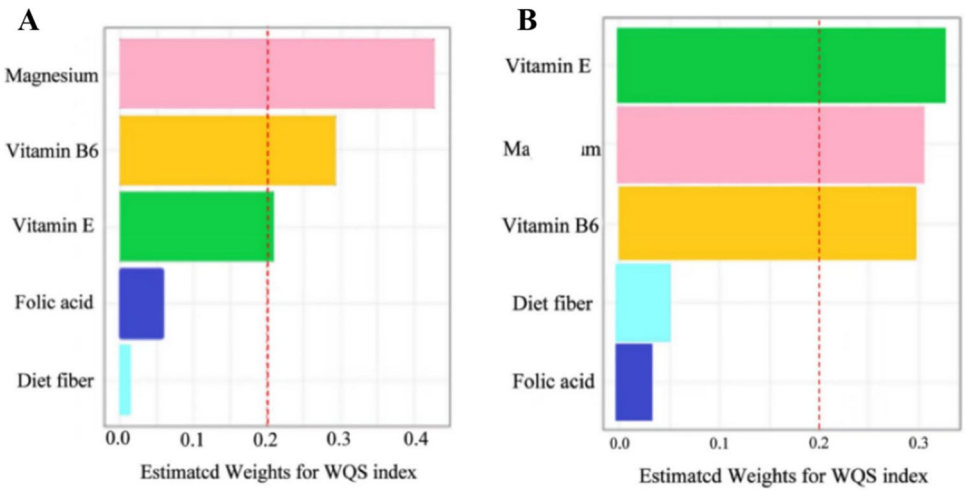

Figure 4. **A** shows the weights of five nutrients in the WQS model analysis in the empty model. **B** shows the weights of five nutrients in the WQS model analysis in the adjusted model.

Group	nutrients	groupPIP	condPIP
Group1 (metal, $r > 0.8$)	**Iron(Fe)**	**0.58**	**0.39**
	Zinc(Zn)	0.58	0.28
	Magnesium(Mg)	0.58	0.33
Group2 (vitamin, $r > 0.8$)	Folic acid	0.56	0.12
	vitamin A	0.56	0.1
	vitamin C	0.56	0.38
	vitamin B2	0.56	0.29
	vitamin B3	0.56	0.05
	β carotene	0.56	0.07
Group3	vitamin B1	0.45	1.00
Group4	**vitamin B6 × 100**	**0.50**	**1.00**
Group5	vitamin B12	0.36	1.00
Group6	**vitamin E**	**0.57**	**1.00**
Group7	Selenium(Se)	0.47	1.00
Group8	**Diet fiber**	**0.73**	**1.00**

Table 5. Posterior inclusion probabilities (PIPs) for group inclusion and conditional inclusion into BKMR model.

WQS model may result in a lower weight if a large number of variables were included, or if there were complex interactions. Two likely important variables would have smaller weights if one of them was highly correlated with another one that was assigned a low weight.

Compared with the GLM and WQS models, BKMR can identify nonlinear effects and explore the interactions between nutrients[32]. In the BKMR model, the risk of MCI decreases with the level of nutrients intake, when all metabolites are at or above their sixtieth percentile, compared to when all nutrients are at their median value (S. Figure 1). In the hierarchical variable selection analyses, the group-PIP and conditional-PIP indicated that iron, vitamin C, vitamin B6, vitamin E, and diet fiber had the highest PIPs within each group and were selected as significant nutrients associated with MCI. The results showed that vitamin E, vitamin B6, and dietary fiber may play an important protective role in MCI, whereas vitamin C showed a inverse relationship and iron showed a U-shaped relationship with MCI.

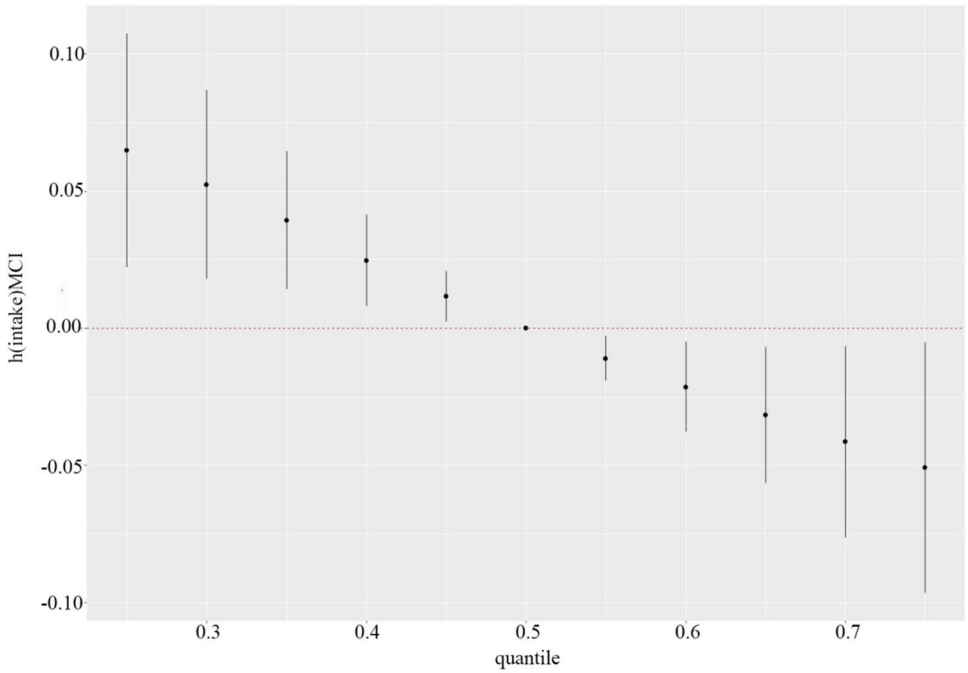

Figure 5. Joint effect (95% CI) of five nutrients on MCI when all the nutrients at particular percentiles were compared to all the chemicals at their fiftieth percentile. The results were assessed by the BKMR model, adjusted for age, gender, resident area, education level, employment status, tobacco smoking, drinking status, LTPA, BMI, daily energy intake, hypertension, and diabetes.

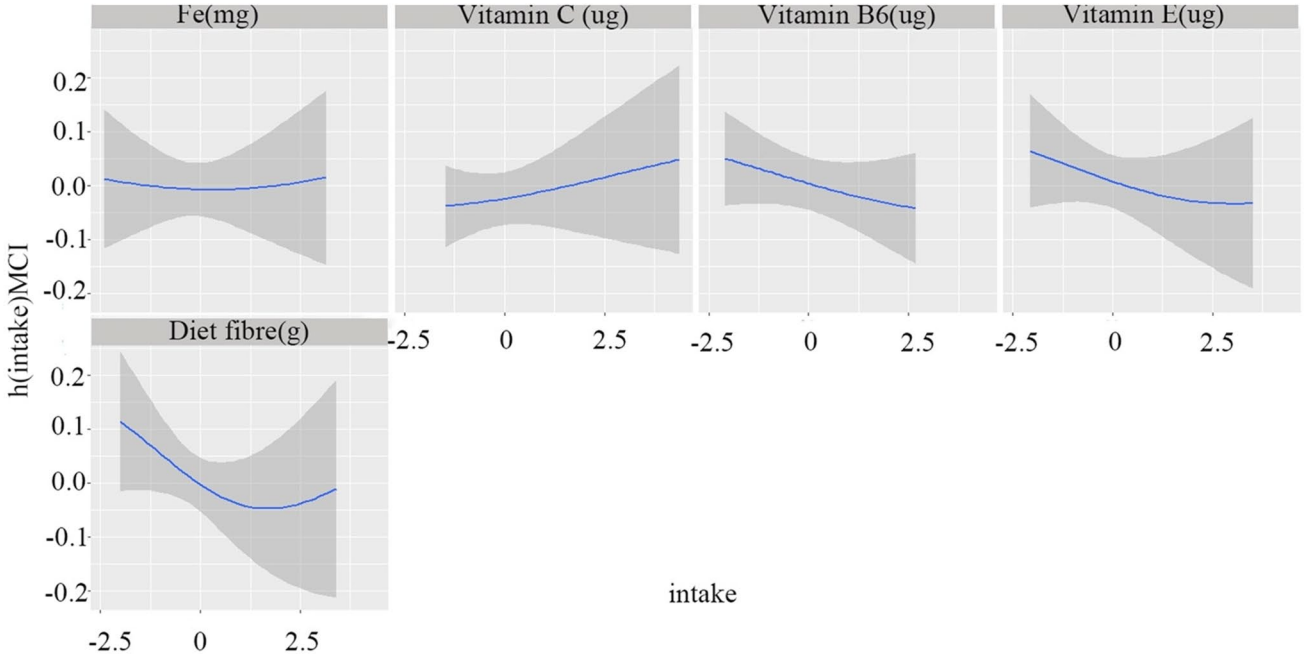

Figure 6. Intake-response function relationship between single nutrient and MCI when all other nutrient intakes were at the median level. The model was adjusted for age, gender, resident area, education level, employment status, tobacco smoking, drinking status, LTPA, BMI, daily energy intake, hypertension, and diabetes.

These results of B vitamins are similar to previous relevant reports. The protective effects of B vitamins on MCI and AD have been reported in population and basic research[12,13,33]. A prospective study involving 2,533 Chinese middle-aged and elderly people with normal initial cognitive ability showed that vitamin B6 were related to better reserves of cognitive function[34]. Folic acid, along with vitamins B12 and B6, is essential in one-carbon metabolism, a network of reactions involving the transfer of one-carbon units[12]. Deficiencies in any of these B vitamins can perturb this complex regulatory network, resulting in hyperhomocysteinemia, which has been demonstrated to be a causal contributor to cognitive decline, MCI, and AD by extensive epidemiological studies in healthy older adults and patient populations.

Magnesium showed a protective effect on MCI in the Lasso models in this study, which was consistent with the existing reports[26–28]. In the results of those three models in this study, dietary fiber had a protective effect on MCI, which may due to dietary fiber's ability to be metabolized into short-chain fatty acids by intestinal flora β-amyloid, which play a protective role in Alzheimer's disease in the neuropathological mechanism[35].

In the hierarchical variable selection analyses, the result shows that the iron s represented a U-shaped relationship with MCI. Either too high or too low iron intake is a risk factor for MCI. Alzheimer's disease has a long preclinical phase. One of the early events in the development of the disease is thought to be oxidative stress[36], due crucially to the actions of redox-active iron[37–39]. Iron deficiency hinders hippocampus-dependent learning processes and impairs cognitive performance. Hippocampal neurons require iron to generate RyR-mediated calcium signals after N-methyl-d-aspartate receptor stimulation, which in turn promotes ERK1/2 activation, an essential step of sustained hippocampal basal synaptic transmission and long-term potentiation[40]. There were reports regarding a higher brain iron concentration with accelerated cognitive decline in iron-loaded mice[41] and the brain iron accumulation in Alzheimer's patients[42] .In a previous study, serum iron parameters were determined in 818 older individuals who participated in a 3-year randomized, placebo-controlled double blind trial; cross-sectional linear regression analyses indicated that higher serum ferritin levels were significantly associated with decreased cognitive function, such as complex speed, and information-processing speed[43]. House et al. compared brain R2 values with serum iron indices, and the results suggested that iron levels in specific gray matter brain regions are influenced by systemic iron status in elderly men[44].

In theory, antioxidant nutrients, including vitamin E, vitamin C, and carotene, counteract these processes by inhibiting lipid peroxidation, the generation of reactive oxygen species, apoptosis, mitochondrial dysfunction, cytotoxic damage to cell membranes, and oxidative damage to proteins and DNA[29]. In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, the result had showed that Vitamin E had no benefit in patients with mild cognitive impairment[30]. Another double-blind, randomized, placebo-controlled trial showed that supplementation with two antioxidants, vitamin C and vitamin A, did not enhance cognitive performance[31].

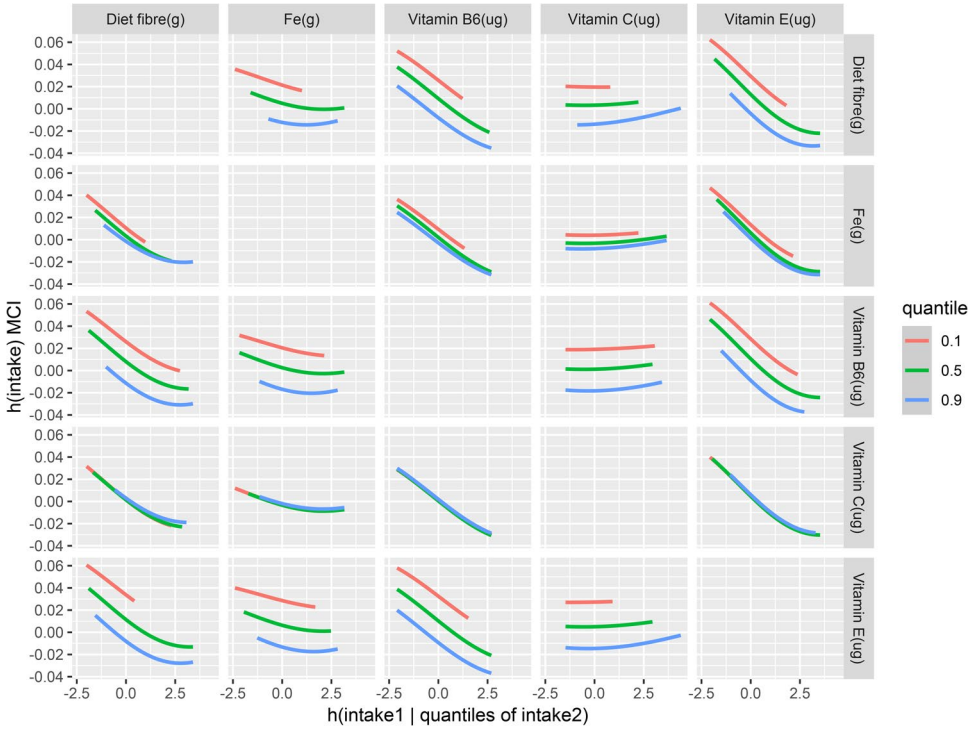

Figure 7. Association between nutrient 1 with MCI, while fixing nutrient 2 at the tenth, fiftieth, and ninetieth quantiles (and holding the remnant predictors to their median level) in the hierarchical variable selection analyses of the BKMR. The model was adjusted for age, gender, resident area, education level, employment status, tobacco smoking, drinking status, LTPA, BMI, daily energy intake, hypertension, and diabetes.

In the present study, as shown in the S. Figure 2, there was little change in the risk of MCI as vitamin a and vitamin c varied, which is similar to the results reported above.

The GLM model can provide a simple relationship between single chemicals and outcomes. The LASSO regression analysis is an advanced variable selection algorithm for data with multi-collinear and/or high-dimensional characteristics, furthermore, the WQS model can explore the effect that a mixed exposure burden has on the outcomes in one direction per occasion. The BKMR model can explore the exposure-response function of each chemical while controlling other chemicals at certain levels, in addition, explore interactions between any two of the chemicals. The potential complicated two-way interactions was found using bivariate exposure-response functions. In the hierarchical variable selection analysis of BKMR, the results of the jointed effects of bivariable on MCI showed a complex interaction between vitamins and minerals.These results provide new insights into the effects of nutrients mixed intake on MCI. Future large populations based epidemiological studies and well-designed intervention studies are warranted to validate the current findings and elucidate the biological mechanisms. Thus, these three models evaluate different aspects, and a joint interpretation will reveal their strengths, limitations, and eventual complementation.

Our study has several limitations. First, because the data in this study were collected at a single point in time, there are limitations in inferring a causal relationship between nutrient intake and MCI. Second, the food frequency questionnaire was used to collect dietary survey data, which cannot well represent the real intake of individuals. Third, the number of people included in this study was relatively small, a larger sample size would make the results more stable and reliable. Fourth, It is very unfortunate that the use of nutritional supplements was not taken into account in the study. Fifth, if there is a group of variables that are highly collinear, LASSO will somewhat arbitrarily select one of these variables for inclusion. While this makes interpretation easier in a sense (fewer variables will have non-zero coefficients), it also makes interpretation more difficult due to the arbitrary nature in which some variables are chosen over others. Finally, there is no previous study have applied BKMR model to examine the association between mixed intake of nutrients and health outcomes, The accuracy and stability of the BKMR model in this scenario need to be further confirmed.

Conclusions

Comparing the three statistical models, we found evidence of higher dietary fiber, vitamin E, and vitamin B6 levels associated with lower MCI, with a potential complicated two-way interactions, whereas vitamin C had the opposite effect. The intake of iron should be moderate. Using these nutrients as a mixture to study their effect on reducing the risk of MCI provides important evidence for study designers to design intervention strategies to reduce the risk of MCI. Future studies need to move from a "one nutrient at a time" approach to simultaneous analyses of multiple nutrients intakes in order to understand and quantify the joint effect of nutrients mixture on human health. Applying multiple methods appropriately for the study questions and data structures may help obtain a more comprehensive picture of the intake-response relationships, as well as ensure the robustness of the findings.

Statistical analyses

We expressed data as mean (SD) and *n* (%) for continuous variables and categorical variables, respectively. We used T-test and χ^2 test to compare the differences between groups.

We selected three methods for the present study: (1) the generalized linear regression (GLM) (2) the Least Absolute Shrinkage and Selection Operator (LASSO) regression and (3) BKMR. These methods were selected because they were suitable for use in this dataset, given that the elements were correlated and had opposing directions.

Data availability

The datasets generated during and/or analysed during the current study are not publiclyavailable due to protect study participant privacy but are available from the correspondingauthor on reasonable request.

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Author contributions

Gao Xian, Wang Yan and Li Qingxia designed the experiment and wrote the paper; Huang Xin, Sun Yan, Zhou Yutian, Zhu Huichen and Liu Shiyao conducted the experiment.

Declarations

Ethical approval

We extracted our data from the CCSNSD, an ongoing longitudinal study established by the National Institute of Nutrition and Health of the Chinese Center for Disease Control and Prevention in 2018–2019. The program was approved by the Institutional Review Board of the National Institute of Nutrition and Health (No. 2017020, November 6, 2017). All participants received and signed informed consent before the investigation.

Competing interests

The authors declare no competing interests.

Additional information

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